UNIVERSIDADE D
COIMBRA

Filipa Lima Ramos Santos Júlio

EVERYDAY EXECUTIVE FUNCTION IN PARKINSON AND HUNTINGTON DISEASE:
A NOVEL ECOLOGICAL APPROACH

Tese de Doutoramento em Psicologia, especialidade em Neuropsicologia, sob orientação da Professora Doutora Maria Cristina Januário dos Santos e co-orientação do Professor Doutor Mário Manuel Rodrigues Simões e da Doutora Maria José Braga Marques Ribeiro, apresentada à Faculdade de Psicologia e de Ciências da Educação da Universidade de Coimbra.

Dezembro de 2022

Faculdade de Psicologia e de Ciências da Educação
da Universidade de Coimbra

Everyday Executive Function in Parkinson and Huntington Disease: a novel ecological approach

Filipa Lima Ramos Santos Júlio

Tese de Doutoramento em Psicologia, especialidade em Neuropsicologia, sob orientação da Professora Doutora Maria Cristina Januário dos Santos e co-orientação do Professor Doutor Mário Manuel Rodrigues Simões e da Doutora Maria José Braga Marques Ribeiro, apresentada à Faculdade de Psicologia e de Ciências da Educação da Universidade de Coimbra.

Dezembro de 2022

1 2 9 0

UNIVERSIDADE D
COIMBRA

The work presented in this thesis was conducted at IBILI - Instituto de Imagem Biomédica e Ciências da Vida, Faculty of Medicine, University of Coimbra, Coimbra, Portugal, at the Neurology Department of the Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal, and at the Faculty of Psychology and Educational Sciences, University of Coimbra, Coimbra, Portugal. The different studies were funded by a PhD scholarship from FCT - Fundação para a Ciência e Tecnologia, Portugal (SFRH/BD/85358/2012), and several grants and sponsor agencies (PTDC/SAU-ENB/112306/2009, PTDC/SAU-ENB/112306/20, UID/NEU/04539/2013, UID/4950/2020, COMPETE/ POCI-01-0145-FEDER-007440, Santa Casa da Misericórdia de Lisboa – PSCNC).

.

O CÉREBRO

O cérebro tem dez milhões de células em contacto
umas com as outras e dez triliões de conexões

Tanta conexão
e tanta solidão

Jorge Sousa Braga
in A Matéria Escura e Outros Poemas, Edição Assírio & Alvim, 2020

Agradecimentos

Aos Doentes, Familiares dos Doentes e Voluntários das Associações de Doentes, esses bravos generosos, altruístas e resilientes. Respect.

Aos Orientadores, pela crítica, pela bússola e pelo amparo (não necessariamente por esta ordem).

Aos Colegas do IBILI, do ICNAS e do CHUC, pelas memórias e caminhos feitos em conjunto.

À Família e aos Amigos, fonte infinita de estâmina, sempre ao meu lado para o que der e vier.

Contents

Abbreviations

ABVD – Actividades Básicas de Vida Diária

ADL – Activities of Daily Living

A-IADL – Functional Incapacity in Advanced Instrumental Activities of Daily Living

APDH – Associação Portuguesa dos Doentes de Huntington

AS – Antisaccade

BADL – Basic Activities of Daily Living

BADS – Behavioural Assessment of Dysexecutive Syndrome battery

BDI-II – Beck Depression Inventory II

CAG – Cytosine-Adenine-Guanine

CHUC – Centro Hospitalar e Universitário de Coimbra

CI – Confidence Intervals

Cognitive – Functional Incapacity due to Cognitive Factors

CTRL – Control/Controls

DH – Doença de Huntington

DHInicial – Doença de Huntington em estadio inicial

DP – Doença de Parkinson

DPEI – Doença de Parkinson em estadio inicial de doença

DPIP – Doença de Parkinson de início precoce

EarlyHD – Early Manifest Huntington's Disease

EcoK – *EcoKitchen*

EF – Executive Functions

EHDN – European Huntington's Disease Network

Emotional – Functional Incapacity due to Emotional Factors

EOPD – Early-Onset Parkinson's Disease

ESPD – Early-Stage Parkinson's Disease

F – Female

FE – Funções Executivas

GFI – Global Functional Incapacity

HADS – SIS – Hospital Anxiety and Depression Scale – Snaith Irritability Scale

H & Y – Hoehn and Yahr scale

HD – Huntington's Disease

H-IADL – Functional Incapacity in Household Instrumental Activities of Daily Living

IADL – Instrumental Activities of Daily Living

IAFAI – The Adults and Older Adults Functional Assessment Inventory

IBILI – Instituto Biomédico de Investigação da Luz e Imagem

IQ – Intelligence Quotient

IQR – Interquartile Range

K-W – Kruskal-Wallis

Low – Lower interval

M – Male

MAS – 1- or 2-back Memory Antisaccade

max – Maximum Score

min – Minimum Score

MoCA – Montreal Cognitive Assessment

MPS – 1- or 2-back Memory Prosaccade

ms – milliseconds

M-W – Mann-Whitney

OculoTMS – a composite score extracted from the sum of the oculomotor items of UHDRS - Motor scale

PD – Parkinson's Disease

Physical – Functional Incapacity due to Physical Factors

PreDH – Doença de Huntington em fase premanifesta

PreHD – Premanifest Huntington's Disease

PS – Prosaccade

QIEC – Full Scale Intelligence Quotient

QIR – Performance Intelligence Quotient

QIV – Verbal Intelligence Quotient

Q1 – First Quartile

Q3 – Third Quartile

ROI – Region Of Interest

RV – Realidade Virtual

SDMT – Symbol Digit Modalities test

SE – Standard Error

TeLPI – Irregular Word Reading Test

TFC – Total Functional Capacity subscale of the UHDRS

TMS – Total Motor Score of the UHDRS

TMT – Trail Making Test

UHDRS – Unified Huntington's Disease Rating Scale

Up – Upper interval

UPDRS – Unified Parkinson's Disease Rating Scale

UPDRS - Motor – Motor scale of the UPDRS

VR – Virtual Reality

WAIS-III – Wechsler Adult Intelligence Scale-III

WCST – Wisconsin Card Sorting Test

y – years

Summary

Neurodegenerative conditions such as Huntington's disease (HD) and Parkinson's disease (PD) have a profound impact not only in the affected person, but also in the extended family and social networks. In HD, the cognitive changes play a key role in the quality of life, as they affect the ability to perform everyday routines. Executive Functions (EF), which are cognitive skills crucial for keeping an independent and adaptive behaviour in daily life and perform complex tasks, are early affected in HD. The dysexecutive symptoms cause significant functional impairments even in mild or preclinical HD stages. Identifying the functional consequences of premature signs of cognitive decline is mandatory to preserve and rehabilitate the everyday cognitive function of patients and prolong their independence and well-being.

However, psychometrically robust tools to evaluate and predict the impact of EF changes in the daily life of HD patients are lacking.

This work sought to create and validate sensitive assessment methods to capture the daily impact of the subtle EF changes shown by persons with HD that maintain their routines such as having a job, driving, cooking, or managing finances.

As one of the earliest HD signs is the disruption of oculomotor behaviour, we first tested an oculomotor task aimed to detect the functional alterations related to inhibitory control deficits and impulsive behaviour in HD (Study 1). This was a saccadic paradigm with increasing working memory and fronto-executive demands that evaluated the oculomotor time and accuracy of persons with premanifest HD (PreHD). Our new assessment method successfully distinguished the PreHD group from a healthy group. The PreHD group, who had a regular performance on conventional neuropsychological tests, showed significant disruptions in their saccade trajectory and latency under more demanding task conditions. So, we were able to deduce functional alterations in PreHD from an experimental saccadic task.

Nevertheless, while holding the potential to identify HD symptoms, it is hard to extrapolate the impact these saccadic deficits have on function. Hence, we developed a

non-immersive virtual reality (VR) assessment task called *EcoKitchen*. This tool was created to capture the functional changes associated with the EF impairments caused by the HD-related basal ganglia disruption. We validated the *EcoKitchen* efficacy to capture cognitive and functional alterations not only in persons with HD (including PreHD), but also in persons with PD (Studies 2 and 3). Also, we showed the *EcoKitchen* efficacy to detect the functional impact of cognitive changes in healthy older adults (Study 4). The simulated kitchen setting allowed to identify and quantify alterations in everyday-like routines involving EF. The *EcoKitchen* confirmed that persons with PreHD and early manifest HD (EarlyHD) have diminished accuracy during task completion and that the EarlyHD group also shows a slower performance time. In persons with early-onset and early-stage PD (EOPD and ESPD), the *EcoKitchen* captured changes in performance time, but not in accuracy – suggesting that some cognitive skills are better preserved in PD than in HD. Lastly, we determined that the *EcoKitchen* was sensitive to the executive decline related to physiological ageing, as the performance time and the number of errors of healthy adults during task completion increased with increasing age.

In sum, we developed and tested novel quantitative assessment methods that proved to be reliable and accurate in discriminating disease stages, nosological entities and age categories. These tools can potentially record intergroup differences, but also changes in individual performance, which is a critical feature in clinical, research and rehabilitation settings. Quantitative data that can track performance changes during executive tasks that mimic daily-life challenges will be vital to predict the impact of the age or disease-related cognitive deterioration on functional status and assess any treatment or rehabilitation effects. This will expedite new and more effective tailored approaches to neurological disorders and to conditions with cognitive and functional alterations, such as healthy ageing.

Finally, the accurate self-report of functional deficits done by study participants showed that the knowledge we have produced can potentially enhance the patients' role in symptom appraisal and management, which will promote more equitable and fair standards of care. Furthermore, the detection of significant changes in the everyday cognitive function of older adults will help design and implement strategies to prevent, rehabilitate and mitigate the cognitive and functional decline in healthy ageing.

Sumário

Doenças neurodegenerativas como a doença de Huntington (DH) ou a doença de Parkinson (DP) têm um impacto profundo não só na pessoa com o diagnóstico, mas também na sua família e círculos sociais.

Na DH, as alterações cognitivas têm um papel fulcral na qualidade de vida, já que afetam a capacidade de desempenhar rotinas diárias. As Funções Executivas (FE) são competências cognitivas precocemente afetadas na DH e que são cruciais para um comportamento diário independente e adaptativo e para o desempenho de tarefas complexas. Estes défices executivos provocam défices funcionais significativos mesmo em fases iniciais ou pré-clinicas da DH. A identificação das consequências funcionais dos sinais precoces de declínio cognitivo é indispensável para a preservação e reabilitação da cognição funcional quotidiana dos doentes, prolongando a sua independência e bem-estar.

Contudo, instrumentos psicometricamente robustos para avaliar e predizer o impacto da disfunção executiva no dia-a-dia das pessoas com DH são ainda escassos.

Este trabalho pretendeu criar e validar métodos de avaliação sensíveis para captar o impacto das alterações subtis nas FE apresentadas por pessoas com DH que mantêm responsabilidades como um emprego, conduzir, cozinhar ou gerir finanças.

Como um dos sinais mais precoces da DH é a disrupção da função oculomotora, começámos por testar uma tarefa oculomotora para detetar as alterações funcionais causadas pelos défices no controlo inibitório e pelo comportamento impulsivo na DH (Estudo 1). Esta era um paradigma sacádico, com exigências crescentes de memória de trabalho e de competências fronto-executivas, que avaliava o tempo e a precisão oculomotora de pessoas com DH premanifesta (PreDH). Este novo método de avaliação conseguiu distinguir o grupo com PreDH de um grupo saudável. O grupo com PreDH, com um desempenho regular em testes neuropsicológicos convencionais, exibiu anomalias significativas em termos da trajetória e latência das sacadas em condições de tarefa mais exigentes. Desta forma, conseguimos inferir alterações funcionais na PreDH a

partir de uma tarefa sacádica experimental.

Apesar do potencial para detetar sintomas da DH, é difícil extrapolar o impacto que os défices sacádicos identificados têm em termos de função. Assim, desenvolvemos uma tarefa de realidade virtual (RV) não imersiva denominada *EcoKitchen*. Este instrumento foi criado para captar os défices funcionais associados aos défices executivos causados pela disrupção dos gânglios da base inerente à DH. Validámos a eficácia da *EcoKitchen* em captar alterações cognitivas e funcionais não só em pessoas com DH (incluindo PreDH), mas também em pessoas com DP (Estudos 2 e 3). Demonstrámos ainda a eficácia da *EcoKitchen* na deteção do impacto funcional das alterações cognitivas em pessoas idosas (Estudo 4). A simulação de uma cozinha permitiu identificar e quantificar as mudanças que ocorrem em rotinas diárias que envolvam FE. A *EcoKitchen* provou que pessoas com PreDH e com DH em estadio inicial (DHInicial) têm um desempenho menos preciso e que o grupo com DHInicial tem ainda um desempenho mais lento. Em pessoas com DP de início precoce e DP em estadio inicial de doença (DPIP e DPEI), a *EcoKitchen* identificou alterações no tempo mas não na precisão de desempenho – o que sugere que algumas áreas cognitivas estão mais preservadas na DP do que na DH. Por último, provámos que a *EcoKitchen* é sensível ao declínio executivo associado ao envelhecimento fisiológico, já que o tempo e o número de erros de desempenho dos adultos saudáveis aumenta com o aumento da idade.

Em suma, desenvolvemos e testámos novos métodos de avaliação quantitativa que provaram ser fiáveis e precisos, discriminando estadios de doença, entidades nosológicas e categorias etárias. Estes instrumentos conseguirão registar diferenças intergrupais mas, também, alterações no desempenho individual, o que é muito relevante nos contextos clínico, de investigação e de reabilitação. Dados quantitativos que consigam detetar alterações no desempenho de tarefas executivas que mimetizam desafios quotidianos serão cruciais para prever o impacto funcional do declínio cognitivo causado por doença ou idade e avaliar o resultado do tratamento ou reabilitação. Isto facilitará abordagens novas, personalizadas e mais eficazes às doenças neurológicas e também a condições que impliquem alterações cognitivas e/ou funcionais, como o envelhecimento saudável.

Por fim, a fidedignidade dos auto-relatos sobre défices funcionais feitos pelos participantes dos estudos mostra que o conhecimento que produzimos poderá reforçar o papel dos doentes na narrativa e gestão dos seus sintomas, o que promoverá uma prestação de cuidados mais equitativa e justa. Além disso, a detecção de alterações significativas na cognição funcional quotidiana de pessoas idosas facilitará o desenho e

implementação de estratégias de prevenção, reabilitação e mitigação do declínio cognitivo e funcional no envelhecimento saudável.

Motivation

The first time I heard about Huntington's disease (HD) was in 2007, when I joined a research team that was developing two studies about emotion recognition and implicit contextual learning in patients with HD at the IBILI – Instituto Biomédico de Investigação da Luz e Imagem, in Coimbra (van Asselen, Almeida, et al., 2012; van Asselen, Júlio, et al., 2012). These two studies resulted from a close collaboration between the Movement Disorder Unit and the Neurogenetics Consultation Service of the Neurology Department of the CHUC - Centro Hospitalar e Universitário de Coimbra (led by Professora Doutora Cristina Januário and Professor Doutor António Freire) and the research group led by Professor Doutor Miguel Castelo-Branco at IBILI. To make a connection between the IBILI and the CHUC project teams that could facilitate a fast and suitable recruitment of study participants, I started to attend the weekly clinical visits of HD families at CHUC. During this time, I also helped preparing the application of the HD team at CHUC, led by Professora Doutora Cristina Januário, to enter the Registry study, promoted by the EHDN – European Huntington's Disease Network (http://www.ehdn.org/pt/). From 2009 until 2017, the consortium CHUC/IBILI became part of the Registry study, one of the largest multi-centre, multi-national, prospective, observational studies ever done in HD or in any other rare neurological disorder (Orth et al., 2010). The Registry study, which involved 17 European countries, aimed to obtain natural history data on as many persons who are part of an HD family as possible, relate phenotypical characteristics (genetic modifiers/wet and dry biomarkers), expedite identification and recruitment of participants for clinical trials, develop and validate sensitive and reliable outcome measures for detecting onset and change over the natural course of premanifest and manifest HD, identify potential outcome measures for use in future clinical trials and clinical care, and help to plan for future research studies (National Institutes of Health, 2012). My role in the Registry was to do the cognitive and behavioural assessments of study participants and coordinate the study visits. I became a regular member of the EHDN in 2010. The Coimbra site was the

second largest Registry site in Portugal and enrolled a total of 114 participants; this has allowed me to get to know and follow a very broad and heterogeneous group of persons affected by HD for many years. As I was getting more involved with HD families, Mrs Ursula Anna Kleibrink, the President of the APDH - Associação Portuguesa dos Doentes de Huntington (https://www.huntington-portugal.com/) at the time, and Professora Doutora Cristina Januário challenged me to become more involved with the HD community in Portugal. The APDH was a quite recent, small, and penniless lay association, representing HD families at a national level and run by a group of volunteers that were family members and friends of HD patients. The organization only had a small office space in Lisboa and representatives in Algarve and in Porto. All the help they could get was more than welcome and so I started to represent the APDH in Coimbra in 2008. I later became President of the Board between 2009 and 2014, and I have been Vice-president of APDH since then. I was also involved as a volunteer in the International Huntington Association between 2011 and 2018 (Board Member at Large) (https://huntington-disease.org/), and I am still actively involved in different international HD organizations, such as the European Huntington Association (Secretary of the Board since 2012) (http://eurohuntington.org/), the Huntington's Disease Youth Organization (Portuguese translator since 2012) (Huntington's Disease Youth Organization, 2017) and HDBuzz (Portuguese translator since 2011) (HDBuzz, 2011). It should be noted that all these organizations lay on the altruism and tenacity of HD family members and friends. I was warmly welcomed and rapidly felt part of a new, energetic, proactive, and multilingual community. And, of course, I did not want to leave. At the end of 2018, I was invited to represent the neurological patient advocates at the new Committee for Ethical and Responsible Conduct of Research, at the i3S consortium of the University of Porto (i3S – University of Porto, 2018). Monthly, I attend the Committee meetings and bring the neurological patient perspective to the research debate. In October 2020, I was invited by the European Huntington Association to become the Project Manager of a project called "MOVING FORWARD - Toward a Future with Effective Disease-Modifying Therapies for Huntington's Disease" (https://ehamovingforward.org/). The main goal of the project is to mobilize the European HD community to show a strong and long-term commitment to research, by increasing trial awareness, increasing health literacy, reducing barriers to study participation, building up the research staff skills on ways to communicate and relate with HD families, and increasing clinical trial readiness (Júlio et al., 2021). I am

extremely happy to be able to work on the improvement of the research experience of HD families and hopefully bring patients closer to effective treatments for this complex disease.

My PhD project started as a direct result of all the experiences, debates, hopes, struggles, laughs, tears, and learnings I shared with the Portuguese and global HD communities. I wanted my project to be meaningful and to have a tangible impact on the lives of patients and families with HD, addressing the challenges emerging from their real-life experiences by investigating a relevant topic that could make a difference to those I know in the HD community.

The keystone for this project came from the many hours I spent observing HD family members and patients interact – either at the Laboratory, the Hospital, or at the HD Association. One intriguing thing for me was that people with a positive genetic test for Huntington's disease but still without any visible symptoms of the disease (in the so-called premanifest or prodromal HD stage - PreHD) often presented a standard performance and results in conventional neuropsychological assessment measures but, at the same time, had several complaints about changes and problems in their everyday routines at home or work. Frequently, the family members corroborated these reports and added relevant and detailed information about subtle but impactful cognitive/behavioural changes in their otherwise asymptomatic HD affected relatives. I did not doubt the veracity of these stories, but when I resorted to commonly used neuropsychological tests to assess these behavioural and cognitive alterations, I could not detect any deficit or impairment. Therefore, I hypothesized that although the cognitive changes were probably real, the assessment methods we used were not sensitive enough to detect them. Moreover, in earlier studies developed at IBILI, the results about cognitive and behavioural changes in preclinical HD were not conclusive (van Asselen, Almeida, et al., 2012; van Asselen, Júlio, et al., 2012).

These observations highlighted the need to develop more realistic and ecologically relevant methods to assess cognition and function. These new tools would be essential to detect and detail the everyday life changes presented by persons with PreHD and help us plan tailored interventions to reduce the impact of these deficits on the quality of life of these families.

The multidisciplinary team at IBILI, that included a wide variety of academic backgrounds – computer engineers, web designers, biomedical engineers, neurologists, neuropsychologists, statisticians, and physicists, just to mention a few – was the perfect

incubator to design, develop, and test new assessment tools that are able to overcome the limitations of more conventional cognitive and functional measures.

So firstly, as changes in oculomotor function and inhibitory control are thought to represent some of the earliest HD alterations, we created an experimental saccadic task that could capture subtle cognitive and motor impairments and be more sensitive to the equivocal PreHD signs and symptoms (Júlio, Caetano, et al., 2019).

Then, secondly, as everyday chores such as meal preparation were among the daily life dimensions to be earlier and more impacted by HD, we decided to create a non-immersive virtual reality (VR) task to assess executive functions in a simulated setting of a kitchen - the *EcoKitchen* (Júlio, Ribeiro, et al., 2019). Specifically, this latter assessment method that we created to address the functional problems caused by the cognitive symptoms associated with Huntington's disease, was recognized by the international HD research and clinical community as an important development in HD assessment – we received the Best Clinical Poster Award at the European Huntington's Disease Network Conference in The Hague – The Netherlands, in 2016 (Júlio et al., 2016). Additionally, several researchers and patient representatives have demonstrated interest in using *EcoKitchen* thereby expanding our results to other HD groups and other clinical conditions.

The main findings of the work described in this thesis were disseminated by the following means: three papers as first author published in international scientific periodicals with referees; two papers as co-author published in international scientific periodicals with referees; one paper as first author submitted to an international scientific periodical with referees; four papers as first author published in conference proceedings; two papers as co-author published in conference proceedings; 11 oral communications (nine as first author and two as co-author) and 24 poster communications (10 as first author and 14 as co-author) presented at national and international scientific meetings.

I hope that these behind-the-scenes stories can contextualize the background of my PhD project and give a glimpse of the path I have started to travel back in 2007, often against all odds.

And, most of all, I hope that this journey continues to be full of marvels and wonders despite the bumps and setbacks that are inextricably linked to a meaningful path.

References

HDBuzz. (2011). Filipa Júlio Tradutor Inglês-Português. https://pt.hdbuzz.net/people/Filipa%20J%C3%BAlio

Huntington's Disease Youth Organization. (2017). HDYO Hot-Seat with Filipa. https://en.hdyo.org/a/527-hdyo-hot-seat-with-filipa

i3S – University of Porto. (2018). Committee for Ethical and Responsible Conduct of Research – Members. https://www.i3s.up.pt/ethics-integrity.php#associationTeam

Júlio, F., Blanco, R., Casanova, J. P., D'Alessio, B., De Schepper, B., De Sousa, D., De Sousa, P., Ferreira, C., Gommans, H., Haselberg, R., Hermant, E., Lis, D., Maffi, S., Olsen, S. O., Papantoniou, M., Squitieri, F., Tretyakova, M., Umakhanova, Z., Václavík, V., Winkelmann, M., … On Behalf Of The European Huntington Association (2021). Perceptions about Research Participation among Individuals at Risk and Individuals with Premanifest Huntington's Disease: A Survey Conducted by the European Huntington Association. *Journal of Personalized Medicine*, *11*(8), 815. https://doi.org/10.3390/jpm11080815

Júlio, F., Caetano, G., Januário, C., & Castelo-Branco, M. (2019). The effect of impulsivity and inhibitory control deficits in the saccadic behavior of premanifest Huntington's disease individuals. *Orphanet Journal of Rare Diseases*, *14*(1), 246. https://doi.org/10.1186/s13023-019-1218-y

Júlio, F., Malhão, A., Pedrosa, F., Gonçalves, H., Simões, M., Simões, M.R., van Asselen, M., Casteolo-Branco, M., & Januário, C. (2016). Everyday Executive Function in Huntington's Disease: Early Deficits Assessed by a Virtual Reality Task. *Journal of Neurology Neurosurgery & Psychiatry, 87* (Suppl 1), A1–A120. http://doi.org/10.1136/jnnp-2016-314597.144

Júlio, F., Ribeiro, M. J., Patrício, M., Malhão, A., Pedrosa, F., Gonçalves, H., Simões, M., van Asselen, M., Simões, M. R., Castelo-Branco, M., & Januário, C. (2019). A Novel Ecological Approach Reveals Early Executive Function Impairments in Huntington's Disease. *Frontiers in Psychology*, *10*, 585. https://doi.org/10.3389/fpsyg.2019.00585

National Institutes of Health. (2012). REGISTRY - an Observational Study of the European Huntington's Disease Network (EHDN) (REGISTRY). ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT01590589

Orth, M., Handley, O. J., Schwenke, C., Dunnett, S. B., Craufurd, D., Ho, A. K., Wild, E., Tabrizi, S. J., Landwehrmeyer, G. B., & Investigators of the European Huntington's Disease Network (2010). Observing Huntington's Disease: The European Huntington's Disease Network's REGISTRY. *PLoS currents, 2,* RRN1184. https://doi.org/10.1371/currents.RRN1184

van Asselen, M., Almeida, I., Júlio, F., Januário, C., Campos, E. B., Simões, M., & Castelo-Branco, M. (2012). Implicit contextual learning in prodromal and early stage Huntington's disease patients. *Journal of the International Neuropsychological Society*, *18*(4), 689–696. https://doi.org/10.1017/S1355617712000288

van Asselen, M., Júlio, F., Januário, C., Campos, E. B., Almeida, I., Cavaco, S., & Castelo-Branco, M. (2012). Scanning Patterns of Faces do not Explain Impaired Emotion Recognition in Huntington Disease: Evidence for a High Level Mechanism. *Frontiers in Psychology*, *3*, 31. https://doi.org/10.3389/fpsyg.2012.00031

Chapter I - General Introduction

In this section of the thesis, we provide an overview of the global definition and main features of Huntington's disease (HD). We pay special attention to the cognitive symptoms caused by this condition and its impact on the functional status of persons with this diagnosis. Specifically, we describe the challenges underlying an accurate assessment of executive functions (EF) and the need to find new tools that can tackle what is known as functional cognition in a more ecological way. Lastly, we discuss the relevance of computer-based assessment tools to overcome the constraints of conventional neuropsychological tests, to capture the impact of EF deficits on daily life-like situations and to predict the functional status of cognitively impaired populations.

Huntington's disease

General Description

Huntington's disease is a rare autosomal dominant neurodegenerative disorder caused by a Cytosine-Adenine-Guanine (CAG) trinucleotide expansion in the Huntingtin gene (≥ 36 repeats). The disease bears the name of the American physician George Huntington, who first provided a comprehensive description of HD in a paper entitled "On Chorea", published in 1872 (Huntington, 1872). Back then, Huntington already pointed some of the key features of this condition: "There are three marked peculiarities in this disease: 1. Its hereditary nature. 2. A tendency to insanity and suicide. 3. Its manifesting itself as a grave disease only in adult life" (Huntington, 1872). For many years, the disease was known as Huntington's Chorea, since chorea was the cornerstone of HD clinical diagnosis. Chorea derives from the Greek word "dance" and describes an

abnormal involuntary movement characterized by brief, abrupt, irregular, unpredictable, non-stereotyped, random flow of muscle contractions that can affect various body parts, and interfere with speech, swallowing, posture, and gait (Ho & Leong, n.d.). However, what was once considered a traditional movement disorder is now better described with three key features of basal ganglia dysfunction: motor abnormalities, psychiatric/behavioural changes, and cognitive decline – and therefore is now known as Huntington's Disease, although its conventional diagnosis is still based on the onset of an unequivocal movement disorder (Paulsen, 2010; Reilmann et al., 2014). This triad of symptoms is particularly challenging for clinical care and research, as there is a huge variability in symptom presentation across patients and even across the disease span of one single patient (Kim et al., 2017; Sax et al., 1989). The mean age of HD clinical onset is around 40 years, and the disease inevitably progresses over a course of 15 to 20 years leading to a premature death, since no effective therapies exist to halt or change the inexorable disease course (Ghosh & Tabrizi, 2018; Roos, 2010; Ross & Tabrizi, 2011; Shoulson & Young, 2011). Usually, it is the concomitant complications of HD which cause death, not HD *per se* (Haines & Conneally, 1986). Pneumonia, often due to aspiration of food caused by lack of swallowing control, is the most frequent cause of death in late-stage HD patients (Haines & Conneally, 1986; Solberg et al., 2018). Suicide is also a much more common cause of death in the HD population compared to the general population (Bindler et al., 2009; Solberg et al., 2018), a fact that emphasizes the need to provide appropriate psychological/psychiatric care to persons with HD. Thus, the disease impact is extremely harsh, with a relentless decline of all the skills that underlie independent living and a marked disruption of the quality of life and functional capacity of persons that were otherwise in their most productive period of life, with the greatest responsibilities at home and/or at work (Claassen, et al., 2021; Shoulson & Young, 2011). Hence, HD involves unrelenting progressive motor, cognitive and psychiatric symptoms (Ghosh & Tabrizi, 2018) that lead to a gradual loss of capacities related to occupation, financial management, domestic tasks, and self-care skills (McAllister, et al., 2021).

The reduced number of persons affected by HD, which has an estimated overall prevalence of 10.6-13.7 individuals per 100,000 in Western populations (McColgan & Tabrizi, 2018), makes it a rather marginalized condition and has delayed the quest for effective disease-modifying treatments. Nevertheless, the current HD research skyline is extremely promising, with several new therapeutic compounds either in clinical

evaluation or on the verge of being so (Bashir, 2019; Dash & Mestre, 2020). Consequently, all the work aimed at validating measures and markers in Huntington's disease to support the development of successful treatments is thought to be urgent and crucial (Tang et al., 2021).

Genetic and Clinical Features

HD is the most common monogenic neurodegenerative disease, a single-gene disorder with autosomal dominant transmission (Ghosh & Tabrizi, 2018; Nopoulos, 2016). The presence of the mutation on either allele leads to the disease and an affected parent has a 50% chance of passing it on to their child (Ghosh & Tabrizi, 2018). The HD genetic mutation is an expanded Cytosine-Adenine-Guanine (CAG) trinucleotide repeat near the start of exon 1 of the Huntingtin gene, which lies on the short arm of chromosome 4 (Ghosh & Tabrizi, 2018). The CAG repeat length ranges from 10 to 35 in the healthy population, with a mean value of 18 CAG repeats (Nopoulos, 2016; Snell et al., 1993). The mutation is fully penetrant at 40 or more CAG repeats, leading to unrelenting symptom presentation. Between 36 and 39 CAG repeats there is reduced penetrance, and carriers may develop HD symptoms in later life or not at all (Rubinsztein et al., 1996). A Huntingtin gene with 27–35 CAG repeats is referred to as an "intermediate allele". Persons who inherit intermediate length alleles are thought to be unaffected, although a behavioural phenotype has now been identified in this group (Killoran, 2013). A longer CAG repeat length correlates with earlier age of onset (Ghosh & Tabrizi, 2018). As with all genetic conditions, a detailed family history is essential to help make a correct diagnosis of HD (Ghosh & Tabrizi, 2018).

Since 1993, with the discovery of the genetic mutation responsible for HD (The Huntington's Disease Collaborative Research Group, 1993), genetic testing by direct mutation analysis has been available to families affected by HD (Craufurd et al., 2015). The genetic test can be used either to confirm a clinical diagnosis of HD in symptomatic people (diagnostic genetic testing) or to predict whether an at-risk person will go on to develop HD (predictive genetic testing) (Craufurd et al., 2015; MacLeod et al., 2013). The latter situation allowed for the offspring of persons with HD to know whether they have inherited the gene mutation (MacLeod et al., 2013). Thus, since the HD mutation was identified, it became possible to determine, prior to symptom onset, who is a carrier of the CAG repeat expansion and one day will develop HD (Craufurd et al., 2015; O'Keeffe

et al., 2009). This breakthrough had a big impact on the natural history of HD, as it enabled to follow the neurodegenerative process many years before symptom onset (Tabrizi et al., 2013). Hence, the HD path could now be divided into "premanifest" and "manifest" periods (Reilmann et al., 2014; Ross, Aylward, et al., 2014). The premanifest period could be further subdivided: initially, persons that carry the HD mutation but apparently do not display any overt symptoms – premanifest HD (PreHD) – are not clinically distinguishable from healthy persons, usually up to 10-15 years before the disease onset; then, they may enter the prodromal HD period, which is characterized by subtle motor, cognitive and behavioural changes with null to minor functional consequences (Ross, Aylward, et al., 2014). Once motor symptoms with functional impact begin, the person is said to have manifest HD and consequently the clinical diagnosis is made and "added" to the genetic diagnosis (Ross, Aylward, et al., 2014). Hence, the onset of manifest disease is said to occur when patients develop definitive motor signs suggestive of HD, which have no other explanation – typically chorea (Ghosh & Tabrizi, 2018). HD differential diagnosis has become easier since the advent of the genetic test, and is typically based on family history, presence of the movement disorder and confirmed mutation on genetic testing (Snowden, 2017).

Historically, HD onset has been defined as the point where motor abnormalities detected at clinical examination are deemed unequivocal signs of HD – with no consideration for cognitive and/or psychiatric changes (Solomon et al., 2008). However, because of the great variety of symptoms and because signs of HD develop gradually, which makes the conversion from a premanifest to a manifest HD stage rather insidious, it is difficult to determine the precise clinical onset of the disease (Paulsen, 2010; Witjes-Ané et al., 2003). The genetic test confirms whether an asymptomatic person will develop symptoms of HD but not when those symptoms will first appear (Snowden, 2017). In fact, having a positive genetic test confirms the presence of an abnormal CAG expansion and provides information on gene status, but not on disease state (O'Keeffe et al., 2009) – since it gives no indication about the clinical condition at the time of testing, how and when HD symptoms will start, or how quickly they will progress (Antoniades et al., 2010; Craufurd et al., 2015; Dumas et al., 2013). Nonetheless, and even though the genetic test is a trait marker rather than a state marker (Craufurd et al., 2015), the CAG-repeat length in the HD gene was found to be inversely correlated with age of onset (Langbehn et al., 2010). Thus, formulae that include variables such as CAG-repeat length and current age were created to predict the time point when HD overt symptoms will begin (Langbehn

et al., 2004; Zhang et al., 2011). While these formulae lack the accuracy to be helpful at an individual level, they provide a valuable proxy of HD clinical onset for research purposes (Snowden, 2017). Adding to the complexity of HD clinical and genetic diagnosis, there is the high incidence of cognitive impairments in HD patients, that often emerge many years prior to the onset of motor symptoms and are important contributors to disability (Ross, Aylward, et al., 2014; Stout et al., 2011). Therefore, a comprehensive evaluation of persons at-risk of HD or with PreHD can be a more accurate and reliable basis for determining the disease clinical onset than sole reliance on judging the motor features of HD (Shoulson et al., 2019). Currently, and although the nature and time course of the earliest HD changes remains a matter of debate, the disease is believed to have a long preclinical period with subtle symptoms, that encompasses not only motor abnormalities, but also impactful cognitive and psychiatric alterations (Reilmann et al., 2014; Ross, Aylward, et al., 2014; Shoulson & Young, 2011; Snowden et al., 2002; Stout et al., 2011).

Neuropathology

HD primarily affects the basal ganglia, causing early damage and death to the neurons of two specific structures of the striatum – the caudate nucleus and the putamen (Aylward, et al., 1996; Rosas et al., 2001; Shoulson & Young, 2011; Vonsattel & DiFiglia, 1998). The basal ganglia comprise a cluster of subcortical nuclei that include the striatum (which contains the caudate nucleus and the putamen, linked together through the fundus), the ventral striatum (the nucleus accumbens and most ventral aspects of caudate and putamen, responsible for reward and aversion), the dorsal striatum (mainly involved in control over conscious motor movements and executive functions), the globus pallidus (internal and external sectors), the substantia nigra, and the subthalamic nucleus (Grahn et al., 2009; Young et al., 2021) (Figure 1).

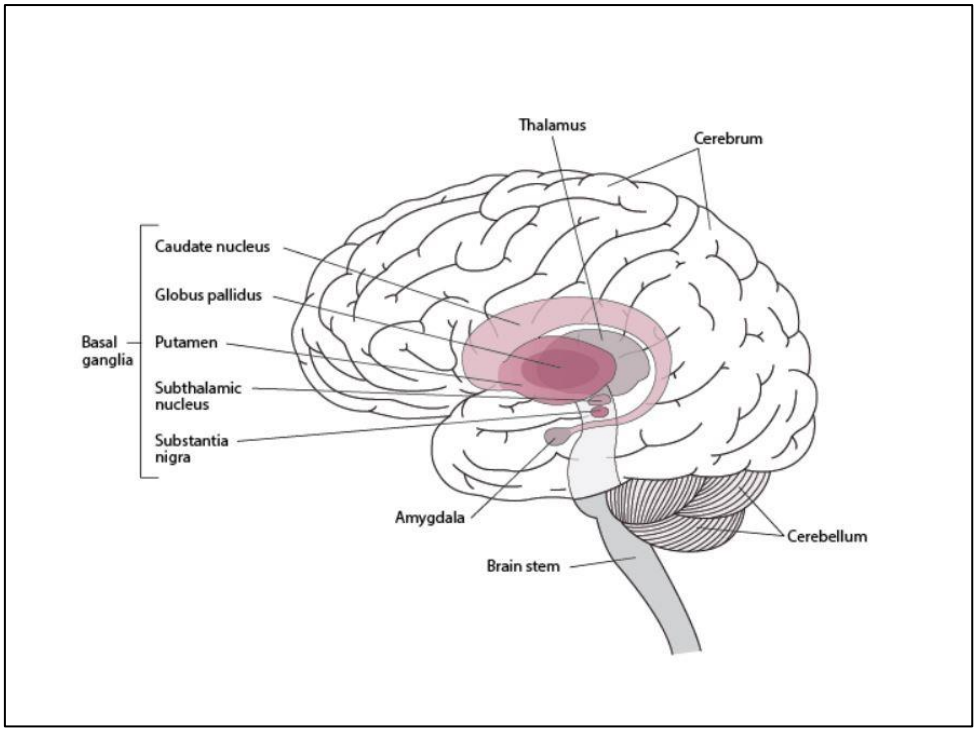

Figure 1 – Basal ganglia (Gonzalez-Usigli, 2022)

The caudate nucleus and putamen are the main input nuclei of the basal ganglia, receiving axons from nearly all parts of the cortex; they are reciprocally interconnected with the substantia nigra, and most of the basal ganglia output is sent via the internal segment of the globus pallidus (GPi) and the substantia nigra pars reticulata (SNr) (Grahn et al., 2009; Matz & Spocter 2022).

The basal ganglia were once thought to be mainly involved in motor function, working as a gate-keeping mechanism for the initiation of movement, effectively choosing which actions to allow and which actions to inhibit (Young et al., 2021). More recently, the basal ganglia and its projections have also become closely associated with cognition, namely executive functions (Marvel et al., 2019; Young et al., 2021). Neuroimaging data indicates that the conventional "motor" structures contain subregions that cooperatively participate in cognitive processes (Marvel et al., 2019). The basal ganglia projections to limbic and prefrontal regions of the thalamus and cortex are related to executive decision-making and emotional stimulation related to reward or aversion (Young et al., 2021), processes which are fundamental to all goal-directed tasks associated with executive functioning (Grahn et al., 2009).

The HD-related striatum atrophy can be detected at least 15 years before the emergence of overt HD clinical symptoms and signs (Farrow et al., 2006; Paulsen, 2010; Shoulson & Young, 2011; Snowden, 2017; Tabrizi et al., 2012). There is a selective and early death of

the cells representing 95% of the striatal neuronal population, which are known as medium spiny neurons (Bergonzoni et al., 2021). Persons with early manifest HD show the most prominent brain pathology in the caudate nucleus, where dramatic degeneration can happen (Filley, 2019). In later stages of the disease, the putamen, frontal cortex, and white matter connections are also affected (O'Callaghan et al., 2014), consistent with frontal-subcortical network involvement and frontostriatal circuitry alterations (Cummings, 1993). Recent research led to the concept of HD as a multisystem degenerative disease of the human brain and not only a neurodegenerative disease predominantly affecting the striatum, given that the brain neurodegeneration in HD is more widespread than previously assumed and also targets the cerebral cortex, pallidum, thalamus, brainstem and cerebellum (Rüb et al., 2016).

The HD neuropathology induces a variety of abnormalities across the motor, psychiatric and cognitive domains (Brooks & Dunnett; Tabrizi et al., 2013), as the brain structures and circuitries mainly affected by this disease are thought to be involved in motor control, emotion regulation and executive functions (Filley, 2019; O'Callaghan et al., 2014).

Interventional Approaches

Regarding the HD therapeutic pipeline, and while there are no disease-modifying treatments yet, there is an exciting silver lining of different therapies being tested or soon to be (Bashir, 2019; Dash & Mestre, 2020). Yet, HD is still incurable and relentlessly progressive, and treatments only comprise pharmacological and non-pharmacological symptomatic therapies that aim to alleviate the motor and mood-based symptoms of this devastating disease (Snowden, 2017). However, a major goal for interventional therapy in HD is to find preventive treatments prior to the onset of disabling symptoms (Langbehn & Hersch, 2020; Ross, Aylward, et al., 2014). This critically depends on the capacity to find suitable, reliable, and sensitive measures to assess both HD clinical signs and therapeutic efficacy (Ross, Aylward, et al., 2014; Stout et al., 2011). The early identification of subtle HD symptoms and the consequent definition of earlier stages of disease offers an opportunity to intervene prior to the onset of profound disability (Brooks & Dunnett, 2013; Tabrizi et al., 2022). Large longitudinal studies such as TRACK-HD (Tabrizi et al., 2013) demonstrated that conventional HD motor and functional assessment scales do not provide feasible measures of change in persons with

PreHD. Hence, novel measures that can capture the complexity of preclinical and clinical HD are urged. Ideally, these measures should objectively pinpoint the current disease status, bring forward the time of detection of the earliest pathologic manifestations of the disease, and accurately reflect any improvement or stabilization resulting from an intervention (i.e., the clinical benefit of the experimental therapy) (Antoniades et al., 2010; Dumas et al., 2013).

Cognition in Huntington's Disease

Cognitive impairment is the most consistent neurological condition of acquired and degenerative brain disorders and is perceived as a significant burden by both patients and carers (Mitchell et al., 2010). Accordingly, while motor changes are the most visible conventional sign of HD clinical onset, the cognitive and behavioural disease features are thought to have the greatest effect on the functional independence and quality of life of persons with HD (Snowden, 2017). A recent study about the patient-reported impact of HD symptoms found that difficulty in thinking was the symptom with the highest life impact score to participants (Glidden et al., 2020). Additionally, a large survey about the symptoms that influence the daily life of persons with HD and their caregivers found that general cognitive decline and, specifically, problems with executive functioning were reported as the most impactful symptoms (Simpson et al., 2016). Thus, from the HD community perspective, cognitive decline is generally considered to be more debilitating to patients and their families than motor symptoms (Papoutsi et al., 2014). Therefore, cognition is an extremely important target for HD therapeutic trials because even subtle cognitive changes account for a significant portion of the variance in functional ability (beyond the influence of demographic, motor and psychiatric factors) and have an impact on meaningful outcomes such as work performance, driving, or quality of life (Paulsen & Long, 2014; Stout et al., 2011). However, and despite being considered a major source of disability, there is no persuasive evidence of benefit in HD cognitive profile from medications used to improve cognition in other dementing disorders (Shoulson & Young, 2011).

While cognitive impairment is increasingly recognized as one of the earliest core symptoms of HD (Dumas et al., 2013; Paulsen & Long, 2014), there are several topics that need further clarification, namely the predictive utility of assessing cognitive functioning

in disease onset and progression (Papp et al., 2011), the heterogeneity of cognitive changes in PreHD (Dumas et al., 2013) and the functional implications of cognitive symptoms (Van Liew et al., 2013). Hence, when addressing cognition in HD, one needs to think about how to efficiently track the cognitive changes over the disease course, how to grasp the functional impact of the cognitive changes and how persons with HD perceive the consequences of the cognitive changes associated with their diagnosis. This work intends to find plausible answers to these problems.

The cognitive deficits displayed in HD match those presented in other disorders associated with striatal-subcortical brain pathology, like Parkinson's disease (Ross, Pantelyat, et al., 2014). HD patients exhibit impairments in attention (sustained and divided attention), working memory and procedural memory, mental flexibility, planning, processing speed, multitasking, organization, problem solving, implicit learning, visuospatial functions, timing and movement sequencing, face and emotion processing and recognition (Dumas et al., 2013; Filley, 2019; Hart et al., 2014; O'Callaghan et al., 2014; Papoutsi et al., 2014; Papp et al., 2011; Ross, Aylward, et al., 2014; Solomon et al., 2008; Stout & Johnson, 2005; Tabrizi et al., 2013; van Asselen, Almeida, et al., 2012; van Asselen, Júlio, et al., 2012). Cognitive domains such as language comprehension, semantic memory, spatial awareness and orientation, and delayed recall are relatively preserved until later stages of disease – which further highlights the subcortical nature of HD neurodegeneration (Dumas et al., 2013; Papoutsi et al., 2014; Papp et al., 2011). Moreover, several deficits occur at the intersection between the cognitive and psychiatric realms of function, namely problems with initiation, lack of awareness, disinhibition, and impulsivity (Ross, Aylward, et al., 2014).

Though cognitive impairments are unanimously accepted in persons with manifest HD, there is not yet a consensus about the nature and extent of premanifest HD cognitive changes (Hart et al., 2014). In fact, the differences found between the brain structure and functioning of persons with premanifest HD and healthy persons are not necessarily accompanied by deficits in task performance or cognitive decline (Rao et al., 2014). Nevertheless, several studies have demonstrated that cognitive alterations are present before the clinical diagnosis of Huntington's disease (Baake et al., 2017; Dumas et al., 2013; Papoutsi et al., 2014; Stout et al., 2011). Some authors suggest that these alterations occur prior to other disease-related changes and become detectable up to 15 years before HD formal diagnosis (Paulsen, 2010; Paulsen & Long, 2014; Papoutsi et al., 2014; Papp et al., 2011; Snowden et al., 2002; Solomon et al., 2008; Stout et al., 2011; Tabrizi et al., 2012).

Other authors suggest that cognitive decline has a relatively acute onset, occurring in a stepwise fashion around the time of HD clinical diagnosis (Snowden et al., 2002). A third group of authors refutes this claim, having failed to find differences between PreHD and healthy cognition (Farrow et al., 2006; Hart et al., 2014; Papp et al., 2011; Rao et al., 2014; Rupp et al., 2010; Witjes-Ané et al., 2003).

Despite this controversy, as researchers are trying to expand clinical trial design to enable the inclusion of PreHD cohorts with observable disease features (Langbehn & Hersch, 2020; Tabrizi et al., 2022) and recent data suggests that the efficacy of experimental therapies is higher in younger and less symptomatic participants (Fox & Harding, 2022), the PreHD phenotype is being increasingly scrutinized. The greater focus on the PreHD profile, namely in terms of cognitive skills, has shown that this group presents an abnormal performance in cognitive measures of attention, working memory, processing speed, visuomotor integration, oculomotor function, psychomotor function, episodic memory, emotion processing, and sensory-perceptual functions (Dumas et al., 2013; Paulsen, 2010; Paulsen & Long, 2014; Rupp et al., 2010; Solomon et al., 2008; Stout et al., 2011; Tabrizi et al., 2013). Deficits in specific EF closely related to everyday life, such as the capacity to dual task, psychomotor speed and the decision-making processes were observed in persons with PreHD (Heim et al., 2020; Reyes et al., 2021; Snowden, 2017). These impairments in domains that engage the fronto-striatal circuitry become clearer as individuals approach the time of HD clinical diagnosis (Solomon et al., 2008). On the contrary, there are typically null to little deficiencies in memory, language, and in measures of global cognitive functioning in PreHD (Dumas et al., 2013).

Notably, besides the lack of agreement regarding premanifest HD cognitive deficits, there is also a lack of agreement regarding the most effective methods to assess cognition at this disease stage, as no single cognitive measure is accepted as sufficiently sensitive to serve in clinical trials and generally no specific scales are recommended for assessing cognition in HD (Dumas et al., 2013; Mestre et al., 2018). Quantifiable measures of cognitive function still lack sensitivity in cohorts of persons with PreHD (Ross, Aylward, et al., 2014) – where cognitive changes often do not represent clinically significant impairments (Papp et al., 2011) and differences from healthy cognition are null or scarce (Farrow et al., 2006; Hart et al., 2014; Papp et al., 2011; Rao et al., 2014; Rupp et al., 2010; Witjes-Ané et al., 2003). As the success of experimental therapies is increasingly measured by their clinical benefit, valid outcome measures that can capture favourable

treatment effects on how a person with PreHD feels, functions or survives is thought to be vital in future clinical trials (Hufnagel, 2019; Langbehn & Hersch, 2020; Lee, n.d.).
Therefore, finding new assessment methods that can detect cognitive deficits before overt motor dysfunction offers a crucial opportunity for identifying key areas to provide earlier clinical care, monitoring clinical progress over time, and evaluating therapeutics from a research and clinical perspective (Papp et al., 2011; Paulsen & Long, 2014). A thorough review about cognitive deficits in HD that analysed more than one hundred strictly selected papers, has found that potential candidates for cognitive biomarkers in PreHD are likely to emerge from the realms of working memory, psychomotor speed, emotion recognition, and/or attentional and visuospatial executive functions, which are the cognitive domains more often mentioned by studies showing changes in preclinical HD (Dumas et al., 2013).

Executive Functions

Definition

Executive Functions (EF) have been consistently identified as one of the earliest and most affected cognitive domains in HD. They comprise a set of interrelated cognitive skills that are crucial for maintaining an independent and adaptive behaviour in everyday life and perform complex tasks (Aron et al., 2003; Gioia & Isquith, 2004; Godefroy et al., 2010; Lezak, 1982; Papagno & Trojano, 2018; Royall et al., 1993). EF generally refer to a collection of related, yet distinct "higher-level" cognitive functions involved in the control and regulation of "lower-level" cognitive processes and goal-directed, future-oriented behaviour – from goal formulation and intention formation to successful execution and processing of the outcome (Alvarez & Emory, 2006; Dirnberger & Jahanshahi, 2013; Gioia & Isquith, 2004). These skills have a regulatory control over cognitive activity, emotional response, and overt behaviour (Crawford, 1998). EF involve a plethora of abilities, such as: the inhibition of automated responses and competing actions or stimuli, the retrieval from declarative memory, the anticipation, initiation, planning, sequencing and monitoring of actions, the ability to sustain attention and resist to interference, task switching and multi-tasking (or the ability to coordinate simultaneous activity), cognitive flexibility or shifting problem-solving strategies flexibly

when necessary (or the ability to maintain and shift set), abstract thinking, the use of feedback, the ability to deal with novelty, and the maintenance, updating and manipulation of information in working memory (or the capacity to hold information actively "online" in the service of problem solving) (Alvarez & Emory, 2006; Gioia & Isquith, 2004; Koerts et al., 2011; Vaughan & Giovanello, 2010). Interestingly, daily life impairments associated with EF have been demonstrated in persons who performed within normal limits to exceptionally well on standard executive and IQ tests (Alvarez & Emory, 2006; Eslinger & Damasio, 1985; Shallice & Burgess, 1991), which may indicate that EF deficits usually manifest only in complex "real-life" situations created by the examiners (Alvarez & Emory, 2006). Any disturbances on these abilities are thought to reflect lesions in structures related to the dorsolateral-prefrontal-subcortical circuit (namely in the dorsolateral frontal cortex projections to the dorsolateral head of the caudate nucleus), which is involved in the management of executive functions and motor programming (Alvarez & Emory, 2006; Cummings, 1993; Hanes et al., 1995). As these brain structures and circuitries are prematurely and strikingly affected in HD, impairments in EF are among the earliest and most impactful cognitive deficits during the disease course. Consequently, an appropriate assessment of executive functions is critical to plan any necessary interventions (Gioia & Isquith, 2004).

Assessment

EF are a key component of everyday applied cognition (Skidmore, 2017) or functional cognition (Wesson et al., 2016), as they allow individuals to engage efficiently in complex daily life goal-directed behaviours and successfully manage the instrumental activities of daily living (IADL) (Chevignard et al., 2008; Katz, 1983). EF are required to optimal functioning in daily life (Godefroy et al., 2010) and considered to be significant predictors of functional status (Aretouli & Brandt, 2010; Bell-McGinty et al., 2002; Cahn-Weiner et al., 2007; Marcotte et al., 2010; Schmitter-Edgecombe et al., 2011). Thus, as neuropsychologists are increasingly being asked to answer questions regarding the effects of cognitive deficits on everyday performance (Schmitter-Edgecombe, et al., 2011), and experimental therapies are measured based on their impact on daily life (Hufnagel, 2019; Lee, n.d.), it becomes more and more relevant to capture the real-world expression of EF changes in everyday activities (Gioia & Isquith, 2004). This is even more relevant because mild EF deficits can result in significant functional deficits, decline in

occupational performance and psychiatric consequences (Eslinger et al., 2011; Foster et al., 2011; Mitchell et al., 2010; Morrison et al., 2013). Hence, this EF "macro-construct" of multiple environmentally sensitive interrelated cognitive subprocesses allow us to solve complex problems and execute complicated decisions (Alvarez & Emory, 2006), and it is exactly because of this complexity that the assessment of EF challenges our traditional testing methodologies (Gioia & Isquith, 2004; Stuss & Buckle, 1992).

Conventional neuropsychological tests provide precise measures of how a patient works cognitively within a controlled environment (Skidmore, 2017) and evaluate changes in specific neuropsychological domains, monitoring their progression and their response to any therapeutic intervention (Porffy et al., 2022; Snowden, 2017). However, these tests are often time-consuming, burdensome, and have low ecological validity, as the actual target for therapy is not a change in the test results but a change in the ability to carry out everyday routine activities (Porffy et al., 2022; Snowden, 2017). Additionally, several commonly used methods to assess EF, such as the Trail Making Test (Cavaco et al., 2013; Reitan, 1958), the Stroop test (Stroop, 1935), or the Wisconsin Card Sorting Test (Heaton, 1981), were developed to differentiate populations with and without gross cerebral pathology and provide limited information about how a person operates in the natural environment (Cicerone et al., 2006; Lai et al., 2018). So, the same tests that were developed to answer diagnostic questions are now used to answer questions about real-world functioning, with very little empirical evidence to support this practice (Chaytor & Schmitter-Edgecombe, 2003). Also, most conventional tests attempt to separate integrated functions into component parts (Burgess et al., 2006; Gioia & Isquith, 2004) and are frequently aimed at measuring a single aspect of executive functioning, such as inhibition or cognitive flexibility – whereas EF in daily life require sustained collaboration between various executive domains (Koerts et al., 2011).

Despite all these limitations posed by conventional cognitive tests, their results are expected to have implications and make predictions for the individual everyday function (Gioia & Isquith, 2004; Schmitter-Edgecombe et al., 2011), as the neuropsychological assessment has shifted from identifying brain injury and lesion location to describing the person's functional strengths and weaknesses in a contemporary cognitive neuroscience perspective of brain/behavioural systems (Cicerone et al., 2006; Lezak, 1982; Lezak et al., 2012; Schmitter-Edgecombe et al., 2011). Therefore, it is more and more obvious that solely relying on standard clinical tests to assess EF does not capture all the nuances of everyday function, since patients often perform well in clinical or laboratory settings but

demonstrate disorganized behaviour in less structured environments (Dirnberger & Jahanshahi, 2013; Godefroy et al., 2010). Hence, there has been a move towards adopting more naturalistic tests to bridge the gap between laboratory tasks of EF and functional outcome measures of everyday activities (Cicerone et al., 2006). Ecologically valid tests of EF, together with measures of activities of daily living, are thought to be particularly valuable for the assessment and management of daily life problems in neurodegenerative disorders (Dirnberger & Jahanshahi, 2013). A comprehensive picture of the individual cognitive and functional potential will integrate all sources of information, including test results, questionnaires, and observational data (Chaytor & Schmitter-Edgecombe, 2003).

In sum, to effectively capture the functional translation of the individual EF status, it is extremely important to ground the assessment of executive functioning on the measurement of observable behaviours that have real-world significance (Alvarez & Emory, 2006) and are a response to real-world demands (Gioia & Isquith, 2004). That is to say, it is crucial to overcome the ecological validity problems of the conventional neuropsychological tests.

Impact on Functional Status

Several studies have shown that there is a close connection between cognitive decline and functional status (Aretouli & Brandt, 2010; Bell-McGinty et al., 2002; Grigsby et al., 1998; Pérès et al., 2008). Many years before the clinical diagnosis of dementia there are subtle changes in IADL that can constitute an early marker of neurological disease (Pérès et al., 2008). Specific executive sub-domains such as inhibitory control, planning, mental flexibility, attention, psychomotor speed, problem solving or sequencing strongly correlate with function and may affect several quality-of-life domains in neurological conditions (Aretouli & Brandt, 2010; Mitchell et al., 2010). Similarly, in healthy older adults, a significant relationship was found between executive abilities and functional independence, particularly cognitive shifting and complex sequencing abilities (Cahn-Weiner et al., 2007; Grigsby et al., 1998). Functional changes may jeopardize the independence, security, or quality of life of neurological patients, and contribute to caregiver burden and community expenses (Aretouli & Brandt, 2010). Thus, the identification of impaired adaptive functioning is essential to provide the appropriate structure and level of care to maintain individual safety and wellbeing and implement

earlier and more effective interventions (Aretouli & Brandt, 2010; Bell-McGinty et al., 2002; Pérès et al., 2008).

HD manifestations include a wide array of impairments in motor control, and behavioural, cognitive, emotional, and social issues that severely limit a person's health-related quality of life and functional capacity (Glidden et al., 2020; Ho et al., 2009; Lai et al., 2018; Ross, Pantelyat, et al., 2014). These symptoms are thought to uniquely and significantly predict functional outcomes (Van Liew et al., 2013). The cognitive and neuropsychiatric changes associated with HD, although less evident than motor alterations, contribute greatly to the loss of functional independence of the affected person and have the greatest impact on families (Beglinger et al., 2010; Hamilton et al., 2003; Snowden, 2017), more than demographic or motor features (Nehl et al., 2004). Specifically, problems in EF have been shown to have a detrimental effect on everyday functioning, level of independence, and quality of life of people with HD (Mayeux et al., 1986; Ready et al., 2008; Snowden, 2017) and were considered by caregivers as having the greatest life impact (Simpson et al., 2016). Symptoms that reflect the HD executive dysfunction, such as generalized slowing in processing speed or the inability to regulate attention are believed to affect interpersonal relationships and independent living (e.g., ability to work and maintain employment, to socially engage, to drive and to manage household chores or to handle finances), to predict functional decline (Eddy & Rickards, 2015; Rothlind et al., 1993; Sheppard et al., 2017; Simpson et al., 2016; Snowden, 2017; Van Liew et al., 2013), and to be present even in persons with PreHD or patients with minimal motor disability (Gibson et al., 2022; Mayeux et al., 1986; Read et al., 2013; van der Zwaan et al., 2021; Williams et al., 2007). Everyday tasks that require psychomotor speed, attention regulation, sequential behaviour, or organization and manipulation of information appear to be particularly affected in mild HD (Mayeux et al., 1986; Ross, Pantelyat, et al., 2014).

Thus, a proper assessment of EF is needed to be able to accurately predict the overall functional status of persons with HD (Eddy & Rickards, 2015; Rothlind et al., 1993; Snowden, 2017). Functional deterioration can be measured as soon as cognitive deterioration is if assessment tools are sensitive enough to detect early and subtle disease manifestations (Pérès et al., 2008). Therefore, we will discuss the importance of having a more integrative and ecologically valid assessment of EF, since the tests of this cognitive domain are notorious for having anecdotally poor ecological validity (Chaytor & Schmitter-Edgecombe, 2003). For the present work, we consider it to be extremely

important to capture the subtle functional deficits caused by the cognitive alterations presented by persons with HD that are still in a so-called premanifest disease stage.

Functional Cognition and Ecological Validity

Functional cognition is a construct that lies at the intersection between everyday performance and cognition and is of key concern both to researchers and clinicians alike (Wesson et al., 2016). It was first described as the ability to complete activities that rely on the critical application of cognitive skills, but this early definition left out the motor/behavioural component of task performance and the environmental constraints in which the task is done (Donovan et al., 2008; Wesson et al., 2017). More recently, functional cognition has been defined as the observable performance of everyday activities resulting from a dynamic interaction between motor abilities, activity demands and the task environment, which is guided by cognitive abilities (Wesson et al., 2016). Thus, functional cognition embodies the performance of IADL, which are complex activities that have a greater cognitive than physical emphasis, that require integration of multiple steps and actions, and that imply sequencing for goal completion (Wesson et al., 2016). When measuring functional cognition, we are measuring both the ability to perform everyday activities and its underlying cognitive skills (Skidmore, 2017; Wesson et al., 2016), as these are thought to determine the person's capacity to be safe, live alone, work, or do any task that is important and meaningful for them in everyday life (Hartman-Maeir et al., 2009). Importantly, measures of everyday cognitive skills should correspond to the cognitive domain under study; for example, it is important to demonstrate the relationship between neuropsychological tests of executive functioning and measures of everyday executive skill, in order to validate the ability of the assessment tools used in clinical or research settings to predict daily function (Chaytor & Schmitter-Edgecombe, 2003).

The assessment of functional cognition is closely related to the notion of ecological validity. In neuropsychological assessment, ecological validity refers to the degree to which test performance corresponds to real world performance (Chaytor & Schmitter-Edgecombe, 2003) and can be defined as the functional and predictive relation between the behaviour on a set of neuropsychological tests and the behaviour in a variety of real-world settings (Sbordone, 1996) – or the challenges imposed by the assessment

procedures and the challenges that the person must confront in real life situations (Neguț et al., 2016). Ecological validity is particularly relevant for the assessment of EF, which coordinate the cognitive and behavioural capacities of the person in real-world or simulated real-world demanding situations (Gioia & Isquith, 2004). An ecologically valid assessment tool has features that are similar to natural behaviours and has value in predicting everyday function (Franzen & Wilhelm, 1996; Gioia & Isquith, 2004) – so it should be effective in capturing functional cognition.

The ecological validity and predictive power of standard neuropsychological tests regarding real-life performance have long been questioned (Porffy et al., 2022) and have two requirements: first, that the demands of the test and the testing conditions resemble the real-world demands (verisimilitude); second, that the performance on a test is empirically related to measures of everyday functioning and predicts some aspect of the individual daily functioning (veridicality) (Chaytor & Schmitter-Edgecombe, 2003; Franzen & Wilhelm, 1996; Gioia & Isquith, 2004). Verisimilitude typically requires abandoning the existing tests and creating new assessments with ecological goals in mind, that attempt to simulate critical everyday cognitive tasks and are more consistently related to outcome measures than the traditional tests (Chaytor & Schmitter-Edgecombe, 2003). Veridicality typically involves the use of statistical techniques to relate performance on traditional neuropsychological tests to measures of real-world functioning, such as employment status, questionnaires, or clinician ratings (Chaytor & Schmitter-Edgecombe, 2003). Hence, the assessment of functional cognition should be able to capture not only the cognitive deficits but also their impact on function, and demands an interdisciplinary approach that links brain, behaviour, and performance in everyday life (Chaytor & Schmitter-Edgecombe, 2003; Hartman-Maeir et al., 2009).

In neurodegenerative conditions such as HD, there is still great need for ecologically valid tasks to assess the patients' reactions to broader aspects of complex everyday problem-solving demands (Gioia & Isquith, 2004). In such cases, measures of functional cognition tackle aspects of cognitive capacity that affect the patients' wellbeing and everyday functioning, offering a basis for targeted intervention (Eddy & Rickards, 2015). The information provided by ecologically relevant assessment tools of functional cognition may help health professionals to work with individuals and their families to facilitate optimal participation in those with cognitive loss (Hartman-Maeir et al., 2009). However, while no specific measures are recommended for assessing cognition in HD (Mestre et al., 2018), also no single assessment method is recommended for estimating

functional cognition (Wesson et al., 2016). Moreover, the estimation of functional impairment is thought to be a greater challenge in the earlier stages of cognitive decline (Gold, 2012; Schmitter-Edgecombe & Parsey, 2014; Wesson et al., 2016). Therefore, novel assessment methods that can depict the functional status of persons with HD in early or premanifest disease stages and offer relevant tips to accommodate the cognitive and motor changes in daily life are much needed.

Neuropsychological Assessment of Functional Cognition

The best measurement of functional cognition involves the assessment of applied cognitive skills within varied activity demands and environments – like performance observation during the real or simulated execution of IADL with high cognitive demands (e.g., meal preparation) (Skidmore, 2017). Self-report, informant-report, and performance-based measures have commonly been used as a proxy for real-world functioning (Schmitter-Edgecombe et al., 2011). Also, the direct observation of real-world performance, which is usually done by occupational therapists, is thought to be a measure of functional cognition (Wesson et al., 2016). Importantly, most of these measures of functional cognition present significant limitations.

Both self- and informant-based assessments of wider functioning often lack objectivity and lead to over- and under-estimations of the real individual cognitive and functional capacity (Porffy et al., 2022; Wesson et al., 2016). Moreover, HD patients present problems with self-awareness and insight (Ho et al., 2006), therefore, the use of this kind of measures can be particularly problematic, as many patients are frequently unaware of their cognitive problems or the implications that these problems bring to their daily life (Fleming et al., 1996; Hartman-Maeir et al., 2009; Katz & Hartman-Maeir, 2011; Prigatano, 2005). Also, time constraints and lack of standardised measures challenge the direct observation of performance in real-world or simulated environments, which introduces reporter bias and compromises the interpretation of results (Wesson et al., 2016). Nevertheless, performance-based measures may detect differences between groups more effectively than other approaches based on self-report or informant-report measures (Jekel et al., 2015; Puente et al., 2014; Sikkes & Rotrou, 2014).

Hence, as neuropsychologists are increasingly asked to capture functional cognition, make predictions about everyday functioning and recommend meaningful

interventions, having ecologically valid assessment tools for this enterprise seems to be vital and, unfortunately, it is still not the rule (Gioia & Isquith, 2004). Specifically, as EF are difficult to comprehensively assess in conventional neuropsychological settings because of the structured nature of the testing environment, they are a fertile cognitive domain in which to study the ecological validity, verisimilitude, and veridicality of new assessment tools (Chaytor & Schmitter-Edgecombe, 2003).

Computer-Based Assessment Tools

Recent developments in technology have enabled us to create assessment measures that can replicate challenges found in everyday life while also maintaining experimental control (Porffy et al., 2022).

Computer-based tools allow for the provision of a controlled stimulus environment in which cognitive challenges can be presented along with the precise delivery and control of environmental variables, such as distracting auditory and visual stimuli (Giovannetti et al., 2006; Morrison et al., 2013; Schultheis et al., 2002). Hence, these measures arise as a promising ecologically valid alternative for classic neuropsychological tests (Neguț et al., 2016). These new technology-based methods to evaluate cognition and function are thought to reliably measure changes in IADL in ecologically valid settings, quantify functional capacity during the execution of supervised tasks in controlled assessments, minimize intra- and inter-rater variability in clinical assessments, reduce the bias created by experience and a priori expectations, and also decrease the sample size of clinical trials, shorten their duration and lower their cost (Artusi et al., 2018).

Specifically, virtual reality (VR) seems to offer numerous assets that may enhance current neuropsychological assessment protocols, address many of the limitations faced by traditional assessment methods and create several opportunities in both clinical and research domains (Schultheis et al., 2002). Measures that mimic real-life settings facilitate an increased flexibility to stimuli presentation that allows participants to bring their personal experience to devise task problems and solutions (Craik & Bialystok, 2006; Schultheis et al., 2002). Virtual environments may be especially well suited to capture the HD-related changes in functional cognition in an ecologically relevant way, as the degree of relevance or similarity that these measures have in relation to the real world is higher than that of classic neuropsychological tests (Schultheis et al., 2002).

The development of novel computer-based assessment tasks within this PhD work had

the primary goal of capturing information in a more efficient and systematic way about the impact of EF deficits on the routine behaviours of populations with both subtle and obvious dysexecutive symptoms.

Outline of the Thesis

This thesis is divided into six main chapters: General Introduction, Study 1, Study 2, Study 3, Study 4 and General Discussion. Each study chapter is an adaptation from the published article (no contents have been changed but the format has been modified to accommodate the thesis design) and is preceded by a short preface. In Chapter I, General Introduction, we concentrated on Huntington's Disease, its genetic, clinical and neuroanatomical features and corresponding impact. We also described the theoretical background underlying our work, namely the challenges of effectively capturing the functional manifestations of HD-related executive deficits, particularly in persons with rare to mild disease symptoms. In Chapter II, Study 1, we focused on HD oculomotor function as an expression of the cognitive symptoms and functional impairments of this clinical condition. We present a saccadic paradigm that has enabled us to capture the subtle EF alterations observed in persons with PreHD, namely inhibitory control deficits and impulsivity. Chapter III, Study 2, and Chapter IV, Study 3, are dedicated to the use of VR assessment methods to increase the ecological validity of the cognitive and function examinations of persons affected by basal ganglia dysfunction. We describe the development of a new computer-based assessment tool, the *EcoKitchen*, and its efficacy in detecting the functional impact of EF changes in both HD and PD. In Chapter V, Study 4, we investigated the *EcoKitchen* proficiency to identify the effect of the age-related EF decline on function. Lastly, in Chapter VI, General Discussion, we analyse and present the main implications of our work for the assessment, follow-up, and rehabilitation of persons with a dysexecutive syndrome. We finish this thesis with some considerations about future work and a set of concluding remarks.

References

Alvarez, J. A., & Emory, E. (2006). Executive function and the frontal lobes: A meta-analytic review. *Neuropsychology Review*, *16*(1), 17–42. https://doi.org/10.1007/s11065-006-9002-x

Antoniades, C. A., Xu, Z., Mason, S. L., Carpenter, R. H., & Barker, R. A. (2010). Huntington's disease: changes in saccades and hand-tapping over 3 years. *Journal of Neurology*, *257*(11), 1890–1898. https://doi.org/10.1007/s00415-010-5632-2

Aretouli, E., & Brandt, J. (2010). Everyday functioning in mild cognitive impairment and its relationship with executive cognition. *International Journal of Geriatric Psychiatry*, *25*(3), 224–233. https://doi.org/10.1002/gps.2325

Aron, A. R., Watkins, L., Sahakian, B. J., Monsell, S., Barker, R. A., & Robbins, T. W. (2003). Task-set switching deficits in early-stage Huntington's disease: Implications for basal ganglia function. *Journal of Cognitive Neuroscience*, *15*(5), 629–642. https://doi.org/10.1162/089892903322307357

Artusi, C. A., Mishra, M., Latimer, P., Vizcarra, J. A., Lopiano, L., Maetzler, W., Merola, A., & Espay, A. J. (2018). Integration of technology-based outcome measures in clinical trials of Parkinson and other neurodegenerative diseases. *Parkinsonism & Related Disorders*, *46 Suppl 1*(Suppl 1), S53–S56. https://doi.org/10.1016/j.parkreldis.2017.07.022

Aylward, E. H., Codori, A. M., Barta, P. E., Pearlson, G. D., Harris, G. J., & Brandt, J. (1996). Basal ganglia volume and proximity to onset in presymptomatic Huntington disease. *Archives of Neurology*, *53*(12), 1293–1296. https://doi.org/10.1001/archneur.1996.00550120105023

Baake, V., Reijntjes, R., Dumas, E. M., Thompson, J. C., REGISTRY Investigators of the European Huntington's Disease Network, & Roos, R. (2017). Cognitive decline in Huntington's disease expansion gene carriers. *Cortex*, *95*, 51–62. https://doi.org/10.1016/j.cortex.2017.07.017

Bashir H. (2019). Emerging therapies in Huntington's disease. *Expert Review of Neurotherapeutics*, *19*(10), 983–995. https://doi.org/10.1080/14737175.2019.1631161

Beglinger, L. J., O'Rourke, J. J., Wang, C., Langbehn, D. R., Duff, K., Paulsen, J. S., & Huntington Study Group Investigators (2010). Earliest functional declines in Huntington disease. *Psychiatry Research*, *178*(2), 414–418. https://doi.org/10.1016/j.psychres.2010.04.030

Bell-McGinty, S., Podell, K., Franzen, M., Baird, A. D., & Williams, M. J. (2002). Standard measures of executive function in predicting instrumental activities of daily living in older adults. *International Journal of Geriatric Psychiatry*, *17*(9), 828–834.

https://doi.org/10.1002/gps.646

Bergonzoni, G., Döring, J., & Biagioli, M. (2021). D1R- and D2R-Medium-Sized Spiny Neurons Diversity: Insights Into Striatal Vulnerability to Huntington's Disease Mutation. *Frontiers in Cellular Neuroscience, 15*, 628010. https://doi.org/10.3389/fncel.2021.628010

Bindler, L., Travers, D., & Millet, B. (2009). Le suicide dans la maladie de Huntington: État actuel des connaissances [Suicide in Huntington's disease: A review]. *Revue Medicale Suisse*, *5*(195), 646–648.

Brooks, S. P., & Dunnett, S. B. (2013). Cognitive deficits in animal models of basal ganglia disorders. *Brain Research Bulletin*, *92*, 29–40. https://doi.org/10.1016/j.brainresbull.2012.04.011

Burgess, P. W., Alderman, N., Forbes, C., Costello, A., Coates, L. M., Dawson, D. R., Anderson, N. D., Gilbert, S. J., Dumontheil, I., & Channon, S. (2006). The case for the development and use of "ecologically valid" measures of executive function in experimental and clinical neuropsychology. *Journal of the International Neuropsychological Society*, *12*(2), 194–209. https://doi.org/10.1017/S1355617706060310

Cahn-Weiner, D. A., Farias, S. T., Julian, L., Harvey, D. J., Kramer, J. H., Reed, B. R., Mungas, D., Wetzel, M., & Chui, H. (2007). Cognitive and neuroimaging predictors of instrumental activities of daily living. *Journal of the International Neuropsychological Society*, *13*(5), 747–757. https://doi.org/10.1017/S1355617707070853

Cavaco, S., Gonçalves, A., Pinto, C., Almeida, E., Gomes, F., Moreira, I., Fernandes, J., & Teixeira-Pinto, A. (2013). Trail Making Test: Regression-based norms for the Portuguese population. *Archives of Clinical Neuropsychology*, *28*(2), 189–198. https://doi.org/10.1093/arclin/acs115

Chaytor, N., & Schmitter-Edgecombe, M. (2003). The ecological validity of neuropsychological tests: a review of the literature on everyday cognitive skills. *Neuropsychology Review*, *13*(4), 181–197. https://doi.org/10.1023/b:nerv.0000009483.91468.fb

Chevignard, M. P., Taillefer, C., Picq, C., Poncet, F., Noulhiane, M., & Pradat-Diehl, P. (2008). Ecological assessment of the dysexecutive syndrome using execution of a cooking task. *Neuropsychological Rehabilitation*, *18*(4), 461–485. https://doi.org/10.1080/09602010701643472

Cicerone, K., Levin, H., Malec, J., Stuss, D., & Whyte, J. (2006). Cognitive rehabilitation interventions for executive function: Moving from bench to bedside in patients with traumatic brain injury. *Journal of Cognitive Neuroscience*, *18*(7), 1212–1222. https://doi.org/10.1162/jocn.2006.18.7.1212

Claassen, D. O., DeCourcy, J., Mellor, J., Johnston, C., & Iyer, R. G. (2021). Impact of Chorea on Self-care Activity, Employment, and Health-care Resource Use in Patients with Huntington's Disease. *Journal of Health Economics and Outcomes Research*, *8*(1), 99–105. https://doi.org/10.36469/001c.24620

Craik, F. I., & Bialystok, E. (2006). Planning and task management in older adults: Cooking breakfast. *Memory & Cognition*, *34*(6), 1236–1249. https://doi.org/10.3758/bf03193268

Craufurd, D., MacLeod, R., Frontali, M., Quarrell, O., Bijlsma, E. K., Davis, M., Hjermind, L. E., Lahiri, N., Mandich, P., Martinez, A., Tibben, A., Roos, R. A., & Working Group on Genetic Counselling and Testing of the European Huntington's Disease Network (EHDN) (2015). Diagnostic genetic testing for Huntington's disease. *Practical Neurology*, *15*(1), 80–84. https://doi.org/10.1136/practneurol-2013-000790

Crawford J. R. (1998). Introduction to the Assessment of Attention and Executive Functioning, *Neuropsychological Rehabilitation, 8*(3), 209-211. https://doi.org/10.1080/713755574

Cummings J. L. (1993). Frontal-subcortical circuits and human behavior. *Archives of Neurology*, *50*(8), 873–880. https://doi.org/10.1001/archneur.1993.00540080076020

Dash, D., & Mestre, T. A. (2020). Therapeutic Update on Huntington's Disease: Symptomatic Treatments and Emerging Disease-Modifying Therapies. *Neurotherapeutics*, *17*(4), 1645–1659. https://doi.org/10.1007/s13311-020-00891-w

Dirnberger, G., & Jahanshahi, M. (2013). Executive dysfunction in Parkinson's disease: A review. *Journal of Neuropsychology*, *7*(2), 193–224. https://doi.org/10.1111/jnp.12028

Donovan, N. J., Kendall, D. L., Heaton, S. C., Kwon, S., Velozo, C. A., & Duncan, P. W. (2008). Conceptualizing functional cognition in stroke. *Neurorehabilitation and Neural Repair*, *22*(2), 122–135. https://doi.org/10.1177/1545968307306239

Dumas, E. M., van den Bogaard, S. J., Middelkoop, H. A., & Roos, R. A. (2013). A review of cognition in Huntington's disease. *Frontiers in Bioscience (Scholar edition)*, *5*(1), 1–18. https://doi.org/10.2741/s355

Eddy, C. M., & Rickards, H. E. (2015). Cognitive deficits predict poorer functional capacity in Huntington's disease: But what is being measured?. *Neuropsychology*, *29*(2), 268–273. https://doi.org/10.1037/neu0000134

Eslinger, P. J., & Damasio, A. R. (1985). Severe disturbance of higher cognition after bilateral frontal lobe ablation: patient EVR. *Neurology*, *35*(12), 1731–1741. https://doi.org/10.1212/wnl.35.12.1731

Eslinger, P. J., Moore, P., Anderson, C., & Grossman, M. (2011). Social cognition, executive functioning, and neuroimaging correlates of empathic deficits in frontotemporal dementia. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *23*(1), 74–82. https://doi.org/10.1176/jnp.23.1.jnp74

Farrow, M., Chua, P., Churchyard, A., Bradshaw, J. L., Chiu, E., & Georgiou-Karistianis, N. (2006).

Proximity to clinical onset influences motor and cognitive performance in presymptomatic Huntington disease gene carriers. *Cognitive and Behavioral Neurology*, *19*(4), 208–216. https://doi.org/10.1097/01.wnn.0000213914.64772.b6

Filley C. M. (2019). History of Subcortical Cognitive Impairment. *Frontiers of Neurology and Neuroscience*, *44*, 108–117. https://doi.org/10.1159/000494958

Fleming, J. M., Strong, J., & Ashton, R. (1996). Self-awareness of deficits in adults with traumatic brain injury: How best to measure?. *Brain Injury*, *10*(1), 1–15. https://doi.org/10.1080/026990596124674

Foster, E. R., Cunnane, K. B., Edwards, D. F., Morrison, M. T., Ewald, G. A., Geltman, E. M., & Zazulia, A. R. (2011). Executive dysfunction and depressive symptoms associated with reduced participation of people with severe congestive heart failure. *The American Journal of Occupational Therapy*, *65*(3), 306–313. https://doi.org/10.5014/ajot.2011.000588

Fox, L., & Harding, R. (January 21, 2022). Finding the silver lining: An update on the Roche GENERATION-HD1 trial data. HDBuzz. https://en.hdbuzz.net/316

Franzen, M. D., & Wilhelm, K. L. (1996). Conceptual foundations of ecological validity in neuropsychological assessment. In R. J. Sbordone & C. J. Long (Eds.), *Ecological Validity of Neuropsychological Testing* (pp. 91–112). Gr Press/St Lucie Press, Inc.

Ghosh, R., & Tabrizi, S. J. (2018). Clinical Features of Huntington's Disease. *Advances in Experimental Medicine and Biology*, *1049*, 1–28. https://doi.org/10.1007/978-3-319-71779-1_1

Gibson, J. S., Rhoten, B. A., Ridner, S. H., & Claassen, D. O. (2022). Perceived Effects of Neuropsychiatric Symptoms on Functional Status in Early-stage Huntington Disease. *Western Journal of Nursing Research*, *44*(2), 141–150. https://doi.org/10.1177/0193945921992545

Gioia, G. A., & Isquith, P. K. (2004). Ecological assessment of executive function in traumatic brain injury. *Developmental Neuropsychology*, *25*(1-2), 135–158. https://doi.org/10.1080/87565641.2004.9651925

Giovannetti, T., Schmidt, K. S., Gallo, J. L., Sestito, N., & Libon, D. J. (2006). Everyday action in dementia: Evidence for differential deficits in Alzheimer's disease versus subcortical vascular dementia. *Journal of the International Neuropsychological Society*, *12*(1), 45–53. https://doi.org/10.1017/S1355617706060012

Glidden, A. M., Luebbe, E. A., Elson, M. J., Goldenthal, S. B., Snyder, C. W., Zizzi, C. E., Dorsey, E. R., & Heatwole, C. R. (2020). Patient-reported impact of symptoms in Huntington disease: PRISM-HD. *Neurology*, *94*(19), e2045–e2053. https://doi.org/10.1212/WNL.0000000000008906

Godefroy, O., Azouvi, P., Robert, P., Roussel, M., LeGall, D., Meulemans, T., & Groupe de

Réflexion sur l'Evaluation des Fonctions Exécutives Study Group (2010). Dysexecutive syndrome: Diagnostic criteria and validation study. *Annals of Neurology*, *68*(6), 855–864. https://doi.org/10.1002/ana.22117

Gold D. A. (2012). An examination of instrumental activities of daily living assessment in older adults and mild cognitive impairment. *Journal of Clinical and Experimental Neuropsychology*, *34*(1), 11–34. https://doi.org/10.1080/13803395.2011.614598

Gonzalez-Usigli, H. A. (2022). Basal ganglia [artwork]. MDS Manual. https://www.msdmanuals.com/home/brain,-spinal-cord,-and-nerve-disorders/movement-disorders/huntington-disease

Grahn, J. A., Parkinson, J. A., & Owen, A. M. (2009). The role of the basal ganglia in learning and memory: neuropsychological studies. *Behavioural Brain Research*, *199*(1), 53–60. https://doi.org/10.1016/j.bbr.2008.11.020

Grigsby, J., Kaye, K., Baxter, J., Shetterly, S. M., & Hamman, R. F. (1998). Executive cognitive abilities and functional status among community-dwelling older persons in the San Luis Valley Health and Aging Study. *Journal of the American Geriatrics Society*, *46*(5), 590–596. https://doi.org/10.1111/j.1532-5415.1998.tb01075.x

Haines, J. L., & Conneally, P. M. (1986). Causes of death in Huntington disease as reported on death certificates. *Genetic Epidemiology*, *3*(6), 417–423. https://doi.org/10.1002/gepi.1370030606

Hamilton, J. M., Salmon, D. P., Corey-Bloom, J., Gamst, A., Paulsen, J. S., Jerkins, S., Jacobson, M. W., & Peavy, G. (2003). Behavioural abnormalities contribute to functional decline in Huntington's disease. *Journal of Neurology, Neurosurgery, and Psychiatry*, *74*(1), 120–122. https://doi.org/10.1136/jnnp.74.1.120

Hanes, K. R., Andrewes, D. G., & Pantelis, C. (1995). Cognitive flexibility and complex integration in Parkinson's disease, Huntington's disease, and schizophrenia. *Journal of the International Neuropsychological Society*, *1*(6), 545–553. https://doi.org/10.1017/s1355617700000679

Hart, E. P., Dumas, E. M., Schoonderbeek, A., Wolthuis, S. C., van Zwet, E. W., & Roos, R. A. (2014). Motor dysfunction influence on executive functioning in manifest and premanifest Huntington's disease. *Movement Disorders*, *29*(3), 320–326. https://doi.org/10.1002/mds.25806

Hartman-Maeir, A., Katz, N., & Baum, C. M. (2009). Cognitive Functional Evaluation (CFE) Process for Individuals with Suspected Cognitive Disabilities. *Occupational Therapy in Health Care*, *23*(1), 1–23. https://doi.org/10.1080/07380570802455516

Heaton, R.K. (1981). *A Manual for the Wisconsin Card Sorting Test.* Psychological Assessment Resources.

Heim, B., Peball, M., Saft, C., von Hein, S. M., Ellmerer, P., Piater, J. M., Seppi, K., & Djamshidian, A. (2020). Time will tell: Decision making in premanifest and manifest Huntington's

disease. *Brain and Behavior*, *10*(11), e01843. https://doi.org/10.1002/brb3.1843

Ho, A. K., Gilbert, A. S., Mason, S. L., Goodman, A. O., & Barker, R. A. (2009). Health-related quality of life in Huntington's disease: Which factors matter most?. *Movement Disorders*, *24*(4), 574–578. https://doi.org/10.1002/mds.22412

Ho, A. K., Robbins, A. O., & Barker, R. A. (2006). Huntington's disease patients have selective problems with insight. *Movement Disorders*, *21*(3), 385–389. https://doi.org/10.1002/mds.20739

Ho, S-L & Leong, H.G. (n.d.). Chorea & Huntington's Disease. International Parkinson and Movement Disorder Society. https://www.movementdisorders.org/MDS/About/Movement-Disorder-Overviews/Chorea--Huntingtons-Disease.htm

Hufnagel, S. B. (2019, September 6). Defining and Assessing Clinical Benefit: A Regulatory Perspective. FDA – U.S. Food and Drug Administration. https://www.fda.gov/media/131585/download

Huntington, G. (1872). On Chorea. *Medical and Surgical Reporter of Philadelphia*, *26*(15), 317–321. https://neuro.psychiatryonline.org/doi/pdf/10.1176/jnp.15.1.109

Jekel, K., Damian, M., Wattmo, C., Hausner, L., Bullock, R., Connelly, P. J., Dubois, B., Eriksdotter, M., Ewers, M., Graessel, E., Kramberger, M. G., Law, E., Mecocci, P., Molinuevo, J. L., Nygård, L., Olde-Rikkert, M. G., Orgogozo, J. M., Pasquier, F., Peres, K., Salmon, E., … Frölich, L. (2015). Mild cognitive impairment and deficits in instrumental activities of daily living: A systematic review. *Alzheimer's Research & Therapy*, *7*(1), 17. https://doi.org/10.1186/s13195-015-0099-0

Katz, N., & Hartman-Maeir, A. (2011). Higher-level cognitive functions enabling participation: Awareness and executive functions. In N. Katz (Ed.), *Cognition, occupation, and participation across the life span: Neuroscience, neurorehabilitation, and models of intervention in occupational therapy* (pp. 13–40). American Occupational Therapy Association.

Katz S. (1983). Assessing self-maintenance: Activities of daily living, mobility, and instrumental activities of daily living. *Journal of the American Geriatrics Society*, *31*(12), 721–727. https://doi.org/10.1111/j.1532-5415.1983.tb03391.x

Killoran, A., Biglan, K. M., Jankovic, J., Eberly, S., Kayson, E., Oakes, D., Young, A. B., & Shoulson, I. (2013). Characterization of the Huntington intermediate CAG repeat expansion phenotype in PHAROS. *Neurology*, *80*(22), 2022–2027. https://doi.org/10.1212/WNL.0b013e318294b304

Kim, E.H., Mehrabi, N., Tippett, L. J., Waldvogel, H. J., & Faull, R. L. M. (2017). Huntington Disease. In D. F. Cechetto & N. Weishaupt (Eds.), *The Cerebral Cortex in Neurodegenerative and Neuropsychiatric Disorders* (pp. 195-221). Academic Press. https://doi.org/10.1016/B978-0-12-801942-9.00008-2

Koerts, J., Van Beilen, M., Tucha, O., Leenders, K. L., & Brouwer, W. H. (2011). Executive

functioning in daily life in Parkinson's disease: Initiative, planning and multi-task performance. *PloS One*, *6*(12), e29254. https://doi.org/10.1371/journal.pone.0029254

Lai, J. S., Goodnight, S., Downing, N. R., Ready, R. E., Paulsen, J. S., Kratz, A. L., Stout, J. C., McCormack, M. K., Cella, D., Ross, C., Russell, J., & Carlozzi, N. E. (2018). Evaluating cognition in individuals with Huntington disease: Neuro-QoL cognitive functioning measures. *Quality of Life Research*, *27*(3), 811–822. https://doi.org/10.1007/s11136-017-1755-6

Langbehn, D. R., Brinkman, R. R., Falush, D., Paulsen, J. S., Hayden, M. R., & International Huntington's Disease Collaborative Group (2004). A new model for prediction of the age of onset and penetrance for Huntington's disease based on CAG length. *Clinical Genetics*, *65*(4), 267–277. https://doi.org/10.1111/j.1399-0004.2004.00241.x

Langbehn, D. R., Hayden, M. R., Paulsen, J. S., & and the PREDICT-HD Investigators of the Huntington Study Group (2010). CAG-repeat length and the age of onset in Huntington disease (HD): A review and validation study of statistical approaches. *American Journal of Medical Genetics. Part B, Neuropsychiatric genetics*, *153B*(2), 397–408. https://doi.org/10.1002/ajmg.b.30992

Langbehn, D. R., & Hersch, S. (2020). Clinical Outcomes and Selection Criteria for Prodromal Huntington's Disease Trials. *Movement Disorders*, *35*(12), 2193–2200. https://doi.org/10.1002/mds.28222

Lee, J. J. (n.d.). Defining Clinical Benefit in Clinical Trials: FDA Perspective. FDA – U.S. Food and Drug Administration. https://celiac.org/main/wp-content/uploads/2015/04/great3-07.pdf

Lezak M. D. (1982). The Problem of Assessing Executive Functions. *International Journal of Psychology*, *17*, 281-297. https://doi.org/10.1080/00207598208247445

Lezak, M. D., Howieson, D. B., Bigler, E. D., & Tranel, D. (2012). *Neuropsychological Assessment* (5th ed.).Oxford University Press.

MacLeod, R., Tibben, A., Frontali, M., Evers-Kiebooms, G., Jones, A., Martinez-Descales, A., Roos, R. A., & Editorial Committee and Working Group 'Genetic Testing Counselling' of the European Huntington Disease Network (2013). Recommendations for the predictive genetic test in Huntington's disease. *Clinical Genetics*, *83*(3), 221–231. https://doi.org/10.1111/j.1399-0004.2012.01900.x

Marcotte, T. D., Scott, J. C., Kamat, R., & Heaton, R. K. (2010). Neuropsychology and the prediction of everyday functioning. In T. D. Marcotte & I. Grant (Eds.), *Neuropsychology of Everyday Functioning* (pp. 5–38). The Guilford Press.

Marvel, C. L., Morgan, O. P., & Kronemer, S. I. (2019). How the motor system integrates with working memory. *Neuroscience and Biobehavioral Reviews*, *102*, 184–194. https://doi.org/10.1016/j.neubiorev.2019.04.017

Matz, O. C., & Spocter, M. (2022). The Effect of Huntington's Disease on the Basal Nuclei: A Review. *Cureus*, *14*(4), e24473. https://doi.org/10.7759/cureus.24473

Mayeux, R., Stern, Y., Herman, A., Greenbaum, L., & Fahn, S. (1986). Correlates of early disability in Huntington's disease. *Annals of Neurology*, *20*(6), 727–731. https://doi.org/10.1002/ana.410200613

McAllister, B., Gusella, J. F., Landwehrmeyer, G. B., Lee, J. M., MacDonald, M. E., Orth, M., Rosser, A. E., Williams, N. M., Holmans, P., Jones, L., Massey, T. H., & REGISTRY Investigators of the European Huntington's Disease Network (2021). Timing and Impact of Psychiatric, Cognitive, and Motor Abnormalities in Huntington Disease. *Neurology*, *96*(19), e2395–e2406. https://doi.org/10.1212/WNL.0000000000011893

McColgan, P., & Tabrizi, S. J. (2018). Huntington's disease: A clinical review. *European Journal of Neurology, 25*(1), 24–34. https://doi.org/10.1111/ene.13413

Mestre, T. A., Bachoud-Lévi, A. C., Marinus, J., Stout, J. C., Paulsen, J. S., Como, P., Duff, K., Sampaio, C., Goetz, C. G., Cubo, E., Stebbins, G. T., Martinez-Martin, P., & Members of the MDS Committee on Rating Scales Development (2018). Rating scales for cognition in Huntington's disease: Critique and recommendations. *Movement Disorders*, *33*(2), 187–195. https://doi.org/10.1002/mds.27227

Mitchell, A.J., Kemp, S., Benito-León, J., & Reuber, M. (2010). The influence of cognitive impairment on health-related quality of life in neurological disease. *Acta Neuropsychiatrica*, *22*, 2-13. https://doi.org/10.1111/j.1601-5215.2009.00439.x

Morrison, M. T., Giles, G. M., Ryan, J. D., Baum, C. M., Dromerick, A. W., Polatajko, H. J., & Edwards, D. F. (2013). Multiple Errands Test-Revised (MET-R): A performance-based measure of executive function in people with mild cerebrovascular accident. *The American Journal of Occupational Therapy*, *67*(4), 460–468. https://doi.org/10.5014/ajot.2013.007880

Neguț, A., Matu, S.-A., Sava, F. A., & David, D. (2016). Task difficulty of virtual reality-based assessment tools compared to classical paper-and-pencil or computerized measures: A meta-analytic approach. *Computers in Human Behavior, 54,* 414–424. https://doi.org/10.1016/j.chb.2015.08.029

Nehl, C., Paulsen, J. S., & Huntington Study Group (2004). Cognitive and psychiatric aspects of Huntington disease contribute to functional capacity. *The Journal of Nervous and Mental Disease*, *192*(1), 72–74. https://doi.org/10.1097/01.nmd.0000106004.67587.57

Nopoulos P. C. (2016). Huntington disease: A single-gene degenerative disorder of the striatum. *Dialogues in Clinical Neuroscience*, *18*(1), 91–98. https://doi.org/10.31887/DCNS.2016.18.1/pnopoulos

O'Callaghan, C., Bertoux, M., & Hornberger, M. (2014). Beyond and below the cortex: The contribution of striatal dysfunction to cognition and behaviour in neurodegeneration. *Journal of Neurology, Neurosurgery, and Psychiatry*, *85*(4), 371–378. https://doi.org/10.1136/jnnp-2012-304558

O'Keeffe, G. C., Michell, A. W., & Barker, R. A. (2009). Biomarkers in Huntington's and Parkinson's Disease. *Annals of the New York Academy of Sciences*, *1180*, 97–110. https://doi.org/10.1111/j.1749-6632.2009.04943.x

Papagno, C., & Trojano, L. (2018). Cognitive and behavioral disorders in Parkinson's disease: An update. I: cognitive impairments. *Neurological Sciences*, *39*(2), 215–223. https://doi.org/10.1007/s10072-017-3154-8

Papoutsi, M., Labuschagne, I., Tabrizi, S. J., & Stout, J. C. (2014). The cognitive burden in Huntington's disease: Pathology, phenotype, and mechanisms of compensation. *Movement Disorders*, *29*(5), 673–683. https://doi.org/10.1002/mds.25864

Papp, K. V., Kaplan, R. F., & Snyder, P. J. (2011). Biological markers of cognition in prodromal Huntington's disease: A review. *Brain and Cognition*, *77*(2), 280–291. https://doi.org/10.1016/j.bandc.2011.07.009

Paulsen J. S. (2010). Early Detection of Huntington Disease. *Future Neurology*, 5(1), 10.2217/fnl.09.78. https://doi.org/10.2217/fnl.09.78

Paulsen, J. S., & Long, J. D. (2014). Onset of Huntington's disease: Can it be purely cognitive?. *Movement Disorders*, *29*(11), 1342–1350. https://doi.org/10.1002/mds.25997

Pérès, K., Helmer, C., Amieva, H., Orgogozo, J. M., Rouch, I., Dartigues, J. F., & Barberger-Gateau, P. (2008). Natural history of decline in instrumental activities of daily living performance over the 10 years preceding the clinical diagnosis of dementia: A prospective population-based study. *Journal of the American Geriatrics Society*, *56*(1), 37–44. https://doi.org/10.1111/j.1532-5415.2007.01499.x

Porffy, L. A., Mehta, M. A., Patchitt, J., Boussebaa, C., Brett, J., D'Oliveira, T., Mouchlianitis, E., & Shergill, S. S. (2022). A Novel Virtual Reality Assessment of Functional Cognition: Validation Study. *Journal of Medical Internet Research*, *24*(1), e27641. https://doi.org/10.2196/27641

Prigatano G. P. (2005). Disturbances of self-awareness and rehabilitation of patients with traumatic brain injury: A 20-year perspective. *The Journal of Head Trauma Rehabilitation*, *20*(1), 19–29. https://doi.org/10.1097/00001199-200501000-00004

Puente, A. N., Terry, D. P., Faraco, C. C., Brown, C. L., & Miller, L. S. (2014). Functional impairment in mild cognitive impairment evidenced using performance-based measurement. *Journal of Geriatric Psychiatry and Neurology*, *27*(4), 253–258. https://doi.org/10.1177/0891988714532016

Rao, J. A., Harrington, D. L., Durgerian, S., Reece, C., Mourany, L., Koenig, K., Lowe, M. J., Magnotta, V. A., Long, J. D., Johnson, H. J., Paulsen, J. S., & Rao, S. M. (2014). Disruption of response inhibition circuits in prodromal Huntington disease. *Cortex*, *58*, 72–85. https://doi.org/10.1016/j.cortex.2014.04.018

Read, J., Jones, R., Owen, G., Leavitt, B. R., Coleman, A., Roos, R. A., Dumas, E. M., Durr, A., Justo, D., Say, M., Stout, J. C., Tabrizi, S. J., Craufurd, D., & TRACK-HD investigators (2013). Quality of life in Huntington's disease: A comparative study investigating the impact for those with pre-manifest and early manifest disease, and their partners. *Journal of Huntington's Disease*, *2*(2), 159–175. https://doi.org/10.3233/JHD-130051

Ready, R. E., Mathews, M., Leserman, A., & Paulsen, J. S. (2008). Patient and caregiver quality of life in Huntington's disease. *Movement Disorders, 23*(5), 721–726. https://doi.org/10.1002/mds.21920

Reilmann, R., Leavitt, B. R., & Ross, C. A. (2014). Diagnostic criteria for Huntington's disease based on natural history. *Movement Disorders, 29*(11), 1335–1341. https://doi.org/10.1002/mds.26011

Reitan, R. M. (1958). Validity of the Trail Making Test as an Indicator of Organic Brain Damage. *Perceptual and Motor* Skills, *8*(3), 271–276. https://doi.org/10.2466/pms.1958.8.3.271

Reyes, A., Bartlett, D. M., Rankin, T. J., Zaenker, P., Turner, K., Teo, W. P., Fu, S. C., Domingos, J., Georgiou-Karistianis, N., Ziman, M., & Cruickshank, T. M. (2021). Clinical Determinants of Dual Tasking in People With Premanifest Huntington Disease. *Physical Therapy*, *101*(4), pzab016. https://doi.org/10.1093/ptj/pzab016

Roos R. A. (2010). Huntington's disease: A clinical review. *Orphanet Journal of Rare Diseases*, *5*, 40. https://doi.org/10.1186/1750-1172-5-40

Rosas, H. D., Goodman, J., Chen, Y. I., Jenkins, B. G., Kennedy, D. N., Makris, N., Patti, M., Seidman, L. J., Beal, M. F., & Koroshetz, W. J. (2001). Striatal volume loss in HD as measured by MRI and the influence of CAG repeat. *Neurology*, *57*(6), 1025–1028. https://doi.org/10.1212/wnl.57.6.1025

Ross, C. A., Aylward, E. H., Wild, E. J., Langbehn, D. R., Long, J. D., Warner, J. H., Scahill, R. I., Leavitt, B. R., Stout, J. C., Paulsen, J. S., Reilmann, R., Unschuld, P. G., Wexler, A., Margolis, R. L., & Tabrizi, S. J. (2014). Huntington disease: Natural history, biomarkers and prospects for therapeutics. *Nature reviews Neurology*, *10*(4), 204–216. https://doi.org/10.1038/nrneurol.2014.24

Ross, C. A., Pantelyat, A., Kogan, J., & Brandt, J. (2014). Determinants of functional disability in Huntington's disease: Role of cognitive and motor dysfunction. *Movement Disorders*, *29*(11), 1351–1358. https://doi.org/10.1002/mds.26012

Ross, C. A., & Tabrizi, S. J. (2011). Huntington's disease: From molecular pathogenesis to clinical

treatment. *The Lancet Neurology*, *10*(1), 83–98.
https://doi.org/10.1016/S1474-4422(10)70245-3

Rothlind, J. C., Bylsma, F. W., Peyser, C., Folstein, S. E., & Brandt, J. (1993). Cognitive and motor correlates of everyday functioning in early Huntington's disease. *The Journal of Nervous and Mental Disease*, *181*(3), 194–199.
https://doi.org/10.1097/00005053-199303000-00008

Royall, D. R., Mahurin, R. K., True, J. E., Anderson, B., Brock, I. P., 3rd, Freeburger, L., & Miller, A. (1993). Executive impairment among the functionally dependent: Comparisons between schizophrenic and elderly subjects. *The American Journal of Psychiatry*, *150*(12), 1813–1819.
https://doi.org/10.1176/ajp.150.12.1813

Rüb, U., Seidel, K., Heinsen, H., Vonsattel, J. P., den Dunnen, W. F., & Korf, H. W. (2016). Huntington's disease (HD): The neuropathology of a multisystem neurodegenerative disorder of the human brain. *Brain Pathology, 26*(6), 726–740.
https://doi.org/10.1111/bpa.12426

Rubinsztein, D. C., Leggo, J., Coles, R., Almqvist, E., Biancalana, V., Cassiman, J. J., Chotai, K., Connarty, M., Crauford, D., Curtis, A., Curtis, D., Davidson, M. J., Differ, A. M., Dode, C., Dodge, A., Frontali, M., Ranen, N. G., Stine, O. C., Sherr, M., Abbott, M. H., … Hayden, M. R. (1996). Phenotypic characterization of individuals with 30-40 CAG repeats in the Huntington disease (HD) gene reveals HD cases with 36 repeats and apparently normal elderly individuals with 36-39 repeats. *American Journal of Human Genetics*, *59*(1), 16–22.

Rupp, J., Blekher, T., Jackson, J., Beristain, X., Marshall, J., Hui, S., Wojcieszek, J., & Foroud, T. (2010). Progression in prediagnostic Huntington disease. *Journal of Neurology, Neurosurgery, and Psychiatry*, *81*(4), 379–384.
https://doi.org/10.1136/jnnp.2009.176982

Sax, D. S., Bird, E. D., Gusella, J. F., & Myers, R. H. (1989). Phenotypic variation in 2 Huntington's disease families with linkage to chromosome 4. *Neurology*, 39(10), 1332–1336.
https://doi.org/10.1212/wnl.39.10.1332

Sbordone, R. J. (1996). Ecological validity: Some critical issues for the neuropsychologist. In R. J. Sbordone & C. J. Long (Eds.), *Ecological validity of neuropsychological testing* (pp. 15–41). Gr Press/St Lucie Press, Inc.

Schmitter-Edgecombe, M., & Parsey, C. M. (2014). Assessment of functional change and cognitive correlates in the progression from healthy cognitive aging to dementia. *Neuropsychology*, *28*(6), 881–893.
https://doi.org/10.1037/neu0000109

Schmitter-Edgecombe, M., Parsey, C., & Cook, D. J. (2011). Cognitive correlates of functional performance in older adults: Comparison of self-report, direct observation, and performance-based measures. *Journal of the International Neuropsychological Society*, *17*(5), 853–864.
https://doi.org/10.1017/S1355617711000865

Schultheis, M. T., Himelstein, J., & Rizzo, A. A. (2002). Virtual reality and neuropsychology: Upgrading the current tools. *The Journal of Head Trauma Rehabilitation*, *17*(5), 378–394. https://doi.org/10.1097/00001199-200210000-00002

Shallice, T., & Burgess, P. W. (1991). Deficits in strategy application following frontal lobe damage in man. *Brain*, *114 (Pt 2)*, 727–741. https://doi.org/10.1093/brain/114.2.727

Sheppard, D. P., Pirogovsky-Turk, E., Woods, S. P., Holden, H. M., Nicoll, D. R., Filoteo, J. V., Corey-Bloom, J., & Gilbert, P. E. (2017). Everyday Functioning in Huntington's Disease: A Laboratory-Based Study of Financial Management Capacity. *Applied Neuropsychology Adult*, *24*(2), 176–182. https://doi.org/10.1080/23279095.2015.1125904

Shoulson, I., Eberly, S., Oakes, D., Kayson, E., Young, A. B., & PHAROS Investigators (2019). Phenotype-genotype discrepancies in the prospective Huntington at-risk observational study. *Annals of Clinical and Translational Neurology*, *6*(6), 1046–1052. https://doi.org/10.1002/acn3.781

Shoulson, I., & Young, A. B. (2011). Milestones in Huntington disease. *Movement Disorders*, *26*(6), 1127–1133. https://doi.org/10.1002/mds.23685

Sikkes, S. A., & Rotrou, J. d. (2014). A qualitative review of instrumental activities of daily living in dementia: What's cooking?. *Neurodegenerative Disease Management*, *4*(5), 393–400. https://doi.org/10.2217/nmt.14.24

Simpson, J. A., Lovecky, D., Kogan, J., Vetter, L. A., & Yohrling, G. J. (2016). Survey of the Huntington's Disease Patient and Caregiver Community Reveals Most Impactful Symptoms and Treatment Needs. *Journal of Huntington's disease*, *5*(4), 395–403. https://doi.org/10.3233/JHD-160228

Skidmore E. R. (2017). Functional Cognition: Implications for Practice, Policy, and Research. *The American Journal of Geriatric Psychiatry*, *25*(5), 483–484. https://doi.org/10.1016/j.jagp.2016.12.020

Snell, R. G., MacMillan, J. C., Cheadle, J. P., Fenton, I., Lazarou, L. P., Davies, P., MacDonald, M. E., Gusella, J. F., Harper, P. S., & Shaw, D. J. (1993). Relationship between trinucleotide repeat expansion and phenotypic variation in Huntington's disease. *Nature Genetics*, *4*(4), 393–397. https://doi.org/10.1038/ng0893-393

Snowden J. S. (2017). The Neuropsychology of Huntington's Disease. *Archives of Clinical Neuropsychology*, *32*(7), 876–887. https://doi.org/10.1093/arclin/acx086

Snowden, J. S., Craufurd, D., Thompson, J., & Neary, D. (2002). Psychomotor, executive, and memory function in preclinical Huntington's disease. *Journal of Clinical and Experimental Neuropsychology*, *24*(2), 133–145. https://doi.org/10.1076/jcen.24.2.133.998

Solberg, O. K., Filkuková, P., Frich, J. C., & Feragen, K. (2018). Age at Death and Causes of Death in Patients with Huntington Disease in Norway in 1986-2015. *Journal of Huntington's disease*, *7*(1), 77–86. https://doi.org/10.3233/JHD-170270

Solomon, A. C., Stout, J. C., Weaver, M., Queller, S., Tomusk, A., Whitlock, K. B., Hui, S. L., Marshall, J., Jackson, J. G., Siemers, E. R., Beristain, X., Wojcieszek, J., & Foroud, T. (2008). Ten-year rate of longitudinal change in neurocognitive and motor function in prediagnosis Huntington disease. *Movement Disorders*, *23*(13), 1830–1836. https://doi.org/10.1002/mds.22097

Stout, J. C., & Johnson, S. A. (2005). Cognitive impairment and dementia in basal ganglia disorders. *Current Neurology and Neuroscience Reports*, *5*(5), 355–363. https://doi.org/10.1007/s11910-005-0059-3

Stout, J. C., Paulsen, J. S., Queller, S., Solomon, A. C., Whitlock, K. B., Campbell, J. C., Carlozzi, N., Duff, K., Beglinger, L. J., Langbehn, D. R., Johnson, S. A., Biglan, K. M., & Aylward, E. H. (2011). Neurocognitive signs in prodromal Huntington disease. *Neuropsychology*, *25*(1), 1–14. https://doi.org/10.1037/a0020937

Stroop, J. R. (1935). Studies of interference in serial verbal reactions. *Journal of Experimental Psychology: General, 18*, 643–662. https://doi.org/10.1037/0096-3445.121.1.15

Stuss, D. T., & Buckle, L. (1992). Traumatic brain injury: Neuropsychological deficits and evaluation at different stages of recovery and in different pathologic subtypes. *The Journal of Head Trauma Rehabilitation*, 7(2), 40–49.

Tabrizi, S. J., Reilmann, R., Roos, R. A., Durr, A., Leavitt, B., Owen, G., Jones, R., Johnson, H., Craufurd, D., Hicks, S. L., Kennard, C., Landwehrmeyer, B., Stout, J. C., Borowsky, B., Scahill, R. I., Frost, C., Langbehn, D. R., & TRACK-HD investigators (2012). Potential endpoints for clinical trials in premanifest and early Huntington's disease in the TRACK-HD study: Analysis of 24-month observational data. *The Lancet Neurology*, *11*(1), 42–53. https://doi.org/10.1016/S1474-4422(11)70263-0 https://doi.org/10.1016/S1474-4422(22)00120-X

Tabrizi, S. J., Scahill, R. I., Owen, G., Durr, A., Leavitt, B. R., Roos, R. A., Borowsky, B., Landwehrmeyer, B., Frost, C., Johnson, H., Craufurd, D., Reilmann, R., Stout, J. C., Langbehn, D. R., & TRACK-HD Investigators (2013). Predictors of phenotypic progression and disease onset in premanifest and early-stage Huntington's disease in the TRACK-HD study: Analysis of 36-month observational data. *The Lancet Neurology*, *12*(7), 637–649. https://doi.org/10.1016/S1474-4422(13)70088-7

Tabrizi, S. J., Schobel, S., Gantman, E. C., Mansbach, A., Borowsky, B., Konstantinova, P., Mestre, T. A., Panagoulias, J., Ross, C. A., Zauderer, M., Mullin, A. P., Romero, K., Sivakumaran, S., Turner, E. C., Long, J. D., Sampaio, C., & Huntington's Disease Regulatory Science

Consortium (HD-RSC) (2022). A biological classification of Huntington's disease: the Integrated Staging System. *The Lancet. Neurology, 21*(7), 632–644.

Tang, H., van Eimeren, T., Sampaio, C., & Mestre, T. A. (2021). Validation of biomarkers in Huntington disease to support the development of disease-modifying therapies: A systematic review and critical appraisal scheme. *Parkinsonism & Related Disorders*, *93*, 89–96. https://doi.org/10.1016/j.parkreldis.2021.10.013

The Huntington's Disease Collaborative Research Group (1993). A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. *Cell*, *72*(6), 971–983. https://doi.org/10.1016/0092-8674(93)90585-e

van Asselen, M., Almeida, I., Júlio, F., Januário, C., Campos, E. B., Simões, M., & Castelo-Branco, M. (2012). Implicit contextual learning in prodromal and early stage Huntington's disease patients. *Journal of the International Neuropsychological Society*, *18*(4), 689–696. https://doi.org/10.1017/S1355617712000288

van Asselen, M., Júlio, F., Januário, C., Campos, E. B., Almeida, I., Cavaco, S., & Castelo-Branco, M. (2012). Scanning Patterns of Faces do not Explain Impaired Emotion Recognition in Huntington Disease: Evidence for a High-Level Mechanism. *Frontiers in Psychology*, *3*, 31. https://doi.org/10.3389/fpsyg.2012.00031

van der Zwaan, K. F., Jacobs, M., van Zwet, E. W., Roos, R., & de Bot, S. T. (2021). Predictors of Working Capacity Changes Related to Huntington's Disease: A Longitudinal Study. *Journal of Huntington's disease*, *10*(2), 269–276. https://doi.org/10.3233/JHD-200446

Van Liew, C., Gluhm, S., Goldstein, J., Cronan, T. A., & Corey-Bloom, J. (2013). The functional implications of motor, cognitive, psychiatric, and social problem-solving states in Huntington's disease. *Psychiatry*, *76*(4), 323–335. https://doi.org/10.1521/psyc.2013.76.4.323

Vaughan, L., & Giovanello, K. (2010). Executive function in daily life: Age-related influences of executive processes on instrumental activities of daily living. *Psychology and Aging*, *25*(2), 343–355. https://doi.org/10.1037/a0017729

Vonsattel, J. P., & DiFiglia, M. (1998). Huntington disease. *Journal of Neuropathology and Experimental Neurology*, *57*(5), 369–384. https://doi.org/10.1097/00005072-199805000-00001

Wesson, J., Clemson, L., Brodaty, H., & Reppermund, S. (2016). Estimating functional cognition in older adults using observational assessments of task performance in complex everyday activities: A systematic review and evaluation of measurement properties. *Neuroscience and Biobehavioral Reviews*, *68*, 335–360. https://doi.org/10.1016/j.neubiorev.2016.05.024

Wesson, J., Clemson, L., Crawford, J. D., Kochan, N. A., Brodaty, H., & Reppermund, S. (2017).

Measurement of Functional Cognition and Complex Everyday Activities in Older Adults with Mild Cognitive Impairment and Mild Dementia: Validity of the Large Allen's Cognitive Level Screen. *The American Journal of Geriatric Psychiatry*, *25*(5), 471–482. https://doi.org/10.1016/j.jagp.2016.11.021

Williams, J. K., Hamilton, R., Nehl, C., McGonigal-Kenney, M., Schutte, D. L., Sparbel, K., Birrer, E., Tripp-Reimer, T., Friedrich, R., Penziner, E., Jarmon, L., & Paulsen, J. (2007). "No one else sees the difference": Family members' perceptions of changes in persons with preclinical Huntington disease. *American Journal of Medical Genetics. Part B, Neuropsychiatric genetics*, *144B*(5), 636–641. https://doi.org/10.1002/ajmg.b.30479

Witjes-Ané, M. N., Vegter-van der Vlis, M., van Vugt, J. P., Lanser, J. B., Hermans, J., Zwinderman, A. H., van Ommen, G. J., & Roos, R. A. (2003). Cognitive and motor functioning in gene carriers for Huntington's disease: A baseline study. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *15*(1), 7–16. https://doi.org/10.1176/jnp.15.1.7

Young, C. B., Reddy, V., & Sonne, J. (2021). *Neuroanatomy, Basal Ganglia*. StatPearls Publishing

Zhang, Y., Long, J. D., Mills, J. A., Warner, J. H., Lu, W., Paulsen, J. S., & PREDICT-HD Investigators and Coordinators of the Huntington Study Group (2011). Indexing disease progression at study entry with individuals at-risk for Huntington disease. *American Journal of Medical Genetics. Part B, Neuropsychiatric genetics*, *156B*(7), 751–763. https://doi.org/10.1002/ajmg.b.31232

Chapter II - Study 1

Preface

Our first study aimed to determine if a saccadic paradigm that heavily depends on executive function is more sensitive at capturing cognitive and behavioural impairments in persons with premanifest Huntington's disease than conventional cognitive tests or simple saccadic tasks.

Although oculomotor measures are not crucial for HD clinical diagnosis as there is a genetic test to identify this disease since 1993, the detection of changes in reproducible saccadic parameters over time might prove to be relevant to track disease onset and progression (Ali et al., 2006).

Saccades are defined as rapid eye movements that bring an image from the periphery into the fovea and shift gaze from one location to another (Anderson & MacAskill, 2013; Blekher et al., 2009; Rupp et al., 2012). Saccades are easily accessible to clinical evaluation and quantification in the laboratory, their dynamic properties are well delineated, and a good part of their neurobiological substrate has been defined (Anderson & MacAskill, 2013; Leigh & Kennard, 2004; Robert et al., 2009). In particular, the basal ganglia and the frontal cortex are deeply involved in the saccadic control circuit and are critical to initiate voluntary saccades and to control reflexive saccades (Hikosaka et al., 2000; Patel et al., 2012; Peltsch et al., 2008). Therefore, saccadic measurement has become a popular method of studying abnormal brain function like the one caused by HD (Ali et al., 2006; Antoniades et al., 2010).

Oculomotor impairments, including saccadic abnormalities, are among the first manifestations of Huntington's Disease (Roos, 2010) and are an unequivocal finding in the clinical evaluation of HD patients (Anderson & MacAskill, 2013; Blekher et al., 2006; Dumas et al., 2013; Golding et al., 2006; Patel et al., 2012; Peltsch et al., 2008; Roos, 2010;

Turner et al., 2011). However, less is known regarding the saccadic abnormalities shown by persons in a premanifest HD stage (PreHD). Though their clinical examination is often normal, some studies using laboratory recordings found oculomotor impairments, while other studies found an intact oculomotor performance (Anderson & MacAskill, 2013; Antoniades et al., 2007, 2010; Blekher et al., 2004, 2006, 2009; Dumas et al., 2013; Golding et al., 2006; Patel et al., 2012; Rupp et al., 2012; Tabrizi et al., 2012; Turner et al., 2011). Nevertheless, those studies that found saccadic impairments, also found significant correlations between timing and trajectory parameters of PreHD saccadic behaviour and estimated time to disease onset (Anderson & MacAskill, 2013; Langbehn et al., 2004), suggesting that this could be an important marker of disease progression. Additionally, a correlation has been found between saccade abnormalities in HD patients and disease severity, as measured by the Unified Huntington's Disease Rating Scale (UHDRS) - motor scale (Anderson & MacAskill, 2013; Huntington Study Group, 1996; Patel et al., 2012).

While intending to design a task that is sensitive to PreHD saccadic impairments, we hypothesized that the combination of an oculomotor response with a cognitively demanding paradigm with increasing executive and/or memory load, can be more effective than simpler saccadic tasks and conventional cognitive tests (Dumas et al., 2013; Robert et al., 2009). Specifically, we were interested to examine the influence of cognitive load in the inhibitory control and impulsivity of the saccadic behaviour of persons in a premanifest HD stage. This hypothesis was based in previous studies with healthy populations that showed that a specific disruption of saccadic inhibition occurs when the experimental task includes high executive and memory demands imposed by an n-back memory saccadic condition (Mitchell et al., 2002; Van der Stigchel, 2010). Also, globally, persons with HD seem to have greater defects in initiating volitional/voluntary (internally) generated saccades than reflexive (externally) generated saccades (Patel et al., 2012), which frequently result in premature and misdirected saccades in the face of more complex oculomotor tasks (Anderson & MacAskill, 2013; Patel et al., 2012; Peltsch et al., 2008; Turner et al., 2011).

With all this in mind, we have put together a four-block saccadic paradigm with increasing executive and memory demands to detect the HD-related performance changes early in the inexorable disease process.

References

Ali, F. R., Michell, A. W., Barker, R. A., & Carpenter, R. H. (2006). The use of quantitative oculometry in the assessment of Huntington's disease. *Experimental Brain Research*, *169*(2), 237–245. https://doi.org/10.1007/s00221-005-0143-6

Anderson, T. J., & MacAskill, M. R. (2013). Eye movements in patients with neurodegenerative disorders. *Nature Reviews Neurology*, *9*(2), 74–85. https://doi.org/10.1038/nrneurol.2012.273

Antoniades, C. A., Altham, P. M., Mason, S. L., Barker, R. A., & Carpenter, R. (2007). Saccadometry: A new tool for evaluating presymptomatic Huntington patients. *Neuroreport*, *18*(11), 1133–1136. https://doi.org/10.1097/WNR.0b013e32821c560d

Antoniades, C. A., Xu, Z., Mason, S. L., Carpenter, R. H., & Barker, R. A. (2010). Huntington's disease: Changes in saccades and hand-tapping over 3 years. *Journal of Neurology*, *257*(11), 1890–1898. https://doi.org/10.1007/s00415-010-5632-2

Blekher, T., Johnson, S. A., Marshall, J., White, K., Hui, S., Weaver, M., Gray, J., Yee, R., Stout, J. C., Beristain, X., Wojcieszek, J., & Foroud, T. (2006). Saccades in presymptomatic and early stages of Huntington disease. *Neurology*, *67*(3), 394–399. https://doi.org/10.1212/01.wnl.0000227890.87398.c1

Blekher, T., Weaver, M. R., Cai, X., Hui, S., Marshall, J., Jackson, J. G., Wojcieszek, J., Yee, R. D., & Foroud, T. M. (2009). Test-retest reliability of saccadic measures in subjects at risk for Huntington disease. *Investigative Ophthalmology & Visual Science*, *50*(12), 5707–5711. https://doi.org/10.1167/iovs.09-3538

Blekher, T. M., Yee, R. D., Kirkwood, S. C., Hake, A. M., Stout, J. C., Weaver, M. R., & Foroud, T. M. (2004). Oculomotor control in asymptomatic and recently diagnosed individuals with the genetic marker for Huntington's disease. *Vision Research*, *44*(23), 2729–2736. https://doi.org/10.1016/j.visres.2004.06.006

Dumas, E. M., van den Bogaard, S. J., Middelkoop, H. A., & Roos, R. A. (2013). A review of cognition in Huntington's disease. *Frontiers in Bioscience (Scholar edition)*, *5*(1), 1–18. https://doi.org/10.2741/s355

Golding, C. V., Danchaivijitr, C., Hodgson, T. L., Tabrizi, S. J., & Kennard, C. (2006). Identification of an oculomotor biomarker of preclinical Huntington disease. *Neurology*, *67*(3), 485–487. https://doi.org/10.1212/01.wnl.0000218215.43328.88

Hikosaka, O., Takikawa, Y., & Kawagoe, R. (2000). Role of the basal ganglia in the control of purposive saccadic eye movements. *Physiological Reviews*, *80*(3), 953–978. https://doi.org/10.1152/physrev.2000.80.3.953

Huntington Study Group (1996). Unified Huntington's Disease Rating Scale: Reliability and

consistency. *Movement Disorders*, *11*(2), 136–142. https://doi.org/10.1002/mds.870110204

Langbehn, D. R., Brinkman, R. R., Falush, D., Paulsen, J. S., Hayden, M. R., & International Huntington's Disease Collaborative Group (2004). A new model for prediction of the age of onset and penetrance for Huntington's disease based on CAG length. *Clinical Genetics*, *65*(4), 267–277. https://doi.org/10.1111/j.1399-0004.2004.00241.x

Leigh, R. J., & Kennard, C. (2004). Using saccades as a research tool in the clinical neurosciences. *Brain127*(Pt 3), 460–477. https://doi.org/10.1093/brain/awh035

Mitchell, J. P., Macrae, C. N., & Gilchrist, I. D. (2002). Working memory and the suppression of reflexive saccades. *Journal of Cognitive Neuroscience, 14*(1), 95–103. https://doi.org/10.1162/089892902317205357

Patel, S. S., Jankovic, J., Hood, A. J., Jeter, C. B., & Sereno, A. B. (2012). Reflexive and volitional saccades: Biomarkers of Huntington disease severity and progression. *Journal of the Neurological Sciences*, *313*(1-2), 35–41. https://doi.org/10.1016/j.jns.2011.09.035

Peltsch, A., Hoffman, A., Armstrong, I., Pari, G., & Munoz, D. P. (2008). Saccadic impairments in Huntington's disease. *Experimental Brain Research*, *186*(3), 457–469. https://doi.org/10.1007/s00221-007-1248-x

Robert, M. P., Nachev, P. C., Hicks, S. L., Golding, C. V., Tabrizi, S. J., & Kennard, C. (2009). Saccadometry of conditional rules in presymptomatic Huntington's disease. *Annals of the New York Academy of Sciences*, *1164*, 444–450. https://doi.org/10.1111/j.1749-6632.2008.03736.x

Roos R. A. (2010). Huntington's disease: A clinical review. *Orphanet Journal of Rare Diseases*, *5*, 40. https://doi.org/10.1186/1750-1172-5-40

Rupp, J., Dzemidzic, M., Blekher, T., West, J., Hui, S., Wojcieszek, J., Saykin, A. J., Kareken, D. A., & Foroud, T. (2012). Comparison of vertical and horizontal saccade measures and their relation to gray matter changes in premanifest and manifest Huntington disease. *Journal of Neurology*, *259*(2), 267–276. https://doi.org/10.1007/s00415-011-6172-0

Tabrizi, S. J., Reilmann, R., Roos, R. A., Durr, A., Leavitt, B., Owen, G., Jones, R., Johnson, H., Craufurd, D., Hicks, S. L., Kennard, C., Landwehrmeyer, B., Stout, J. C., Borowsky, B., Scahill, R. I., Frost, C., Langbehn, D. R., & TRACK-HD investigators (2012). Potential endpoints for clinical trials in premanifest and early Huntington's disease in the TRACK-HD study: Analysis of 24-month observational data. *The Lancet Neurology*, *11*(1), 42–53. https://doi.org/10.1016/S1474-4422(11)70263-0

Turner, T. H., Goldstein, J., Hamilton, J. M., Jacobson, M., Pirogovsky, E., Peavy, G., & Corey-Bloom, J. (2011). Behavioral measures of saccade latency and inhibition in manifest and premanifest Huntington's disease. *Journal of Motor Behavior*, *43*(4), 295–302. https://doi.org/10.1080/00222895.2011.580390

Van der Stigchel S. (2010). The search for oculomotor inhibition: Interactions with working memory. *Experimental Psychology*, *57*(6), 429–435. https://doi.org/10.1027/1618-3169/a000053

Study 1

The Effect of Impulsivity and Inhibitory Control Deficits in the Saccadic Behaviour of Premanifest Huntington's Disease Individuals

Adapted from: **Júlio, F.**, Caetano, G., Januário, C., & Castelo-Branco, M. (2019). The effect of impulsivity and inhibitory control deficits in the saccadic behavior of premanifest Huntington's disease individuals. *Orphanet Journal of Rare Diseases*, *14*(1), 246. https://doi.org/10.1186/s13023-019-1218-y

Abstract

Introduction: This study aims to test response inhibition in persons with premanifest Huntington's disease (PreHD), in the context of a saccadic paradigm with working memory demands and fronto-executive load as a way to measure inhibitory control deficits and impulsive behaviour in Huntington's disease (HD).

Material and Methods: The oculomotor function of 15 persons with PreHD and 22 Controls was assessed using an experimental paradigm comprising four horizontal

saccadic tasks: prosaccade (PS), antisaccade (AS), 1- or 2-back memory prosaccade (MPS), and 1- or 2-back memory antisaccade (MAS). Success rate, latency, directional and timing errors were calculated for each task. A comprehensive battery of neuropsychological tests was also used to assess the overall cognitive functioning of study participants. Statistical correlations between oculomotor, clinical and cognitive measures were computed for the PreHD group.

Results: PreHD participants showed reduced success rate in the AS task, increased direction errors in the AS and MAS tasks and decreased latency in the MAS task when compared to Controls, despite presenting similar executive and memory scores in the conventional neuropsychological tests applied. Significant associations were identified between specific AS and MAS parameters and disease-related measures, cognitive skills and other oculomotor results of PreHD participants.

Discussion: Our results show that oculomotor performance in premanifest Huntington's disease deteriorates once inhibitory control, working memory and/or fronto-executive load are added to the task. A more automatic pattern of performance, including a faster response time and directionally erroneous eye movements were detected in the oculomotor behaviour of the PreHD group—these alterations were significantly correlated with disease stage and cognitive status. Our saccadic paradigm was able to capture impulsivity and inhibitory control deficits in a group of persons with PreHD on average far from symptom onset, thus holding the potential to identify the earliest disease-related changes.

Introduction

Huntington's disease (HD) is an autosomal inherited neurodegenerative disorder caused by a Cytosine-Adenine-Guanine (CAG) trinucleotide repeat expansion in the Huntingtin gene. HD is characterized by motor abnormalities, emotional and behavioural changes, and a general cognitive decline (Roos, 2010; Shoulson & Young, 2011; Walker, 2007). Testing positive for HD supplies only information on gene status, but not on disease state, as the test result gives little indication on how and when the triad of symptoms will start (Dumas et al., 2013; O'Keeffe et al., 2009). The proper identification and quantification of the signs and symptoms exhibited by persons that tested positive for HD but are still in a premanifest stage is vital to implement and assess the efficacy of any

therapeutic interventions (Weir et al., 2011).

Although there is now a consensual idea that cognitive impairments emerge years before HD clinical diagnosis and that the progression of cognitive decline is gradual (Diamond et al., 1992; Harrington et al., 2012; Ross, Aylward, et al., 2014; Stout et al., 2011), the conversion of an individual from a premanifest to a manifest HD status is classically defined solely on the basis of motor signs, with no consideration for cognitive and/or psychiatric disturbances (Roos, 2010; Shoulson & Young, 2011; Solomon et al., 2008). Nevertheless, the cognitive changes associated with HD need also to be fully addressed in disease progression and characterization (Novak & Tabrizi, 2011)—impairments in inhibitory control, attention, working memory, executive functions, mental flexibility, psychomotor functions, planning, processing speed, multitasking, organization, problem solving, implicit learning, visuospatial functions, timing and movement sequencing, face and emotion processing and recognition (Carvalho et al., 2016; Coppen et al., 2018; Dumas et al., 2013; Hart et al., 2014; Nasr & Rosas, 2019; Papoutsi et al., 2014; Papp et al., 2011; Paulsen, 2010; Paulsen & Long, 2014; Ross, Aylward, et al., 2014; Rupp et al., 2010; Solomon et al., 2008; Stout et al., 2011, 2014; Tabrizi et al., 2013; van Asselen, Almeida, et al., 2012; van Asselen, Júlio, et al., 2012). One of the cognitive symptoms most peculiar to HD is the executive dysfunction syndrome, a condition that encompasses disinhibition, attentional deficits, poor impulse control, and perseveration (Novak & Tabrizi, 2011; Rosenblatt, 2007). In HD, these changes in different aspects of top-down control mechanisms are associated with the disruption of the corticostriatal circuitry, especially the prefrontal-striatal connections (Balci et al., 2009; Bari & Robbins, 2013; Dalley et al., 2011; Paulsen, 2010; Rosas et al., 2005). This circuitry is important for the planning of an instrumental performance, temporal control over motor output, and response inhibition in general (Balci et al., 2009; Bari & Robbins, 2013; Rao et al., 2014). Accordingly, individuals with established basal ganglia damage, such as those with HD or Parkinson's Disease (PD), experience difficulty selecting a preferred motor activity and inhibiting undesired responses, frequently displaying impulsivity and altered behaviour inhibition in their performance (Dalley et al., 2011; Duff et al., 2007; Gorges et al., 2014; Henderson et al., 2011; Manfré et al., 2016; Zhang, Nombela, et al., 2016; Zhang, Rittman, et al., 2016).

Thus, impulsivity can be defined as the observable behavioural manifestation of a failure of the prefrontal cortex in inhibiting an overt motor act or response (Bari & Robbins, 2013). Despite the multitude of studies about impulsivity in PD (Bayard et al., 2016; Vela

et al., 2016; Zhang, Nombela, et al., 2016; Zhang, Rittman, et al., 2016), impulsive behaviour in HD needs to be further investigated. Harrington et al. (2012) pinpoint that fact, referring to a large, multi-center prospective study (PREDICT-HD) to indicate that one of the domains that has been inadequately assessed in HD is inhibition. Also, as stated by Bari and Robbins (2013), there are many unanswered questions about the mechanisms underlying abnormal impulsive behaviour.

Considering these outstanding questions, we aimed at assessing response inhibition and, hence, impulsivity, in an objective manner, by using an oculomotor paradigm with a component of inhibitory motor control and increasing cognitive load. Oculomotor impairments are precisely among the first manifestations of HD, with saccadic abnormalities having been frequently described in persons with HD (Anderson & MacAskill, 2013; Blekher et al., 2004; Dumas et al., 2013; Golding et al., 2006; Patel et al., 2012; Peltsch et al., 2008; Roos, 2010; Tabrizi et al., 2012, 2013; Turner et al., 2011; Vaca-Palomares et al., 2019). Although mixed findings have been reported about premanifest HD individuals' oculomotor performance (Anderson & MacAskill, 2013; Antoniades et al., 2010; Blekher et al., 2004, 2006; Dumas et al., 2013; Golding et al., 2006; Patel et al., 2012; Rupp et al., 2012), studies have shown significant alterations in antisaccade and memory-guided saccade measures of latency, higher variability of saccade latency and increased error rates (Anderson & MacAskill, 2013; Dumas et al., 2013; Patel et al., 2012; Rupp et al., 2012; Tabrizi et al., 2012). Findings include higher disinhibition (impaired saccade suppression), higher number of anticipatory saccades (that is, timing errors), increased errors in memory-guided saccade tasks, prolonged latency for initiating voluntary saccades, and an increase in latency for reflexive prosaccades (Anderson & MacAskill, 2013; Antoniades et al., 2007, 2010; Blekher et al., 2004; Turner et al., 2011). Nevertheless, Gorges et al. (2014) suggest that a comprehensive explanation for the lack of inhibition control at the saccadic or eye movement level in HD remains to be identified. Saccadic paradigms designed to assess inhibition and impulsivity processes in HD can further help to identify underlying deficits and mechanisms. Also, most cognitive/executive tasks, including those explicitly devised as a measure of behavioural inhibition, have been criticized for suffering from low reliability (Bari & Robbins, 2013). Thus, as stated by Zhang, Rittman, et al. (2016), the use of saccadic measures to test deficits in inhibitory oculomotor control with an emphasis on impulsive response patterns can benefit the objective assessment of this cognitive and behavioural trait.

Finally, a number of studies suggest that task complexity (higher cognitive/executive

load) is essential for discriminating persons with PreHD and controls in the majority of saccadic paradigms (Antoniades et al., 2007; Peltsch et al., 2008; Turner et al., 2011). The known frontostriatal impairment in Huntington's disease, and the proven influence of this circuitry in the inhibitory component of antisaccades, imply that increasingly complex executive and memory saccadic tasks are expected to be more sensitive to disease onset than simple ones (Mitchell et al., 2002; Robert et al., 2009; Van der Stigchel, 2010).

This study aims to test if inhibitory control demanding oculomotor paradigms, embedded with an increasing fronto-executive and memory load, may provide a sensitive and objective measure of impulsivity, hence failure in inhibiting a motor act, in persons with premanifest HD.

Materials and Methods

Participants

Thirty-seven participants completed the neuropsychological assessment and thirty-six participants completed the saccade/eye-tracking protocol (due to technical problems, the oculomotor data of one participant with PreHD could not be recorded).

Study participants were primarily recruited from the Neurological Department – Neurogenetics Consultation Service of Coimbra University Hospital. They were also recruited through the Huntington's disease Portuguese Association. All participants gave their informed written consent after the study protocol had been explained to them. Informed consent was obtained according to the Declaration of Helsinki and all procedures were approved by the local Ethics Committee (Faculty of Medicine, University of Coimbra).

Exclusion criteria included history of alcohol or drug abuse/dependence, concurrent neurological illness, severe ophthalmic disease, and use of psychotropic medication (the last criterion only applied to controls). The Montreal Cognitive Assessment test score, a mild cognitive impairment and dementia screening tool, was also an exclusion criterion (Freitas et al., 2011; Nasreddine et al., 2005) — a below the established normative reference score based on age and education (Freitas et al., 2011) was presumed to indicate the presence of mild cognitive impairment and, thus, the participant would no

longer take part in the study.

Clinical history, current medications (Table 1.1), and any other information considered to be important for taking part in this study were registered as well. Participants were assigned to two groups (Table 1.2):

Persons with Premanifest Huntington's Disease (PreHD): 15 persons with an expanded HD gene (≥36 CAG repeats) who demonstrated either no signs or soft signs of motor abnormalities, i.e., had a diagnostic confidence score of 0–3 on the Unified Huntington's Disease Rating Scale – Motor scale (UHDRS-Motor), a Total Motor Score (TMS) of ≤ 5, and a Total Functional Capacity (TFC) score of 13 in this UHDRS subscale (Huntington Study Group, 1996).

Controls (CTRL): 22 non-gene carriers, defined as those persons with two unexpanded HD alleles (<36 CAG repeats - gene negative status), or healthy volunteers who were not at risk for HD and had no known neurological disorder (spouses and healthy participants from the community).

Table 1.1 Classes of medication for Premanifest HD (PreHD) and Control (CTRL) groups

(number of participants on)	*CTRL*	*PreHD*
No Medication	22	11
Antidepressants	0	4
Anxiolytics, Sedatives and Hypnotics	0	2
Antipsychotics	0	0

CTRL – Control participants; PreHD – Premanifest HD participants

Table 1.2 Demographic characteristics of the CTRL and PreHD groups

	CTRL=22		*PreHD=15*		*Chi-Square /Mann-Whitney*	
					χ^2/ *U*	*p*
	Gender (F:M) 15:7		Gender (F:M) 8:7		0.836	0.361
	Handedness (R:L) 19:3		Handedness (R:L) 15:0		3.058	0.383
	Median	*IQR*	*Median*	*IQR*		
Age (years)	34	12	37	12	161.5	0.914
Education (years)	11.5	2	12	7	155.5	0.766
CAG repeats	-	-	41	2	-	-
Time to HD Onset (years)	-	-	21.1	11	-	-
UHDRS - TMS	-	-	1	3	-	-
UHDRS - OculoTMS	-	-	0	1	-	-
UHDRS - TFC	-	-	13	0	-	-

No significant differences were found between PreHD and Controls in any of the Demographic variables
IQR – Interquartile Range; CAG repeats – CAG repeat expansion confirmed by a genetic test; Estimated Time to HD Onset – number of years to the formal diagnosis of manifest HD, calculated with the Langbehn's formula (Langbehn et al., 2004); UHDRS – Unified Huntington's Disease Rating Scale (Huntington Study Group, 1996); TMS – Total Motor Scale of the UHDRS; OculoTMS – a composite score extracted from the sum of the oculomotor items of UHDRS-Motor scale; TFC – Total Functional Capacity scale of the UHDRS

Clinical evaluation

An experienced movement disorder neurologist administered the motor subscale of the Unified Huntington's Disease Rating Scale (Huntington Study Group, 1996) to the PreHD participants to establish, with at least 99% certainty, whether individuals had motor manifestations of HD. The neurologist assigned an overall confidence rating that represented the likelihood of motor abnormalities be attributable to HD. The persons with a Total Motor Score (TMS) of ≤ 5 and a rating from 0 to 3 in the diagnostic confidence score were classified as PreHD. A higher TMS indicates worse clinical symptoms. A cut-off of 5 points was used to determine the premanifest status of the participant, in accordance with the European Huntington's Disease Network (EHDN) – Registry study's guidelines (Orth et al., 2010). A composite score (OculoTMS) was computed from the oculomotor component of the UHDRS-Motor scale—ocular pursuit, saccade initiation and saccade velocity items. The Total Functional Capacity subscale (TFC) of the UHDRS was also administered to all the participants of the clinical group, to assess their functional status and determine their premanifest HD stage (Huntington Study Group, 1996; Tabrizi et al., 2012). The TFC uses a rating between 0 and 13 of different functional domains, and a higher score means higher autonomy and independence in the activities of daily living.

Oculomotor Experiment

Participants had to complete four horizontal saccadic tasks, where saccadic movements were recorded using an iViewX Hi-speed eye tracking system (Sensor Motoric Instruments, 2002-2009) – Figure 1.1. This paradigm was designed considering former findings in healthy individuals, that showed specific disruption of saccadic inhibition when the oculomotor task was conjoint to an increasing executive load via an n-back memory task (Mitchell et al., 2002; Van der Stigchel, 2010).

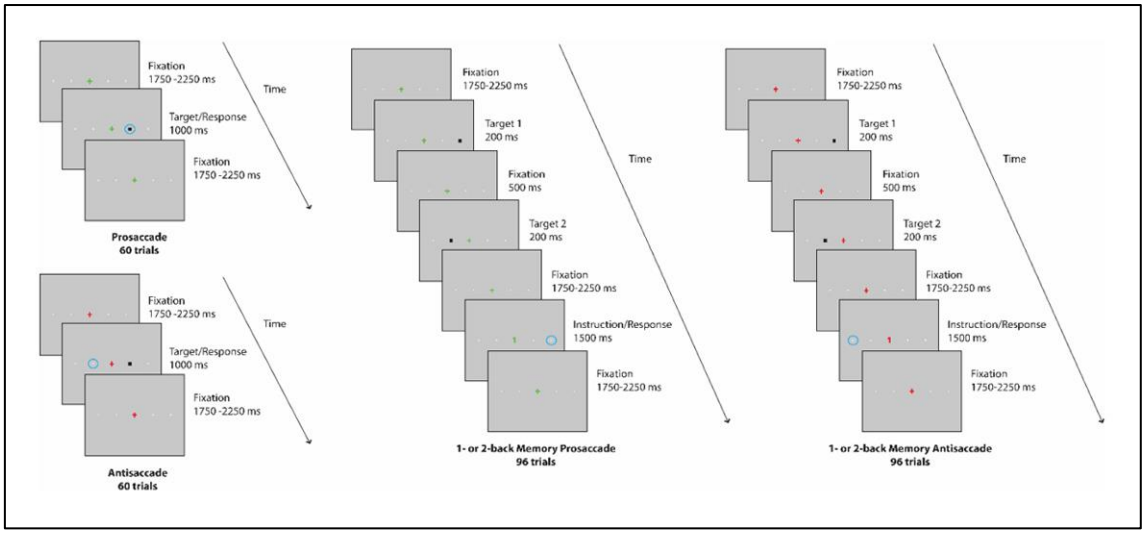

Figure 1.1 Experimental design of the four horizontal saccadic tasks

Oculomotor Testing Procedure

Participants were seated in front of a 17-inch monitor with their heads placed in a stable chin rest that was positioned 52 cm from the screen. Prior to each oculomotor task, the examiner instructed verbally the participant to ensure that the goal of each task was fully understood, followed by a practice block to discard potential novelty effects in task performance. Eye-tracking recordings were performed after a 9-point calibration using the subject's dominant eye. The saccade protocol was administered over a period of 40 to 60 minutes, in a fixed order, with an increasing working memory and fronto-executive load.

The experiment was compound of four conditions. In each, a central fixation point was defined (cross, 1º diameter in visual angle), and peripheral visual targets (black square, 0.6º visual angle) were randomly assigned to four possible positions at ± 6º or ± 12º visual angle. Small position cues were present throughout the experiment at each of the four possible target positions (* symbols, 0.24 º visual angle, light gray in colour).

- Prosaccade task (PS): The participant was instructed to fixate gaze on a central illuminated green cross, and to look to the peripheral target as rapidly as possible once it appeared, and then return to the central fixation cross. This task consisted of 60 trials.
- Antisaccade task (AS): The participant was instructed to fixate gaze on a central illuminated red cross, and to look to the opposite direction of the visual target once it appeared, i.e., the mirror-image location of the target at an equal distance

from the central fixation cross. Afterwards, the participant was asked to return to the central fixation cross. This task also consisted of 60 trials.

- 1- or 2-back Memory Prosaccade task (MPS): The participant was instructed to fixate gaze on a central green cross. While two peripheral squares appeared, the participant was asked to continue to fixate the central green cross. The task period was assigned once the central fixation cross was replaced by a digit, either a green one or a green two, when the participant had to generate a saccade to a remembered position. If the digit was one, the participant was asked to look at the remembered position where the first square had appeared. If the digit was two, the participant was asked to look at the remembered position where the second square had appeared. Then, the participant had to return to the central fixation cross. This task consisted of 96 trials.
- 1- or 2-back Memory Antisaccade task (MAS): The participant was instructed to fixate gaze on a central red cross. The task period was assigned once the central fixation cross was replaced by a digit, either a red one or a red two, when the participant had to generate a saccade. If the digit was one, the participant was asked to look to the opposite direction (i.e., the mirror-image location) of the remembered position where the first square appeared. If the digit was two, the participant was asked to look to the opposite direction of the remembered position where the second square appeared. Then, the participant had to return to the central fixation red cross. This task also consisted of 96 trials.

Oculomotor Data Processing

Regarding the psychophysics task, BeGaze software (Sensor Motoric Instruments, 2014) was used to create experiments based on saccade detection: peak velocity threshold 40^0/ms; saccade velocity initiation and termination of 15^0/ms and 85^0/ms, respectively; minimum fixation duration of 50 ms; minimum saccade duration of 22 ms. Computed data on saccades and blinks were extracted and further analysed with the Matlab software toolbox (The MathWorks, 2013).

Identification of valid trials for each task was performed applying the following criteria: *i)* initiation and termination had to be within a region of interest ($\pm$ 2.5^0 x $\pm$ 4^0 visual angle) of the fixation and target position, respectively; *ii)* the primary saccade initiated within the central fixation ROI, had an amplitude enabling termination outside the ROI

(horizontally), was performed in the correct direction, and had a latency higher than 80 ms; *iii)* if the latency was below 80 ms it was considered an anticipatory saccade error (latency-type error); *iv)* if the saccade was performed in the opposite horizontal direction it was considered a direction error; *v)* the primary saccade had a latency below 700 ms (PS and AS tasks) or 1000 ms (MPS and MAS tasks), otherwise it was considered a long-latency error (latency-type error); *vi)* the total saccadic movement finished within the ROI for the intended target position, prior to return to the central fixation position. Additionally, trials contaminated by blinks or other abnormalities were discarded from the analysis.

For every participant, measures were computed for each of the PS, AS, MPS and MAS tasks, namely: percentage of successful trials – trials free of errors; percentage of direction errors – resulting from a reflexive saccade in the opposite direction of the correct hit; percentage of anticipatory saccade errors – resulting from a premature saccade, in which the participant took less than 80 ms to start the saccade; latency – saccadic reaction time, that is time from stimulus appearance to the onset of the primary saccade (milliseconds). The calculation of mean latencies included only correct trials that met the inclusion criteria.

Only participants that had at least 25% of successful trials (i.e., trials free of any kind of error type) were included in the analysis, for each of the oculomotor tasks (Table 1.3).

Table 1.3 Number of included and excluded participants after identification of valid trials per saccadic task (25% criterion)

Task	*Included*	*Excluded (less than 25% valid trials)*	*Excluded (did not perform the task)*
Prosaccade	22 CTRL	0 CTRL	0 CTRL
	14 PreHD	0 PreHD	1 PreHD
Antisaccade	22 CTRL	0 CTRL	0 CTRL
	14 PreHD	0 PreHD	1 PreHD
Memory Prosaccade	21 CTRL	1 CTRL	0 CTRL
	14 PreHD	0 PreHD	1 PreHD
Memory Antisaccade	20 CTRL	2 CTRL	0 CTRL
	13 PreHD	1 PreHD	1 PreHD

CTRL – Control participants; PreHD – Premanifest HD participants

Neuropsychological Assessment

We have used a comprehensive neuropsychological test battery that was designed to maximize sensitivity to the frontostriatal neural circuitry and cognitive control abilities, and that mainly incorporated widely used executive and memory tests (Table 1.4).

We aimed at tapping the major cognitive functions known to be affected in the early stages of HD (Orth et al., 2010; Paulsen & Long, 2014; Snowden et al., 2002; Solomon et al., 2008; Stout et al., 2011; Tabrizi et al., 2013). We computed two main composite scores from this battery — Executive and Memory — to have a baseline depiction of the cognitive abilities involved in the saccadic paradigm created for this study, and to acknowledge any significant differences between the overt cognitive profile of PreHD and Control participants that could otherwise explain the potential differences found in their oculomotor behaviour.

An Executive Composite Score was computed from six neuropsychological test scores [Stroop word reading test – total correct; Stroop colour naming test – total correct; Stroop interference test – total correct; Symbol digit modality test – total correct; Verbal fluency test (letters-PMR) – total correct; Verbal fluency test (category-animals) – total correct]. A Memory Composite Score was computed from six neuropsychological test scores [Benton visual retention test – total correct; Auditory verbal learning test (trials-1-5) – total correct; Auditory verbal learning test (recall) – total correct; Auditory verbal learning test (recognition) – total correct; Corsi block tapping task (direct) – total correct; Corsi block tapping task (inverse) – total correct].

Table 1.4 Neuropsychological Assessment Protocol

Tool	*Goal/Assessment Domain*
Montreal Cognitive Assessment – MoCA (Freitas et al., 2011; Nasreddine et al., 2005)	mild cognitive impairment and dementia screening
Stroop Test – Color Naming, Word Reading, and Interference tasks (Stroop, 1935; Trenerry et al., 1989)	executive function – cognitive flexibility and processing speed
Edinburgh Handedness Inventory – Portuguese adaptation (Oldfield, 1971)	handedness definition
Digit Symbol subtest of the Wechsler Adult Intelligence Scale-III (WAIS-III) (Wechsler, 1997, 2008)	psychomotor speed and working memory
Rey Auditory Verbal Learning test – Portuguese version (Cavaco et al., 2015; Rey, 1964) – total trials 1-5	verbal memory
12-item short form of the Raven Advanced Progressive Matrices (Raven et al., 1993)	indication of non-verbal intelligence and to control for individual differences in IQ that are unrelated to illness
Corsi Block-Tapping task (Berch et al., 1998; Kessels et al., 2000)	psychomotor speed, working memory and executive functioning – the product of the total number of correct trials and the length of the largest sequence was calculated
Benton Visual Retention test (Benton, 1974)	visual memory
Rey Auditory Verbal Learning test – Portuguese version (Cavaco et al., 2015; Rey, 1964) – recall and recognition trials	verbal memory
Benton Visual Form Discrimination test (Benton et al., 1983)	visual perception
Phonemic Verbal Fluency test: 3 letters – P, M, R (Lezak, 1995)	executive function – working memory, word generation and inhibition
Semantic Verbal Fluency test: category – animals (Ardila et al., 2006)	executive function – working memory, word generation and inhibition
Vocabulary of the WAIS-III (Wechsler, 1997, 2008)	indication of verbal intelligence and control for individual differences in intelligence that are unrelated to illness
Hospital Anxiety and Depression Scale – Snaith Irritability Scale (HADS-SIS) (Pais-Ribeiro et al., 2007; Snaith et al., 1978; Zigmond & Snaith, 1983)	psychiatric symptoms and prevalence of depression and anxiety

Additionally, we have assessed the global cognitive status, the verbal and non-verbal intelligence level, the visual perception abilities, and the neuropsychiatric symptoms of study participants using standardized measures of these domains.

The neuropsychological battery was administered over a period of one and a half hours, in a strictly prescribed order, to avoid interference problems related to evaluating the same contents or assessing the same domain in several tasks in a row, and to respect the time intervals required by certain tests.

Statistics

Statistical analysis was performed with the software IBM SPSS Statistics (Version 24), adopting a level of significance of $\alpha = 0.05$, and only significant results were reported and further debated in the "Results" and "Discussion" sections.

Outliers were excluded from data analysis for each oculomotor parameter in the four saccadic tasks—values below Q1-1.5xIQR and above Q3+1.5xIQR (Table 1.5).

Table 1.5 Number of outliers per group for each of the four oculomotor parameters across the four saccadic tasks

	% Successful Trials		*% Direction Errors*		*% Anticipatory Saccade Errors*		*Latency*	
	CTRL	*PreHD*	*CTRL*	*PreHD*	*CTRL*	*PreHD*	*CTRL*	*PreHD*
PS	2	1	0	2	1	1	1	0
AS	1	0	2	0	0	2	1	0
MPS	1	1	1	1	2	0	1	0
MAS	0	0	2	0	3	0	0	1

CTRL – Control participants; PreHD – Premanifest HD participants
PS – Prosaccade; AS – Antisaccade; MPS – 1- or 2-back memory Prosaccade; MAS – 1- or 2-back memory Antisaccade
Successful trials – trials free of errors (%); Direction errors – resulting from a reflexive saccade in the opposite direction of the correct hit (%); Anticipatory saccade errors – resulting from a premature saccade: participant takes less than 80 ms to start the saccade (%); Latency – saccadic reaction time: time from stimulus appearance to the onset of the first saccade (milliseconds)

When comparing the neuropsychological and saccadic performance of the PreHD and Control groups, ANCOVA statistical analysis was performed with age as a covariate, given that this variable is known to affect cognition and reflexive and voluntary eye movements both in clinical and healthy populations (Antoniades et al., 2010; Butler et al., 1999; Murman, 2015; Patel et al., 2012). Mann-Whitney *U* tests were used to compare the demographic variables of the two groups. Comparisons of nominal/categorical variables between groups were performed resorting to Chi-square tests of independence. Wilcoxon-Signed rank tests were used to further examine the effects of task condition (PS, AS, MPS and MAS) in the PreHD participants' saccadic performance. Spearman rank correlation coefficients were calculated to analyse the associations between the performance of the PreHD participants in the oculomotor measures where a group difference was found and other clinical, cognitive and oculomotor data of the PreHD group. Benjamini–Hochberg corrections with false positive rate established at 0.05 were used to deal with multiple comparisons.

Results

The PreHD and CTRL participants enrolled in our study were matched in terms of age, education level, gender, and handedness (Table 1.2).

Oculomotor Results

The comparison of the saccadic performance of the two groups (Table 1.6 and Figure 1.2) revealed that alterations of oculomotor performance were present in the clinical group compared to controls, especially in the tasks with higher executive and/or memory load, namely the AS and MAS tasks.

Table 1.6 Comparison of the Oculomotor results of the CTRL and PreHD groups across the four saccadic tasks

	% Successful Trials		*% Direction Errors*		*% Anticipatory Saccade Errors*		*Latency*	
	F	*p*	*F*	*p*	*F*	*p*	*F*	*p*
PS	(1,30) 3.299	0.079	(1,31) 0.203	0.655	(1,31) 0.124	0.728	(1,32) 0.954	0.336
AS	(1,32) 5.200	0.029*	(1,31) 7.278	0.011*	(1,31) 0.984	0.329	(1,32) 0.132	0.719
MPS	(1,30) 0.081	0.778	(1,30) 0.158	0.694	(1,30) 0.516	0.478	(1,31) 1.186	0.285
MAS	(1,30) 1.287	0.266	(1,28) 5.480	0.027*	(1,27) 1.984	0.170	(1,29) 12.272	0.002*

PS – Prosaccade; AS – Antisaccade; MPS – 1- or 2-back memory Prosaccade; MAS – 1- or 2-back memory Antisaccade
** PreHD ≠ CTRL (ANCOVA, p≤ 0.05 – controlling for the effect of age)*

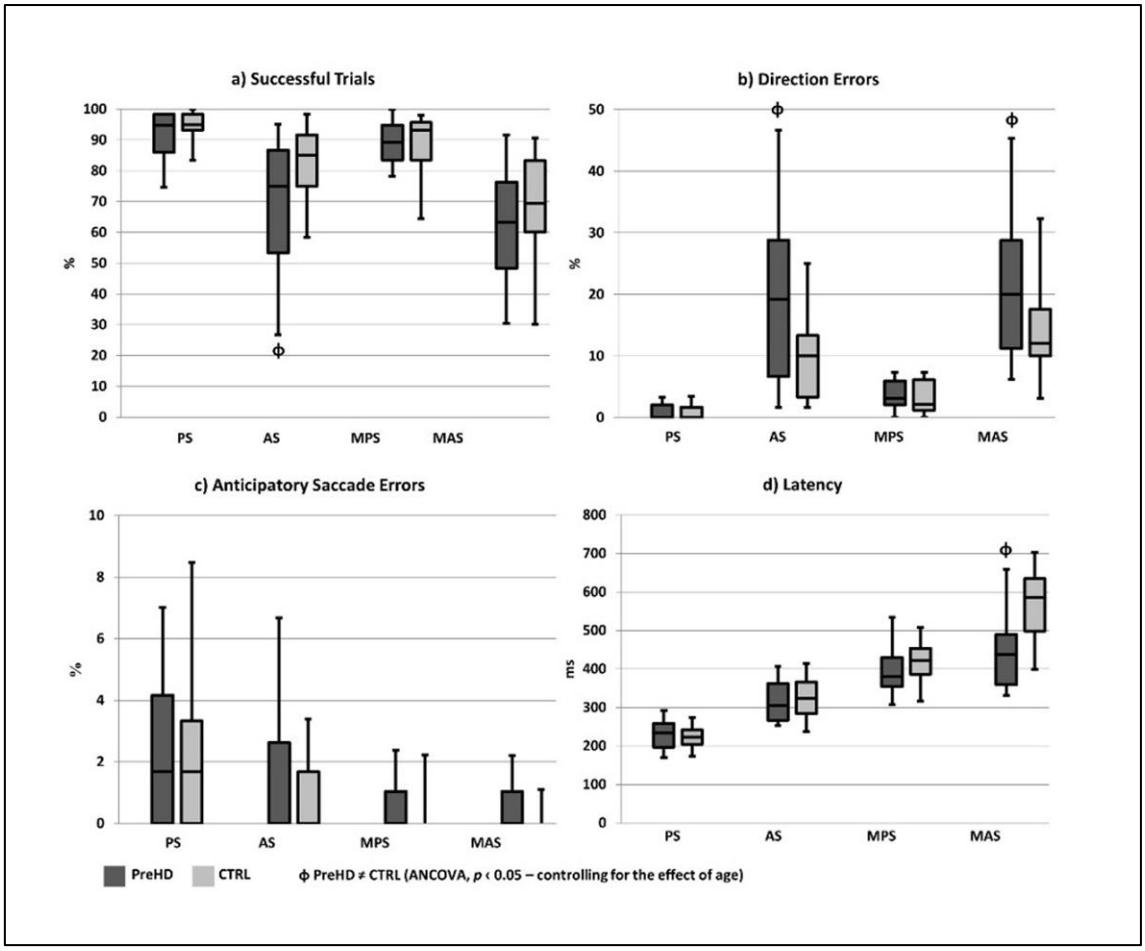

Figure 1.2 Oculomotor results of the CTRL and PreHD groups across the four saccadic tasks

Box plot (line, median; box, 1st and 3rd quartiles; whiskers, minimum and maximum. PS – Prosaccade; AS – Antisaccade; MPS – 1- or 2-back memory Prosaccade; MAS – 1- or 2-back memory Antisaccade. PreHD – Premanifest HD participants; CTRL – Control participants.
a) Successful trials – trials free of errors (%); b) Direction errors – resulting from a reflexive saccade in the opposite direction of the correct hit (%); c) Anticipatory saccade errors – resulting from a premature saccade: participant takes less than 80 ms to start the saccade (%); d) Latency – saccadic reaction time: time from stimulus appearance to the onset of the first saccade (milliseconds)
***ϕ** PreHD ≠ CTRL (ANCOVA, p ‹ 0.05 – controlling for the effect of age)*

In addition, the analysis of the performance of PreHD participants across the four saccadic conditions revealed that both accuracy and timing measures reflected the impact of the incremental executive and memory demands of the saccadic tasks (Table 1.7).

Table 1.7 Significant differences in the PreHD group performance across the four saccadic tasks

PreHD	*Successful Trials (n= 12)*		*Direction Errors (n= 11)*		*Anticipatory Saccade Errors (n= 11)*		*Latency (n= 12)*	
	Z	*p*	*Z*	*p*	*Z*	*p*	*Z*	*p*
PS - AS	-3.059	0.002*	-2.845	0.004*	-1.272	0.203	-3.059	0.002*
PS - MPS	-1.334	0.182	-2.851	0.004*	-2.371	0.018*	-3.059	0.002*
PS - MAS	-3.059	0.002*	-2.934	0.003*	-2.371	0.018*	-3.059	0.002*
AS - MPS	-2.845	0.004*	-2.667	0.008*	-1.761	0.078	-3.059	0.002*
AS - MAS	-1.647	0.099	-1.156	0.248	-1.490	0.136	-3.059	0.002*
MPS -MAS	-3.059	0.002*	-2.803	0.005*	-0.730	0.465	-2.275	0.023*

PreHD – Premanifest HD participants; PS – Prosaccade; AS – Antisaccade; MPS – 1- or 2-back memory Prosaccade; MAS – 1- or 2-back memory Antisaccade; Successful trials – trials free of errors (%); Direction errors – resulting from a reflexive saccade in the opposite direction of the correct hit (%); Anticipatory saccade errors – resulting from a premature saccade: participant takes less than 80 ms to start the saccade (%); Latency – saccadic reaction time: time from stimulus appearance to the onset of the first saccade (milliseconds)
*Wilcoxon Signed Ranks Test * Significant differences p≤ 0.05*

For the percentage of successful trials, an important statistically significant difference was found between PreHD and CTRL participants in the AS condition ($F(1,32)= 5.200$, $p= 0.029$). This result suggests that once an executive load or inhibitory demand was introduced into an otherwise simple reflexive saccadic task, the PreHD group started to show an abnormal oculomotor behaviour, with a significantly decrease in their success rate due to the switch in the protocol.

Notably, for the percentage of direction errors, again a statistically significant difference was found between PreHD and CTRL participants in the AS condition ($F(1,31)= 7.278$, $p= 0.011$) and in the MAS condition ($F(1,28)= 5.480$, $p= 0.027$). These results suggest that, when an executive load is added to the task, either independently or combined with memory demands, the oculomotor performance of PreHD participants fails to adapt to the new goal and inhibition deficits emerge.

For the percentage of anticipatory saccade errors, no statistically significant differences were found between PreHD and CTRL participants across the four saccadic conditions. These results suggest that both groups exhibit a similar rate of premature saccades along the different task conditions, albeit the reduced accuracy displayed by PreHD participants in the more demanding AS and MAS tasks.

Finally, for the primary saccade latency, a statistically significant difference was found between PreHD and CTRL participants in the MAS condition, where PreHD participants showed a faster saccadic reaction time compared to controls ($F(1,29)= 12.272$, $p= 0.002$). These findings suggest that for the premanifest HD participants, latency in the context of

the most demanding saccadic condition can illustrate a more automatic response pattern when the task demands increase.

The analysis of the saccadic performance of the PreHD participants across the four different task conditions (PS, AS, MPS and MAS) revealed significant effects of the increasing cognitive load in the percentage of successful trials, percentage of direction errors, percentage of anticipatory errors and latency (Table 1.7). Latency and the percentage of direction errors seemed to be particularly sensitive measures for capturing the decremental impact of the increasing executive and memory demands of the oculomotor task on the behaviour of premanifest HD participants [all significant differences $|Z| \geq 2.803$, $p \leq 0.05$]. Interestingly, only the primary saccade latency differed between the AS and MAS oculomotor performance of the PreHD group ($Z = -3.059$, $p = 0.002$), which suggests that in saccadic conditions with inhibition demands the behaviour of the clinical group is globally similar (and equally compromised), whereas a more automatic response pattern emerges when the task demands increase (MAS task).

Neuropsychological Results

No significant differences were found between PreHD and CTRL participants in the Executive and Memory Composite scores computed from the neuropsychological battery used, nor in any of the other neuropsychological and neuropsychiatric measures used (Table 1.8). These results suggest that both groups had a similar cognitive and psychiatric status, as assessed with conventional tests and scales, which might indicate that the oculomotor differences found between the two groups cannot be explained by disparate executive, memory or psychiatric conditions.

Table 1.8 Neuropsychological test results of the CTRL and PreHD groups

	CTRL		*PreHD*		*ANCOVA*	
	Median	*IQR*	*Median*	*IQR*	*F*	*p*
Executive Composite Score	321	65	307	74	(1,34) 0.313	0.579
Memory Composite Score	206.5	32	203	61	(1,34) 0.225	0.638
Vocabulary - WAIS III	36.5	15	37	13	(1,34) 0.271	0.606
Raven Matrices	8	2	9	3	(1,34) 0.105	0.748
Montreal Cognitive Assessment	26	3	26	3	(1,34) 0.248	0.622
Benton Visual Form Discrimination	30.5	3	30	4	(1,34) 0.310	0.861
HADS-SIS – Depression	4	5	4	6	(1,34) 0.150	0.700
HADS-SIS – Anxiety	6	7	5	5	(1,34) 0.197	0.660

No significant differences found between PreHD and Controls in any of the Neuropsychological Measures
IQR – Interquartile Range; HADS-SIS - Hospital Anxiety and Depression Scale – Snaith Irritability Scale
Executive Composite Score = Stroop word reading test (total correct) + Stroop color naming test (total correct) + Stroop interference test (total correct) + Symbol digit modality test (total correct) + Verbal fluency test (letters-PMR) (total correct) + Verbal fluency test (category-animals) (total correct)
Memory Composite Score = Benton visual retention test (total correct) + Auditory verbal learning test (trials-1-5) (total correct) + Auditory verbal learning test (recall) (total correct) + Auditory verbal learning test (recognition) (total correct) + Corsi block tapping task (direct) (total correct) + Corsi block tapping task (inverse) (total correct)

Correlational Analysis

In the PreHD group, the four oculomotor parameters that statistically differed from the CTRL group were significantly correlated with their results in other clinical, cognitive and oculomotor measures included in our study protocol (Table 1.9, and Table 1.10).

Table 1.9 Correlations between the oculomotor, clinical and cognitive results of the PreHD group

PreHD	*AS Successful Trials n = 14*		*AS Direction Errors n = 14*		*MAS Direction Errors n = 13*		*MAS Latency n = 12*	
	rho	*p*	*rho*	*p*	*rho*	*p*	*rho*	*p*
CAG	-0.089	0.763	0.000	1.000	-0.220	0.469	0.303	0.339
Time to HD Onset (years)	0.420	0.135	-0.310	0.281	-0.014	0.964	-0.620	0.032*
UHDRS-TMS	-0.356	0.212	0.314	0.274	0.284	0.347	-0.096	0.766
UHDRS-OculoTMS	-0.473	0.088	0.533	0.049*	0.609	0.027*	0.096	0.767
Executive Score	0.459	0.099	-0.257	0.375	-0.325	0.279	0.133	0.681
Memory Score	0.533	0.050*	-0.300	0.298	-0.660	0.014*	0.186	0.564

AS – Antisaccade; MAS – 1- or 2-back memory Antisaccade
CAG repeats – CAG repeat expansion confirmed by a genetic test; Estimated Time to HD Onset – number of years to the formal diagnosis of manifest HD; UHDRS – Unified Huntington's Disease Rating Scale; TMS – Total Motor Scale of the UHDRS; OculoTMS – a composite score extracted from the sum of the oculomotor items of UHDRS-Motor scale
** Correlation is significant at 0.05 level (two-tailed)*

Importantly, the percentage of direction errors of the PreHD group in the AS and MAS conditions were significantly correlated with the UHDRS-OculoTMS (*rs*= 0.533, *p*= 0.049 and *rs*= 0.609, *p*= 0.027, respectively), which reflects oculomotor abnormalities detected at neurological examination. Moreover, the PreHD primary saccade latency in the MAS condition was significantly correlated with the Time to HD Onset (*rs*= -0.620, *p*= 0.032). Finally, we have found that the memory composite score was significantly associated with the AS percentage of successful trials and the MAS percentage of direction errors in the PreHD group (*rs*= 0.533, *p*= 0.050 and *rs*= -0.660, *p*= 0.014, respectively). These results suggest that changes in specific oculomotor parameters prior to the onset of clinically relevant motor disturbances are significantly associated with important disease-related features and cognitive skills in premanifest HD individuals. Additionally, the significant associations found between antisaccade trajectory and timing measures in the PreHD group indicate that executively demanding oculomotor tasks seem to induce a consistently erroneous and impulsive saccadic behaviour in premanifest HD individuals.

Table 1.10 Correlations between the oculomotor results in the PreHD group

PreHD	*AS Successful Trials n = 14*		*AS Direction Errors n = 14*		*MAS Direction Errors n = 13*		*MAS Latency n = 12*	
	rho	*p*	*rho*	*P*	*rho*	*p*	*rho*	*p*
PS								
Successful Trials	0.771	0.001**	-0.676	0.008*	-0.138	0.654	-0.182	0.572
Direction Errors	-0.272	0.347	0.149	0.611	0.275	0.363	-0.233	0.466
Anticipatory Errors	-0.477	0.084	0.419	0.136	0.327	0.275	-0.086	0.791
Latency	-0.046	0.875	-0.207	0.478	-0.071	0.817	0.147	0.649
AS								
Successful Trials	1.000		-0.887	0.000**	-0.364	0.222	-0.263	0.409
Direction Errors	-0.887	0.000**	1.000		0.383	0.197	0.347	0.269
Anticipatory Errors	-0.837	0.000**	0.747	0.002**	0.356	0.233	-0.105	0.746
Latency	-0.460	0.098	0.260	0.370	0.093	0.762	0.441	0.152
MPS								
Successful Trials	0.549	0.042*	-0.258	0.373	-0.295	0.328	0.319	0.312
Direction Errors	-0.251	0.386	0.288	0.318	0.271	0.370	-0.152	0.638
Anticipatory Errors	-0.539	0.047*	0.284	0.325	0.513	0.073	0.431	0.161
Latency	-0.282	0.329	0.176	0.547	0.049	0.873	0.629	0.028*
MAS								
Successful Trials	0.449	0.107	-0.095	0.747	-0.401	0.174	0.049	0.880
Direction Errors	-0.385	0.173	0.264	0.361	1.000		-0.196	0.542
Anticipatory Errors	-0.262	0.366	0.054	0.855	0.322	0.283	-0.303	0.339
Latency	-0.154	0.599	0.077	0.793	-0.115	0.707	1.000	

PS – Prosaccade; AS – Antisaccade; MPS – 1- or 2-back memory Prosaccade; MAS – 1- or 2-back memory Antisaccade
Successful trials – trials free of errors (%); Direction errors – resulting from a reflexive saccade in the opposite direction of the correct hit (%); Anticipatory saccade errors – resulting from a premature saccade: participant takes less than 80 ms to start the saccade (%); Latency – saccadic reaction time: time from stimulus appearance to the onset of the first saccade (milliseconds)
** Correlation is significant at 0.05 level (two-tailed)*
*** Correlation is significant after Benjamini-Hochberg correction: AS % valid trails p≤ 0.001; AS % direction errors p≤ 0.002; MAS % direction errors p≤ 0.01; MAS latency p≤ 0.02*

Discussion

The current study addressed the role of saccadic movement parameters, and specifically saccadic inhibition with or without memory and fronto-executive load, as a potential marker of impulsive behaviour in premanifest Huntington's disease. We hypothesized that an oculomotor experiment embedded with a cognitively demanding paradigm (Bari & Robbins, 2013; Mitchell et al., 2002; Van der Stigchel, 2010), aimed at increasing fronto-executive load whilst tapping onto the inhibitory component of saccadic eye movements, could be more sensitive in detecting the earliest HD-related alterations than formerly investigated paradigms (Antoniades et al., 2007; Blekher et al., 2006; Golding et al., 2006; Robert et al., 2009; Turner et al., 2011; Winder & Roos, 2018), conventional cognitive tests that evaluate executive function and working memory (Ardila et al., 2006; Berch et al., 1998; Kessels et al., 2000; Lezak, 1995; Stroop, 1935; Trenerry et al., 1989), and standard clinical evaluation of oculomotor function (Huntington Study Group, 1996; Winder & Roos, 2018). Particularly, the influence of frontal-executive load in oculomotor inhibition processes was analysed in this study and tested as a potential trigger of impulsive response patterns in persons with premanifest HD.

We have found that PreHD participants with a similar executive and memory performance in conventional tests to controls, show statistically significant saccadic impairments in an oculomotor paradigm that encloses inhibition and increasing cognitive demands.

The PreHD group has shown impairments particularly in oculomotor tasks with an inhibitory component, exhibiting a decreased success rate in the AS task, a higher percentage of direction errors in the AS and MAS tasks, and a reduced response latency in the MAS condition when compared to controls. The timing and trajectory abnormalities shown by the PreHD group of our study illustrate the impaired saccade suppression in premanifest HD reported by Anderson and MacAskill (2013), the higher incidence of unusually early saccades in premanifest individuals reported by Antoniades et al. (2010) and Rupp et al. (2012), and the HD patients' inability to stifle saccades especially in highly demanding memory and executive tasks reported by Ali et al. (2006). The lower percentage of success rate in the AS task and the reduced saccade latency shown by the premanifest HD group in the MAS task may be interpreted as indicators of more impulsive oculomotor behaviour/automatic response pattern due to early impairments in inhibitory control mechanisms. Farrow et al. (2006) suggested that in

cognitive tasks with increasing executive load, persons with premanifest HD have greater difficulty overcoming the more demanding executive conditions and are more likely to inappropriately make more automatic responses. Our data seems to be in line with this statement — control participants seem to show a stable oculomotor performance along the four different saccadic tasks, increasing their response latency in the more demanding conditions, as part of the strategy to ensure a successful performance and to keep good accuracy levels, whereas PreHD participants tend to give more erroneous responses in the tasks with higher executive and memory load, and show a faster saccadic reaction time compared to controls. The changes in saccade timing (latency) observed in the clinical group might represent automatic processes and work as a proxy for the impulsivity and inhibitory control deficits often described in Huntington's disease. This impulsivity-related response pattern matches the speed-accuracy trade-off described by Heitz (2014) where faster responses entail less accumulated evidence, and hence less informed decisions. This finding is also in line with the study of Vaportzis et al. (2015) that reported that HD participants were affected differently than controls with respect to the competing goals of speed and accuracy. Moreover, these results seem to have similarities with the reflection impulsivity attributed to PD patients during rapid decision paradigms (Kagan et al., 1966), that is, a tendency to "jump to conclusions" without gathering enough information (Zhang, Nombela, et al., 2016).

Rao et al. (2014) claim that response-inhibition failure in premanifest HD is associated with functional changes in inhibitory control, attentional reorienting, and motor-control systems. Because neural degeneration in HD begins in the basal ganglia, and saccadic suppression and inhibitory control mechanisms appear to be affected directly by these changes, measures of saccadic suppression, specifically, may be an effective early indicator of disease onset and impulsivity symptoms in premanifest HD, as response inhibition can serve as a "proxy" for the study of impulsivity and its neurobiological underpinnings (Bari & Robbins, 2013; Peltsch et al., 2008).

We hypothesized that an oculomotor paradigm with increment of executive and/or working-memory load might be more sensitive to the earliest HD-related changes if tapping onto the inhibition of saccades, since the frontostriatal circuitry is known to be affected one to two decades prior to estimated disease clinical onset (Gómez-Tortosa et al., 2001; Paulsen et al., 2008; Rosas et al., 2006). This is relevant when searching for sensitive and low-cost markers of earliest functional changes due to HD

neurodegenerative processes. In contrast to studies in healthy individuals (Mitchell et al., 2002; Van der Stigchel, 2010) we embedded the n-back memory component in the saccadic task, instead of a separate auditory or visual presentation of letters, respectively. We envisioned this would allow to discard interference from other sensory modalities and to better disentangle impairment in oculomotor inhibition in scope of HD neurodegeneration. Despite former findings of oculomotor alterations in premanifest HD (Ali et al., 2006; Antoniades et al., 2007, 2010; Blekher et al., 2004, 2006; Golding et al., 2006; Henderson et al., 2011; Patel et al., 2012; Peltsch et al., 2008; Robert et al., 2009; Rupp et al., 2010, 2012; Turner et al., 2011), our study remains one of the few to have significant results on a sample of PreHD participants that are on average far from estimated clinical onset (Rupp et al., 2010, 2012; Turner et al., 2011). Furthermore, even though age is known to affect performance of reflexive and voluntary eye movements, both in healthy and clinical populations (Munoz et al., 1998; Rodríguez-Labrada et al., 2019), previous studies have not controlled systematically for such effects, which might affect the positive results reported. Also, in former studies, the criterion for the categorization of premanifest and manifest HD individuals has been based on subjective confidence ratings (for example, see Blekher et al., 2006), and not in a clear and standardized cut-off score as in the UHDRS-Motor scale (Huntington Study Group, 1996). At last, the application of pattern classification algorithms to oculomotor data has already shown promising results in differentiating premanifest HD individuals from control participants (Miranda et al., 2016; Wiecki et al., 2016), yet the interpretation of results in view of the dysfunction of inhibitory motor control remains elusive.

Regarding the conventional neuropsychological assessment results, the comparable cognitive baseline performance of the PreHD and Control participants in our study is in accordance with previous studies that did not detect differences between the cognitive profile of gene positive and gene negative/healthy control individuals (Antoniades et al., 2007; Farrow et al., 2006; Papp et al., 2011; Rupp et al., 2010; Solomon et al., 2008; Witjes-Ané et al., 2003). Even in large sample size studies (e.g., PREDICT-HD and TRACK-HD), the only robust cognitive deficits were detected in individuals that were close to estimated clinical onset (HD symptom presentation) and in the more executive demanding tests (Paulsen, 2010; Tabrizi et al., 2012, 2013). Our sample of PreHD participants was composed by individuals that were on average far from estimated clinical onset (73% had 15 or more years to the time of HD clinical diagnosis, according to Langbehn's formula (Langbehn et al., 2004)), which might have had an important

impact in our overall results (e.g., small effect sizes). Furthermore, these results suggest that the differences found in oculomotor performance between persons with PreHD and CTRL individuals cannot be otherwise explained by the two groups having a distinct overt cognitive baseline.

Finally, the significant correlations found between specific oculomotor parameters and HD clinical and cognitive features reinforce the view that the saccadic behaviour of PreHD individuals, particularly under more executively demanding conditions, reliably mirrors the often subtle and underestimated cognitive and motor alterations that characterize the premanifest stage of HD, and also gives important information about disease onset and progression. This is in line with former findings in persons with premanifest HD: impaired oculomotor functioning was shown to be associated to worse performance on cognitive tasks (Carvalho et al., 2016); response accuracy in a visual processing task was found to be significantly correlated with an index of disease progression (Nasr & Rosas, 2019); reaction time in a sequential button pressing task was significantly associated with estimated time to disease onset (Farrow et al., 2006); increased error rates in antisaccade and memory guided saccade tasks were demonstrated to be associated to more abnormalities in the UHDRS motor scale and to a closer estimated disease onset (Blekher et al., 2006; Rupp et al., 2010); higher cognitive impairment was shown to be significantly related to increased oculomotor changes (Biglan et al., 2013); and, antisaccade error rate has been found to increase proportionally with disease progression (Tabrizi et al., 2009). Thus, quantitative measures of oculomotor inhibitory control and impulsivity such as the ones computed from the AS and MAS tasks of our study protocol seem to be sensitive indicators of the disease status and progression stage of persons with premanifest HD.

In conclusion, our results indicate that the temporal and spatial properties of oculomotor function in persons with PreHD reflect an imbalance between goal oriented and automatic behaviour, due to early inhibitory control deficits. Moreover, our data suggest that the failure of the inhibitory control mechanisms that are involved in simple and complex oculomotor responses can induce an impulsive eye movement pattern in otherwise asymptomatic carriers of the genetic mutation that matches the HD executive dysfunction syndrome described by Rosenblatt (2007). Hence, saccadic timing and trajectory measures may be an effective early indicator of disease onset in HD, namely of motor disinhibition and impulsivity signs. Furthermore, the manifestation of timing or spatial deviations in the saccadic behaviour of premanifest HD individuals might

depend on the task, and the levels of inhibition involved as well as executive load.

Limitations

The small sample size makes it difficult to further subdivide the PreHD group into those far and close from estimated clinical onset. Large longitudinal studies like TRACK-HD or PREDICT-HD found the most significant differences between the cognitive performance of asymptomatic HD gene carriers and controls in those participants closer to clinical onset (Paulsen, 2010; Tabrizi et al., 2012, 2013); this might indicate that a stratification is necessary if one wants to find robust evidence of cognitive changes in premanifest HD. Moreover, the relatively small sample size enrolled in our study prevents us from being able to generalize our results — further work is essential to validate and replicate our findings in a larger sample. Finally, the fact that significant differences were absent at the level of conventional neuropsychological test results between PreHD and CTRL participants leads us to hypothesize that the neuropsychological test battery used, even if extensive, was not sufficiently sensitive to the subtle and earliest changes that occur in HD cognition—subtle changes synonymous of small effect sizes, might need larger samples of premanifest gene carriers for testing novel hypotheses. Also, having a set of more ecological neuropsychological tests would probably help to better distinguish between the PreHD and CTRL groups, as cognitive assessment methods that resemble daily-life tasks have proven to be more successful at differentiating premanifest HD individuals far from estimated disease onset and controls (Stout et al., 2016).

Conclusion

Our saccadic task results suggest that the performance of persons with PreHD deteriorates when a fronto-executive or/and memory load is added to the task. Moreover, the PreHD group appears to have deficits in goal-oriented oculomotor behaviour — more automatic responses or impulsivity at the cost of timed-strategy for accurate decision making. Our findings also suggest that specific horizontal saccadic parameters that enclose inhibition and memory demands seem to be accurate indicators of disease-related features in persons with premanifest HD. Hence, measures of inhibitory control mechanisms in the context of eye movement paradigms may provide

sensitive markers of clinical disease onset in Huntington's disease and help understand the neurobehavioral underpinnings of impulsivity as a trait of HD phenotype. Lastly, new quantitative tools that can detect the earliest disease-related changes and provide information about premanifest HD subtle signs and symptoms are thought to be extremely relevant for the design and implementation of interventional strategies aimed at delaying the onset or progression of Huntington's disease.

References

Ali, F. R., Michell, A. W., Barker, R. A., & Carpenter, R. H. (2006). The use of quantitative oculometry in the assessment of Huntington's disease. *Experimental Brain Research, 169*(2), 237–245. https://doi.org/10.1007/s00221-005-0143-6

Anderson, T. J., & MacAskill, M. R. (2013). Eye movements in patients with neurodegenerative disorders. *Nature Reviews Neurology, 9*(2), 74–85. https://doi.org/10.1038/nrneurol.2012.273

Antoniades, C. A., Altham, P. M., Mason, S. L., Barker, R. A., & Carpenter, R. (2007). Saccadometry: A new tool for evaluating presymptomatic Huntington patients. *Neuroreport, 18*(11), 1133–1136. https://doi.org/10.1097/WNR.0b013e32821c560d

Antoniades, C. A., Xu, Z., Mason, S. L., Carpenter, R. H., & Barker, R. A. (2010). Huntington's disease: Changes in saccades and hand-tapping over 3 years. *Journal of Neurology, 257*(11), 1890–1898. https://doi.org/10.1007/s00415-010-5632-2

Ardila, A., Ostrosky-Solís, F., & Bernal, B. (2006). Cognitive testing toward the future: The example of Semantic Verbal Fluency (ANIMALS), *International Journal of Psychology, 41*(5), 324-332. https://doi.org/10.1080/00207590500345542

Balci, F., Day, M., Rooney, A., & Brunner, D. (2009). Disrupted temporal control in the R6/2 mouse model of Huntington's disease. *Behavioral Neuroscience, 123*(6), 1353–1358. https://doi.org/10.1037/a0017650

Bari, A., & Robbins, T. W. (2013). Inhibition and impulsivity: Behavioral and neural basis of response control. *Progress in Neurobiology, 108*, 44–79. https://doi.org/10.1016/j.pneurobio.2013.06.005

Bayard, S., Joly, E., Ghisletta, P., Rossignol, A., Herades, Y., Geny, C., Gély-Nargeot, M. C., & Rochat, L. (2016). A multidimensional approach to impulsivity in Parkinson's disease:

Measurement and structural invariance of the UPPS Impulsive Behaviour Scale. *Psychological Medicine, 46*(14), 2931–2941. https://doi.org/10.1017/S0033291716001586

Benton A.L. (1974). *The revised visual retention test: Clinical and experimental applications (*4th ed.). Psychological Corporation.

Benton AL., Hamsher, K. D., Varney, N. R., & Spreen, O. (1983). *Contributions to neuropsychological assessment: a clinical manual (*1st ed.). Oxford University Press.

Berch, D. B., Krikorian, R., & Huha, E. M. (1998). The Corsi block-tapping task: Methodological and theoretical considerations. *Brain and Cognition, 38*(3), 317–338. https://doi.org/10.1006/brcg.1998.1039

Biglan, K. M., Zhang, Y., Long, J. D., Geschwind, M., Kang, G. A., Killoran, A., Lu, W., McCusker, E., Mills, J. A., Raymond, L. A., Testa, C., Wojcieszek, J., Paulsen, J. S., & PREDICT-HD Investigators of the Huntington Study Group (2013). Refining the diagnosis of Huntington disease: The PREDICT-HD study. *Frontiers in Aging Neuroscience, 5,* 12. https://doi.org/10.3389/fnagi.2013.00012

Blekher, T., Johnson, S. A., Marshall, J., White, K., Hui, S., Weaver, M., Gray, J., Yee, R., Stout, J. C., Beristain, X., Wojcieszek, J., & Foroud, T. (2006). Saccades in presymptomatic and early stages of Huntington disease. *Neurology, 67*(3), 394–399. https://doi.org/10.1212/01.wnl.0000227890.87398.c1

Blekher, T. M., Yee, R. D., Kirkwood, S. C., Hake, A. M., Stout, J. C., Weaver, M. R., & Foroud, T. M. (2004). Oculomotor control in asymptomatic and recently diagnosed individuals with the genetic marker for Huntington's disease. *Vision Research, 44*(23), 2729–2736. https://doi.org/10.1016/j.visres.2004.06.006

Butler, K. M., Zacks, R. T., & Henderson, J. M. (1999). Suppression of reflexive saccades in younger and older adults: Age comparisons on an antisaccade task. *Memory & Cognition, 27*(4), 584–591. https://doi.org/10.3758/bf03211552

Carvalho, J. O., Long, J. D., Westervelt, H. J., Smith, M. M., Bruce, J. M., Kim, J. I., Mills, J. A., Paulsen, J. S., & PREDICT-HD Investigators and Coordinators of The Huntington Study Group (2016). The impact of oculomotor functioning on neuropsychological performance in Huntington disease. *Journal of Clinical and Experimental Neuropsychology, 38*(2), 217–226. https://doi.org/10.1080/13803395.2015.1101054

Cavaco, S., Gonçalves, A., Pinto, C., Almeida, E., Gomes, F., Moreira, I., Fernandes, J., & Teixeira-Pinto, A. (2015). Auditory Verbal Learning Test in a Large Nonclinical Portuguese Population. *Applied Neuropsychology Adult, 22*(5), 321–331. https://doi.org/10.1080/23279095.2014.927767

Coppen, E. M., van der Grond, J., Hart, E. P., Lakke, E., & Roos, R. (2018). The visual cortex and visual cognition in Huntington's disease: An overview of current literature. *Behavioural Brain Research, 351*, 63–74. https://doi.org/10.1016/j.bbr.2018.05.019

Dalley, J. W., Everitt, B. J., & Robbins, T. W. (2011). Impulsivity, compulsivity, and top-down cognitive control. *Neuron, 69*(4), 680–694. https://doi.org/10.1016/j.neuron.2011.01.020

Diamond, R., White, R. F., Myers, R. H., Mastromauro, C., Koroshetz, W. J., Butters, N., Rothstein, D. M., Moss, M. B., & Vasterling, J. (1992). Evidence of presymptomatic cognitive decline in Huntington's disease. *Journal of Clinical and Experimental Neuropsychology, 14*(6), 961–975. https://doi.org/10.1080/01688639208402547

Duff, K., Paulsen, J. S., Beglinger, L. J., Langbehn, D. R., Stout, J. C., & Predict-HD Investigators of the Huntington Study Group (2007). Psychiatric symptoms in Huntington's disease before diagnosis: The predict-HD study. *Biological Psychiatry, 62*(12), 1341–1346. https://doi.org/10.1016/j.biopsych.2006.11.034

Dumas, E. M., van den Bogaard, S. J., Middelkoop, H. A., & Roos, R. A. (2013). A review of cognition in Huntington's disease. *Frontiers in Bioscience, 5*, 1–18. https://doi.org/10.2741/s355

Farrow, M., Chua, P., Churchyard, A., Bradshaw, J. L., Chiu, E., & Georgiou-Karistianis, N. (2006). Proximity to clinical onset influences motor and cognitive performance in presymptomatic Huntington disease gene carriers. *Cognitive and Behavioral Neurology, 19*(4), 208–216. https://doi.org/10.1097/01.wnn.0000213914.64772.b6

Freitas, S., Simões, M. R., Alves, L., & Santana, I. (2011). Montreal Cognitive Assessment (MoCA): Normative study for the Portuguese population. *Journal of Clinical and Experimental Neuropsychology, 33*(9), 989–996. https://doi.org/10.1080/13803395.2011.589374

Golding, C. V., Danchaivijitr, C., Hodgson, T. L., Tabrizi, S. J., & Kennard, C. (2006). Identification of an oculomotor biomarker of preclinical Huntington disease. *Neurology, 67*(3), 485–487. https://doi.org/10.1212/01.wnl.0000218215.43328.88

Gómez-Tortosa, E., MacDonald, M. E., Friend, J. C., Taylor, S. A., Weiler, L. J., Cupples, L. A., Srinidhi, J., Gusella, J. F., Bird, E. D., Vonsattel, J. P., & Myers, R. H. (2001). Quantitative neuropathological changes in presymptomatic Huntington's disease. *Annals of Neurology, 49*(1), 29–34. https://doi.org/10.1002/1531-8249(200101)49:1<29::AID-ANA7>3.0.CO;2-B

Gorges, M., Pinkhardt, E. H., & Kassubek, J. (2014). Alterations of eye movement control in neurodegenerative movement disorders. *Journal of Ophthalmology*, 2014, 658243. https://doi.org/10.1155/2014/658243

Harrington, D. L., Smith, M. M., Zhang, Y., Carlozzi, N. E., Paulsen, J. S., & PREDICT-HD Investigators of the Huntington Study Group (2012). Cognitive domains that predict time to diagnosis in prodromal Huntington disease. *Journal of Neurology, Neurosurgery, and Psychiatry, 83*(6), 612–619. https://doi.org/10.1136/jnnp-2011-301732

Hart, E. P., Dumas, E. M., Schoonderbeek, A., Wolthuis, S. C., van Zwet, E. W., & Roos, R. A. (2014). Motor dysfunction influence on executive functioning in manifest and premanifest Huntington's disease. *Movement Disorders, 29*(3), 320–326. https://doi.org/10.1002/mds.25806

Heitz R. P. (2014). The speed-accuracy tradeoff: History, physiology, methodology, and behavior. *Frontiers in Neuroscience, 8*, 150. https://doi.org/10.3389/fnins.2014.00150

Henderson, T., Georgiou-Karistianis, N., White, O., Millist, L., Williams, D. R., Churchyard, A., & Fielding, J. (2011). Inhibitory control during smooth pursuit in Parkinson's disease and Huntington's disease. *Movement Disorders, 26*(10), 1893–1899. https://doi.org/10.1002/mds.23757

Huntington Study Group (1996). Unified Huntington's Disease Rating Scale: Reliability and consistency. *Movement Disorders, 11*(2), 136–142. https://doi.org/10.1002/mds.870110204

Kagan, J., Pearson, L., & Welch, L. (1966). Conceptual impulsivity and inductive reasoning. *Child Development, 37*(3), 583–594. https://doi.org/10.1111/j.1467-8624.1966.tb04308.x

Kessels, R. P., van Zandvoort, M. J., Postma, A., Kappelle, L. J., & de Haan, E. H. (2000). The Corsi Block-Tapping Task: Standardization and normative data. *Applied Neuropsychology, 7*(4), 252–258. https://doi.org/10.1207/S15324826AN0704_8

Langbehn, D. R., Brinkman, R. R., Falush, D., Paulsen, J. S., Hayden, M. R., & International Huntington's Disease Collaborative Group (2004). A new model for prediction of the age of onset and penetrance for Huntington's disease based on CAG length. *Clinical Genetics, 65*(4), 267–277. https://doi.org/10.1111/j.1399-0004.2004.00241.x

Lezak MD. (1995). *Neuropsychological assessment* (3rd ed). Oxford University Press.

Manfré, G., Doyère, V., Bossi, S., Riess, O., Nguyen, H. P., & El Massioui, N. (2016). Impulsivity trait in the early symptomatic BACHD transgenic rat model of Huntington disease. *Behavioural Brain Research, 299*, 6–10. https://doi.org/10.1016/j.bbr.2015.11.007

MATLAB and Statistics Toolbox Release (2013a). The MathWorks, Inc. [Software]. Natick, Massachusetts, United States. https://www.mathworks.com/company/newsroom/mathworks-announces-release-2013a-of-the-matlab-and-simulink-product-families.html

Miranda, Â., Lavrador, R., Júlio, F., Januário, C., Castelo-Branco, M., & Caetano, G. (2016). Classification of Huntington's disease stage with support vector machines: A study on oculomotor performance. *Behavior Research Methods, 48*(4), 1667–1677. https://doi.org/10.3758/s13428-015-0683-z

Mitchell, J. P., Macrae, C. N., & Gilchrist, I. D. (2002). Working memory and the suppression of

reflexive saccades. *Journal of Cognitive Neuroscience, 14*(1), 95–103. https://doi.org/10.1162/089892902317205357

Munoz, D. P., Broughton, J. R., Goldring, J. E., & Armstrong, I. T. (1998). Age-related performance of human subjects on saccadic eye movement tasks. *Experimental Brain Research*, *121*(4), 391–400. https://doi.org/10.1007/s002210050473

Murman D. L. (2015). The Impact of Age on Cognition. *Seminars in Hearing, 36*(3), 111–121. https://doi.org/10.1055/s-0035-1555115

Nasr, S., & Rosas, H. D. (2019). Impact of Huntington's Disease on Mental Rotation Performance in Motor Pre-Symptomatic Individuals. *Journal of Huntington's Disease, 8*(3), 339–356. https://doi.org/10.3233/JHD-190348

Nasreddine, Z. S., Phillips, N. A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., Cummings, J. L., & Chertkow, H. (2005). The Montreal Cognitive Assessment, MoCA: A brief screening tool for mild cognitive impairment. *Journal of the American Geriatrics Society, 53*(4), 695–699. https://doi.org/10.1111/j.1532-5415.2005.53221.x

Novak, M. J., & Tabrizi, S. J. (2011). Huntington's disease: Clinical presentation and treatment. *International Review of Neurobiology, 98*, 297–323. https://doi.org/10.1016/B978-0-12-381328-2.00013-4

O'Keeffe, G. C., Michell, A. W., & Barker, R. A. (2009). Biomarkers in Huntington's and Parkinson's Disease. *Annals of the New York Academy of Sciences, 1180*, 97–110. https://doi.org/10.1111/j.1749-6632.2009.04943.x

Oldfield R. C. (1971). The assessment and analysis of handedness: The Edinburgh inventory. *Neuropsychologia, 9*(1), 97–113. https://doi.org/10.1016/0028-3932(71)90067-4

Orth, M., Handley, O. J., Schwenke, C., Dunnett, S. B., Craufurd, D., Ho, A. K., Wild, E., Tabrizi, S. J., Landwehrmeyer, G. B., & Investigators of the European Huntington's Disease Network (2010). Observing Huntington's Disease: The European Huntington's Disease Network's REGISTRY. *PLoS Currents, 2,* RRN1184. https://doi.org/10.1371/currents.RRN1184

Pais-Ribeiro, J., Silva, I., Ferreira, T., Martins, A., Meneses, R., & Baltar, M. (2007). Validation study of a Portuguese version of the Hospital Anxiety and Depression Scale. *Psychology, Health & Medicine*, *12*(2), 225–237. https://doi.org/10.1080/13548500500524088

Papoutsi, M., Labuschagne, I., Tabrizi, S. J., & Stout, J. C. (2014). The cognitive burden in Huntington's disease: Pathology, phenotype, and mechanisms of compensation. *Movement Disorders, 29*(5), 673–683. https://doi.org/10.1002/mds.25864

Papp, K. V., Kaplan, R. F., & Snyder, P. J. (2011). Biological markers of cognition in prodromal Huntington's disease: A review. *Brain and Cognition, 77*(2), 280–291.

https://doi.org/10.1016/j.bandc.2011.07.009

Patel, S. S., Jankovic, J., Hood, A. J., Jeter, C. B., & Sereno, A. B. (2012). Reflexive and volitional saccades: Biomarkers of Huntington disease severity and progression. *Journal of the Neurological Sciences, 313*(1-2), 35–41. https://doi.org/10.1016/j.jns.2011.09.035

Paulsen J. S. (2010). Early Detection of Huntington Disease. *Future Neurology, 5*(1), 10.2217/fnl.09.78. https://doi.org/10.2217/fnl.09.78

Paulsen, J. S., Langbehn, D. R., Stout, J. C., Aylward, E., Ross, C. A., Nance, M., Guttman, M., Johnson, S., MacDonald, M., Beglinger, L. J., Duff, K., Kayson, E., Biglan, K., Shoulson, I., Oakes, D., Hayden, M., & Predict-HD Investigators and Coordinators of the Huntington Study Group (2008). Detection of Huntington's disease decades before diagnosis: The Predict-HD study. *Journal of Neurology, Neurosurgery, and Psychiatry, 79*(8), 874–880. https://doi.org/10.1136/jnnp.2007.128728

Paulsen, J. S., & Long, J. D. (2014). Onset of Huntington's disease: Can it be purely cognitive?. *Movement Disorders, 29*(11), 1342–1350. https://doi.org/10.1002/mds.25997

Peltsch, A., Hoffman, A., Armstrong, I., Pari, G., & Munoz, D. P. (2008). Saccadic impairments in Huntington's disease. *Experimental Brain Research, 186*(3), 457–469. https://doi.org/10.1007/s00221-007-1248-x

Rao, J. A., Harrington, D. L., Durgerian, S., Reece, C., Mourany, L., Koenig, K., Lowe, M. J., Magnotta, V. A., Long, J. D., Johnson, H. J., Paulsen, J. S., & Rao, S. M. (2014). Disruption of response inhibition circuits in prodromal Huntington disease. *Cortex, 58,* 72–85. https://doi.org/10.1016/j.cortex.2014.04.018

Raven, J., Raven, J. C., & Court, J. H. (1993). *Manual for Raven's progressive matrices and vocabulary scales*. Sections 1–7 (3rd ed.) Oxford Psychologists Press.

Rey A. (1964). *Rey verbal learning test. L'examen clinique en psychologie* (2nd ed.) Presses Universitaires de France.

Robert, M. P., Nachev, P. C., Hicks, S. L., Golding, C. V., Tabrizi, S. J., & Kennard, C. (2009). Saccadometry of conditional rules in presymptomatic Huntington's disease. *Annals of the New York Academy of Sciences, 1164*, 444–450. https://doi.org/10.1111/j.1749-6632.2008.03736.x

Rodríguez-Labrada, R., Vázquez-Mojena, Y., & Velázquez-Pérez, L. (2019). *Eye Movement Abnormalities in Neurodegenerative Diseases*. In (Ed.), Eye Motility. IntechOpen. https://doi.org/10.5772/intechopen.81948

Roos R. A. (2010). Huntington's disease: A clinical review. *Orphanet Journal of Rare Diseases*, *5*, 40. https://doi.org/10.1186/1750-1172-5-40

Rosas, H. D., Hevelone, N. D., Zaleta, A. K., Greve, D. N., Salat, D. H., & Fischl, B. (2005). Regional cortical thinning in preclinical Huntington disease and its relationship to cognition. *Neurology, 65*(5), 745–747.

https://doi.org/10.1212/01.wnl.0000174432.87383.87

Rosas, H. D., Tuch, D. S., Hevelone, N. D., Zaleta, A. K., Vangel, M., Hersch, S. M., & Salat, D. H. (2006). Diffusion tensor imaging in presymptomatic and early Huntington's disease: Selective white matter pathology and its relationship to clinical measures. *Movement Disorders, 21*(9), 1317–1325. https://doi.org/10.1002/mds.20979

Rosenblatt A. (2007). Neuropsychiatry of Huntington's disease. *Dialogues in Clinical Neuroscience, 9*(2), 191–197. https://doi.org/10.31887/DCNS.2007.9.2/arosenblatt

Ross, C. A., Aylward, E. H., Wild, E. J., Langbehn, D. R., Long, J. D., Warner, J. H., Scahill, R. I., Leavitt, B. R., Stout, J. C., Paulsen, J. S., Reilmann, R., Unschuld, P. G., Wexler, A., Margolis, R. L., & Tabrizi, S. J. (2014). Huntington disease: Natural history, biomarkers and prospects for therapeutics. *Nature Reviews Neurology, 10*(4), 204–216. https://doi.org/10.1038/nrneurol.2014.24

Rupp, J., Blekher, T., Jackson, J., Beristain, X., Marshall, J., Hui, S., Wojcieszek, J., & Foroud, T. (2010). Progression in prediagnostic Huntington disease. *Journal of Neurology, Neurosurgery, and Psychiatry, 81*(4), 379–384. https://doi.org/10.1136/jnnp.2009.176982

Rupp, J., Dzemidzic, M., Blekher, T., West, J., Hui, S., Wojcieszek, J., Saykin, A. J., Kareken, D. A., & Foroud, T. (2012). Comparison of vertical and horizontal saccade measures and their relation to gray matter changes in premanifest and manifest Huntington disease. *Journal of Neurology, 259*(2), 267–276. https://doi.org/10.1007/s00415-011-6172-0

Sensor Motoric Instruments (2002-2009). iViewX [Apparatus]. https://www.tilburguniversity.edu/sites/default/files/download/iViewX-System-Manual.pdf

Sensor Motoric Instruments (2014). BeGaze [Software]. https://psychologie.unibas.ch/fileadmin/user_upload/psychologie/Forschung/N-Lab/SMI_BeGaze_Manual.pdf

Shoulson, I., & Young, A. B. (2011). Milestones in Huntington disease. *Movement Disorders*, *26*(6), 1127–1133. https://doi.org/10.1002/mds.23685

Snaith, R. P., Constantopoulos, A. A., Jardine, M. Y., & McGuffin, P. (1978). A clinical scale for the self-assessment of irritability. *The British Journal of Psychiatry, 132,* 164–171. https://doi.org/10.1192/bjp.132.2.164

Snowden, J. S., Craufurd, D., Thompson, J., & Neary, D. (2002). Psychomotor, executive, and memory function in preclinical Huntington's disease. *Journal of Clinical and Experimental Neuropsychology, 24*(2), 133–145. https://doi.org/10.1076/jcen.24.2.133.998

Solomon, A. C., Stout, J. C., Weaver, M., Queller, S., Tomusk, A., Whitlock, K. B., Hui, S. L.,

Marshall, J., Jackson, J. G., Siemers, E. R., Beristain, X., Wojcieszek, J., & Foroud, T. (2008). Ten-year rate of longitudinal change in neurocognitive and motor function in prediagnosis Huntington disease. *Movement Disorders, 23*(13), 1830–1836. https://doi.org/10.1002/mds.22097

Stout, J. C., Glikmann-Johnston, Y., & Andrews, S. C. (2016). Cognitive assessment strategies in Huntington's disease research. *Journal of Neuroscience Methods, 265,* 19–24. https://doi.org/10.1016/j.jneumeth.2015.12.007

Stout, J. C., Paulsen, J. S., Queller, S., Solomon, A. C., Whitlock, K. B., Campbell, J. C., Carlozzi, N., Duff, K., Beglinger, L. J., Langbehn, D. R., Johnson, S. A., Biglan, K. M., & Aylward, E. H. (2011). Neurocognitive signs in prodromal Huntington disease. *Neuropsychology, 25*(1), 1–14. https://doi.org/10.1037/a0020937

Stout, J. C., Queller, S., Baker, K. N., Cowlishaw, S., Sampaio, C., Fitzer-Attas, C., Borowsky, B., & HD-CAB Investigators (2014). HD-CAB: A cognitive assessment battery for clinical trials in Huntington's disease 1,2,3. *Movement Disorders, 29*(10), 1281–1288. https://doi.org/10.1002/mds.25964

Stroop, J. R. (1935). Studies of interference in serial verbal reactions. *Journal of Experimental Psychology, 18*(6), 643–662. https://doi.org/10.1037/h0054651

Tabrizi, S. J., Langbehn, D. R., Leavitt, B. R., Roos, R. A., Durr, A., Craufurd, D., Kennard, C., Hicks, S. L., Fox, N. C., Scahill, R. I., Borowsky, B., Tobin, A. J., Rosas, H. D., Johnson, H., Reilmann, R., Landwehrmeyer, B., Stout, J. C., & TRACK-HD investigators (2009). Biological and clinical manifestations of Huntington's disease in the longitudinal TRACK-HD study: Cross-sectional analysis of baseline data. *The Lancet Neurology, 8*(9), 791–801. https://doi.org/10.1016/S1474-4422(09)70170-X

Tabrizi, S. J., Reilmann, R., Roos, R. A., Durr, A., Leavitt, B., Owen, G., Jones, R., Johnson, H., Craufurd, D., Hicks, S. L., Kennard, C., Landwehrmeyer, B., Stout, J. C., Borowsky, B., Scahill, R. I., Frost, C., Langbehn, D. R., & TRACK-HD investigators (2012). Potential endpoints for clinical trials in premanifest and early Huntington's disease in the TRACK-HD study: Analysis of 24-month observational data. *The Lancet Neurology, 11*(1), 42–53. https://doi.org/10.1016/S1474-4422(11)70263-0

Tabrizi, S. J., Scahill, R. I., Owen, G., Durr, A., Leavitt, B. R., Roos, R. A., Borowsky, B., Landwehrmeyer, B., Frost, C., Johnson, H., Craufurd, D., Reilmann, R., Stout, J. C., Langbehn, D. R., & TRACK-HD Investigators (2013). Predictors of phenotypic progression and disease onset in premanifest and early-stage Huntington's disease in the TRACK-HD study: Analysis of 36-month observational data. *The Lancet Neurology, 12*(7), 637–649. https://doi.org/10.1016/S1474-4422(13)70088-7

Trenerry, M.R., Crosson, B., DeBoe, J., & Lebel, W.R. (1989). *Stroop Neuropsychological Screening Test (SNTC).* Psychological Assessment Resources.

Turner, T. H., Goldstein, J., Hamilton, J. M., Jacobson, M., Pirogovsky, E., Peavy, G., & Corey-Bloom, J. (2011). Behavioral measures of saccade latency and inhibition in manifest and premanifest Huntington's disease. *Journal of Motor Behavior, 43*(4), 295–302. https://doi.org/10.1080/00222895.2011.580390

Vaca-Palomares, I., Brien, D. C., Coe, B. C., Ochoa-Morales, A., Martínez-Ruano, L., Munoz, D. P., & Fernandez-Ruiz, J. (2019). Implicit learning impairment identified via predictive saccades in Huntington's disease correlates with extended cortico-striatal atrophy. *Cortex, 121*, 89–103. https://doi.org/10.1016/j.cortex.2019.06.013

van Asselen, M., Almeida, I., Júlio, F., Januário, C., Campos, E. B., Simões, M., & Castelo-Branco, M. (2012). Implicit contextual learning in prodromal and early stage Huntington's disease patients. *Journal of the International Neuropsychological Society, 18*(4), 689–696. https://doi.org/10.1017/S1355617712000288

van Asselen, M., Júlio, F., Januário, C., Campos, E. B., Almeida, I., Cavaco, S., & Castelo-Branco, M. (2012). Scanning Patterns of Faces do not Explain Impaired Emotion Recognition in Huntington Disease: Evidence for a High-Level Mechanism. *Frontiers in Psychology, 3*, 31. https://doi.org/10.3389/fpsyg.2012.00031

Van der Stigchel S. (2010). The search for oculomotor inhibition: Interactions with working memory. *Experimental Psychology, 57*(6), 429–435. https://doi.org/10.1027/1618-3169/a000053

Vaportzis, E., Georgiou-Karistianis, N., Churchyard, A., & Stout, J. C. (2015). Dual task performance in Huntington's disease: A comparison of choice reaction time tasks. *Neuropsychology, 29*(5), 703–712. https://doi.org/10.1037/neu0000172

Vela, L., Martínez Castrillo, J. C., García Ruiz, P., Gasca-Salas, C., Macías Macías, Y., Pérez Fernández, E., Ybot, I., Lopez Valdés, E., Kurtis, M. M., Posada Rodriguez, I. J., Mata, M., Ruiz Huete, C., Eimil, M., Borrue, C., Del Val, J., López-Manzanares, L., Rojo Sebastian, A., & Marasescu, R. (2016). The high prevalence of impulse control behaviors in patients with early-onset Parkinson's disease: A cross-sectional multicenter study. *Journal of the Neurological Sciences, 368*, 150–154. https://doi.org/10.1016/j.jns.2016.07.003

Walker F. O. (2007). Huntington's Disease. *Seminars in Neurology, 27*(2), 143–150. https://doi.org/10.1055/s-2007-971176

Wechsler D. (1997). *WAIS-III administration and scoring manual* (3rd ed.) The Psychological Corporation.

Wechsler D. (2008). *WAIS-III: Escala de Inteligência de Wechsler para adultos – Manual (*3rd ed.)Portuguese Version [Wechsler Adult Intelligence Scale - WAIS-III]. Cegoc.

Weir, D. W., Sturrock, A., & Leavitt, B. R. (2011). Development of biomarkers for Huntington's disease. *The Lancet Neurology, 10*(6), 573–590. https://doi.org/10.1016/S1474-4422(11)70070-9

Wiecki, T. V., Antoniades, C. A., Stevenson, A., Kennard, C., Borowsky, B., Owen, G., Leavitt, B., Roos, R., Durr, A., Tabrizi, S. J., & Frank, M. J. (2016). A Computational Cognitive Biomarker for Early-Stage Huntington's Disease. *PloS One, 11*(2), e0148409. https://doi.org/10.1371/journal.pone.0148409

Winder, J. Y., & Roos, R. (2018). Premanifest Huntington's disease: Examination of oculomotor abnormalities in clinical practice. *PloS One, 13*(3), e0193866. https://doi.org/10.1371/journal.pone.0193866

Witjes-Ané, M. N., Vegter-van der Vlis, M., van Vugt, J. P., Lanser, J. B., Hermans, J., Zwinderman, A. H., van Ommen, G. J., & Roos, R. A. (2003). Cognitive and motor functioning in gene carriers for Huntington's disease: A baseline study. *The Journal of Neuropsychiatry and Clinical Neurosciences, 15*(1), 7–16. https://doi.org/10.1176/jnp.15.1.7

Zhang, J., Nombela, C., Wolpe, N., Barker, R. A., & Rowe, J. B. (2016). Time on timing: Dissociating premature responding from interval sensitivity in Parkinson's disease. *Movement Disorders, 31*(8), 1163–1172. https://doi.org/10.1002/mds.26631

Zhang, J., Rittman, T., Nombela, C., Fois, A., Coyle-Gilchrist, I., Barker, R. A., Hughes, L. E., & Rowe, J. B. (2016). Different decision deficits impair response inhibition in progressive supranuclear palsy and Parkinson's disease. *Brain, 139*(Pt 1), 161–173. https://doi.org/10.1093/brain/awv331

Zigmond, A. S., & Snaith, R. P. (1983). The hospital anxiety and depression scale. *Acta Psychiatrica Scandinavica, 67*(6), 361–370. https://doi.org/10.1111/j.1600-0447.1983.tb09716.x

Chapter III – Study 2

Preface

In Study 2, we were interested in confronting the ability of a non-immersive virtual reality task to grasp the functional impact of EF deficits in highly functioning preclinical and clinical populations versus: 1.) a subjective (self-report) functional measure - "The Adults and Older Adults Functional Assessment Inventory – IAFAI" (Sousa et al., 2015); 2.) a set of neuropsychological assessment tasks that try to overcome the ecological issues of standard executive tests (the "Behavioural Assessment of Dysexecutive Syndrome battery – BADS" (Wilson et al., 1996)); and 3.) a conventional neuropsychological test battery. Additionally, we were interested in understanding if a multi-modal approach combining objective and subjective assessment methods would facilitate the identification of subtle deficits on the functional cognition of persons with early manifest and premanifest HD.

In Study 1, we tested inhibitory control executive skills in the context of an abstract task difficult to translate to everyday deficits (Júlio et al., 2019). This means that, although we observed deficits in persons with HD, it was difficult to conclude that those deficits were significant in their everyday functional cognition.

Therefore, we have developed the *EcoKitchen*, a novel computerized performance-based assessment measure that simulates different executive-demanding routine tasks done in a kitchen setting to capture the functional impact of the cognitive changes displayed by persons with HD. Meal preparation is a good example of a real-life executive task, since it requires the ability to formulate and implement a plan, and monitor and accomplish different subgoals, while bearing in mind the overall goal of having different foods properly cooked and ready at the same time (Craik & Bialystok, 2006; Shallice, 1982; Ward, 2004). Successful meal preparation is highly dependent on both planning (plan

and monitor one's own progress to perform several tasks at the same time) and response inhibition (to undertake certain tasks while refraining from completing other tasks) (Morrison et al., 2013), two core EF skills. In addition, daily-life meal preparation often involves the performance of competing tasks under distracting and unsupportive conditions (Chaytor & Schmitter-Edgecombe, 2003) – which is the essence of EF.

In the presence of subtle EF impairments, those deficits are only detectable when tested with performance-based tests that use functional tasks with structured rules and goals (Burgess et al., 2006; Kibby et al., 1998; Morrison et al., 2013; Shallice & Burgess, 1991), in complex situations that ideally require multitasking (Burgess et al., 2006; Katz & Maeir, 2011). This approach is believed to be more sensitive to the EF impact on function than conventional or construct-driven neuropsychological tests and tasks (Manchester et al., 2004; Morrison et al., 2013).

The development of the *EcoKitchen* followed previous indications about important features of effective EF assessment, namely the use of several overlapping task demands, the need to choose between different action strategies, switch to adjust to changing circumstances and monitor task progression, the addition of time pressure, or the use of multiple and interleaved task scenarios versus single tasks (Kalaitzakis & Pearce, 2009; Wesson et al., 2016). Additionally, the findings of our oculomotor study (Júlio et al., 2019) pointed out the relevance of steadily rising the cognitive load of the assessment task to be able to capture the functional impact of mild EF deficits in preclinical HD. This influenced the design of different levels of task complexity, i.e., increasingly demanding *EcoKitchen* blocks, which simulate the complex demands found in naturalistic settings while still maintaining the experimental control over stimulus presentation and response measurement required for rigorous scientific analysis (Schultheis et al., 2002).

One of the study aims was to use a multi-modal assessment approach to characterize the functional cognition of persons with HD and to establish the construct validity of the *EcoKitchen*, by examining the relationship between the performance on the *EcoKitchen* and on commonly used neuropsychological assessment measures. For these we included in the study classic paper-and-pencil executive tests, a more ecological set of executive tasks (BADS), and a self-report functional measure (IAFAI). The latter was added to the protocol because patient reported outcomes (i.e., the voice of persons with HD) are increasingly seen as invaluable resources to help design and implement meaningful interventions, measure the benefits of a treatment on the ability to function and effectively describe the symptom experience (Simpson et al., 2016).

We predicted that the novel and dynamic nature of test conditions, which simulate real-life stressors and replicate the cognitive challenges and distractors found in day-to-day situations (Morrison et al., 2013; Neguț et al., 2016) would be more effective at capturing the cognitive impact on function in persons with subtle dysexecutive symptoms. Notably, assessment tools like the *EcoKitchen* may be more inherently motivating to examinees because results are easily recognized as relevant to everyday life (Morrison et al., 2013; Schutz & Wanlass, 2009).

In sum, this study was intended to validate a novel assessment tool, the *EcoKitchen*, as a valuable option to identify the functional impact of the cognitive deficits exhibited by preclinical and clinical HD populations in a more ecologically relevant way.

References

Burgess, P. W., Alderman, N., Forbes, C., Costello, A., Coates, L. M., Dawson, D. R., Anderson, N. D., Gilbert, S. J., Dumontheil, I., & Channon, S. (2006). The case for the development and use of "ecologically valid" measures of executive function in experimental and clinical neuropsychology. *Journal of the International Neuropsychological Society*, *12*(2), 194–209. https://doi.org/10.1017/S1355617706060310

Chaytor, N., & Schmitter-Edgecombe, M. (2003). The ecological validity of neuropsychological tests: A review of the literature on everyday cognitive skills. *Neuropsychology Review*, *13*(4), 181–197. https://doi.org/10.1023/b:nerv.0000009483.91468.fb

Craik, F. I., & Bialystok, E. (2006). Planning and task management in older adults: Cooking breakfast. *Memory & Cognition*, *34*(6), 1236–1249. https://doi.org/10.3758/bf03193268

Júlio, F., Caetano, G., Januário, C., & Castelo-Branco, M. (2019). The effect of impulsivity and inhibitory control deficits in the saccadic behavior of premanifest Huntington's disease individuals. *Orphanet Journal of Rare Diseases*, *14*(1), 246. https://doi.org/10.1186/s13023-019-1218-y

Kalaitzakis, M. E., & Pearce, R. K. (2009). The morbid anatomy of dementia in Parkinson's disease. *Acta Neuropathologica*, *118*(5), 587–598. https://doi.org/10.1007/s00401-009-0597-x

Katz, N., & Maeir, A. (2011). Higher-level cognitive functions enabling participation: Awareness and executive functions. In N. Katz (Ed.), *Cognition, occupation, and participation across the life span: Neuroscience, neurorehabilitation, and models of intervention in occupational*

therapy (pp. 13–40). American Occupational Therapy Association.

Kibby, M. Y., Schmitter-Edgecombe, M., & Long, C. J. (1998). Ecological validity of neuropsychological tests: Focus on the California Verbal Learning Test and the Wisconsin Card Sorting Test. *Archives of Clinical Neuropsychology*, *13*(6), 523–534.

Manchester, D., Priestley, N., & Jackson, H. (2004). The assessment of executive functions: Coming out of the office. *Brain Injury*, *18*(11), 1067–1081. https://doi.org/10.1080/02699050410001672387

Morrison, M. T., Giles, G. M., Ryan, J. D., Baum, C. M., Dromerick, A. W., Polatajko, H. J., & Edwards, D. F. (2013). Multiple Errands Test-Revised (MET-R): A performance-based measure of executive function in people with mild cerebrovascular accident. *The American Journal of Occupational Therapy*, *67*(4), 460–468. https://doi.org/10.5014/ajot.2013.007880

Neguț, A., Matu, S-A., Sava, F. A., & David, D. (2016). Task difficulty of virtual reality-based assessment tools compared to classical paper-and-pencil or computerized measures: A meta-analytic approach. *Computers in Human Behavior, 54,* 414-424. https://doi.org/10.1016/j.chb.2015.08.029

Schultheis, M. T., Himelstein, J., & Rizzo, A. A. (2002). Virtual reality and neuropsychology: Upgrading the current tools. *The Journal of Head Trauma Rehabilitation*, *17*(5), 378–394. https://doi.org/10.1097/00001199-200210000-00002

Schutz, L. E., & Wanlass, R. L. (2009). Interdisciplinary assessment strategies for capturing the elusive executive. *American Journal of Physical Medicine & Rehabilitation*, *88*(5), 419–422. https://doi.org/10.1097/PHM.0b013e3181a0e2d3

Shallice T. (1982). Specific impairments of planning. *Philosophical Transactions of the Royal Society of London. Series B, Biological sciences*, *298*(1089), 199–209. https://doi.org/10.1098/rstb.1982.0082

Shallice, T., & Burgess, P. W. (1991). Deficits in strategy application following frontal lobe damage in man. *Brain*, *114(Pt 2)*, 727–741. https://doi.org/10.1093/brain/114.2.727

Simpson, J. A., Lovecky, D., Kogan, J., Vetter, L. A., & Yohrling, G. J. (2016). Survey of the Huntington's Disease Patient and Caregiver Community Reveals Most Impactful Symptoms and Treatment Needs. *Journal of Huntington's Disease*, *5*(4), 395–403. https://doi.org/10.3233/JHD-160228

Sousa, L. B., Prieto, G., Vilar, M., Firmino, H., & Simões, M. R. (2015). The Adults and Older Adults Functional Assessment Inventory: A Rasch Model Analysis. *Research on Aging*, *37*(8), 787–814. https://doi.org/10.1177/0164027514564469

Ward, G. D. (2004). Planning and Executive Control of Thought and Action. In R. Morris & G. D. Ward (Eds.), *The Cognitive Psychology of Planning. Current Issues in Thinking and Reasoning* (pp. 89-110). Taylor & Francis Group. ISBN 978-0-415-64677-2

Wesson, J., Clemson, L., Brodaty, H., & Reppermund, S. (2016). Estimating functional cognition in

older adults using observational assessments of task performance in complex everyday activities: A systematic review and evaluation of measurement properties. *Neuroscience and Biobehavioral Reviews*, *68*, 335–360. https://doi.org/10.1016/j.neubiorev.2016.05.024

Wilson, B., Alderman, N., Burgess, P., Emslie, H., & Evans, J. (1996). *Behavioural Assessment of the Dysexecutive Syndrome.* Thames Valley Test Company.

Study 2

A Novel Ecological Approach reveals Early Executive Function Impairments in Huntington's Disease

Adapted from: **Júlio, F.**, Ribeiro, M. J., Patrício, M., Malhão, A., Pedrosa, F., Gonçalves, H., Simões, M., van Asselen, M., Simões, M. R., Castelo-Branco, M., & Januário, C. (2019). A Novel Ecological Approach Reveals Early Executive Function Impairments in Huntington's Disease. *Frontiers in Psychology*, *10*, 585.
https://doi.org/10.3389/fpsyg.2019.00585

Abstract

Introduction: Impairments in executive functions are common in neurogenetic disorders such as Huntington's disease (HD) and are thought to significantly influence the patient's functional status. Reliable tools with higher ecological validity that can assess and predict the impact of executive dysfunction in daily-life performance are needed. This study aimed to develop and validate a novel non-immersive virtual reality task (*EcoKitchen*) created with the purpose of capturing cognitive and functional changes

shown by HD carriers without clinical manifestations of the disease (Premanifest HD), in a more realistic setting.

Materials and Methods: We designed a virtual reality task with three blocks of increasing executive load. The performance of three groups (Controls, CTRL; Persons with Premanifest HD, PreHD; Persons with Early Manifest HD, EarlyHD) was compared in four main components of the study protocol: the *EcoKitchen*; a subjective (self-report) measure - "The Adults and Older Adults Functional Assessment Inventory (IAFAI)"; the "Behavioural Assessment of Dysexecutive Syndrome battery (BADS)"; and a conventional neuropsychological test battery. We also examined statistical associations between the *EcoKitchen* and the other executive, functional and clinical measures used.

Results: The EarlyHD group showed deficits in all the assessment methods used. In contrast, the PreHD group was only found to be impaired in the *EcoKitchen* task, particularly in the most cognitively demanding blocks, where they showed a higher number of errors compared to the CTRL group. Statistically significant correlations were identified between the *EcoKitchen*, measures of the other assessment tools, and HD clinical features.

Discussion: The *EcoKitchen* task, developed as an ecological executive function assessment tool, was found to be sensitive to early deficits in this domain. Critically, in persons with premanifest HD, it identifies dysfunction prior to symptom onset. Further it adds a potential tool for diagnosis and management of the patients' real-life problems.

Introduction

Huntington's disease (HD) is a neurodegenerative genetic movement disorder mainly characterized by subcortical pathology involving the basal ganglia and the frontostriatal circuitry, with prominent cell loss and atrophy in the caudate and putamen (Shoulson & Young, 2011). Testing positive for HD only indicates that someone carries the gene defect, does not equate to having the disease (O'Keeffe et al., 2009), as the test result does not inform about how and when the symptoms will start, nor about the current disease status (Dumas et al., 2013). Individuals who carry the genetic mutation but who do not yet meet the criteria for an HD clinical diagnosis are considered to be in a premanifest HD phase. The conversion from a premanifest to a manifest HD stage is traditionally

based on the onset of unequivocal motor symptoms. Nevertheless, cognitive, behavioural and neuroanatomical changes have been reported to occur before any clinically detectible motor signs (Aylward et al., 2004; Paulsen, 2010; Roos, 2010; Rosas et al., 2005; Rosenblatt, 2007).

Huntington's disease clinical presentation includes motor, behavioural and cognitive alterations that typically arise in middle adulthood, when family and career responsibilities are often greatest (Nehl et al., 2004). Impairments in executive functions are frequent in persons with HD, even in premanifest or early manifest disease stages (Novak &Tabrizi, 2010; Paulsen, 2011; Stout et al., 2011; Tabrizi et al., 2011) and are thought to significantly influence their functional status and to be major contributors to everyday deficits, disability and loss of autonomy (Godefroy et al., 2010; Reilmann et al., 2014; Ross, Aylward, et al., 2014; Stout et al., 2011). The executive dysfunction associated with HD includes deficits in planning and multitasking, sequencing, set-shifting, attentional control, response inhibition and perseveration (Dumas, et al., 2013; Novak & Tabrizi, 2011; Rosenblatt, 2007). These changes are thought to reflect HD brain alterations , namely the disruption of the frontal-subcortical, and specifically, prefrontal-striatal circuitry, and the altered functioning of brain circuits that are important for organizing behaviour, cognitive flexibility, the planning of an instrumental performance, response inhibition, attention, and temporal control over motor output (Balci et al., 2009; Paulsen, 2010; Rao et al., 2014; Rosas et al., 2005). These executive deficits need to be properly acknowledged and assessed as they can have a considerable impact on the quality of life and daily functioning of persons with HD (Beglinger et al., 2010; Hamilton et al., 2003; Hoth et al., 2007; Mörkl et al., 2016; Nehl et al., 2004).

Executive functions can be defined as the "capacities that enable a person to engage successfully in independent, purposive, self-serving behaviour" (Lezak et al., 2012). These complex, higher-order abilities are needed to be able to adapt in a flexible manner to many daily life situations that require task conceptualization, planning, action and evaluation (Dumas et al., 2013). As executive functioning requires so many integrated cognitive functions and supervisory processes, impairments in this domain tend to be supramodal and affect the expression of all aspects of behaviour (Lezak, 1982). To drive a car, pay bills, take the medication at the right time of the day, prepare a meal – these are all examples of Instrumental Activities of Daily Living (IADL) that involve executive functions, and these are exactly the kind of activities that are reportedly impaired early in the course of HD (Beglinger et al., 2010; Williams et al., 2011), even when individuals

show a relatively unimpaired performance in conventional executive tests or present average scores in functional measures such as the widely used Total Functional Capacity scale - TFC (Shoulson & Fahn, 1979). As Lezak (1982) states, impairments in executive functions can compromise a person's capacity to maintain an independent and productive life no matter how well he can see and hear, walk and talk, and perform tests. This seems to apply perfectly to the premanifest HD condition, where changes in day-to-day function are more likely to be experienced in tasks that require multiple cognitive, motor and behavioural abilities (Williams et al., 2011), such as doing routine work, manage finances or drive safely (Beglinger et al., 2010), rather than in the performance of single and more abstract tests.

In fact, the subtle changes in behaviour and cognition observed in persons who do not yet display disease-related motor alterations (premanifest HD stage) and persons with early manifest HD are often missed in highly structured examinations (Reilmann et al., 2014; Stout et al., 2007, 2016), as traditional cognitive and functional measures seem insensitive to the initial changes in HD. Backing this idea, a thorough review of studies about cognition in HD by Dumas et al. (2013) found almost equal support for and against the presence of executive deficits in premanifest gene carriers, highlighting the need for further research. Moreover, in neuropsychology, few objective methods for assessing the functional impact of executive impairments are available, as traditional tests measure cognitive abilities in isolated and artificial situations, which bear little similarity to the situations that patients encounter in their daily life (Allain et al., 2014; Chaytor et al., 2006). These type of clinical tools are urgently needed to demonstrate daily life functional changes besides cognitive efficacy as evaluated by classical neuropsychological testing (Royall et al., 2007), so that the success of interventions can be progressively evaluated in terms of the effects they have on quality of life and functional independence, and not merely in terms of efficacy in reducing primary symptoms (Moore et al., 2007). Therefore, new, more ecological, and more sensitive assessment tools that are able to document the insidious onset of subtle executive alterations in the daily functioning of HD affected individuals and that are able to demonstrate changes in day-to-day function in HD, and specifically in premanifest HD, are urged (Downing et al., 2014).

To address these issues and understand the inconsistencies often found between the results obtained in formal examinations and the real-life complaints about the cognitive and functional status of premanifest and early manifest HD individuals, a new

assessment tool was created at our Lab: the *EcoKitchen*, a non-immersive virtual reality task consisting of preparing meals in a kitchen. The *EcoKitchen* was based in two main premises: on the one hand, cooking is a good example of a real-world task that often draws heavily on executive functioning (Tanguay et al., 2014); on the other hand, different assessment and rehabilitation studies of clinical populations have successfully used kitchen settings to address functional and executive impairments (Allain et al., 2014; Baum & Edwards, 1993; Bialystok et al., 2008; Craik & Bialystok, 2006; Giovannetti et al., 2008; Ruse et al., 2014; Zhang et al., 2003). Notably, the *EcoKitchen* improves on the existing tools for several reasons: it is more portable and standardized than some of the methods that are done in real kitchens or involve manipulating props (e.g., Baum & Edwards, 1993; Giovannetti et al., 2008); outputs combine time and error measures, whereas some existing methods rely more heavily on only one dimension and omit valuable information about the changes in speed/accuracy trade-off often seen in clinical populations (e.g., Craik & Bialystok, 2006; Giovannetti et al., 2008); focus more on the examinee and less on the examiner, having less observational bias and less external cues that can prompt action or improve action correctness (Ruse et al., 2014; Zhang et al., 2003); it informs about the impact of increasing executive load on the participants behaviour, having different levels of complexity (e.g., Allain et al., 2014); has higher realism, as the virtual scenario created tried to include known food and beverage brands and more life-like stimuli than previous studies (e.g., Craik & Bialystok, 2006).

The inclusion of real-world scenarios and virtual reality tasks in clinical studies might provide a good mean to evidence the impact of executive impairment on the patients' life (Albani et al., 2010; Frisch et al., 2012) – delivering sensitive measures of everyday function and a valid testing ground to assess the impact of executive deficits in daily-life (Frisch et al., 2012; Moore et al., 2007; Poliakoff & Smith-Spark, 2008). Few studies have used or developed performance-based tools to assess everyday functioning in HD. Nicoll et al. (2014) used the "Memory for Intentions Screening Test" as a standardized performance-based measure of prospective memory in HD and Sheppard et al. (2017) used the "Advanced Finances Test" as a performance-based measure of the participants' ability to manage finances. Both studies were done in semi-naturalistic settings (real materials and props handled in a laboratory) and resorted to observational methods to infer about the mild-moderate HD patients' performance level. In our view, the *EcoKitchen* has the potential to increase the objectivity and sensitivity of HD executive and functional assessments such as the ones mentioned for several reasons: it proposes a

more refined definition of the executive sub-domains being evaluated; makes a clearer link to conventional executive and functional tools often used in HD clinical practice; evaluates the impact of different executive loads over individual performance as it manipulates the task executive demands; it provides quantitative data about the performance time and accuracy of the examinee.

EcoKitchen was designed to evaluate planning, multi-tasking, set-shifting, cognitive flexibility, self-monitoring, sequencing, divided attention, and scanning skills. As Dumas et al. (2013) stated, it is often very difficult to pinpoint just one specific executive function that is responsible for the correct performance of a task. Moreover, as Craik and Bialystok (2006) indicate, the choice of a real-life task means that the specificity of measurement of individual cognitive functions is limited, as there are no unitary constructs involved in daily-life performance – we think that the same principle might apply to computer-simulated tasks. Consequently, each one of the parameters considered in the *EcoKitchen* performance analysis can be associated not with one executive function but rather with a sub-set of executive domains. This association is further detailed in the "Materials and Methods" section.

To our knowledge, this is the first study where a virtual reality task was created specifically for the assessment of functional deficits related to executive impairments in persons with HD, particularly in persons with premanifest HD. Thus, this work was essentially planned as an exploratory feasibility study, aimed at checking if the *EcoKitchen* was well-tolerated by the clinical groups and if it was able to differentiate healthy participants from persons with HD, particularly premanifest HD participants. Furthermore, this study aimed to identify which variables computed from the *EcoKitchen* task might be more sensitive to the earliest disease-related cognitive and functional alterations and, thus, withhold the potential to be used in clinical, research and rehabilitation settings in the future.

We tested the executive function of persons with EarlyHD, PreHD and healthy Controls using the newly developed *EcoKitchen* tool and compared the results with other executive and functional measures in a wider assessment protocol that included a subjective (self-report) functional measure – "The Adults and Older Adults Functional Assessment Inventory – IAFAI" (Sousa et al., 2015), a more ecological executive test battery – the "Behavioural Assessment of Dysexecutive Syndrome – BADS" (Wilson et al., 1996), and a conventional neuropsychological test battery. "The Adults and Older Adults Functional Assessment Inventory – IAFAI" (Sousa et al., 2015) was used as a

subjective (self-report) verbal functional measure, since it was considered to be more accurate and broad than other subjective functional assessments, namely the Total Functional Capacity scale (Huntington Study Group, 1996). The "Behavioural Assessment of Dysexecutive Syndrome" battery – BADS (Wilson et al., 1996) was included in the protocol as a more close to daily-life like situations traditional executive tool (Norris & Tate, 2000; Wilson et al., 1998). Importantly, to our knowledge, BADS has been scarcely used with HD patients (Nimmagadda et al., 2011), with no reports in premanifest HD found, and this is the first time IAFAI was used with HD affected individuals.

Finally, the conventional neuropsychological battery, composed by a set of widely known executive tests, was used as a description of the executive status of the premanifest and early manifest HD participants enrolled in this study. The tests included in this battery were chosen because they were proven to be sensitive to basal ganglia damage and HD earliest cognitive changes (Dumas et al., 2013; Lemiere et al., 2002; Lezak et al., 2012; Paulsen, 2010). Moreover, these tests are extensively used in clinical settings (some are part of the cognitive section of the main standardized HD assessment scale, the Unified Huntington's Disease Rating Scale – Huntington Study Group, 1996) and in large multinational longitudinal observational studies [e.g., Registry Study (Baake et al., 2017); TRACK-HD (Tabrizi et al., 2009); PREDICT-HD (Paulsen et al., 2006); HD-CAB (Stout et al., 2014)]. Finally, the executive sub-domains assessed by these tests are thought to correspond to the executive sub-domains involved in *EcoKitchen* task performance and, thus, we expected performance in both components of our study protocol to be correlated, helping us to describe the cognitive skills elicited by the *EcoKitchen*.

In summary, this study aimed to test *EcoKitchen* as a new performance-based tool to detect the earliest signs of executive and functional changes in HD prior to the onset of clinical symptoms and overcome the limitations often posed by the traditional assessment methods.

Materials and Methods

Participants

A total of 15 Early Manifest HD participants (EarlyHD), 15 Premanifest HD participants (PreHD) and 19 Control participants (CTRL) completed the four protocol components and entered the data analysis, after the exclusion of 1 EarlyHD and 1 CTRL participants for presenting a score in the "Montreal Cognitive Assessment" - MoCA (Freitas et al., 2011; Nasreddine et al., 2005) below the established cut-off for their age and education level. Due to time constraints, 2 CTRL participants did not complete IAFAI.

EarlyHD and PreHD participants were recruited from the Neurogenetics Consultation Service of the Neurological Department of Coimbra University Hospital. All but 3 CTRL participants were gene negative or non-at-risk relatives of the HD affected participants. All subjects gave written informed consent in accordance with the Declaration of Helsinki to participate in the study approved by our Institutional Ethics Committees (Faculty of Medicine and Coimbra University Hospital).

The participants were assigned to one of three groups according to the following criteria:

- Early manifest HD (EarlyHD): patients with mild HD symptoms - stages I-II (Shoulson & Fahn, 1979), that had a UHDRS Total Functional Capacity scale of 10-13 (Huntington Study Group, 1996) and a positive HD genetic test result which confirms a CAG length of ≥36 (n=15).
- Premanifest HD (PreHD): participants that showed no clinical symptoms of HD, that had a UHDRS Total Motor score ≤ 5 (Huntington Study Group, 1996) and a positive HD genetic test result which confirms a CAG length of ≥36 (n=15).

Exclusion criteria for the clinical groups included dementia, severe depression, history of substance abuse, and any other neurological condition.

- Controls (CTRL): healthy participants, with no history of dementia, depression, substance abuse, any neurological and/or psychiatric condition and no current use of psychotropic medication (n=19).

The clinical groups were assessed by an experienced neurologist using the "Unified Huntington's Disease Rating Scale" (UHDRS) – Motor and Total Functional Capacity scales (Huntington Study Group, 1996). The UHDRS Total Motor score can range from 0 to 124 and higher scores indicate increased severity of motor symptoms. The UHDRS

Total Functional Capacity scale can range from 0 to 13 – lower scores indicate increased disability. Disease duration was defined for each early manifest HD participant as the number of years since HD clinical diagnosis. Langbehn's formula (Langbehn et al., 2004) was used to calculate the estimated time (in number of years) to disease onset of the PreHD participants, although no further classification of the premanifest participants was done according to this parameter. Information about the CAG repeat number was collected for both clinical groups.

To avoid cognitive confounds, we used the "Montreal Cognitive Assessment" - MoCA (Freitas et al., 2011; Nasreddine et al., 2005) as a mild cognitive impairment and dementia screening tool and excluded any subjects that were below the expected score on this test. The "Beck Depression Inventory – II" (Beck et al., 1996; Campos & Gonçalves, 2011) was used as a neuropsychiatric measure and also as an exclusion criterion if moderate to severe depressive symptoms were signalled. The "Irregular Word Reading Test – TeLPI" (Alves et al., 2012) was administered to provide an estimate of the level of premorbid intelligence of all the participants. The "Edinburgh Handedness Inventory" (Oldfield, 1971) was used to define subject's handedness.

The demographic characteristics of the three groups are presented in Table 2.1.

The study protocol included four different components: *EcoKitchen*, IAFAI, BADS and a conventional neuropsychological test battery.

Table 2.1 Demographic characteristics with Kruskal-Wallis and Mann-Whitney comparisons across groups

	CTRL=19 *Gender (F:M) 15:4* *Handedness (R:L) 18:1*	*PreHD=15* *Gender (F:M) 12:3* *Handedness (R:L) 15:0*	*EarlyHD=15* *Gender (F:M) 10:5* *Handedness (R:L) 14:1*	*K-W*	*M-W* *PreHD* *vs* *CTRL*	*M-W* *EarlyHD* *vs* *CTRL*	*M-W* *PreHD* *vs* *EarlyHD*
Demographic Characteristics	*Median (IQR; min-max)*	*Median (IQR; min-max)*	*Median (IQR; min-max)*	χ^2 *(p-value)*	*U (p-value)*	*U (p-value)*	*U (p-value)*
Age (years)	41 (12; 25-57)	36 (16; 22-52)	46 (6; 25-69)	6.075 * (0.048)	95 (0.099)	112.5 (0.297)	56 # (0.019)
Education (years)	11 (7; 6-17)	14 (7; 6-17)	9 (6; 6-16)	6.582 * (0.037)	111 (0.270)	95 (0.095)	53.5 # (0.013)
CAG	-	42 (5; 39-49)	43 (2; 38-50)	-	-	-	97.5 (0.529)
Disease Duration (years)	-	-	5 (6; 1-10)	-	-	-	-
Years to HD Onset	-	16.46 (10.43; 7.37-43.34)	-	-	-	-	-
UHDRS - TFC	-	13 (0; 13-13)	12 (2; 10-13)	-	-	-	45 # (0.001)
UHDRS - Motor	-	0 (3; 0-5)	24 (20; 5-44)	-	-	-	1 # (‹ 0.001)
MoCA	26 (4; 22-30)	27 (4; 21-30)	23 (4; 18-29)	10.218 * (0.006)	119 (0.411)	67 ¥ (0.008)	45 # (0.005)
BDI-II	3 (4; 0-24)	6 (9; 0-23)	17 (17; 0-23)	8.715 * (0.013)	121.5 (0.464)	62 ¥ (0.005)	61 # (0.032)
TeLPI (QIEC)	113.54 (15.35; 67.44-125.82)	116.60 (13.05; 91.64-126.09)	103.18 (19.98; 84.72-121.98)	8.303 * (0.016)	116.5 (0.367)	78.5 ¥ (0.026)	49 # (0.008)
TeLPI (QIV)	114.83 (15.89; 71.76-127.67)	117.88 (14.31; 94.31-127.67)	103.28 (19.68; 87.01-123.88)	8.592 * (0.014)	117.5 (0.385)	79.5 ¥ (0.029)	46 # (0.006)
TeLPI (QIR)	109.72 (11.25; 70.58-118.91)	111.72 (9.19; 91.16-118.91)	102.51 (16.45; 84.98-115.82)	8.230 * (0.016)	118.5 (0.405)	78.5 ¥ (0.026)	49 # (0.008)

CTRL – Controls; PreHD – Premanifest HD; EarlyHD – Early Manifest HD; IQR – Interquartile Range; min-max – Minimum and Maximum scores (Range); K-W – Kruskal-Wallis; M-W – Mann-Whitney; CAG – CAG repeat expansion confirmed by a genetic test; Disease Duration – Years since HD clinical diagnosis (only computed for HD); Years to HD Onset – Years to estimated HD clinical diagnosis according to Langbehn's formula (only computed for HP); UHDRS - TFC – Total Functional Capacity scale of the Unified Huntington's Disease Rating Scale; UHDRS - Motor – Motor scale of the Unified Huntington's Disease Rating Scale; MoCA – Montreal Cognitive Assessment; BDI-II – Beck Depression Inventory II; TeLPI – The Irregular Word Reading Test (TeLPI); QIEC – Full Scale Intelligence Quotient; QIV – Verbal Intelligence Quotient; QIR – Performance Intelligence Quotient
** Significant group effect (Kruskal-Wallis, p ‹ 0.05) ¥ EarlyHD ≠ CTRL (Mann-Whitney, p ‹ 0.05); # PreHD ≠ EarlyHD (Mann-Whitney, p ‹ 0.05)*

EcoKitchen

As previously mentioned, *EcoKitchen* is a new assessment tool created at our laboratory to add performance-based information to the other executive and functional measures used. *EcoKitchen* is a non-immersive virtual reality task that aims to objectively evaluate the cognitive and functional status of the study participants using a realistic scenario – a computer-generated kitchen.

EcoKitchen design and procedures

EcoKitchen was implemented on a desktop PC, with a 23'' monitor (large screen size of 23-inch), in full screen mode (1920 x 1200). The stimuli were generated with Vizard (WorldViz, 2002). The participant experienced the kitchen environment from a first-hand perspective and used the computer mouse to move around the scenario.

EcoKitchen was designed as a non-immersive desktop computer task, which involves a flat-screen presentation of the virtual kitchen setting. This option in comparison with a fully-immersive virtual reality display has several advantages. It is more portable than a three-dimensional environment, thus facilitating assessment in clinical settings (Allain et al., 2014); it limits the risk of simulation sickness, which could pose a problem for elderly participants or clinical groups (Attree et al., 1996; Kawano et al., 2012); it is more appropriate for individuals less familiarized with computers; finally, it creates very little memory demands to the study participants – individuals did not need to navigate through the scenario, having the risk of forgetting where the requested items were.

The task included three different blocks, with an increasing executive load. Each condition was preceded by a practice block. There was also a first global practice block, to guarantee that each participant was completely familiarized with the apparatus before the assessment blocks begun (Figure 2.1).

- Global Practice Block - The participant had to explore the kitchen environment and grab a specific list of items - all the items that he/she was going to need in the following blocks were on that list, as well as distracter items.
- Block 1 - A picture list with all the items needed to prepare a cup of coffee with milk (Task A) was displayed on the upper part of the screen. The list was left in full view during the block to reduce constraints on memory. Participants were instructed to collect each item, in the order they appeared in the list, as fast and

accurately as possible. They had to attend and turn off the stove as soon as and only when the clock was completely red. Participants had to plan and monitor their behaviour to complete this level successfully.

- Block 2 - Participants had to perform Task A, as described in the first block, while, simultaneously, paying attention and monitoring a boiling kettle that was on the stove. They were instructed to press the kettle every time and as soon as smoke came out and a red signal appeared on the right upper part of the screen, to prevent water from spilling. The kettle was set up to burst three times during the block, at random moments, so participants had to check smoke and the red signal appearance periodically. Participants had to recruit the same executive skills as before, plus divide their attention to complete this level successfully.
- Block 3 - Participants had to perform the tasks described in the first and the second blocks (Task A and boiling kettle). Additionally, participants were instructed to also prepare toasts with butter (Task B). A picture list with all the items needed to prepare the second snack was displayed on the upper part of the screen. Participants were instructed to alternate between the two lists (Task A and Task B) to make sure that both tasks were completed at the same time. Participants had to apply the same skills used in the previous block, plus switch/alternate between tasks to complete this level successfully.

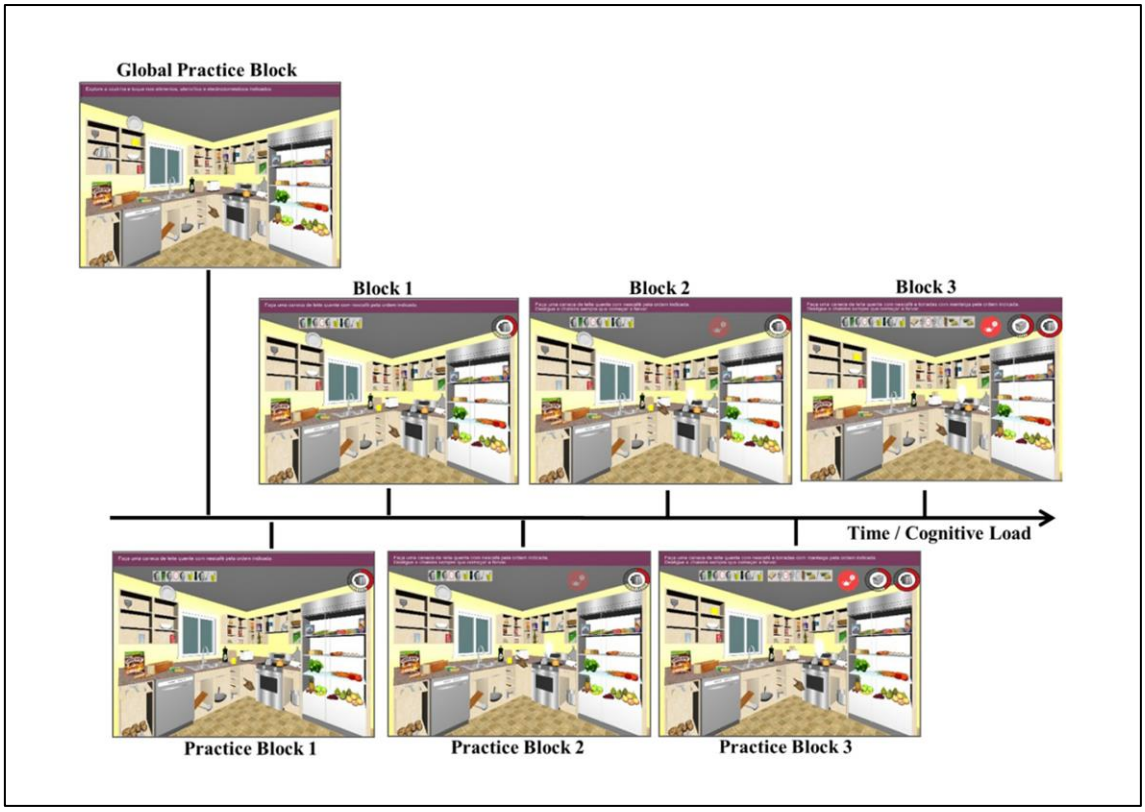

Figure 2.1 *EcoKitchen* Task Design

EcoKitchen included three different blocks (each preceded by a practice trial), with increasing executive demands. In Block 1, the participant had to prepare a cup of coffee with milk – Task A. In Block 2, while performing Task A, the participant had to turn off a boiling kettle that burst at several random moments. In Block 3, the participant had to perform the tasks previously described, whilst preparing toasts with butter (Task B).

The interactions with the different items needed to perform the tasks were facilitated – e.g., if the participant touched the jar, it would go automatically to the stove. This was settled not only to help the participants who globally did not have much experience with computer interaction, but also to focus on the cognitive aspects of task performance rather than on the motor coordination/control aspects – which can be problematic in a movement disorder. The *EcoKitchen* aimed to analyse executive functioning while minimizing the impact of computer interaction difficulties (Allain et al., 2014). To reduce memory constraints, the instructions and the lists with the requested items and actions needed to perform either Task A or Task B were left in full view during the whole block. With the same purpose, there were no closed cabinets or drawers in the *EcoKitchen*, all items were on full display. Finally, to increase the realism of the task (and thus its ecological validity), known commercial brands were used to depict the foods and beverages included in the kitchen setting.

EcoKichen data analysis

Several parameters were defined for the analysis of the *EcoKitchen* performance of each participant, considering Time and Error variables. Although the performance of tasks that simulate daily-life routines requires a plethora of cognitive functions and executive sub-domains that are difficult to disentangle, we have added some information about the executive functions that, in our view, are reflected by each *EcoKitchen* parameter.

- Performance Time Task A – the time the participant was engaged in the preparation of a cup of coffee with milk (time elapsed from the moment the first item of the list was picked to the moment the last item of the list was picked and used). This parameter reflects psychomotor and processing speed, planning, and motor time.
- Performance Time Task B – the time the participant was engaged in the preparation of toasts with butter (time elapsed from the moment the first item of the list was picked to the moment the last item of the list was picked and used). This parameter reflects the same executive domains as Performance Time Task A, plus task switching.
- Reaction Time Stove – the amount of time the participant took to react and turn off the stove once the clock was completely red (which was the cue for the behaviour to take place and for the participant to initiate the response). This parameter gives indications about behaviour monitoring, response initiation, divided attention, and set-shifting.
- Reaction Time Kettle – the amount of time the participant took to react and turn off the kettle once smoke appeared and a red signal blinked in the right upper part of the computer screen (which were the cues for the behaviour to take place and for the participant to initiate the response). This parameter reflects divided attention, sustained alertness, response initiation, and set-shifting.
- Reaction Time Toaster – the amount of time the participant took to react and turn off the toaster once the clock was completely red (which was the cue for the behaviour to take place and for the participant to initiate the response). This parameter gives indications about the same executive domains tackled by Reaction Time Stove, plus task switching.
- Reaction Time per Block – the mean of the different reaction times extracted from each *EcoKitchen* block. This parameter reflects all the executive sub-domains

involved in the different reaction times to specific cues.

- Sequencing Errors – the number of times the participant failed to follow the proper sequence of the task (e.g., tried to mix the coffee with the spoon before adding the milk). This parameter reflects planning, behaviour monitoring, and working memory.
- Item Errors – the number of times the participant picked items of the *EcoKitchen* scenario that were not needed to prepare either Task A or Task B (e.g., selected a pineapple instead of coffee). This parameter reflects attention and behaviour monitoring.
- Impulsivity Errors Stove – the number of times the participants tried to turn off the stove before the proper time (before the clock being completely red). This parameter reflects response inhibition or inhibitory control, and attention.
- Impulsivity Errors Toaster – the number of times the participants tried to turn off the toaster before the proper time (before the clock being completely red). This parameter reflects the same executive sub-domains involved in Impulsivity Errors Stove, plus task switching.
- Total Errors/Performance Time Task A – the number of errors per minute the participants did during the completion of Task A (cup of coffee with milk). This parameter gives indication about the speed-accuracy balance in task completion.

$$\frac{total\ errors}{performance\ time\ task\ A} \text{ x } 60$$

- Total Errors/Performance Time Task B – the number of errors per minute the participants did during the completion of Task B (toasts with butter). This parameter gives the same indication as the previous one, plus indication about task switching abilities.

$$\frac{total\ errors}{performance\ time\ task\ B} \text{ x } 60$$

IAFAI – the Adults and Older Adults Functional Assessment Inventory

We have used "IAFAI" (Sousa et al., 2015) as a verbal and subjective measure of the functional status of study participants. In IAFAI, the participant must rate his level of self-perceived difficulties in performing Basic and Instrumental Activities of Daily

Living (BADL and IADL, respectively), such as bathing, using an ATM card or cooking a meal. Each activity can have a score of 0 (representing the absence of difficulty/dependence in the execution of the ADL) or a score of 1 (representing the presence of difficulty/dependence in the execution of the ADL) (Sousa et al., 2015). Moreover, the participant must indicate if each of the signalled difficulties is explained by physical, cognitive or emotional restrictions. Seven incapacity percentages were computed from IAFAI: Global Functional Incapacity (GFI), Functional Incapacity in Basic Activities of Daily Living (ABVD), Functional Incapacity in Household Instrumental Activities of Daily Living (H-IADL), Functional Incapacity in Advanced Instrumental Activities of Daily Living (A-IADL), Functional Incapacity due to Physical Factors (Physical), Functional Incapacity due to Cognitive Factors (Cognitive), and Functional Incapacity due to Emotional Factors (Emotional).

BADS – the Behavioural Assessment of Dysexecutive Syndrome battery

For the executive functions assessment, we used the "BADS" (Wilson et al., 1996), created by Barbara Wilson to overcome the ecological validity constraints of other traditional executive tests (Burgess et al., 1998, 2006). This battery is composed by six sub-tests, all of which imply skills and materials that try to resemble daily-life like situations. Seven variables were extracted from BADS: Total Score, Rule Shift Cards Test Score, Action Program Test Score, Key Search Test Score, Temporal Judgement Test Score, Zoo Map Test Score, and Modified Six Elements Test Score.

Neuropsychological test battery

The conventional neuropsychological test battery used as a baseline description of the executive status of the study participants assembled several classic executive tests widely employed in clinical and research settings. The Phonemic Verbal Fluency test: three letters – P, M, R (Cavaco et al., 2013a) and the Semantic Verbal Fluency test – category animals (Cavaco et al., 2013a) were used to assess working memory, word generation and inhibition. The Stroop test – Naming, Interference and Reading tasks (Stroop, 1935) were used to assess cognitive flexibility and processing speed. The Symbol Digit Modalities Test (Smith, 1982) was used to assess working memory, attention and

integration, and psychomotor speed. The Digit Span Test (Forward and Backward) of the WAIS-III – Wechsler Adult Intelligence Scale-third edition (Wechsler, 1997, 2008) was used to assess working memory. The Trail Making Test – parts A and B (Cavaco et al., 2013b; Reitan, 1958) was used to assess scanning, sequencing, divided attention, psychomotor speed and cognitive flexibility. Finally, the Wisconsin Card Sorting Test (Heaton, 1981) was used to assess abstract behaviour and set shifting. All the tests were applied in a strictly prescribed order, to avoid any interference effects or content overlapping. Twenty scores were extracted from this test battery.

Statistical analyses

Comparisons of quantitative variables between the three groups (EarlyHD, PreHD, and Controls) were performed resorting to Kruskal-Wallis tests. When statistically significant differences were detected (effect of group), post hoc comparisons were performed between two groups using the Mann-Whitney *U* tests. Comparisons of nominal/categorical variables between groups were performed resorting to Chi-square tests of independence. Wilcoxon-Signed rank tests were used to analyse the effects of the increasing cognitive load in the participants' performance across the three EcoKitchen blocks. Spearman rank correlation coefficients were calculated to examine the associations of *EcoKitchen*, the other assessment methods and HD features for the clinical groups (PreHD and EarlyHD). Benjamini-Hochberg corrections with false positive rate established at 0.05 were used to deal with multiple comparisons, and only the correlations that survived these corrections were mentioned in the "Results" section and further examined in the "Discussion" section. To reduce the number of pairwise correlations and enhance interpretability, in the correlation analyses, the variables related to *EcoKitchen* were averaged across the three blocks. In the correlations with clinical variables, it is of note that disease duration (in years) was only considered for the early manifest HD group (n=15) and estimated years to likely onset was only considered for the premanifest HD group (n=15), thus reducing the sample size considered for computing the correlation coefficients in this case. Finally, given the high intra-group variability detected in the *EcoKitchen* performance of the early manifest HD participants (as reflected in the boxplots depicted in Figures 2.2-2.4), there was a possibility that the differences observed in our study were driven by just a few patients within this group. To test this hypothesis, we checked for outliers using the following logical conditions

[($xi \geq$ Q3 + 1.5 * IQR) and ($xi \leq$ Q1 -1.5 * IQR)]. For each of the *EcoKitchen* variables computed there was a maximum of two outliers within the EarlyHD group. In total, six of the 15 persons with early manifest HD enrolled in our study presented outlier results in at least one of the *EcoKitchen* computed measures, but there was no participant whose performance was identified as an outlier in all variables. Moreover, this sub-group of patients was demographically and clinically matched to the other early manifest HD participants ($p \geq 0.05$ in all the variables displayed in Table 2.1). Lastly, no EarlyHD outliers were found on four of the *EcoKitchen* measures, namely, in Performance Time Task A (Block 1 and Block 2), in Reaction Time per Block (Block 3), and in Reaction Time per Cue (Stove). Kruskal-Wallis and Mann-Whitney U comparisons were performed as described above excluding the outliers identified in the EarlyHD group. Importantly, the statistical results were equivalent to the results obtained including all data points. As high intra-group variability reflects the phenotypic variability that is reportedly one of the key features of this disease (Folstein et al., 1984; Mehrabi et al., 2016; Waldvogel et al., 2012), these early manifest HD outliers were considered to be clinically and scientifically relevant, and therefore we decided not to exclude them from our main analyses presented in this paper. All calculations were performed with IBM SPSS Statistics (Version 24), adopting a level of significance of $\alpha = 0.05$.

Results

EcoKitchen

The several time and error variables extracted from the participants' performance in the *EcoKitchen* task gave us important indications about how well HD affected individuals could perform executively demanding tasks similar to daily-life routines and, thus, about their functional status. Moreover, the analysis of the *EcoKitchen* data gave us relevant information about the impact of increasing executive load on the behaviour of clinical and healthy populations. We defined three main categories for the *EcoKitchen* data analysis: accuracy, time, and cognitive load. Only significant results are reported.

EcoKitchen Accuracy Measures

EcoKitchen errors

We computed three types of errors from the *EcoKitchen* performance data – sequencing errors (participant failed to follow the proper sequence of the task), item errors (participant picked items not needed to complete the task), and impulsivity errors (participant turned off the stove or toaster before the proper time). Sequencing errors reflected difficulties in the planning and monitoring of actions. We found a significant group effect for the percentage of participants with sequencing errors in Block 1 and Block 3 of *EcoKitchen* [($\chi 2(2)= 13.253$, $p= 0.001$) and ($\chi 2(2)= 8.964$, $p= 0.011$), respectively] (Table 2.2). Interestingly, post hoc tests comparing the different groups revealed that a significantly higher percentage of PreHD participants than controls failed to plan and correctly sequence their actions, but only in the more executive challenging *EcoKitchen* Block 3 ($\chi 2(1)= 4.437$, $p= 0.035$). The early manifest HD group also showed more sequencing errors than controls in Block 1 and Block 3 [$\chi 2(1)= 9.188$, $p= 0.002$, and $\chi 2(1)= 6.689$, $p= 0.010$, respectively], and was also worse than PreHD participants in Block 1 ($\chi 2(1)= 8.889$, $p= 0.003$). We also found a significant group effect in terms of impulsivity errors in Block 3 of *EcoKitchen* ($\chi 2(2)= 12.621$, $p= 0.002$). This might reflect deficits in inhibitory control and increased impulsivity in the early manifest HD group, as a higher percentage of EarlyHD than CTRL and PreHD participants tried to stop the stove before the proper time in the more cognitively demanding *EcoKitchen* condition [($\chi 2(1)= 7.425$, $p= 0.006$) and ($\chi 2(1)= 6.000$, $p= 0.014$), respectively].

Table 2.2 Percentage of participants that had a score ≠ 0 in the Sequencing, Item and Impulsivity Error Variables of the *EcoKitchen* Task

	CTRL			*PreHD*			*EarlyHD*		
EcoKitchen	*Block 1*	*Block 2*	*Block 3*	*Block 1*	*Block 2*	*Block 3*	*Block 1*	*Block 2*	*Block 3*
Sequencing Errors	15.8	26.3	52.6	13.3	20	86.7 ϕ	66.7 ¥#	40	93.3 ¥
Item Errors	0	0	5.3	6.7	6.7	20	6.7	20	13.3
Impulsivity Errors - Stove	10.5	5.3	0	6.7	6.7	0	13.3	20	33.3 ¥#

CTRL – Controls; PreHD – Premanifest HD; EarlyHD – Early Manifest HD ϕ PreHD ≠ Control (Chi-square test for independence – p ‹ 0.05);
¥ EarlyHD ≠ Control (Chi-square test for independence – p ‹ 0.05); # EarlyHD ≠ PreHD (Chi-square test for independence – p ‹ 0.05)

EcoKitchen errors/time

We calculated the number of errors per minute as a measure of speed-accuracy trade-off in each group of participants. We found a significant group effect in the number of errors per minute during the preparation of a cup of coffee with milk ($\chi 2(2)= 8.174$, $p= 0.017$) (Figure 2.2). Importantly, in the post hoc tests, PreHD participants showed a decrease in the quality of their task performance, committing more errors per minute during Task A than controls ($U= 86$, $p= 0.048$). The persons with early manifest HD also showed a diminished quality of their task performance, as they presented a higher number of sequencing, item and impulsivity errors per minute than controls during both Task A and Task B completion ($U= 65.5$, $p= 0.007$ and $U= 80.5$, $p= 0.029$, respectively).

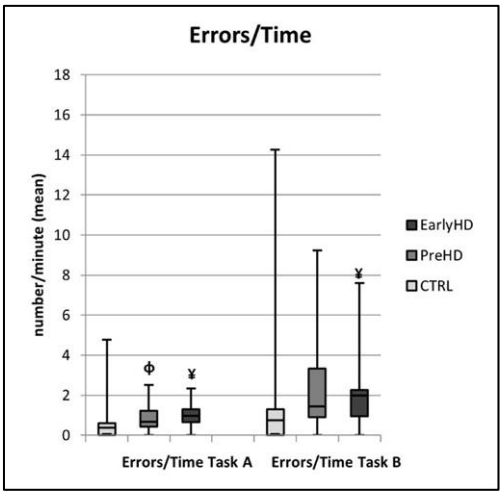

Figure 2.2 *EcoKitchen* Number of Total Errors *per* minute of Performance Time Task A and Number of Total Errors per minute of Performance Time Task B (mean) and significant differences between groups

Boxplots: central mark - median; edges of box - 25th and 75th percentiles; whiskers - most extreme data points (minimum and maximum).
ϕ PreHD ≠ Control (Mann-Whitney, p ‹ 0.05); ¥ EarlyHD ≠ Control (Mann-Whitney, p ‹ 0.05)

EcoKitchen Time Measures

EcoKitchen performance time

We analysed and compared the time it took the participants from the three groups to prepare a cup of coffee with milk (Task A) and toasts with butter (Task B), to see whether group differences would emerge. We found a statistically significant group effect in Task A and Task B performance times in all *EcoKitchen* conditions [Task A: Block 1 - $\chi 2(2)= 21.972$, $p< 0.001$; Block 2 - $\chi 2(2)= 12.512$, $p= 0.002$; Block 3 - $\chi 2(2)= 13.959$,

p= 0.001; Task B: $\chi 2(2)$= 16.475, p< 0.001] (Figure 2.3). Notably, we found no differences between PreHD and control participants in total task time suggesting that the motor and cognitive times of persons with premanifest HD were not affected. In contrast, we found that persons with early manifest HD already displayed a motor and cognitive slowness that influenced their timely performance both in single and multitasking conditions, as they were slower compared to controls [Task A: Block 1 - U= 25, p< 0.001; Block 2 - U= 46, p= 0.001; Block 3 - U= 46, p= 0.001; Task B: U= 41, p< 0.001], and to premanifest participants [Task A: Block 1 - U= 14, p< 0.001; Block 2 - U= 46, p= 0.006; Block 3 - U= 38, p= 0.002; Task B: U= 27, p< 0.001] across all EcoKitchen Blocks and Tasks.

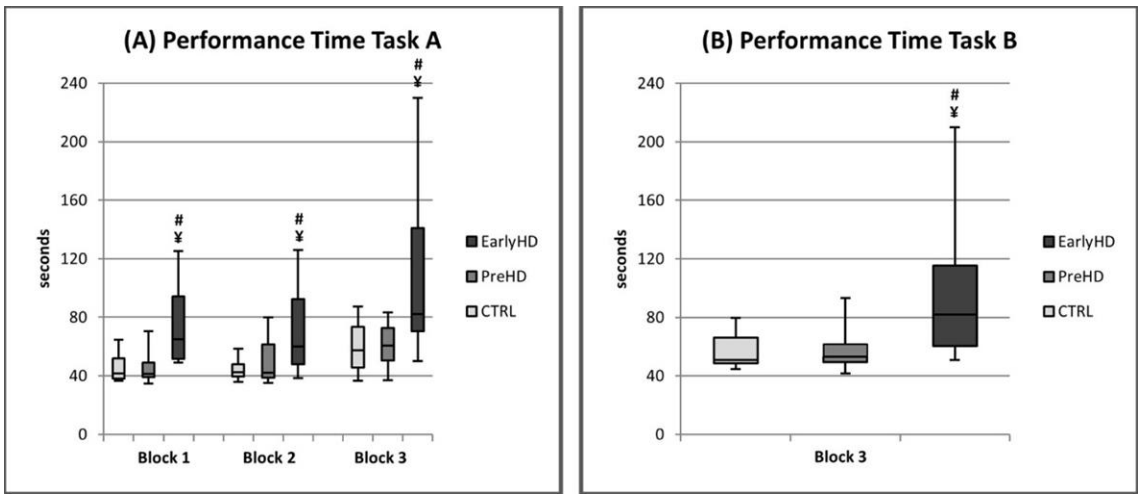

Figure 2.3 *EcoKitchen* Performance Time Task A (A) and Performance Time Task B (B) and significant differences between groups

Boxplots: central mark - median; edges of box - 25th and 75th percentiles; whiskers - most extreme data points (minimum and maximum).
¥ EarlyHD ≠ Control (Mann-Whitney, p ‹ 0.05); # EarlyHD ≠ PreHD (Mann-Whitney, p ‹ 0.05)

EcoKitchen reaction time

We analysed the amount of time participants took to react to the different cues included in the *EcoKitchen* scenario (stove, kettle, and toaster). These reaction time measures reflect cognitive functions like response initiation, monitoring, divided attention, set shifting and task switching skills. The average reaction time across the different cues presented a significant group effect in the more demanding *EcoKitchen* Blocks 2 and 3 [$\chi 2(2)$= 13.680, p= 0.001 and $\chi 2(2)$= 7.727, p= 0.021, respectively] (Figure 2.4). No differences were found between the PreHD and CTRL groups. Reversely, persons with EarlyHD took longer than CTRL and PreHD participants to react to the target stimuli while engaged in a primary task, even when prompt action indications were given. We

found that the EarlyHD group was significantly slower than CTRL and PreHD participants in Blocks 2 and 3 (U= 38.5, p< 0.001 and U= 68, p= 0.010; U= 48, p= 0.007 and U= 60.5, p= 0.031, respectively). When considering the *EcoKitchen* cues separately, again a significant group effect was found in the reaction times to turn off the stove and to turn off the boiling kettle [$\chi 2(2)$= 9.152, p= 0.010 and $\chi 2(2)$= 14.458, p= 0.001, respectively]. Persons with EarlyHD showed a slower response initiation to attend the stove and the kettle than controls (U= 59, p= 0.004 and U= 51, p= 0.002, respectively), and were also slower than PreHD participants to react to the kettle (U= 33, p= 0.001). Interestingly, there was a trend for the PreHD group to be slower to turn off the stove than controls (U= 86.5, p= 0.052), although this did not reach statistical significance.

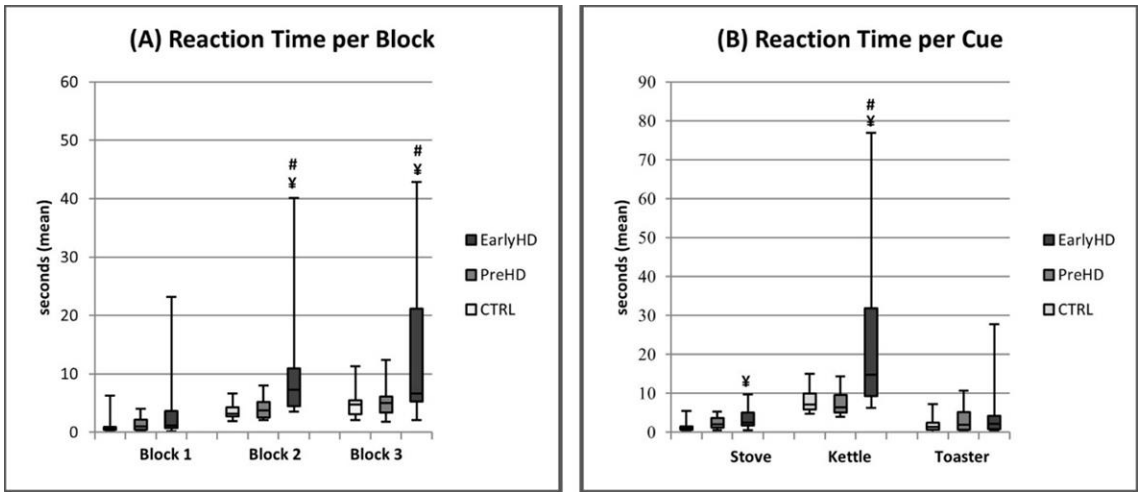

Figure 2.4 *EcoKitchen* Reaction Time per Block (A) and Reaction Time per Cue (B) - Stove, Kettle, and Toaster (Mean of the 3 blocks) and significant differences between groups

Boxplots: central mark - median; edges of box - 25th and 75th percentiles; whiskers - most extreme data points (minimum and maximum).
¥ EarlyHD ≠ Control (Mann-Whitney, p ‹ 0.05); # EarlyHD ≠ PreHD (Mann-Whitney, p ‹ 0.05)

EcoKitchen Cognitive Load

Next, we analysed the effects of increasing cognitive load in the participants' performance across the three *EcoKitchen* blocks to see whether the behaviour of study participants reflected the impact of the task executive demands. The incremental complexity of the *EcoKitchen* had a negative impact in performance accuracy, as we found a significant increase in the percentage of participants that failed to follow the proper sequence of the task in Block 3 compared to Blocks 1 and 2 (Z= -4.690, p< 0.001 and Z= -4.271, p< 0.001, respectively). This was paralleled by an increase in the number

of errors per minute during the completion of Task A in Block 3 compared to Block 1 and 2 (Z= -5.077, p< 0.001 and Z= -3.972, p< 0.001, respectively). The increasing cognitive demands of the *EcoKitchen* also had a negative impact in terms of timing measures, as the time participants devoted to Task A in Block 3 was significantly higher than in Block 1 and Block 2 (Z= -5.287, p< 0.001 and Z= -5.217, p< 0.001, respectively). Finally, the reaction time to the stove cue also reflected the *EcoKitchen* increasing complexity, as it was significantly higher in Block 3 compared to Block 1 and 2 (Z= -3831, p< 0.001 and Z= -4.153, p< 0.001, respectively).

IAFAI – the Adults and Older Adults Functional Assessment Inventory

The IAFAI results gave us relevant information about the self-reported functional status of study participants and about the insight the clinical groups have about their ability to perform different daily-life tasks. We found that a higher percentage of persons with early manifest HD than CTRL and PreHD participants report difficulties in the performance of both BADL and IADL (Table 2.3). Namely, a significantly higher percentage of EarlyHD than CTRL and PreHD participants signalled functional difficulties in basic activities of daily living, in household IADL, and in advanced IADL. Furthermore, a significantly higher percentage of EarlyHD than CTRL and PreHD participants attributed the cause of the experienced functional difficulties to physical, cognitive, and emotional factors. These results suggest that persons with early manifest HD have insight about the deficits they experience when performing simple and complex daily-life tasks, as well as about the factors that might be causing these deficits. Importantly, persons with PreHD and CTRL individuals rated themselves equally capable, with no statistically significant differences between the two groups on any of the variables extracted from IAFAI. Thus, PreHD participants are not aware of functional changes in their daily routines, perceiving their everyday performance at the control level and reporting significantly less difficulties than EarlyHD participants in all the IAFAI measures considered.

Table 2.3 Percentage of participants that had a score ≠ 0 in IAFAI

	CTRL	*PreHD*	*EarlyHD*	*Chi-Square PreHD vs CTRL*	*Chi-Square EarlyHD vs CTRL*	*Chi-Square PreHD vs EarlyHD*
IAFAI		*%*		χ^2 *(p-value)*	χ^2 *(p-value)*	χ^2 *(p-value)*
Global Functional Incapacity	17.6	26.7	93.3	0.379 (0.538)	18.331 ¥ (‹ 0.001)	13.889 # (‹ 0.001)
Functional Incapacity in BADL	0	20	80	3.752 (0.053)	21.760 ¥ (‹ 0.001)	10.800 # (0.001)
Functional Incapacity in H-IADL	0	13.3	93.3	2.418 (0.120)	28.207 ¥ (‹ 0.001)	19.286 # (‹ 0.001)
Functional Incapacity in A-IADL	17.6	13.3	80	0.112 (0.737)	12.441 ¥ (‹ 0.001)	13.393 # (‹ 0.001)
Functional Incapacity - Physical	0	20	80	3.752 (0.053)	21.760 ¥ (‹ 0.001)	10.800 # (0.001)
Functional Incapacity - Cognitive	11.8	13.3	93.3	0.018 (0.893)	21.208 ¥ (‹ 0.001)	19.286 # (‹ 0.001)
Functional Incapacity - Emotional	11.8	13.3	60	0.018 (0.893)	8.219 ¥ (0.004)	7.033 # (0.008)

CTRL – Controls; PreHD – Premanifest HD; EarlyHD – Early Manifest HD; IAFAI - the Adults and Older Adults Functional Assessment Inventory; BADL – Basic Activities of Daily Living; IADL – Instrumental Activities of Daily Living
¥ EarlyHD ≠ Control (Chi-square test – p ‹ 0.05); # EarlyHD ≠ PreHD (Chi-square test– p ‹ 0.05)

BADS – the Behavioural Assessment of Dysexecutive Syndrome battery

The BADS results were important to determine if a neuropsychological test battery with higher ecological validity than conventional executive tests could be better at differentiating the clinical and control groups. We found a statistically significant group effect in the Total Score and in several of the subtests that comprise it, namely in the Rule Shift Cards Test, the Action Program Test, and the Zoo Map Test (Table 2.4). Persons with early manifest HD presented lower scores when compared to controls and premanifest participants in all these subtests. Notably, PreHD and CTRL participants presented similar scores in all the computed BADS measures, which suggests that even with tasks that try to simulate daily-life executive demands, the PreHD group did not differ from CTRL participants.

Table 2.4 BADS (the Behavioural Assessment of Dysexecutive Syndrome battery) results with Kruskal-Wallis and Mann-Whitney comparisons across groups

	CTRL	*PreHD*	*EarlyHD*	*K-W*	*M-W PreHD vs CTRL*	*M-W EarlyHD vs CTRL*	*M-W PreHD vs EarlyHD*
BADS	*Median (IQR; min-max)*	*Median (IQR; min-max)*	*Median (IQR; min-max)*	χ^2 *(p-value)*	*U (p-value)*	*U (p-value)*	*U (p-value)*
Total	17 (3; 13-22)	18 (6; 12-21)	12 (5; 9-18)	16.985 * (‹ 0.001)	130 (0.662)	31 ¥ (‹ 0.001)	36 # (0.001)
Rule Shift Cards Test	4 (1; 1-4)	4 (1; 3-4)	3 (2; 0-4)	9.676 * (0.008)	140 (0.916)	76 ¥ (0.013)	50 # (0.005)
Action Program Test	4 (0; 2-4)	4 (0; 0-4)	3 (2; 1-4)	11.069 * (0.004)	129 (0.447)	69 ¥ (0.002)	66 # (0.029)
Key Search Test	3 (2; 0-4)	2 (2; 0-4)	2 (2; 0-4)	5.110 (0.078)	97.5 (0.106)	82.5 ¥ (0.032)	102.5 (0.669)
Temporal Judgment Test	2 (1; 0-3)	1 (1; 0-3)	1 (1; 0-2)	3.284 (0.194)	101 (0.123)	103.5 (0.137)	105 (0.731)
Zoo Map Test	2 (2; 0-4)	3 (2; 0-4)	1 (2; 0-3)	10.632 * (0.005)	103 (0.159)	74 ¥ (0.014)	44 # (0.004)
Modified 6 Elements Test	4 (1; 1-4)	4 (1; 2-4)	3 (2; 0-4)	4.656 (0.097)	139.5 (0.906)	91.5 (0.056)	72.5 (0.073)

*CTRL – Controls; PreHD – Premanifest HD; EarlyHD – Early Manifest HD; IQR – Interquartile Range; min-max – Minimum and Maximum scores (Range); BADS – The Behavioural Assessment of Dysexecutive Syndrome battery; K-W – Kruskal-Wallis; M-W – Mann-Whitney * Significant group effect (Kruskal-Wallis, p ‹ 0.05) ¥ EarlyHD ≠ Controls (Mann-Whitney, p ‹ 0.05); # PreHD ≠ EarlyHD (Mann-Whitney, p ‹ 0.05)*

Neuropsychological test battery

The results obtained in the conventional neuropsychological tests applied gave us a comprehensive picture about the participants' cognitive status in the different executive sub-domains tapped by this battery. We observed a statistically significant group effect in several of the executive measures applied, namely in the Phonemic Verbal Fluency – PMR total correct, letter P and letter R correct scores; the Stroop Word Reading, Colour Naming and Interference tests; the Semantic Verbal Fluency – total correct; the Symbol Digit Modalities Test – total correct; the Digit Span Test – backward and total scores; the Trail Making Test A and B time measures; and the Wisconsin Card Sorting Test - percentage of errors (Table 2.5). The *post hoc* analyses showed us that the persons with early manifest HD presented deficits in most of the tests applied when compared to control participants, namely in the Phonemic Verbal Fluency – PMR total correct, the Stroop Word Reading, Colour Naming and Interference tests, the Semantic Verbal Fluency – total correct, the Symbol Digit Modalities Test – total correct, the Digit Span Test – backward and total scores, the Trail Making Test A and B time measures, and the Wisconsin Card Sorting Test – percentage of errors and perseverative errors. Statistically significant differences were also found between the EarlyHD and PreHD conventional executive test profiles, namely in the Phonemic Verbal Fluency – PMR total, letter P and letter R; the Stroop Word Reading, Colour Naming and Interference tests; the Semantic Verbal Fluency – total correct; the Symbol Digit Modalities Test – total correct; the Digit Span Test – forward, backward and total scores, and the Trail Making Test A and B time measures.

Interestingly, persons with PreHD presented a similar performance to controls in all the variables extracted from this battery, showing the same executive profile as healthy participants. The results of the early manifest HD group suggest that tests with time constraints and that assess processing/psychomotor speed are more sensitive to HD executive changes. Furthermore, these results, together with BADS results, seem to indicate that the overall executive status of the PreHD and CTRL groups is similar, and that any subtle cognitive changes due to HD might remain undetectable with the use of these type of conventional assessment approaches (e.g., paper and pencil tests).

Table 2.5 Neuropsychological Test Battery results with Kruskal-Wallis and Mann-Whitney comparisons across groups

Neuropsychological Test Battery	*CTRL* *Median (IQR;min-max)*	*PreHD* *Median (IQR;min-max)*	*EarlyHD* *Median (IQR;min-max)*	*K-W* χ^2 *(p-value)*	*M-W PreHD vs CTRL* *U (p-value)*	*M-W EarlyHD vs CTRL* *U (p-value)*	*M-W PreHD vs EarlyHD* *U (p-value)*
Phonemic Verbal Fluency – PMR correct	29 (21; 13-59)	35 (17; 18-59)	23 (20; 11-46)	7.634 * (0.022)	115 (0.340)	84.5 ¥ (0.044)	50 # (0.009)
Phonemic Verbal Fluency – P correct	12 (9; 5-24)	13 (6; 6-23)	8 (7; 1-18)	7.673 * (0.022)	109 (0.243)	92.5 (0.082)	47 # (0.006)
Phonemic Verbal Fluency – M correct	9 (8; 4-19)	12 (4; 5-19)	7 (8; 2-15)	4.383 (0.112)	129 (0.639)	92.5 (0.082)	68 (0.064)
Phonemic Verbal Fluency – R correct	10 (6; 3-20)	10 (5; 6-19)	7 (6; 2-14)	6.274 * (0.043)	127.5 (0.601)	90.5 (0.070)	53 # (0.013)
Stroop Word Reading – correct	88 (23; 53-118)	90 (21; 50-110)	58 (17; 20-88)	20.768 * (‹ 0.001)	128.5 (0.627)	22 ¥ (‹ 0.001)	24 # (‹ 0.001)
Stroop Colour Naming – correct	68 (15; 40-100)	71 (23; 45-90)	45 (10; 26-67)	21.693 * (‹ 0.001)	142 (0.986)	19 ¥ (‹ 0.001)	21.5 # (‹ 0.001)
Stroop Interference – correct	43 (8; 26-62)	48 (7; 25-60)	26 (9; 10-37)	26.001 * (‹ 0.001)	90 (0.068)	19 ¥ (‹ 0.001)	9.5 # (‹ 0.001)
Semantic Verbal Fluency – correct	22 (9; 12-36)	20 (5; 13-39)	15 (5; 8-19)	19.954 * (‹ 0.001)	108.5 (0.237)	23 ¥ (‹ 0.001)	32 # (0.001)
Symbol Digit Modalities Test – correct	52 (12; 35-75)	56 (19; 30-70)	30 (13; 16-42)	27.584 * (‹ 0.001)	122 (0.476)	6.5 ¥ (‹ 0.001)	7.5 # (‹ 0.001)
Symbol Digit Modalities Test – errors	0 (0; 0-5)	0 (1; 0-2)	0 (1; 0-4)	1.540 (0.463)	115 (0.248)	119 (0.310)	112 (0.981)
Digit Span – forward	8 (5; 4-12)	9 (5; 5-14)	7 (2; 4-11)	4.409 (0.110)	109 (0.241)	110 (0.254)	64 # (0.042)
Digit Span – backward	5 (2; 3-10)	6 (3; 3-11)	4 (2; 2-7)	12.176 * (0.002)	138.5 (0.887)	46 ¥ (0.001)	51 # (0.010)
Digit Span – total	13 (8; 7-21)	15 (7; 8-22)	11 (3; 7-17)	8.329 * (0.016)	121.5 (0.464)	76 ¥ (0.020)	50 # (0.009)
Trail Making Test – part A time	26 (7; 14-41)	24 (15; 15-63)	42 (31; 27-74)	19.098 * (‹ 0.001)	129.5 (0.651)	22 ¥ (‹ 0.001)	32 # (0.001)
Trail Making Test – part A errors	0 (0; 0-1)	0 (0; 0-1)	0 (1; 0-2)	1.875 (0.392)	138.5 (0.804)	118.5 (0.209)	96.5 (0.340)
Trail Making Test – part B time	62 (33; 36-120)	58 (31; 36-222)	156 (97; 64-366)	21.389 * (‹ 0.001)	129.5 (0.652)	18 ¥ (‹ 0.001)	24 # (‹ 0.001)
Trail Making Test – part B errors	0 (1; 0-3)	1 (1; 0-3)	1 (2; 0-3)	3.498 (0.174)	111.5 (0.223)	96 (0.074)	96 (0.469)
WCST – trials administered	87 (24; 70-128)	86 (55; 70-128)	94 (37; 73-128)	3.785 (0.151)	134.5 (0.780)	87.5 (0.056)	79.5 (0.169)
WCST – percentage of errors	17.24 (10.16; 8.57-41.41)	16.85 (24.64; 10-52.34)	26.61 (14.78; 10.96-41-41)	6.037 * (0.049)	121.5 (0.466)	69.5 ¥ (0.011)	79 (0.164)
WCST – perseverative errors	9 (10; 5-29)	11 (21; 5-51)	19 (21; 5-42)	5.592 (0.061)	112 (0.288)	74 ¥ (0.017)	84.5 (0.244)

*CTRL – Controls; PreHD – Premanifest HD; EarlyHD – Early Manifest HD; IQR – Interquartile Range; min-max – Minimum and Maximum scores (Range); K-W – Kruskal-Wallis; M-W – Mann-Whitney; WCST – Wisconsin Card Sorting Test * Significant group effect (Kruskal-Wallis, p ‹ 0.05) ¥ EarlyHD ≠ Controls (Mann-Whitney, p ‹ 0.05); # EarlyHD ≠ PreHD (Mann-Whitney, p ‹ 0.05)*

Correlational analyses

We have found that the time parameters of the *EcoKitchen* were significantly correlated with the different measures included in the study protocol. Specifically, the time the clinical groups took to prepare the cup of coffee with milk (Performance Time Task A) and to prepare the toasts with butter (Performance Time Task B) and the time they took to react to the different *EcoKitchen* cues, particularly the boiling kettle (Reaction Time *per* Block and Reaction Time Kettle), were significantly correlated with their self-reported functional difficulties as measured by IAFAI, except for the Functional Incapacity due to Emotional Factors (all significant correlations $r_s \geq 0.46$, $p < 0.05$). Thus, the subjective perception of the clinical groups about their ability to perform basic and complex activities of daily living is associated with the time features of their objective performance in a simulated kitchen task. The *EcoKitchen* performance and reaction time parameters were also significantly correlated with several conventional neuropsychological tests, particularly those that had time constraints, such as the Phonemic and Semantic Verbal Fluency Tests, the Stroop Word Reading, Colour Naming and Interference Tests, the Symbol Digit Modalities Test – total correct and the Trail Making Test A and B Time measures (all significant correlations $|r_s| \geq 0.51$, $p < 0.05$). The significant correlations found between the *EcoKitchen* time measures and the classical neuropsychological tests shed further light on the different cognitive sub-domains involved in *EcoKitchen* task completion, namely cognitive flexibility, divided attention, sequencing, psychomotor/processing speed, inhibition, and working memory. Finally, the performance time and reaction time of the PreHD and EarlyHD groups in the *EcoKitchen* were significantly correlated with the Motor and Functional Capacity scores obtained in the UHDRS – Unified Huntington's Disease Rating Scale (all significant correlations $|r_s| \geq 0.52$, $p < 0.05$), which suggests that the *EcoKitchen* time measures capture some of the main HD clinical features, namely the motor symptoms severity, and the subjective functional status ascribed by an experienced neurologist. In contrast, no statistically significant correlations were found between the *EcoKitchen* accuracy parameters and the other executive and functional measures included in the study protocol, nor HD clinical features. Furthermore, no statistically significant correlations were found between any of the *EcoKitchen* variables and the different BADS sub-scores.

The significant associations found between the *EcoKitchen* and the different well-

established assessment methods indicate which functional areas and which executive sub-domains are captured by the time variables computed from this novel virtual tool, adding further validation and clarification about what is being measured during the performance of simulated household tasks. Moreover, the significant correlations found between the *EcoKitchen* and HD symptom severity give important indications about the functional implications of HD clinical phenotype to daily-life like tasks.

Discussion

The *EcoKitchen*, a novel virtual reality task that evaluates executive skills and their functional outcome using a performance-based setup, was able to distinguish between EarlyHD, PreHD and control participants. Notably, this novel task showed that persons with PreHD present diminished accuracy during the performance of daily life- like routines. This study also confirmed that persons with early manifest HD already present cognitive and functional alterations, revealed by all the assessment tools used – *EcoKitchen*, IAFAI, BADS and conventional neuropsychological tests.

The difference found between the PreHD and CTRL participants enrolled in this study is notable because these were high functioning (TFC median=13) and far from estimated disease onset (Years to Onset median=16) individuals, and measures that detect functional changes in premanifest HD populations with this clinical profile have been challenging to find (Downing et al., 2014). Nevertheless, these measures are critical to use if relevant lessons are to be drawn from research studies and clinical trials. The identification and quantification of subtle disease-related alterations in individuals that carry the abnormal gene but who do not yet meet the criteria for an HD clinical diagnosis (premanifest HD) provides a window of opportunity for interventions aimed at preventing or delaying symptom onset (Weir et al., 2011). Furthermore, reliable and accurate assessment methods that can discriminate between disease stages and record changes in the persons' performance are extremely important to clinical, research and rehabilitation settings (Baum & Edwards, 1993).

As noted by Stout et al. (2016), researchers still know very little about how people with HD perform in everyday life, as there have been no studies that examined cognitive performance in the natural setting. While relatively common in other clinical models,

like Traumatic Brain Injury or Alzheimer's Disease (Allain et al., 2014; Baum & Edwards, 1993; Giovannetti et al., 2008; Tanguay et al., 2014; Zhang et al., 2003), few studies have used performance-based tasks to assess function in HD. *EcoKitchen* was designed to assess the executive skills (like planning, sequencing, scanning, dividing attention, set shifting or multi-tasking) involved in a routine action such as meal preparation in a controlled performance-based format. Virtual reality technology is considered pivotal to improve the knowledge about the cognitive features underlying functional disability in HD, given the constraints of conventional methods to detect subtle alterations in premanifest HD populations.

In fact, there is an ongoing debate about the low sensitivity and diminished ecological validity of the more traditional neuropsychological tests (Allain et al., 2014; Chaytor et al., 2006; Parsons et al., 2015). Measures of executive function aim to assess a number of constructs: selective attention, inhibitory control, planning, impulsivity, problem solving, and some aspects of short-term memory (Parsons et al., 2015). However, these hypothetical constructs may have little relevance to real-world behaviours (Burgess et al., 2006; Parsons et al., 2015), which can lead to inconsistencies as low scores on classical measures of executive function do not necessarily imply poor executive behaviour in everyday life and, conversely, a good performance on classical executive measures can be accompanied by severely dysexecutive behaviour in everyday life (Tanguay et al., 2014). While the persons with early manifest HD were impaired in all the conventional executive measures used, the persons with PreHD enrolled in our study presented a similar performance to controls, showing the same executive profile as healthy participants. These results are in line with other studies that did not find significant cognitive differences between far from estimated onset persons with premanifest HD and controls (Baake et al., 2017; Dumas et al., 2013; Tabrizi et al., 2013; van Asselen et al., 2012). Moreover, no differences were found between the PreHD and CTRL groups in any of the BADS measures, which supports the claim that, although having higher ecological validity than classic executive tests and mimicking real-world situations (Burgess et al., 2006), BADS may not be sensitive to executive impairments in relatively high functioning individuals (Sohlberg & Mateer, 2001). The PreHD and CTRL groups gave similar self-reports of functional status, as assessed by the IAFAI. This is in line with the description of Reilmann et al. (2014) of a HD phase where signs and symptoms have only minor impact on function and where, although some intra-individual decline may occur from the premorbid level of functioning, this is not usually detectable on

subjective measures like TFC (or IAFAI, we add). In our study, IAFAI was unable to differentiate a group of premanifest HD participants that already display performance deficits in the *EcoKitchen* from healthy individuals. Furthermore, the impairments revealed by the IAFAI results of the early manifest HD group suggest that despite lack of insight being often reported in Huntington's disease (Ho et al., 2006; Sitek et al., 2014), the patients enrolled in our study appeared to be at least self-aware of their functional deficits. This observation is in line with previous findings that showed that in HD, and particularly in earlier stages of HD, self-awareness of functional dysfunction (impairments in the performance of activities of daily living) is better preserved than the self-awareness of the motor, cognitive or psychiatric changes associated with this clinical condition (McCusker et al., 2014; Sitek et al., 2011; Snowden et al., 1998).

Robust differences were found between the persons with premanifest HD and controls in our study in the number of errors in the more cognitively demanding block of the *EcoKitchen*, where multi-tasking, divided attention and set shifting were required. Also, the fact that the PreHD group exhibited mainly sequencing errors, reveals the existence of early impairments in planning, behaviour monitoring and/or working memory prior to HD clinical diagnosis. The PreHD participants presented a performance time similar to healthy controls, but this was done at a cost of having an increased number of errors and a trend to show slower reaction times – which might be a reflection of the speed-accuracy trade-off that often occurs in clinical populations (Heitz, 2014). Furthermore, the *EcoKitchen* performance of PreHD participants consubstantiates the claim of Williams et al. (2015) that functional changes during the prodromal HD period may well reflect subtle changes in everyday cognitive functioning that predate a motor diagnosis of HD – deficits were observed not in the performance time by itself (which could be linked to early changes in motor speed, for example) rather in the time to react to parallel cues, in the number of errors, and in the number of errors per minute committed, particularly in the *EcoKitchen* blocks with higher executive load. Thus, the cognitive and functional profile shown by the persons with PreHD in our study corroborates the allegation of Stout et al. (2016) that the study of functional cognition (how well an individual operates cognitively in everyday life) may allow to observe the effects of HD with greater sensitivity and ecological validity than conventional cognitive and/or functional assessment methods, and that computerized assessments open new horizons for investigating that topic. Similarly to what Allain et al. (2014) suggested for Alzheimer's disease patients, the *EcoKitchen* demonstrated that virtual reality environments

(ecologically valid, controlled and safe scenarios) are a promising alternative that can be used for the detection of everyday action impairments in premanifest and early manifest Huntington's disease stages. Also, as Keefe et al. (2016) indicate, performance-based functional capacity measures do not involve subjective judgments about one's own abilities nor require informants, so they might help to reduce the burden on investigators and participants in future clinical studies. Moreover, the IAFAI and the *EcoKitchen* results of the PreHD group seem to be in line with the findings of Nicoll et al. (2014) in a study about prospective memory in HD, where a discrepancy between the participants' performance-based and self-reported function was identified. This further highlights the importance of using objective measures to assess the functional and cognitive status of persons with premanifest HD, as the self-report methods to assess function are susceptible to bias and the classic cognitive tests often lack the sensitivity to subtle executive impairments and do not inform about their relevance to everyday performance.

Importantly, the several statistically significant correlations found between the *EcoKitchen* and the other cognitive and functional assessment measures used, as well as HD clinical features, further validate the scope and aim of this novel virtual reality task that we have created for persons with HD. Namely, the time variables extracted from the *EcoKitchen* (performance time and reaction time) were significantly correlated with the other protocol components used, except for the BADS, as well as with HD clinical features. These statistically significant associations showed us which of the cognitive sub-domains assessed by conventional neuropsychological tests were related to the variables computed from the *EcoKitchen* and, thus, underlie the performance of daily life-like tasks. Our correlational analysis suggests that cognitive flexibility, speed of thinking and acting, divided and sustained attention, scanning, sequencing, and integration skills, inhibitory control and working memory are closely associated with the timely performance of household chores, specifically kitchen tasks. In our view, unravelling the cognitive architecture that frames the performance of routine tasks is extremely relevant for the planning of tailored interventions that aim to prevent, delay or rehabilitate specific functional deficits, as it allows to identify and stimulate the different cognitive sub-domains underlying the function loss. This is in line with the claim of Parsons et al. (2015) that virtual environments may add to an existing neuropsychological battery when attempting to make accurate predictions about a person's behaviour in the real world, as they allow to measure the functional output of constructs within the

complexity of a real-world environment. Furthermore, the robust correlations found between the IAFAI and the *EcoKitchen* variables signalled the existence of a high convergent validity between the two measures (both seem to assess the same construct - function) and indicate which self-reported daily-life functional incapacities assessed by the IAFAI were related to the *EcoKitchen*'s performance (both BADL and IADL were associated with the virtual performance of kitchen chores). As Moore et al. (2007) state, performance-based instruments may be improved by being co-normed with subjective reports of functioning, and this study seems to support this view, as it combines subjective and objective information about the functional skills of study participants. The correlations found between the *EcoKitchen* parameters and HD clinical variables, such as the severity of motor symptoms and the patients' functional capacity rated by the neurologist (UHDRS – Motor and TFC scores) gave us indications about which disease features were most strongly associated with the behaviour of the EarlyHD and PreHD groups on this novel functional task, and corroborate the thoroughly reported increasing functional incapacity due to motor impairments associated with this condition (Ross, Pantelyat, et al., 2014; Rothlind et al., 1993). Finally, the lack of correlation between the error variables computed from the *EcoKitchen* and the other assessment methods that integrated the study protocol suggests that the *EcoKitchen* provides additional information regarding the cognitive and functional status of persons with HD that is not conveyed by the other methods.

In sum, the *EcoKitchen* has proven capable of adding a significant contribution to the detection of the earliest impairments in Huntington's disease, which in turn may facilitate an improvement in the management of these deficits - prolonging functioning at work, increasing social integration, and fostering independence in persons with premanifest HD (Reilmann et al., 2014). In our view, the several parameters computed from the *EcoKitchen* and the way they relate to the different executive skills, to the self-reported functional incapacities and to the HD clinical symptomatology, can work as a proxy of the patients' global cognitive and functional status and be extremely relevant to the design and implementation of pharmacological and non-pharmacological approaches to tackle specific domains. Improving the quality of life of persons with HD and settling a solid ground for effective interventions with disease-modifying goals is one of the main aims in the HD research field. The *EcoKitchen* task has the potential to be included in that effort. As some authors suggest (Eddy & Rickards, 2015; Nehl et al. 2004), acknowledging that the cognitive component of HD has an additional negative

impact on functional capacity makes way for compensatory strategies to be implemented to offset some of the effects of cognitive decline on functional abilities. The *EcoKitchen* seems to be prone to be used as a rehabilitation tool or cognitive stimulation method, as it provides quantitative data that can track any subtle individual changes in the performance of simple and complex executive demanding tasks that simulate everyday-life routines. Finally, a better understanding of the dynamics between cognition and function in HD will improve the standards of care of persons with HD and guide the choice of outcome measures for future studies.

Limitations

Functional capacity as tackled by performance-based measures is not fully synonymous of everyday functioning (Moore et al., 2007), as observed behaviour during simulated tasks may differ greatly from what the individual does spontaneously in the environment (Williams et al., 2015). Virtual reality tools often cannot fully replicate the uncertainties of everyday life nor the compensatory aids/strategies that the individual uses to obtain a successful performance (McGuire, 2014). However, the use of virtual reality tasks in clinical research has several gains compared to real world settings, namely in terms of affordability, safety, efficiency, applicability to a wide range of conditions, and facility of data capturing and scoring, among others (Allain et al., 2014; Parsons et al., 2015; Ruse et al., 2014). Another possible limitation of the *EcoKitchen* is that it might be somewhat difficult to isolate which specific executive functions are impaired and contribute to the performance deficits observed, as the three blocks involve complex tasks that rely on multiple cognitive skills. Yet, the several correlations computed between the *EcoKitchen* and the other cognitive and functional measures, namely the conventional executive test battery, may help to clarify what is in fact being measured – the *EcoKitchen* was proved to be mostly related to psychomotor/processing speed, planning, attention, set shifting and cognitive flexibility tests.

On the other hand, IAFAI was only used as a self-report functional measure due to logistic constraints. Consequently, IAFAI results might not have fully captured the participants' functional status, as lack of insight/awareness or anosognosia have been often described in HD and represent a challenge for the use of self-report assessment methods (Ho et al., 2006; Sitek et al., 2014). As Hoth et al. (2007) claim, family member/friend/caregiver ratings can potentially provide more reliable information

about patients' deficits than do patients' reports. However, other authors like Giovannetti et al. (2008), state that reliance on caregiver questionnaires to assess everyday action is also prone to bias and offers only a very gross assessment of performance. We tried to provide some additional information about the subjects' functional status using the UHDRS-TFC scores (which is a rating done by a neurologist). Furthermore, we were interested to see if there were disparities between the patients' perception about their functional status and their objective performance in the *EcoKitchen* – as it was the case for the PreHD group.

Finally, studies with larger sample sizes are needed to confirm the functionally significant executive deficits observed in persons with PreHD. Also, caution must be taken regarding the conclusions withdrawn from the comparisons of the two clinical groups, as differences in age and education level were detected between the EarlyHD and PreHD participants enrolled in our study and these variables might explain at least in part the differences observed in their performance. Moreover, future studies with other clinical conditions will further validate the *EcoKitchen* as a sensitive assessment tool for patients with functional impairment due to executive deficits.

Conclusion

We offer evidence that the *EcoKitchen* task can detect functionally significant deficits in early manifest non-demented persons with HD and persons with premanifest HD. Given that this is an exploratory feasibility study, we would like to highlight several points that need to be addressed in future work to consubstantiate and expand the current findings. This new assessment tool must be validated in larger sample sizes, preferably including patients at different stages of HD severity, subdividing persons with premanifest HD into those far and close from estimated disease onset, and including other neurological conditions with similar brain driven cognitive impairments (e.g., Parkinson's disease). Longitudinal studies would be beneficial to track individual and group changes along a timeline and to see whether targeting specific executive sub-domains with cognitive rehabilitation/enhancement strategies would have a positive impact in the *EcoKitchen* performance. Moreover, as previously mentioned, performance-based measures are not fully synonymous of everyday functioning. Thus, a study exploring the relations between the *EcoKitchen* performance and a real-life kitchen performance (preferably at home and not in a Lab setting) would help to corroborate its

ecological validity.

From a clinical perspective, given the high variability demonstrated by the EarlyHD participants in the *EcoKitchen* task, individual assessments are considered necessary to have a nuanced characterization of each patient and accurately predict the person's actual functional and executive status. This personalized and targeted approach is important to improve the efficacy of intervention and rehabilitation programs. In our view, the *EcoKitchen* can be an important asset contributing to a better understanding of the HD phenotype, clarifying the relation between cognition and daily living activities, facilitating the planning of tailored interventions, and, thus, improving the quality of life of those affected by HD.

References

Albani, G., Raspelli, S., Carelli, L., Morganti, F., Weiss, P. L., Kizony, R., Katz, N., Mauro, A., & Riva, G. (2010). Executive functions in a virtual world: A study in Parkinson's disease. *Studies in Health Technology and Informatics*, *154*, 92–96. https://doi.org/10.3233/978-1-60750-561-7-92

Allain, P., Foloppe, D. A., Besnard, J., Yamaguchi, T., Etcharry-Bouyx, F., Le Gall, D., Nolin, P., & Richard, P. (2014). Detecting Everyday Action Deficits in Alzheimer's Disease using a Nonimmersive Virtual Reality Kitchen. *Journal of the International Neuropsychological Society, 20*(5), 468–477. https://doi.org/10.1017/S1355617714000344

Alves, L., Simões, M. R., & Martins, C. (2012). The Estimation of Premorbid Intelligence Levels among Portuguese Speakers: The Irregular Word Reading Test (TeLPI). *Archives of Clinical Neuropsychology, 27*(1), 58–68. https://doi.org/10.1093/arclin/acr103

Attree, E. A, Brooks, B. M., Rose, F. D., Andrews, T. K., Leadbetter, A. G., & Clifford, B. R. (1996). Memory Processes and Virtual Environments: I Can't Remember What Was There, but I Can Remember How I Got There. Implications for People with Disabilities. In Paul M. Sharkey (Ed.), *Proceedings of the First European Conference on Disability, Virtual Reality, and Associated Technology*. Reading, UK: ECDVRAT & University of Reading, 117–123.

Aylward, E.H., Sparks, B. F., Field, K. M., Yallapragada, V., Shpritz, B. D., Rosenblatt, A., Brandt, J., Gourley, L. M., Liang, K., Zhou, H., Margolis, R.L., & Ross, C. A. (2004). Onset and Rate of Striatal Atrophy in Preclinical Huntington Disease. *Neurology, 63*(1), 66-72. https://doi.org/10.1212/01.WNL.0000132965.14653.D1

Baake, V., Reijntjes, R. H. A. M., Dumas, E. M., Thompson, J. C., REGISTRY Investigators of the European Huntington's Disease Network, & Roos, R. A. C. (2017). Cognitive Decline in Huntington's Disease Expansion Gene Carriers. *Cortex, 95*, 51–62. https://doi.org/10.1016/j.cortex.2017.07.017

Balci, F., Day, M., Rooney, A., & Brunner, D. (2009). Disrupted Temporal Control in the R6/2 Mouse Model of Huntington's Disease. *Behavioral Neuroscience, 123*(6), 1353-1358. https://doi.org/10.1037/a0017650

Baum, C., & Edwards, D. F. (1993). Cognitive Performance in Senile Dementia of the Alzheimer's Type: The Kitchen Task Assessment. *The American Journal of Occupational Therapy, 47*(5), 431–436. https://doi.org/10.5014/ajot.47.5.431

Beck, A. T., Steer, R. A., & Brown, G. K. (1996). Manual for the Beck Depression Inventory-II. Psychological Corporation.

Beglinger, L. J., O'Rourke, J. J. F., Wang, C., Langbehn, D. R., Duff, K., Paulsen, J. S., & Huntington Study Group Investigators (2010). Earliest Functional Declines in Huntington Disease. *Psychiatry Research, 178*(2), 414–418. https://doi.org/10.1016/j.psychres.2010.04.030

Bialystok, E., Craik, F. I. M., & Stefurak, T. (2008). Planning and Task Management in Parkinson's Disease: Differential Emphasis in Dual-Task Performance. *Journal of the International Neuropsychological Society, 14*, 257–265. https://doi.org/10.1017/S1355617708080296

Burgess, P. W., Alderman, N., Evans, J., Emslie, H., & Wilson, B. A. (1998). The Ecological Validity of Tests of Executive Function. *Journal of the International Neuropsychological Society, 4*(6), 547–558. https://doi.org/10.1017/S1355617798466037

Burgess, P. W., Alderman, N., Forbes, C., Costello, A., Coates, L. M.-A., Dawson, D. R., Anderson, N. D., Gilbert, S. J., Dumontheil, I., & Channon, S. (2006). The Case for the Development and Use of "Ecologically Valid" Measures of Executive Function in Experimental and Clinical Neuropsychology. *Journal of the International Neuropsychological Society, 12*(2), 194–209. https://doi.org/10.1017/S1355617706060310

Campos, R. C., & Gonçalves, B. (2011). The Portuguese Version of Beck Depression Inventory-II (BDI-II): Preliminary Psychometric Data with Two Non-Clinical Samples. *European Journal of Psychological Assessment, 27*(4), 258–264. http://hdl.handle.net/10174/3952

Cavaco, S., Gonçalves, A., Pinto, C., Almeida, E., Gomes, F., Moreira, I., Fernandes, J., Teixeira-Pinto, A. (2013a). Semantic Fluency and Phonemic Fluency: Regression-based Norms for the Portuguese Population. *Archives of Clinical Neuropsychology, 28*(3), 262–271. https://doi.org/10.1093/arclin/act001

Cavaco, S., Gonçalves, A., Pinto, C., Almeida, E., Gomes, F., Moreira, I., Fernandes, J., & Teixeira-

Pinto, A. (2013b). Trail Making Test: Regression-Based Norms for the Portuguese Population. *Archives of Clinical Neuropsychology, 28*(2), 189–198. https://doi.org/10.1093/arclin/acs115

Chaytor, N., Schmitter-Edgecombe, M., & Burr, R. (2006). Improving the Ecological Validity of Executive Functioning Assessment. *Archives of Clinical Neuropsychology, 21*, 217–227. https://doi.org/10.1016/j.acn.2005.12.002

Craik, F. I. M., & Bialystok, E. (2006). Planning and Task management in Older Adults: Cooking Breakfast. *Memory & Cognition, 34*(6), 1236–1249. https://doi.org/10.3758/BF03193268

Downing, N. R., Kim, J.-I., Williams, J. K., Long, J. D., Mills, J. A., Paulsen, J. S., & The PREDICT-HD Investigators and Coordinators of the Huntington Study Group (2014). WHODAS 2.0 in Prodromal Huntington Disease: Measures of Functioning in Neuropsychiatric Disease. *European Journal of Human Genetics, 22*(8), 958–963. https://doi.org/10.1038/ejhg.2013.275

Dumas, E. M., van den Bogaard, S. J., Middelkoop, H. A., & Roos, R. A. (2013). A Review of Cognition in Huntington's Disease. *Frontiers in Bioscience, 5*(2), 1–18. http://dx.doi.org/10.2741/S355

Eddy, C. M., & Rickards, H. E. (2015). Cognitive Deficits Predict Poorer Functional Capacity in Huntington's disease: But What is Being Measured? *Neuropsychology, 29*(2), 268–273. https://doi.org/10.1037/neu0000134

Folstein, S.E., Abbott, M.H., Franz, M.L., Huang, S., Chase, G.A., & Folstein, M.F. (1984). Phenotypic Heterogeneity in Huntington Disease. *Journal of Neurogenetics, 1*(2), 175-184. https://doi.org/10.3109/01677068409107083

Freitas, S., Simões, M. R., Alves, L., & Santana, I. (2011). Montreal Cognitive Assessment (MoCA): Normative Study for the Portuguese Population. *Journal of Clinical and Experimental Neuropsychology, 33*(9), 989–996. https://doi.org/10.1080/13803395.2011.589374

Frisch, S., Förstl, S., Legler, A., Schöpe, S., & Goebel, H. (2012). The Interleaving of Actions in Everyday Life Multitasking Demands. *Journal of Neuropsychology, 6*(2), 257–269. https://doi.org/10.1111/j.1748-6653.2012.02026.x

Giovannetti, T., Bettcher, B. M., Brennan, L., Libon, D. J., Kessler, R. K., & Duey, K. (2008). Coffee With Jelly or Unbuttered Toast: Commissions and Omissions Are Dissociable Aspects of Everyday Action Impairment in Alzheimer's Disease. *Neuropsychology, 22*(2), 235–245. https://doi.org/10.1037/0894-4105.22.2.235

Godefroy, O., Azouvi, P., Robert, P., Roussel, M., LeGall, D., & Meulemans, T. on Behalf of the Groupe de Réflexion sur l'Evaluation des Fonctions Exécutives Study Group (2010). Dysexecutive Syndrome: Diagnostic Criteria and Validation Study. *Annals of Neurology, 68*(6), 855–864. https://doi.org/10.1002/ana.22117

Hamilton, J. M., Salmon, D. P., Corey-Bloom, J., Gamst, A., Paulsen, J. S., Jerkins, S., Jacobson, M.

W., & Peavy, G. (2003). Behavioural Abnormalities Contribute to Functional Decline in Huntington's Disease. *Journal of Neurology, Neurosurgery and Psychiatry, 74*(1), 120–122. https://doi.org/10.1136/jnnp.74.1.120

Heaton, R. K. (1981). *A Manual for the Wisconsin Card Sorting Test.* Psychological Assessment Resources.

Heitz, R. P. (2014). The Speed-Accuracy Tradeoff: History, Physiology, Methodology, and Behavior. *Frontiers in Neuroscience, 8*(150). https://doi.org/10.3389/fnins.2014.00150

Ho, A., Robbins, A.O.G., & Barker, R. A. (2016). Huntington's Disease Patients Have Selective Problems with Insight. *Movement Disorders, 21*(3), 385-389 https://doi.org/10.1002/mds.20739

Hoth, K. F., Paulsen, J. S., Moser, D. J., Tranel, D., Clark, L. A., & Bechara, A. (2007). Patients with Huntington's Disease have Impaired Awareness of Cognitive, Emotional, and Functional Abilities. *Journal of Clinical and Experimental Neuropsychology, 29*(4), 365–376. https://doi.org/10.1080/13803390600718958

Huntington Study Group. (1996). Unified Huntington's Disease Rating Scale: Reliability and Consistency. *Movement Disorders, 11*(2), 136–142. https://doi.org/10.1002/mds.870110204

Kawano, N., Iwamoto, K., Ebe, K., Aleksic, B., Noda, A., Umegaki, H., Kuzuya, M., Iidaka, T., & Ozaki, N. (2012). Slower adaptation to driving simulator and simulator sickness in older adults. *Aging Clinical and Experimental Research, 24*(3), 285–289. https://doi.org/10.1007/BF03325260

Keefe, R. S. E., Davis, V. G., Atkins, A. S., Vaughan, A., Patterson, T., Narasimhan, M., & Harvey, P. D. (2016). Validation of a Computerized Test of Functional Capacity. *Schizophrenia Research, 175*(1–3), 90–96. https://doi.org/10.1016/j.schres.2016.03.038

Langbehn, D. R., Brinkman, R. R., Falush, D., Paulsen, J. S., & Hayden, M. R. on behalf of an International Huntington's Disease Collaborative Group (2004). A New Model for Prediction of the Age of Onset and Penetrance for Huntington's Disease Based on CAG Length. *Clinical Genetics, 65*(4), 267–277. https://doi.org/10.1111/j.1399-0004.2004.00241.x

Lemiere, J., Decruyenaere, M., Evers-Kiebooms, G., Vandenbussche, E., & Dom, R. (2002). Longitudinal study evaluating neuropsychological changes in so-called asymptomatic carriers of the Huntington's disease mutation after 1 year. *Acta Neurologica Scandinavica*, *106*(3), 131–141. https://doi.org/10.1034/j.1600-0404.2002.01192.x

Lezak, M.D. (1982). The Problem of Assessing Executive Functions. *International Journal of Psychology, 17,* 281–297. https://doi.org/10.1080/00207598208247445

Lezak, M. D., Howieson, D. B., Bigler, E. D., & Tranel, D. (2012). *Neuropsychological Assessment* (5th

ed.). Oxford University Press.

McCusker, E., & Loy, C. T. (2014). The Many Facets of Unawareness in Huntington Disease. *Tremor and other Hyperkinetic Movements, 4,* 257 https://doi.org/10.7916/D8FJ2FD3

McGuire, B. E. (2014). Assessing Complex Executive Functions with Computerized Tests: Is That Toast Burning? *Frontiers in Behavioral Neuroscience, 8*(362), https://doi.org/10.3389/fnbeh.2014.00362

Mehrabi, N.F., Waldvogel, H.J., Tippett, L.J., Hogg, V.M., Synek, B.J., & Faull, R.L.M. (2016). Symptom Heterogeneity in Huntington's Disease Correlates with Neuronal Degeneration in the Cerebral Cortex. *Neurobiology of Disease, 96,* 67-74 https://doi.org/10.1016/j.nbd.2016.08.015

Moore, D. J., Palmer, B. W., Patterson, T. L., & Jeste, D. V. (2007). A Review of Performance-Based Measures of Functional Living Skills. *Journal of Psychiatric Research, 41,* 97-118 https://doi.org/10.1016/j.jpsychires.2005.10.008

Mörkl, S., Müller, N. J., Blesl, C., Wilkinson, L., Tmava, A., Wurm, W., Holl, A. K., & Painold, A. (2016). Problem Solving, Impulse Control and Planning in Patients with Early- and Late-Stage Huntington's Disease. *European Archives of Psychiatry and Clinical Neuroscience, 266*(7), 663–671. https://doi.org/https://dx.doi.org/10.1007/s00406-016-0707-4

Nasreddine, Z. S., Phillips, N. A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., Cummings, J. L., & Chertkow, H. (2005). The Montreal Cognitive Assessment, MoCA: A Brief Screening Tool for Mild Cognitive Impairment. *Journal of the American Geriatrics Society, 53*(4), 695–699. https://doi.org/10.1111/j.1532-5415.2005.53221.x

Nehl, C., Paulsen, J. S., & The Huntington Study Group. (2004). Cognitive and Psychiatric Aspects of Huntington Disease Contribute to Functional Capacity. *The Journal of Nervous and Mental Disease, 192*(1), 72–74. https://doi.org/10.1097/01.nmd.0000106004.67587.57

Nicoll, D. R., Pirogovsky, E., Woods, S. P., Holden, H. M., Filoteo, J. V., Gluhm, S., Corey-Bloom, J., & Gilbert, P. E. (2014). "Forgetting to Remember" in Huntington's Disease: A Study of Laboratory, Semi-Naturalistic, and Self-Perceptions of Prospective Memory. *Journal of the International Neuropsychological Society, 20*(2), 192–199. https://doi.org/10.1017/S1355617713001355

Nimmagadda, S. R., Agrawal, N., Worrall-Davies, A., Markova, I., & Rickards, H. (2011). Determinants of Irritability in Huntington's Disease. *Acta Neuropsychiatrica, 23*(6), 309–314. https://doi.org/10.1111/j.1601-5215.2011.00563.x

Norris, G., & Tate, R. L. (2000). The Behavioural Assessment of the Dysexecutive Syndrome (BADS): Ecological, Concurrent and Construct Validity. *Neuropsychological Rehabilitation, 10*(1), 33–45. https://doi.org/10.1080/096020100389282

Novak, M. J. U., & Tabrizi, S. J. (2010). Huntington's disease. *British Medical Journal, 340*(3), c3109. https://doi.org/10.1136/bmj.c3109

Novak, M. J., & Tabrizi, S. J. (2011). Huntington's disease: Clinical Presentation and Treatment. *International Review of Neurobiology, 98,* 297–323. https://doi.org/10.1016/B978-0-12-381328-2.00013-4

O'Keeffe, G. C., Michell, A. W., & Barker, R. A. (2009). Biomarkers in Huntington's and Parkinson's Disease. *Annals of the New York Academy of Science, 1180,* 97-110. http://doi.org/10.1111/j.1749-6632.2009.04943.x

Oldfield, R. C. (1971). The Assessment and Analysis of Handedness: The Edinburgh Inventory. *Neuropsychologia, 9*(1), 97–113. https://doi.org/10.1016/0028-3932(71)90067-4

Parsons, T. D., Carlew, A. R., Magtoto, J., & Stonecipher, K. (2015). The Potential of Function-Led Virtual Environments for Ecologically Valid Measures of Executive Function in Experimental and Clinical Neuropsychology. *Neuropsychological Rehabilitation, 27*(5), 777–807. https://doi.org/10.1080/09602011.2015.1109524

Paulsen, J. S. (2010). Early Detection of Huntington Disease. *Future Neurology, 5*(1), 85-104. https://doi.org/10.2217/fnl.09.78

Paulsen, J. S. (2011). Cognitive Impairment in Huntington Disease: Diagnosis and Treatment. *Current Neurology and Neuroscience Reports, 11*(5), 474–483. https://doi.org/10.1007/s11910-011-0215-x

Paulsen, J.S., Hayden, M., Stout, J.C., Langbehn, D.R., Aylward, E., Ross, C.A., Guttman, M., Nance, M., Kieburtz, K., Oakes, D., Shoulson, I., Kayson, E., Johnson, S., Penziner, E. & Predict HD investigators. (2006). Preparing for Preventive Clinical Trials: The Predict-HD study. *Archives of Neurology, 63*(6):883–90. https://doi.org/10.1001/archneur.63.6.883

Poliakoff, E., & Smith-Spark, J. H. (2008). Everyday Cognitive Failures and Memory Problems in Parkinson's Patients Without Dementia. *Brain and Cognition, 67*(3), 340–350. https://doi.org/10.1016/j.bandc.2008.02.004

Rao, J. A., Harrington, D. L., Durgerian, S., Reece, C., Mourany, L., Koenig, K., & Rao, S. M. (2014). Disruption of Response Inhibition Circuits in Prodromal Huntington Disease. *Cortex, 58,* 72-85. https://doi.org/10.1016/j.cortex.2014.04.018

Reilmann, R., Leavitt, B. R., & Ross, C. A. (2014). Diagnostic Criteria for Huntington's Disease Based on Natural History. *Movement Disorders, 29*(11), 1335–1341. https://doi.org/10.1002/mds.26011

Reitan, R. M. (1958). Validity of the Trail Making Test as an Indicator of Organic Brain Damage. *Perceptual and Motor* Skills, *8*(3), 271–276. https://doi.org/10.2466/pms.1958.8.3.271

Roos, R. A. (2010). Huntington's disease: A Clinical Review. *Orphanet Journal of Rare Diseases, 5,* 40.

http://doi.org/10.1186/1750-1172-5-40

Rosas, H. D., Hevelone, N. D., Zaleta, A. K., Greve, D. N., Salat, D. H., & Fischl, B. (2005). Regional Cortical Thinning in Preclinical Huntington Disease and its Relationship to Cognition. *Neurology, 65*(5), 745-747.
https://doi.org/10.1212/01.wnl.0000174432.87383.87

Rosenblatt, A. (2007). Neuropsychiatry of Huntington's disease. *Dialogues in Clinical Neuroscience, 9*(2), 191-197.
https://doi.org/10.31887/DCNS.2007.9.2/arosenblatt

Ross, C. A., Aylward, E. H., Wild, E. J., Langbehn, D. R., Long, J. D., Warner, J. H., Scahill, R. I., Leavitt, B. R., Stout, J. C., Paulsen, J. S., Reilmann, R., Unschuld, P. G., Wexler, A., Margolis, R. L., & Tabrizi, S. J. (2014). Huntington Disease: Natural History, Biomarkers and Prospects for Therapeutics. *Nature Reviews Neurology, 10*(4), 204–216.
https://doi.org/10.1038/nrneurol.2014.24

Ross, C. A, Pantelyat, A., Kogan, J., & Brandt, J. (2014). Determinants of Functional Disability in Huntington's Disease: Role of Cognitive and Motor Dysfunction. *Movement Disorders, 29*(11), 1351–1358.
https://doi.org/10.1002/mds.26012

Rothlind, J. C., Bylsma, F. W., Peyser, C., Folstein, S. E., & Brandt, J. (1993). Cognitive and Motor Correlates of Everyday Functioning in Early Huntington's Disease. *The Journal of Nervous and Mental Disease, 181*(3), 194–199.
https://doi.org/10.1097/00005053-199303000-00008

Royall, D. R., Lauterbach, E. C., Kaufer, D., Malloy, P., Coburn, K. L., Black, K. J., & The Committee on Research of the American Neuropsychiatric Association (2007). The Cognitive Correlates of Functional Status: A Review from the Committee on Research of the American Neuropsychiatric Association. *Journal of Neuropsychiatry and Clinical Neurosciences, 19*(3), 249–265.
https://doi.org/10.1176/appi.neuropsych.19.3.249

Ruse, S. A, Davis, V. G., Atkins, A. S., Krishnan, K. R. R., Fox, K. H., Harvey, P. D., & Keefe, R. S. E. (2014). Development of a Virtual Reality Assessment of Everyday Living Skills. *Journal of Visualized Experiments, (86),* e51405.
https://doi.org/10.3791/51405

Sheppard, D. P., Pirogovsky-Turk, E., Woods, S. P., Holden, H. M., Nicoll, D. R., Filoteo, J. V., Corey-Bloom, J., & Gilbert, P. E. (2017). Everyday Functioning in Huntington's Disease: A Laboratory-Based Study of Financial Management Capacity. *Applied Neuropsychology: Adult, 24*(2), 176–182.
https://doi.org/10.1080/23279095.2015.1125904

Shoulson, I., & Fahn, S. (1979). Huntington Disease: Clinical Care and Evaluation. *Neurology, 29(*1), 1–3.
https://doi.org/10.1212/WNL.29.1.1

Shoulson, I., & Young, A. B. (2011). Milestones in Huntington Disease. *Movement Disorders, 26*(6),

1127–1133.
https://doi.org/10.1002/mds.23685

Sitek, E.J., Sołtan, W., Wieczorek, D., Schinwelski, M., Robowski, P., Reilmann, R., Guzińska, K., Harciarek, M., Krysa, W., and Sławek, J. (2011). Self-awareness of Motor Dysfunction in Patients with Huntington's Disease in Comparison to Parkinson's Disease and Cervical Dystonia. *Journal of the International Neuropsychological Society, 17*(5), 788-795.
https://doi.org/10.1017/S1355617711000725

Sitek, E. J., Thompson, J. C., Craufurd, D., & Snowden, J. S. (2014). Unawareness of deficits in Huntington's disease. *Journal of Huntington's Disease*, *3*(2), 125–135.
https://doi.org/10.3233/JHD-140109

Smith, A. (1982). *Symbol Digits Modalities Test (SDMT) Manual* (Revised). Western Psychological Services.

Snowden, J.S., Craufurd, D., Griffiths, H.L., and Neary, D. (1998). Awareness of Involuntary Movements in Huntington Disease. *Archives of Neurology, 55*, 801–805
https://doi.org/10.1001/archneur.55.6.801

Sohlberg, M. M., & Mateer, C. A. (2001). *Cognitive Rehabilitation: An Integrative Neuropsychological Approach*. Guilford Press

Sousa, L. B., Prieto, G., Vilar, M., Firmino, H., & Simões, M. R. (2015). The Adults and Older Adults Functional Assessment Inventory: A Rasch Model Analysis. *Research on Aging, 37*(8), 787–814.
https://doi.org/10.1177/0164027514564469

Stout, J. C., Glikmann-Johnston, Y., & Andrews, S. C. (2016). Cognitive Assessment Strategies in Huntington's Disease Research. *Journal of Neuroscience Methods, 265,* 19-24.
https://doi.org/10.1016/j.jneumeth.2015.12.007

Stout, J. C., Paulsen, J. S., Queller, S., Solomon, A. C., Whitlock, K. B., Campbell, J. C., Carlozzi, N., Duff, K., Beglinger, L. J., Langbehn, D. R., Johnson, S. A., Biglan, K. M., Aylward, E. H., & the PREDICT-HD Investigators and Coordinators of the Huntington Study Group. (2011). Neurocognitive Signs in Prodromal Huntington Disease. *Neuropsychology, 25*(1), 1–14.
https://doi.org/10.1037/a0020937

Stout, J. C., Queller, S., Baker, K. N., Cowlishaw, S., Sampaio, C., Fitzer-Attas, C., & HD-CAB-Investigators. (2014). HD-CAB: A Cognitive Assessment Battery for Clinical Trials in Huntington's disease. *Movement Disorders, 29*(10), 1281-1288.
https://doi.org/10.1002/mds.25964

Stout, J. C., Weaver, M., Solomon, A. C., Queller, S., Hui, S., Johnson, S. A., Gray, J., Beristain, X., Wojcieszek, J., and Foroud, T. (2007). Are Cognitive Changes Progressive in Prediagnostic HD? *Cognitive and Behavioral Neurology, 20*(4), 212–218.
https://doi.org/10.1097/WNN.0b013e31815cfef8

Stroop, J. R. (1935). Studies of Interference in Serial Verbal Reactions. *Journal of Experimental Psychology, 18,* 643–662.
https://doi.org/10.1037/0096-3445.121.1.15

Tabrizi, S.J., Langbehn, D.R., Leavitt, B.R., Roos, R.A., Durr, A., Craufurd, D., Stout, J.C., & TRACK-HD Investigators. (2009). Biological and Clinical Manifestations of Huntington's disease in the Longitudinal TRACK-HD Study: Cross-Sectional Analysis of Baseline Data. *The Lancet Neurology, 8,* 791–801. https://doi.org/10.1016/S1474-4422(09)70170-X

Tabrizi, S. J., Scahill, R. I., Durr, A., Roos, R. A. C., Leavitt, B. R., Jones, R., Landwehrmeyer, G. B., Fox, N. C., Johnson, H., Hicks, S. L., Kennard, C., Craufurd, D., Frost, C., Langbehn, D. R., Reilmann, R., Stout, J. C., and the TRACK-HD investigators (2011). Biological and Clinical Changes in Premanifest and Early Stage Huntington's Disease in the TRACK-HD Study: The 12-Month Longitudinal Analysis. *The Lancet Neurology, 10*(1), 31–42. https://doi.org/10.1016/S1474-4422(10)70276-3

Tabrizi, S. J., Scahill, R. I., Owen, G., Durr, A., Leavitt, B. R., Roos, R. A., Borowsky, B., Landwehrmeyer, B., Frost, C., Johnson, H., Craufurd, D., Reilmann, R., Stout, J. C., Langbehn, D. R., and the TRACK-HD Investigators (2013). Predictors of Phenotypic Progression and Disease Onset in Premanifest and Early-Stage Huntington's Disease in the TRACK-HD Study: Analysis of 36-Month Observational Data. *The Lancet Neurology, 12*(7), 637–649. https://doi.org/10.1016/S1474-4422(13)70088-7

Tanguay, A. N., Davidson, P. S. R., Guerrero Nuñez, K. V., & Ferland, M. B. (2014). Cooking Breakfast After a Brain Injury. *Frontiers in Behavioral Neuroscience, 8*(272) https://doi.org/10.3389/fnbeh.2014.00272

van Asselen, M., Júlio, F., Januário, C., Bobrowicz-Campos, E., Almeida, I., Cavaco, S., & Castelo-Branco, M. (2012). Scanning Patterns of Faces do Not Explain Impaired Emotion Recognition in Huntington Disease: Evidence for a High-Level Mechanism. *Frontiers in Psychology, 3*(31). https://doi.org/10.3389/fpsyg.2012.00031

Waldvogel, H. J., Kim, E. H., Thu, D. C., Tippett, L. J., & Faull, R. L. (2012). New Perspectives on the Neuropathology in Huntington's Disease in the Human Brain and its Relation to Symptom Variation. *Journal of Huntington's Disease*, *1*(2), 143–153. https://doi.org/10.3233/JHD-2012-120018

Wechsler, D. (1997). *WAIS¬III Administration and Scoring Manual* (3rd ed.). The Psychological Corporation.

Wechsler, D. (2008). *Escala de Inteligência de Wechsler para Adultos − Manual* (3a edição) [Wechsler Adult Intelligence Scale.3rd edition]. Cegoc.

Weir, D. W., Sturrock, A., & Leavitt, B. R. (2011). Development of Biomarkers for Huntington's disease. *The Lancet Neurology, 10*(6), 573-590. https://doi.org/10.1016/S1474-4422(11)70070-9

Williams, J., Downing, N., Vaccarino, A.L., Guttman, M., & Paulsen, J.S. (2011). Self-Reports of Day-to-Day Function in a Small Cohort of People with Prodromal and Early HD. *PLoS Currents, 3,* RRN1254

https://doi.org/10.1371/currents.RRN1254

Williams, J. K., Kim, J., Downing, N., Farias, S., Harrington, D. L., Long, J. D., Mills, J. A., Paulsen, J. S., and The PREDICT-HD Investigators and Coordinators of the Huntington Study Group (2015). Everyday Cognition in Prodromal Huntington Disease. *Neuropsychology, 29*(2), 255–267.
https://doi.org/10.1037/neu0000102

Wilson, B. A., Alderman, N., Burgess, P. W., Emslie, H., & Evans, J. J. (1996). *Behavioural Assessment of Dysexecutive Syndrome.* Thames Valley Test Company.

Wilson, B. A., Evans, J. J., Emslie, H., Alderman, N., & Burgess, P. (1998). The Development of an Ecologically Valid Test for Assessing Patients with a Dysexecutive Syndrome. *Neuropsychological Rehabilitation, 8*(3), 213–228.
https://doi.org/10.1080/713755570

WorldViz (2002). Vizard (Version 4.0) [Software].
https://www.worldviz.com/vizard-virtual-reality-software

Zhang, L., Abreu, B. C., Seale, G. S., Masel, B., Christiansen, C. H., & Ottenbacher, K. J. (2003). A Virtual Reality Environment for Evaluation of a Daily Living Skill in Brain Injury Rehabilitation: Reliability and Validity. *Archives of Physical Medicine and Rehabilitation, 84*(8), 1118–1124.
https://doi.org/10.1016/S0003-9993(03)00203-X

Chapter IV – Study 3

Preface

Our third study was set to compare two clinical models of basal ganglia disorders, Parkinson's disease (PD) and Huntington's disease (HD), regarding the impact of cognitive impairments on performance of daily life- like tasks. Moreover, we aimed to assess the level of insight of persons with HD and PD by contrasting their self-report about everyday function with their actual performance on daily life- like tasks. Our intention was to provide meaningful clues for the planning of disease-tailored pharmacological and non-pharmacological interventions, for involving patients in symptom report and management and for further validating the utility of our tasks in the neuropsychological examination of neurodegenerative disorders with an EF impact.

The two most mentioned classical diseases of the basal ganglia are Huntington's disease and Parkinson's disease, in which prominent neuropathology is found in the subcortical regions of the brain and frontostriatal circuitry (Filley, 2019; Lee et al., 2014; Stout & Johnson, 2005; Young et al., 2021). In early disease stages, the two conditions have distinct neuropathological focuses – the putamen and related motor function are more affected in PD and the caudate nucleus and related cognitive role are more affected in HD (Bhatia & Marsden, 1994; Cope et al., 1996; DeLong & Georgopoulos, 1981; Dickson, 2018; Geevarghese et al., 2015; Peinemann et al., 2005; Sprengelmeyer et al., 1995; Starkstein et al., 1992; Waldvogel et al., 2015; Wichmann & DeLong, 1993). Consequently, the functional impact of both diseases is expected to be different, with daily life more altered by cognitive deficits in mild HD and by impaired motor functioning in mild PD (Lundervold et al., 1994; McIsaac et al., 2018; Roman et al., 1998; Stout & Johnson, 2005). As PD and HD patients are often seen in the same movement disorder unit by the same expert team, it will be relevant to disentangle their phenotypic profiles (Erro et al., 2013;

Mehrabi et al., 2016) to be able to implement more focused and effective care and support strategies.

With this in mind, we tested the functional cognition of two groups of patients with Parkinson's disease (early-onset and early-stage PD) using the *EcoKitchen* task and compared their results with a group of persons with early manifest HD and a group of healthy controls.

The knowledge about the patients' subjective awareness of cognitive impairments is thought to be crucial in clinical practice (Koerts et al., 2011). If patients are not aware of their cognitive impairments, they do not report them and, consequently, these deficits remain untreated and continue to impact daily life (Koerts et al., 2011). Moreover, we cannot assume that persons with suspected cognitive deficits, such as patients with HD and PD, have a realistic view of their condition (Hartman-Maeir et al., 2009).

Consequently, to link and confront the level of functional awareness and the level of functional cognition in PD and HD, we compared the self-report of these groups regarding the everyday life consequences of their clinical conditions using "The Adults and Older Adults Functional Assessment Inventory – IAFAI" (Sousa et al., 2015) and analysed this information in light of their performance in the *EcoKitchen*.

The outcomes of this study were intended to help health care professionals to engage patients in their own rehabilitation and treatment process (Hartman-Maeir et al., 2009; Koerts et al., 2011).

References

Bhatia, K. P., & Marsden, C. D. (1994). The behavioural and motor consequences of focal lesions of the basal ganglia in man. *Brain*, *117(Pt 4)*, 859–876. https://doi.org/10.1093/brain/117.4.859

Cope, M. T., Georgiou, N., Bradshaw, J. L., Iansek, R., & Phillips, J. G. (1996). Simon effect and attention in Parkinson's disease: A comparison with Huntington's disease and Tourette's syndrome. *Journal of Clinical and Experimental Neuropsychology*, *18*(2), 276–290. https://doi.org/10.1080/01688639608408282

DeLong, M.R., & Georgopoulos, A.P. (1981). Motor function of the basal ganglia. In J.M. Brookhart, V.B. Mountcastle & V.B. Brooks (Eds), *Handbook of physiology: The nervous system. Motor control, part I* (vol.11). American Physiological Society.

Dickson D. W. (2018). Neuropathology of Parkinson disease. *Parkinsonism & Related Disorders*, *46 Suppl 1* (Suppl 1), S30–S33. https://doi.org/10.1016/j.parkreldis.2017.07.033

Erro, R., Vitale, C., Amboni, M., Picillo, M., Moccia, M., Longo, K., Santangelo, G., De Rosa, A., Allocca, R., Giordano, F., Orefice, G., De Michele, G., Santoro, L., Pellecchia, M. T., & Barone, P. (2013). The heterogeneity of early Parkinson's disease: A cluster analysis on newly diagnosed untreated patients. *PloS One*, *8*(8), e70244. https://doi.org/10.1371/journal.pone.0070244

Filley C. M. (2019). History of Subcortical Cognitive Impairment. *Frontiers of Neurology and Neuroscience*, *44*, 108–117. https://doi.org/10.1159/000494958

Geevarghese, R., Lumsden, D. E., Hulse, N., Samuel, M., & Ashkan, K. (2015). Subcortical structure volumes and correlation to clinical variables in Parkinson's disease. *Journal of Neuroimaging*, *25*(2), 275–280. https://doi.org/10.1111/jon.12095

Hartman-Maeir, A., Katz, N., & Baum, C. M. (2009). Cognitive Functional Evaluation (CFE) Process for Individuals with Suspected Cognitive Disabilities. *Occupational Therapy in Health Care*, *23*(1), 1–23. https://doi.org/10.1080/07380570802455516

Koerts, J., Van Beilen, M., Tucha, O., Leenders, K. L., & Brouwer, W. H. (2011). Executive functioning in daily life in Parkinson's disease: Initiative, planning and multi-task performance. *PloS One*, *6*(12), e29254. https://doi.org/10.1371/journal.pone.0029254

Lee, H. M., Kwon, K. Y., Kim, M. J., Jang, J. W., Suh, S. I., Koh, S. B., & Kim, J. H. (2014). Subcortical grey matter changes in untreated, early stage Parkinson's disease without dementia. *Parkinsonism & Related Disorders*, *20*(6), 622–626. https://doi.org/10.1016/j.parkreldis.2014.03.009

Lundervold, A. J., Karlsen, N. R., & Reinvang, I. (1994). Assessment of 'subcortical dementia' in patients with Huntington's disease, Parkinson's disease, multiple sclerosis and AIDS by a neuropsychological screening battery. *Scandinavian Journal of Psychology*, *35*(1), 48–55. https://doi.org/10.1111/j.1467-9450.1994.tb00932.x

McIsaac, T. L., Fritz, N. E., Quinn, L., & Muratori, L. M. (2018). Cognitive-Motor Interference in Neurodegenerative Disease: A Narrative Review and Implications for Clinical Management. *Frontiers in Psychology*, *9*, 2061. https://doi.org/10.3389/fpsyg.2018.02061

Mehrabi, N. F., Waldvogel, H. J., Tippett, L. J., Hogg, V. M., Synek, B. J., & Faull, R. L. (2016). Symptom heterogeneity in Huntington's disease correlates with neuronal degeneration in the cerebral cortex. *Neurobiology of Disease*, *96*, 67–74. https://doi.org/10.1016/j.nbd.2016.08.015

Peinemann, A., Schuller, S., Pohl, C., Jahn, T., Weindl, A., & Kassubek, J. (2005). Executive

dysfunction in early stages of Huntington's disease is associated with striatal and insular atrophy: A neuropsychological and voxel-based morphometric study. *Journal of the Neurological Sciences*, *239*(1), 11–19. https://doi.org/10.1016/j.jns.2005.07.007

Roman, M. J., Delis, D. C., Filoteo, J. V., Demadura, T. L., Paulsen, J., Swerdlow, N. R., Swenson, M. R., Salmon, D., Butters, N., & Shults, C. (1998). Is there a "subcortical" profile of attentional dysfunction? A comparison of patients with Huntington's and Parkinson's diseases on a global-local focused attention task. *Journal of Clinical and Experimental Neuropsychology*, *20*(6), 873–884. https://doi.org/10.1076/jcen.20.6.873.1111

Sousa, L. B., Prieto, G., Vilar, M., Firmino, H., & Simões, M. R. (2015). The Adults and Older Adults Functional Assessment Inventory: A Rasch Model Analysis. *Research on Aging*, *37*(8), 787–814. https://doi.org/10.1177/0164027514564469

Sprengelmeyer, R., Canavan, A. G., Lange, H. W., & Hömberg, V. (1995). Associative learning in degenerative neostriatal disorders: Contrasts in explicit and implicit remembering between Parkinson's and Huntington's diseases. *Movement Disorders*, *10*(1), 51–65. https://doi.org/10.1002/mds.870100110

Starkstein, S. E., Brandt, J., Bylsma, F., Peyser, C., Folstein, M., & Folstein, S. E. (1992). Neuropsychological correlates of brain atrophy in Huntington's disease: A magnetic resonance imaging study. *Neuroradiology*, *34*(6), 487–489. https://doi.org/10.1007/BF00598956

Stout, J. C., & Johnson, S. A. (2005). Cognitive impairment and dementia in basal ganglia disorders. *Current Neurology and Neuroscience Reports, 5*(5), 355–363. https://doi.org/10.1007/s11910-005-0059-3

Waldvogel, H. J., Kim, E. H., Tippett, L. J., Vonsattel, J. P., & Faull, R. L. (2015). The Neuropathology of Huntington's Disease. *Current Topics in Behavioral Neurosciences*, *22*, 33–80. https://doi.org/10.1007/7854_2014_354

Wichmann, T., & DeLong, M. R. (1993). Pathophysiology of parkinsonian motor abnormalities. *Advances in Neurology*, *60*, 53–61.

Young, C. B., Reddy, V., & Sonne, J. (2021). Neuroanatomy, Basal Ganglia. In *StatPearls [Internet]*. StatPearls Publishing

Study 3

Cognition, Function and Awareness of Disease Impact in Early Parkinson's and Huntington's Disease

Adapted from: **Júlio, F.,** Ribeiro, M. J., Morgadinho, A., Sousa, M., van Asselen, M., Simões, M. R., Castelo-Branco, M., & Januário, C. (2022). Cognition, function and awareness of disease impact in early Parkinson's and Huntington's disease. *Disability and Rehabilitation*, *44*(6), 921-939.
https://doi.org/10.1080/09638288.2020.1783001

Abstract

Introduction: Patients with Parkinson's and Huntington's Disease (PD and HD) present impairments in cognitively challenging everyday activities. This study contrasts these two basal ganglia disorders on the ability to perform daily life- like tasks and their level of awareness regarding the disease impact on function.

Materials and Methods: 19 controls, 10 persons with early-onset PD, 20 persons with early-stage PD, and 15 persons with early manifest HD patients were compared in the *EcoKitchen*, a virtual reality task with increasing executive load, the "Behavioural Assessment of Dysexecutive Syndrome battery – BADS", and "The Adults and Older

Adults Functional Assessment Inventory – IAFAI", a self-report functional questionnaire. The *EcoKitchen* clinical correlates were investigated.

Results: All clinical groups presented slower *EcoKitchen* performance than controls, however, only persons with HD showed decreased accuracy. Persons with HD and PD exhibited reduced BADS scores compared to the other study participants. Importantly, on the IAFAI, persons with PD signalled more physically related incapacities and persons with HD indicated more cognitively related incapacities. Accordingly, the *EcoKitchen* performance was significantly associated with PD motor symptom severity.

Discussion: Our findings suggest differential disease impact on cognition and function across persons with PD and HD, with preserved awareness regarding disease- related functional alterations. These observations have important implications for clinical management, research and rehabilitation.

Introduction

Idiopathic Parkinson's disease (PD) is one of the most common neurodegenerative diseases and is associated with a progressive loss of dopamine neurons in the nigrostriatal system, particularly the posterior putamen in the early disease stages (Dirnberger & Jahanshahi, 2013; O'Keeffe et al., 2009). Huntington's disease (HD) is a rare autosomal dominant progressive disease caused by a cytosine-adenine-guanine (CAG) trinucleotide repeat expansion in the Huntingtin gene that results in an early and selective prominent cell loss and atrophy of the caudate nucleus and putamen (Shoulson & Young, 2011).

While both conditions are within the family of subcortical neurodegenerative movement disorders that primarily affect the basal ganglia and disrupt the frontostriatal circuitry (Stout & Johnson, 2005), the structural and functional neuronal alterations and the pathophysiological changes associated with PD and HD are complex and involve increasingly broader regions and circuits of the brain as the diseases progress (Huang et al., 2007; Montoya et al., 2006). In Parkinson's disease, there is a progressive disruption in circuits formed by cortico-basal ganglia-thalamo-cortical connections, which mediate cognitive and motor function (Dickson, 2018; Hünerli et al., 2019; Rodriguez-Oroz et al., 2009); with disease evolution, there are widespread cortical and subcortical changes and

increasingly abnormal network activity (Berti et al., 2012; Huang et al., 2007). In Huntington's disease, neuroanatomical changes have been detected even in premanifest disease stages (Tabrizi et al., 2009), where neuronal degeneration occurs preferentially within the striatum (Montoya et al., 2006). With HD relentless progression, the pathological process expands to other brain regions, and at death the brain might have lost as much as 25% of its volume (Andrews & Brooks, 1998; Montoya et al., 2006; Rosas et al., 2003).

Nevertheless, in the early disease stages, there is a greater involvement of the putamen in Parkinson's disease and a greater involvement of the caudate nucleus in Huntington's disease (Dickson, 2018; Lee et al., 2014; Waldvogel et al., 2015; Wichmann & DeLong, 1993). As the putamen is a structure more related to motor function and the caudate nucleus has a predominantly cognitive role (Bhatia & Marsden, 1994; Cope et al., 1996; DeLong & Georgopoulos, 1981; Geevarghese et al., 2015; Peinemann et al., 2005; Sprengelmeyer et al., 1995; Starkstein et al., 1992), the disease-related cognitive and functional manifestations are expected to be different. Moreover, though motor symptoms are the hallmark of the formal diagnosis of both diseases (PD as a hypokinetic and HD as a hyperkinetic movement disorder (Cope et al., 1996; Glosser, 2001)), patients exhibit a broad spectrum of motor, cognitive and emotional changes (Stout & Johnson, 2005), and considerable phenotypic heterogeneity (Erro et al., 2013; Mehrabi et al., 2016). Therefore, the distinct clinico-neuropathological features of these two diseases could lead to diagnosis-specific cognitive and functional impairments in these patients (Lundervold et al., 1994; McIsaac et al., 2018; Roman et al., 1998; Stout & Johnson, 2005).

Amidst the several cognitive alterations associated with PD and HD, many of them already present at prodromal disease stages (Aarsland et al., 2017; Paulsen & Long, 2014), bradyphrenia and executive functioning deficits stand out as important and early symptoms of these conditions (Roman et al., 1998). Bradyphrenia refers to disproportionately slowed cognition/information processing and is one of the central features of frontal subcortical neuropathology (Glosser, 2001; Hanes et al., 1995; Lanni et al., 2014). Executive functions (EF) are higher-order capacities that enable the successful engagement in independent, purposive, self-serving behaviour and flexible adaptation to daily-life situations (Dumas et al., 2013; Lezak et al., 2012). The dysexecutive profile of PD and HD includes problems with organizing, planning, sequencing, monitoring and completing tasks, cognitive flexibility, attentional control, set-shifting, inhibitory control, dual task performance and multitasking, judgement and decision-making (Bialystok et

al., 2008; Dirnberger & Jahanshahi, 2013; Dumas et al., 2013; Kudlicka et al., 2018; Novak & Tabrizi, 2011; Rosenblatt, 2007; Stout & Johnson, 2005). Impairments in EF have been consistently identified in early manifest HD patients (Novak & Tabrizi, 2010; Paulsen, 2011; Stout et al., 2011; Tabrizi et al., 2011). In contrast, the findings of executive dysfunction in PD have been somewhat uneven and the rate of cognitive impairment in early-stage PD has been a source of controversy, as deficits can be quite subtle and are usually less severe than those found in HD (Hanes et al., 1995; Stout & Johnson, 2005). Particularly, early-onset PD patients (EOPD), which have a PD diagnosis before 45 years, often progress more slowly, present a more preserved cognitive function than late-onset PD patients, and rarely develop dementia (Glosser, 2001; Schrag & Schott, 2006; Tang et al., 2016). The identification of different cognitive subtypes in PD is thought to be important, as homogeneous groups have a stronger clinical, pathological, and genetic coherence that will facilitate tailored interventional strategies (van Rooden et al., 2011).

Executive deficits are robust determinants of functional status and disability in these disorders, even more frequently than motor impairments, and also compared to deficits in other cognitive domains, such as memory, language or visuospatial abilities (Devos et al., 2012; Dumas et al., 2013; Jacobs et al., 2018; Petkus et al., 2020; Rothlind et al., 1993; Svenningsson et al., 2012). In fact, EF abnormalities can have a negative impact on the cognitive decline rate, quality of life, awareness level, autonomy and everyday functioning of patients, and on the burden of caregivers (Aldaz et al., 2019; Andrews et al., 2018; Beglinger et al., 2010; Ceravolo et al., 2012; Cipresso et al., 2014; Glosser, 2001; Godefroy et al., 2010; Hamilton et al., 2003; Hoth et al., 2007; Kudlicka et al., 2013; Mörkl et al., 2016; Nehl et al., 2004; Reilmann et al., 2014; Ross et al., 2014; Stout et al., 2011). However, these associations between executive deficits and function in persons with PD and HD have been mainly deduced from neuropsychological assessments that are "construct driven" rather than "function" led (Burgess et al., 2006). In fact, few sensitive and ecologically relevant methods for documenting the impact of executive deficits on everyday function are available, as traditional tests focus on cognitive skills in isolated and artificial situations that bear little similarity to real life (Allain et al., 2014; Chaytor et al., 2006; Kudlicka et al., 2018). On the other hand, there is a lack of knowledge about the subjective experience of disease impact on daily life (Ceravolo et al., 2012). Although there has been an increasing number of studies looking into functional determinants in persons with PD and HD, there is still a shortage of measures that can accurately capture small but meaningful changes in function in earlier disease stages (Deck et al., 2019;

Mestre et al., 2018). The patients' report is particularly valuable for the identification and management of problems in everyday routines (Dirnberger & Jahanshahi, 2013). Nevertheless, as inaccurate self-appraisal is commonly seen in disorders with prefrontal cortex involvement and is often associated with impairments in EF, it is important to complement self-report measures with objective assessments to corroborate the patients' subjective view and reduce the potential bias that awareness problems can exert in the reliable evaluation of the patients' status (Andrews et al., 2018; Kudlicka et al., 2013).

Different studies have previously demonstrated that persons with PD and HD frequently exhibit lack of insight about the disease-related changes that impact their performance (e.g., Ho et al., 2006; Hoth et al., 2007; Kudlicka et al., 2013; Leritz et al., 2004). However, while there is a substantial number of studies showing impairment of awareness or insight in PD and HD, there is also growing evidence that lack of insight is not an unitary construct, rather is thought to have significant variability in its magnitude and expression among patients (Caine & Shoulson, 1983). Moreover, awareness deficits are relatively independent of general disease progression alone, as quantified by the number of years of disease duration, and more linked to cognitive and emotional symptoms, namely executive dysfunction (Hoth et al., 2007; Koerts et al., 2012; Kudlicka et al., 2013; Sitek et al., 2011). Finally, insight in basal ganglia disorders is thought to fall on a continuum, with patients having limited awareness rather than lacking awareness all together (Hoth et al., 2007). Taking all this into account, the evaluation of the level of insight that persons with PD and HD have about the impact of their symptoms on everyday life activities is believed to be of utterly importance, given its consequences to patient involvement in symptom report and management, performance monitoring, and clinical and rehabilitation decisions.

In this study, we compared the ability of persons with early Parkinson's and Huntington's disease to perform executively demanding tests and daily life- like tasks (objective assessment) and their self-report of perceived difficulties in everyday chores (subjective assessment).

The ability to complete daily life tasks was evaluated using a performance-based assessment tool created at our laboratory, the *EcoKitchen*. This was important to overcome the inconsistencies often found between the results obtained with conventional cognitive assessment methods and the real-life functional complaints of these patients (Chaytor et al., 2006; Parsons et al., 2017; Shallice & Burgess, 1991). The *EcoKitchen* is a non-immersive virtual reality task that involves preparing meals in a

kitchen scenario (Júlio et al., 2019). Virtual reality environments that resemble everyday settings and tasks seem to be a good testing ground to measure executive skills in an ecologically valid, controlled and secure way and evidence their impact on function in a fast, quantifiable and easy manner (Albani et al., 2010; Cipresso et al., 2014; Frisch et al., 2012; McIsaac et al., 2018; Moore et al., 2007; Poliakoff & Smith-Spark, 2008; Vlagsma et al., 2017).

To depict the baseline executive status of study participants, the "Behavioural Assessment of Dysexecutive Syndrome battery – BADS" (Wilson et al., 1996) was also included in our study protocol. This is a set of executive tests that reportedly has higher ecological validity than more conventional paper-and-pencil assessments (Burgess et al., 1998, 2006; Norris & Tate, 2000; Wilson et al., 1998), as it involves abilities and materials that try to resemble everyday like situations. Importantly, to our knowledge, BADS has been seldom used with persons with HD and PD (Kamei et al., 2008; Nimmagadda et al., 2011; Perfetti et al., 2010) and we did not find reports of BADS comparisons of these two clinical conditions.

Participants' perceived difficulties in everyday chores were assessed with a subjective functional measure – "The Adults and Older Adults Functional Assessment Inventory – IAFAI" (Sousa et al., 2015). In IAFAI, participants rate their level of self-perceived difficulties in performing basic and instrumental activities of daily living and indicate the type of constraints that they think underlie the experienced functional problems. As Lanni et al. (2014) state, self-report questionnaires can capture relevant data about the cognitive skills needed to complete real-world tasks. Moreover, solely relying on clinical or computerized tests to assess EF has been much debated, as patients often perform well in experimental settings but demonstrate disorganized behaviour at home or in less structured environments (Dirnberger & Jahanshahi, 2013; Godefroy et al., 2010). Thus, it seemed crucial to include a tool that could capture the everyday functioning of persons with PD and HD and signal their self-perceived difficulties in real-life situations.

To understand the clinical correlates of the executive performance of persons with PD and HD, we further examined the associations emerging between the variables computed from the *EcoKitchen* task and the disease features of the clinical groups.

In summary, this study intends to surpass the limitations often posed by traditional neuropsychological tools and have an ecologically valid depiction of the impact of clinical symptoms on the functional ability and awareness status of persons with early-stage and early-onset PD (ESPD and EOPD, respectively) without dementia in

comparison to early manifest persons with HD without dementia (EarlyHD) and healthy controls (CTRL). This assessment was based on their objective performance of an executive demanding virtual reality task and their subjective rating of daily function. A conventional battery of executive tests was also used to characterize the baseline executive skills of study participants. We have formerly demonstrated cognitive and functional deficits not only in early manifest, but also in premanifest HD individuals using a similar protocol (Júlio, et al., 2019). We have shown that the early manifest HD group presented deficits in all the assessment measures used and that the premanifest HD group was only found to be impaired in the *EcoKitchen* task. This new study uses the data previously acquired with persons with EarlyHD and healthy participants and compares their performance with two groups of persons with Parkinson's disease (early-onset and early-stage). Our aim was to further validate the *EcoKitchen* task and the IAFAI as reliable tools to assess the functional impact of executive deficits in basal ganglia disorders. This was thought to be of great relevance, as the understanding of the impact of PD and HD on the performance of executively demanding everyday activities and on the person's awareness of their own difficulties is still incomplete and is imperative for appropriate symptom management, development of tailored interventions and planning of rehabilitation strategies.

Our hypothesis was that the differences in the affected striatum structures would reveal distinct impairments in the behaviour of the clinical groups and also play a role in their self-appraisal of functional deficits. We expected there would be an inter-group continuum from healthy to mildly/moderately defective executive and functional skills: controls (CTRL) > persons with early-onset PD (EOPD) > persons with early-stage idiopathic PD (ESPD) > persons with early manifest HD (EarlyHD). This would mirror the disparate neuroanatomical regions selectively involved in early PD and HD – the motor role of the putamen and the cognitive role of the caudate nucleus, respectively (Bhatia & Marsden, 1994; DeLong et al., 1981; Glosser, 2001). We estimated to find that persons with early-onset PD would present a relatively preserved cognitive status and motor abnormalities that would have a minor functional impact; persons with early-stage PD would present worse motor symptomatology and cognitive changes compared to persons with EOPD, that would be more obvious under more challenging task conditions and in terms of performance time/pace; finally, in accordance to previous results (Júlio et al., 2019), we expected that persons with early manifest HD would display a global cognitive impairment and motor alterations that would negatively

impact their performance of executively demanding tests and tasks, regardless of difficulty level.

To our knowledge, this is the first study comparing the performance of persons with mild Parkinson's and Huntington's disease without dementia with a virtual reality measure designed to address cognitive skills and functional ability in basal ganglia disorders.

Materials and Methods

Participants

Persons with Parkinson's Disease were divided into two groups given the following criteria:

- Early-Stage Idiopathic PD (ESPD): persons with a diagnosis of idiopathic PD according to the UK Brain Bank Diagnostic Criteria (Hughes et al., 1992), ≤ 5 years disease duration, disease onset after 45 years, mild PD symptoms, and a Hoehn and Yahr score ≤ 2.5 (Hoehn & Yahr, 1967)
- Early-Onset PD (EOPD): persons with a diagnosis of PD according to the UK Brain Bank Diagnostic Criteria (Hughes et al., 1992), disease onset prior to 45 years, mild PD symptoms, and a Hoehn and Yahr score ≤ 2.5 (Hoehn & Yahr, 1967)

The group of persons with Huntington's disease and the group of healthy participants, (previously reported in Júlio, et al. (2019)) were assembled with the following criteria:

- Early Manifest HD (EarlyHD): persons with a genetic test result confirming a CAG-repeat length of≥ 36, mild HD symptoms (stages I-II Shoulson & Fahn (Shoulson & Fahn, 1979)), and a Total Functional Capacity scale of 10-13 (Huntington Study Group, 1996)
- Controls (CTRL): healthy participants with no history of dementia, depression, substance abuse, any neurological and/or psychiatric condition and no current use of psychotropic medication

This paper presents and discusses the data from 20 Early-Stage Idiopathic PD (ESPD), 10

Early-Onset PD (EOPD), 15 Early Manifest HD (EarlyHD) and 19 Control (CTRL) participants. Two persons with ESPD did not perform *EcoKitchen* due to motor fluctuations and two CTRL participants did not complete IAFAI due to time constraints. Persons with ESPD, EOPD and EarlyHD were recruited from the Movement Disorders Unit and the Neurogenetics Consultation Service of the Neurological Department of Coimbra University Hospital and assessed in their regular on-state of medication – which is displayed in Table 3.1**.**

Table 3.1 Classes of medication for the clinical groups

(number of participants on)	*EarlyHD*	*EOPD*	*ESPD*
No Medication	2	0	2
Antidepressants	11	0	9
Anxiolytics, Sedatives and Hypnotics	10	4	3
Antipsychotics	5	0	0
Anticonvulsants	1	2	4
Antiparkinsonians	1	10	18

EarlyHD – Early Manifest Huntington's Disease; EOPD – Early-Onset Parkinson's Disease; ESPD – Early-Stage Parkinson's Disease

Exclusion criteria for the clinical groups included dementia, severe depression, history of substance abuse, and any other neurological condition.

All participants gave written informed consent in accordance with the Declaration of Helsinki to participate in the study approved by our Institutional Ethics Committees (Faculty of Medicine and Coimbra University Hospital).

The demographic characteristics of the four groups are presented in Table 3.2.

Table 3.2 Demographic characteristics of the four groups

Demographics	*CTRL=19* *Gender (F:M) 15:4* *Handedness (R:L) 18:1* *Median (IQR) [95% CI]*	*EarlyHD=15* *Gender (F:M) 10:5* *Handedness (R:L) 14:1* *Median (IQR) [95% CI]*	*EOPD=10* *Gender (F:M) 5:5* *Handedness (R:L) 10:0* *Median (IQR) [95% CI]*	*ESPD=20* *Gender (F:M) 10:10* *Handedness (R:L) 17:3* *Median (IQR) [95% CI]*	*Kruskal-Wallis* χ^2	*p-value*	η^2
Age (y)	41 (12) [37-48]	46 (6) [41-47]	47 (11) [41-51.49]	60.50 (11) c e f [57.50-66.97]	35.558	<0.001 *	0.543
Education (y)	11 (7) [9-15]	9 (6) [6-12]	10 (9) [6-15]	9 (8) [4-10.50]	5.240	0.155	0.037
CAG	-	43 (2) [42-44]	-	-	-	-	-
Hoehn and Yahr	-	-	2 (1) [1-2]	1.25 (1) [1-2]	-	-	-
Disease Duration (y)	-	5 (6) [4-7.95]	5 (5) [3.50-8.50]	3 (3) [2-4.50]	5.845	0.054	0.092
UHDRS - TFC	-	12 (2) [11-13]	-	-	-	-	-
UHDRS - Motor	-	24 (20) [12-28]	-	-	-	-	-
UPDRS - Motor	-	-	23.5 (15) [12.54-28.99]	22.5 (13) [14-24.50]	-	-	-
MoCA	26 (4) [24.51-28]	23 (4) a [21-25]	25 (3) [24-27]	23 (4) c [22-25]	10.698	0.013 *	0.128
BDI-II	3 (4) [2-5]	17 (17) a [12-21]	10 (15) b [4-18.50]	12.5 (19) c [8.50-24]	14.215	0.003 *	0.187
TeLPI (QIEC)	113.54 (15.35) [105.48-117.38]	103.18 (19.98) [93.56-113.49]	104.32 (24.19) [91.65-122.75]	102.41 (20.83) [97.81- 111.05]	5.512	0.138	0.042
TeLPI (QIV)	114.83 (15.89) [106.51-118.80]	103.28 (19.68) [95.61-114.83]	105.49 (24.95) [95.65-121.11]	103.46 (20.89) [97.74- 111.83]	5.374	0.146	0.040
TeLPI (QIR)	109.72 (11.25) [103.54-112.77]	102.51 (16.45) [93.24-109.61]	102.51 (18.47) [94.81-113.77]	100.97 (16.43) [98.42-108.17]	5.110	0.164	0.035

CTRL – Controls; EarlyHD – Early Manifest Huntington's Disease; EOPD – Early-Onset Parkinson's Disease; ESPD – Early-Stage Parkinson's Disease
IQR – Interquartile Range [95% Confidence Interval for median]
y – years: CAG – cytosine-adenine-guanine trinucleotide repeat expansion confirmed by a genetic test; UHDRS - TFC – Total Functional Capacity scale of the Unified Huntington's Disease Rating Scale; UHDRS - Motor – Motor scale of the Unified Huntington's Disease Rating Scale; UPDRS - Motor – Motor scale of the Unified Parkinson's Disease Rating Scale; MoCA – Montreal Cognitive Assessment; BDI-II – Beck Depression Inventory II; TeLPI – The Irregular Word Reading Test; QIEC – Full Scale Intelligence Quotient; QIV – Verbal Intelligence Quotient; QIR – Performance Intelligence Quotient
** Kruskal-Wallis p< 0.05*
a CTRL ≠ EarlyHD; b CTRL≠ EOPD; c CTRL≠ ESPD; d EarlyHD ≠ EOPD; e EarlyHD ≠ ESPD; f EOPD≠ ESPD (Mann-Whitney, p< 0.05)

Clinical, Cognitive and Neuropsychiatric Screening Measures

The "Movement Disorders Society – Unified Parkinson's Disease Rating Scale part-III" (UPDRS) (Goetz et al., 2008) and the "Hoehn and Yahr" scale (Hoehn & Yahr, 1967) were used to determine the severity of motor symptoms and the disease stage of persons with EOPD and ESPD. The UPDRS (Goetz et al., 2008) is composed by 18 items (e.g., action tremor, postural stability, or bradykinesia) that the rater must observe when evaluating the motor function of persons with PD. Each item is individually scored, using 0 for normal or no problems, 1 for minimal problems, 2 for mild problems, 3 for moderate problems, and 4 for severe problems; the higher the score, the higher the degree of motor incapacity. The "Hoehn and Yahr" scale (Hoehn & Yahr, 1967) is often used in combination with the previous motor scale and indicates how PD symptoms progress (e.g., unilateral motor symptom or motor symptom on both sides) and grades PD severity or the level of disability in a scale ranging from 0 "No signs of disease" to 5 "Needing a wheelchair or bedridden unless assisted."

The "Unified Huntington's Disease Rating Scale" (UHDRS) – Motor and Total Functional Capacity scales (Huntington Study Group, 1996) were used to determine the severity of motor symptoms and the functional level of persons with HD. The UHDRS – Motor Assessment provides a uniform clinical rating of the motor function of persons with HD. It includes 15 items (e.g., chorea, dystonia, rigidity), rated individually on a range from 0 "normal" to 4 "cannot perform/severe problems;" again, higher scores indicate increased motor dysfunction. The UHDRS Total Functional Capacity scale is a broad measure of functional capacity used by a rater after an interview with the person with HD (and relevant informants). It has five global items that assess occupation, finances, domestic chores, activities of daily living, and care level; the total score ranges from 0 to 13 – with greater scores indicating higher functioning capacity.

We have used the "Montreal Cognitive Assessment" (Freitas et al., 2011; Nasreddine et al., 2005) to screen for mild cognitive impairment and dementia, the "Beck Depression Inventory – II" (Beck et al., 1996; Campos & Gonçalves, 2011) to assess neuropsychiatric symptoms, the "Irregular Word Reading Test" (Alves et al., 2012) to estimate the level of premorbid intelligence, and the "Edinburgh Handedness Inventory" (Oldfield, 1971) to define handedness.

The scores of the four groups on these measures are shown in Table 3.2.

EcoKitchen

This non-immersive virtual reality task was implemented on a desktop PC, in which participants had a flat-full screen presentation of a kitchen setting in a 23'' monitor and used the computer mouse to navigate around the scenario. The *EcoKitchen* included three different blocks, each preceded by a practice block, with increasing executive demands. There was also a first global practice block, to guarantee that each participant was completely familiarized with the apparatus, instructions and aim of the task before the assessment blocks begun (Figure 3.1).

In Block 1, participants had to prepare a cup of coffee with milk – Task A. In Block 2, while performing Task A, participants had to turn off a kettle that boiled at several randomly defined moments. In Block 3, participants had to perform the tasks previously described, whilst performing an equally demanding concurrent task – preparing toasts with butter (Task B).

As the *EcoKitchen* aimed to evaluate executive functioning, several precautions were adopted to reduce the impact of other factors such as motor problems, computer interaction difficulties or memory constraints on task performance. The interactions with the different items needed to perform the tasks were facilitated (e.g., the participant just touched an item, and it would move automatically), the instructions and the lists with the requested items and actions needed were left in full view during the whole block, and all items were on full display in the scenario.

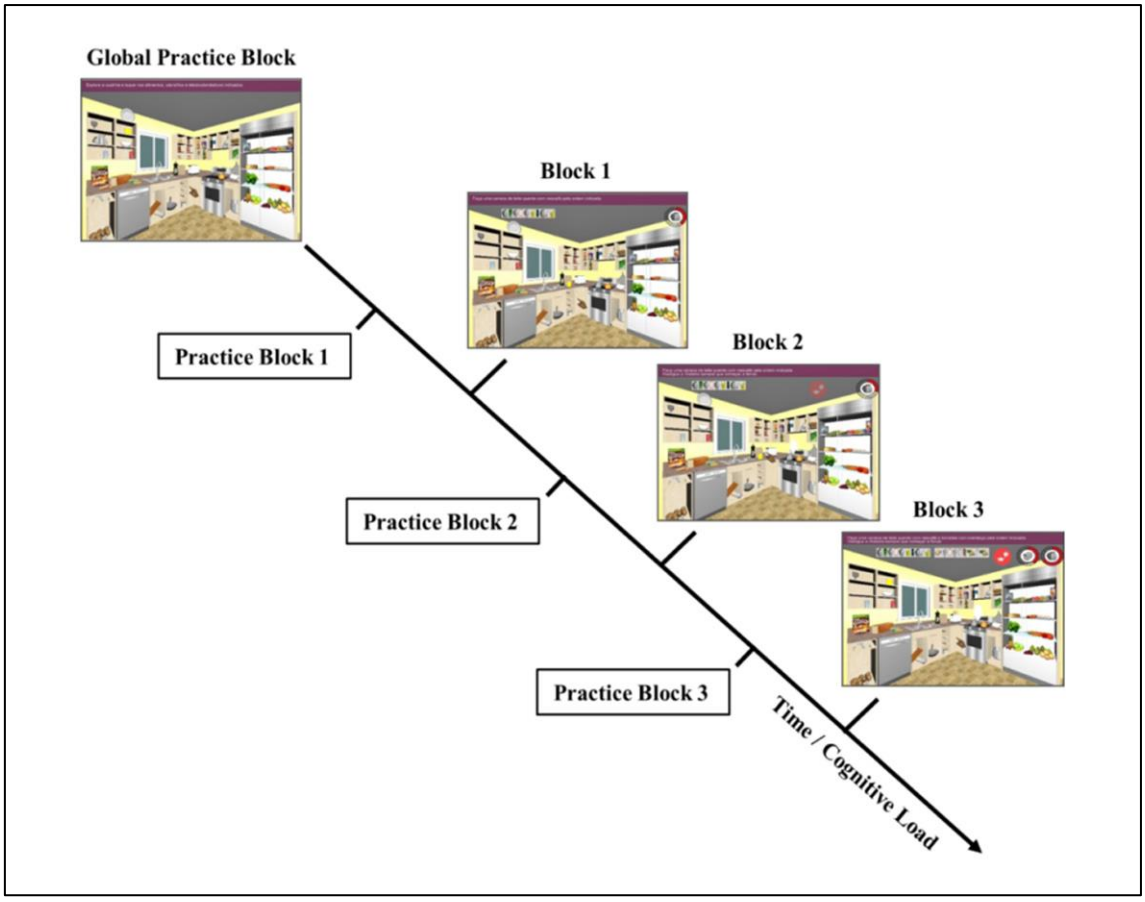

Figure 3.1 *EcoKitchen* Task Design

Block 1 - participants had to prepare a cup of coffee with milk (Task A); Block 2 - while performing Task A, participants had to turn off a kettle that boiled at several moments; Block 3 - participants had to perform the tasks previously described, whilst preparing toasts with butter (Task B)

Several parameters were defined for the *EcoKitchen* data analysis, considering the different cognitive skills and executive sub-domains that in our view are involved in task performance. The *EcoKitchen* design, procedures, and data analysis are fully detailed elsewhere (Júlio, et al., 2019).

- Performance Time Task A and Performance Time Task B – the amount of time participants were engaged in the preparation of a cup of coffee with milk (Task A)/ toasts with butter (Task B); this parameter reflects psychomotor and processing speed, planning, motor time, and task switching skills
- Reaction Time Stove and Reaction Time Toaster – the amount of time participants took to react and turn off the stove/ the toaster once the clock was completely red (indication to prompt the action); this parameter reflects behaviour monitoring, response initiation, divided attention, set-shifting, and task switching skills
- Reaction Time Kettle – the amount of time participants took to react and turn off

the kettle at random moments throughout the block when the signal for behavioural initiation appeared; this parameter reflects divided attention, sustained alertness, response initiation, and set-shifting skills

- Reaction Time *per* Block – the mean of the different reaction times extracted from each *EcoKitchen* block; this parameter reflects all the executive sub-domains involved in the different reaction times to specific cues
- Sequencing Errors – the number of times participants failed to follow the proper sequence of the task (e.g., tried to mix the coffee with the spoon before adding the milk); this parameter reflects planning, behaviour monitoring, and working memory skills
- Item Errors – the number of times participants picked items of the scenario that were not needed to prepare Task A or Task B (e.g., selected a pineapple instead of coffee); this parameter reflects attention and behaviour monitoring skills]
- Impulsivity Errors Stove and Impulsivity Errors Toaster – the number of times participants tried to turn off the stove/ the toaster before the proper time (i.e., before the clock being completely red); this parameter reflects response inhibition or inhibitory control, attention, and task switching skills
- Total Errors/Performance Time Task A and Total Errors/Performance Time Task B – the number of errors per minute participants committed during the completion of Task A/ Task B; this parameter reflects speed-accuracy balance in task completion and task switching skills

BADS – the Behavioural Assessment of Dysexecutive Syndrome battery

We used the "Behavioural Assessment of Dysexecutive Syndrome battery – BADS" (Wilson et al., 1996) to have a global baseline depiction of the executive skills of study participants. This battery is composed by six sub-tests that capture different aspects of the dysexecutive syndrome using tasks and materials analogous to those required in everyday life activities involving executive functioning (Wilson et al., 1998):

- The Rule Shift Card test examines the ability to shift from one simple rule to another more complex rule. In this sub-test, participants must respond "Yes" or "No" to a set of playing cards that is showed to them, one at a time. In the first part, participants are asked to say "Yes" to a red playing card and "No" to a

black playing card; in the second part, the rule is changed, and participants are asked to respond "Yes" if the card is the same colour as the previous card and "No" if it is a different colour. The score involves the time taken and the number of errors made (Evans et al., 1997; Wilson et al., 1998)

- The Action Program test requires the ability to develop a plan of action to solve a novel and practical task without guidance. In this sub-test, different props are put in front of the participant: a large container that has water inside and a removable lid with a small hole; a tall thin container with a cork loose in the bottom; a piece of wire which is not long enough for reaching the cork; and a small cylindrical tube to which a top can be attached. Participants are asked to remove the cork out of the tube using any of the objects in front of them. The task requires five steps for its solution, which the participant ideally must take without any action prompt. The score is based on the number of steps independently completed (Evans et al., 1997; Wilson et al., 1998)
- The Key Search test evaluates the ability to plan and monitor an efficient course of action without any supervision. In this sub-test, participants are provided with an A4 piece of paper with a large square and a small black dot 50 mm below the square. Participants are asked to imagine that the square is a large field in which they have lost their keys and they must draw a line, starting on the black dot, to show the path they would take to search this field and find the lost keys. The score depends on the efficacy of the search pattern adopted according to the examples provided in the test manual (Evans et al., 1997; Wilson et al., 1996, 1998)
- The Temporal Judgement test examines the ability to make sensible estimates about the time length of different activities. In this sub-test, participants must answer four questions regarding how long it takes to achieve different events (e.g., "how long does it take to blow up a party balloon" or "how long do most dogs live for"). The score of each answer is attributed according to the degree of deviation from the answers most commonly provided by the BADS normative sample (Evans et al., 1997; Wilson et al., 1998)
- The Zoo Map test evaluates complex planning skills in low-demanding (clear instructions provided) and high-demanding (no aid/structure provided) conditions. In this sub-test, a paper with a map of a zoo and a paper with instructions are given to the participants and they have to draw a line to show how they would visit a series of designated locations on this map. When

planning the route, they must obey to certain rules (e.g., use a path just once). The test has two parts: in the first part, the order in which the visits should take place is not provided; in the second part, another identical map is given to the participant and the visits' order is clearly specified. The score involves the number of errors/rule breaks made, the number of places correctly visited and the planning and executing times (Evans et al., 1997; Wilson et al., 1998)

- The Modified Six Elements test taps the ability to plan, organize and monitor behaviour, and prospective memory and set-shifting skills. In this sub-test, participants must do three tasks (dictation, arithmetic, and picture naming), each of which is divided into two parts called A and B. During a 10-minute period, participants need to attempt doing something from each of the six sub-tasks, while obeying to one rule – they are not allowed to do the two parts of the same task consecutively. The score considers the number of tasks attempted, the number of rule breaks made, and the maximum time spent on any of the tasks (Evans et al., 1997; Wilson et al., 1998)

Seven variables were extracted from BADS (each sub-test was reduced to a single raw score, range 0-4): Total Score, Rule Shift Cards Test Score, Action Program Test Score, Key Search Test Score, Temporal Judgement Test Score, Zoo Map Test Score, and Modified Six Elements Test Score.

IAFAI – the Adults and Older Adults Functional Assessment Inventory

The self-reported functional status of study participants was assessed with the IAFAI (Sousa et al., 2015). This inventory includes items that cover several important functional domains: feeding, dressing, bathing and continence, mobility and transference, conversation and telephone use, meal preparation, housekeeping, home security, comprehension and communication, health-related decision making, finances, going out and transportation use, and leisure and interpersonal relationships (Sousa et al., 2015). These domains are translated into specific sentences, such as "Buttoning clothes", "Dialling a phone number", "Cooking a meal" or "Taking medications as prescribed". Participants rated their level of self-perceived difficulties in performing each inventoried Basic and Instrumental Activity of Daily Living (BADL and IADL, respectively) – a score

of 0 represented the absence and a score of 1 represented the presence of difficulty/dependence. When difficulty/dependence was signalled, participants assigned it either to physical, cognitive or emotional causes. Seven incapacity percentages were computed: Global Functional Incapacity – GFI, Functional Incapacity in Basic Activities of Daily Living – BADL, Functional Incapacity in Household Instrumental Activities of Daily Living – H-IADL, Functional Incapacity in Advanced Instrumental Activities of Daily Living – A-IADL, Functional incapacity due to Physical Factors – Physical, Functional Incapacity due to Cognitive Factors – Cognitive, and Functional Incapacity due to Emotional Factors – Emotional.

Statistical analyses

Kruskal-Wallis tests were used to compare the quantitative results of the four groups. When a statistically significant effect of group was detected, Mann-Whitney *U* test *post-hoc* comparisons were performed between groups. Nominal/categorical variables were compared resorting to Chi-square tests of independence. Effect sizes (Cramér's *V* and η^2) were determined and reported when appropriate[1]. Spearman rank correlation coefficients were calculated to examine the associations between the *EcoKitchen* results and the clinical features of EarlyHD, EOPD and ESPD participants. To reduce the number of pairwise correlations and enhance interpretability, in the correlation analyses, the variables related to *EcoKitchen* were averaged across the three Blocks. Given the exploratory nature of this study and given that a comprehensive and detailed description of our results is presented (effect sizes, confidence intervals and raw *p*-values), a strict adjustment for multiple comparisons was thought to be less critical and to potentially neglect the clinical and scientific relevance of the findings (Althouse, 2016; Rothman, 1990; Saville, 1990), so all calculations (performed with IBM SPSS Statistics (Version 24) adopted a level of significance of $a = 0.05$.

[1]According to Cohen (1988), a Cramér's *V* for $k = 4$ between 0.06 – < 0.17 corresponds to a small effect size, between 0.17 – < 0.29 corresponds to a medium effect size, and of ≥ 0.29 corresponds to a large effect size. A Cramér's *V* for $k = 2$ between 0.10 – < 0.30 corresponds to a small effect size, between 0.30 – < 0.50 corresponds to a medium effect size, and of ≥ 0.50 corresponds to a large effect size (Cohen, 1988). Fritz et al. (2012) indicate that a $\eta 2$ value of 0.010 corresponds to Cohen's $d = 0.2$, which is considered a small effect size; a $\eta 2$ value of 0.059 corresponds to Cohen's $d = 0.5$, which is considered a medium effect size and a $\eta 2$ value of 0.14 corresponds to Cohen's $d = 0.8$, which is considered a large effect size.

Results

EcoKitchen

EcoKitchen Accuracy Measures

In the *EcoKitchen* task, the two PD groups showed relatively preserved task completion abilities, performing with the same accuracy level of healthy controls or even better in terms of inhibitory control skills, as implied by the level of Impulsivity Errors – Toaster. In contrast, persons with EarlyHD exhibited an increased error rate when compared to the other study participants, which might reflect impairments in action planning and monitoring, attention, and response inhibition. It is of note that the comparison between persons with EarlyHD and healthy individuals was previously reported in Júlio, et al. (2019); now, the EarlyHD reduced accuracy was also seen in the comparison to ESPD and EOPD affected individuals.

Specifically, we found a significant group effect for the percentage of participants that exhibited Sequencing Errors in Blocks 1 and 3 of the *EcoKitchen*, Item Errors in Block 2, Impulsivity Errors – Stove in Block 3, and Impulsivity Errors – Toaster in Block 3 (Table 3.3).

Table 3.3 Percentage of participants that had a score ≠ 0 in the Sequencing, Item and Impulsivity Error Variables of the *EcoKitchen* Task

	CTRL	*EarlyHD*	*EOPD*	*ESPD*	*Chi-Square*		
EcoKitchen Errors	% *[95% CI]*	% *[95% CI]*	% *[95% CI]*	% *[95% CI]*	χ^2	*p-value*	*Cramér's V*
Sequencing Block 1	15.8 [3.4-39.6]	66.7 a [38.4-88.2]	40 [12.2-73.8]	38.9 [17.3-64.3]	9.156	0.027 *	0.384
Sequencing Block 2	26.3 [9.1-51.2]	40 [16.3-66.7]	20 [2.5-55.6]	44.4 [21.5-69.2]	2.493	0.477	0.201
Sequencing Block 3	52.6 [28.9-75.6]	93.3 a d [68.1-99.8]	30 [6.7-65.2]	66.7 [41-86.7]	11.560	0.009 *	0.432
Item Block 1	0 [0-17.6]	6.7 [2-31.9]	0 [0-30.8]	0 [0-18.5]	3.185	0.364	0.227
Item Block 2	0 [0-17.6]	20 a e [4.3-48.1]	0 [0-30.8]	0 [0-18.5]	9.878	0.020 *	0.399
Item Block 3	5.3 [1,26]	13.3 [1.7-40.5]	20 [2.5-55.6]	5.6 [1-27.3]	2.222	0.528	0.189
Impulsivity Stove Block 1	10.5 [1.3-33.1]	13.3 [1.7-40.5]	0 [0-30.8]	0 [0-18.5]	3.631	0.304	0.242
Impulsivity Stove Block 2	5.3 [1-26]	20 [4.3-48.1]	20 [2.5-55.6]	5.6 [1-27.3]	3.174	0.366	0.226
Impulsivity Stove Block 3	0 [0-17.6]	33.3 a e [11.8-61.6]	10 [3-44.5]	5.6 [1-27.3]	10.303	0.016 *	0.408
Impulsivity Toaster	42.1 [20.3-66.5]	53.3 d e [26.6-78.7]	10 [3-44.5]	5.6 c [1- 27.3]	12.449	0.006 *	0.448

CTRL – Controls; EarlyHD – Early Manifest Huntington's Disease; EOPD – Early-Onset Parkinson's Disease; ESPD – Early Stage Parkinson's Disease
[Clopper-Pearson 95% Confidence Intervals]
* Chi-square p< 0.05
a CTRL ≠ EarlyHD; b CTRL≠ EOPD; c CTRL≠ ESPD; d EarlyHD ≠ EOPD; e EarlyHD ≠ ESPD; f EOPD≠ ESPD (Chi-square test for independence p < 0.05)

Post-hoc tests showed that persons with EarlyHD presented diminished accuracy in their *EcoKitchen* performance not only compared to controls but also, interestingly, when compared to persons with EOPD and ESPD. More persons with EarlyHD than controls gave Sequencing Errors in Blocks 1 and 3 [$\chi^2(1)= 9.188$, $p= 0.002$, Cramér's $V= 0.520$, and $\chi^2(1)= 6.689$, $p= 0.010$, Cramér's $V= 0.444$, respectively], and more persons with EarlyHD than persons with EOPD showed Sequencing Errors in Block 3 ($\chi^2(1)= 11.060$, $p= 0.001$, Cramér's $V= 0.665$). Similarly, a higher percentage of persons with EarlyHD than persons with ESPD and controls presented Item Errors in Block 2 [$\chi^2(1)= 3.960$, $p= 0.047$, Cramér's $V= 0.346$, and $\chi^2(1)= 4.168$, $p= 0.041$, Cramér's $V= 0.350$, respectively]. Additionally, more persons with EarlyHD than persons with ESPD and controls showed Impulsivity Errors – Stove in Block 3 [$\chi^2(1)= 4.244$, $p= 0.039$, Cramér's $V= 0.359$, and $\chi^2(1)= 7.425$, $p= 0.006$, Cramér's $V= 0.467$, respectively]. Finally, an increased number of

persons with EarlyHD compared to persons with EOPD and ESPD exhibited Impulsivity Errors – Toaster [(χ^2(1)= 4.890, p= 0.027, Cramér's V= 0.442) and (χ^2(1)= 9.416, p= 0.002, Cramér's V= 0.534), respectively]. A significant difference was also found between the percentage of ESPD and CTRL participants that presented Impulsivity Errors – Toaster (χ^2(1)= 6.708, p= 0.010, Cramér's V= 0.426), with controls revealing a worse performance. Lastly, we found a significant group effect in the number of errors per minute during Task A and Task B (Figure 3.2 and Table 3.4).

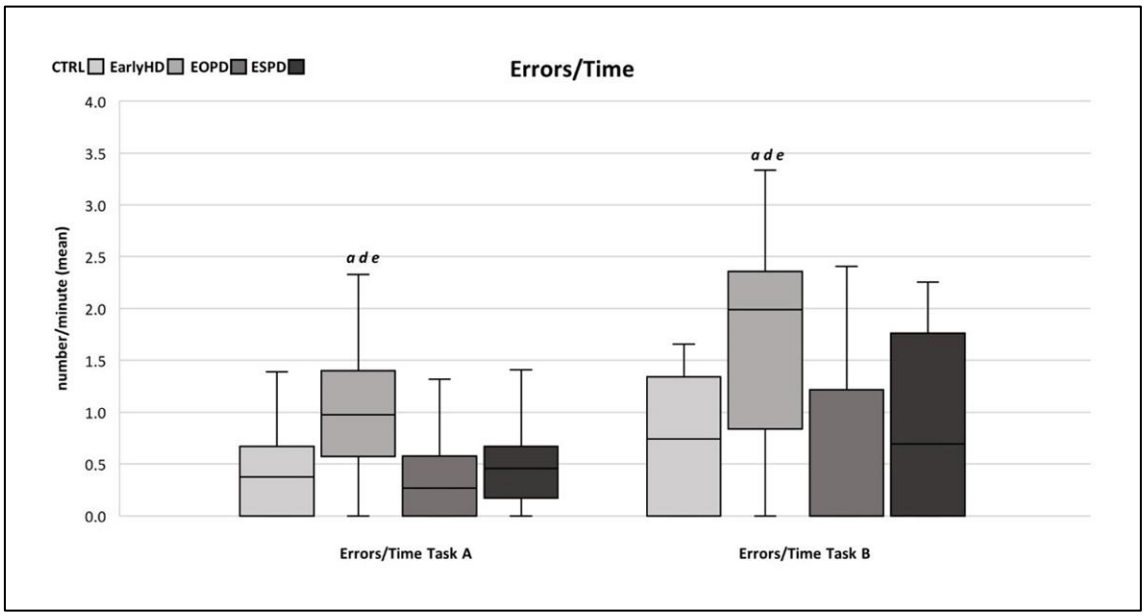

Figure 3.2 *EcoKitchen* Number of Total Errors per minute of Performance Time Task A and Number of Total Errors per minute of Performance Time Task B (Mean) and significant differences between groups.

Boxplots: central mark - median; edges of box - 25th and 75th percentiles; whiskers - most extreme data points (minimum and maximum). ***a*** *CTRL ≠ EarlyHD;* ***b*** *CTRL ≠ EOPD;* ***c*** *CTRL ≠ ESPD;* ***d*** *EarlyHD ≠ EOPD;* ***e*** *EarlyHD ≠ ESPD;* ***f*** *EOPD ≠ ESPD (Mann-Whitney p < 0.05)*

Table 3.4 *EcoKitchen* variables with Kruskal-Wallis and Mann-Whitney comparisons across groups

	CTRL	*EarlyHD*	*EOPD*	*ESPD*			
					Kruskal-Wallis		
EcoKitchen	*Median (IQR) [95% CI]*	*Median (IQR) [95% CI]*	*Median (IQR) [95% CI]*	*Median (IQR) [95% CI]*	χ^2	*p-value*	η^2
Errors / Time A	0.37 (0.67) [0-0.54]	0.97 (0.82) a d e [0.66-1.40]	0.27 (0.58) [0-0.54]	0.46 (0.50) [0.20-0.55]	11.936	0.008 *	0.154
Errors / Time B	0.74 (1.34) [0-1.26]	1.99 (1.52) a d e [0.89-2.36]	0 (1.22) [0-1.18]	0.70 (1.76) [0.13-1.52]	9.187	0.027 *	0.107
Performance Time A – Block 1	41.75 (13.99) [38.56-49.54]	64.89 (42.73) a [51.47-93.35]	71.76 (74.96) b [46.39-120.02]	80.93 (57.27) c [63.97-118.92]	27.193	< 0.001 *	0.417
Performance Time A – Block 2	42.25 (8.39) [40.07-45.68]	59.97 (44.53) a [47.84-90.62]	63.39 (49.48) b [44.24-97.85]	82.29 (47.86) c [60.29-98.77]	21.536	< 0.001 *	0.320
Performance Time A – Block 3	57.28 (27.67) [47.48-71.95]	82.21 (70.28) a [70.63-130.02]	74.25 (36.31) b [56.77-96.64]	111.53 (59.39) c f [87.68-138.71]	22.794	< 0.001 *	0.341
Performance Time B	50.88 (17.58) [48.75- 64.53]	81.82 (55.34) a [65.66-111.78]	80.52 (47.26) b [60.85-101.76]	112.55 (85.96) c [79.82-152.79]	22.079	< 0.001 *	0.329
Reaction Time – Block 1	0.56 (0.54) [0.48- 0.81]	1.15 (2.99) a [0.69-3.62]	2.15 (7.70) b [0.82-7.33]	1.39 (4.28) c [0.83-4.06]	14.234	0.003 *	0.194
Reaction Time – Block 2	3.20 (2.11) [2.80- 4.15]	7.28 (7.31) a [4.49-10.92]	8.38 (6.53) b [4.21-10.45]	7.74 (9.19) c [4.09-11.13]	21.084	< 0.001 *	0.312
Reaction Time – Block 3	4.71 (2.85) [3.21-5.16]	6.69 (18.76) a [5.30-24.06]	5.60 (4.37) [4.48-9.73]	8.86 (8.22) c f [5.73-13.40]	15.720	0.001 *	0.219
Reaction Time – Stove	1.24 (0.87) [0.75-1.46]	2.45 (4.14) a [1.86-5.07]	3.65 (3.22) b [1.60-5.30]	3.25 (9.09) c [2.18-10.54]	18.369	< 0.001 *	0.265
Reaction Time – Kettle	7.14 (5.61) [5.97- 8.52]	14.84 (23.32) a [9.29-32.56]	11.42 (11.13) [7.05-19.79]	12.84 (8.31) c [8.65-16.62]	15.573	0.001 *	0.217
Reaction Time – Toaster	1.38 (2.28) [0.81-2.08]	2.21 (4.60) [0.62-5.22]	2.85 (4.05) [2.33-6.89]	4.16 (8.90) [1.92-9.80]	7.214	0.065	0.073

CTRL – Controls; EarlyHD – Early Manifest Huntington's Disease; EOPD – Early-Onset Parkinson's Disease; ESPD – Early-Stage Parkinson's Disease
*IQR – Interquartile Range [95% Confidence Interval for median] * Kruskal-Wallis p< 0.05*
a CTRL ≠ EarlyHD; b CTRL≠ EOPD; c CTRL≠ ESPD; d EarlyHD ≠ EOPD; e EarlyHD ≠ ESPD; f EOPD≠ ESPD (Mann-Whitney p < 0.05)

Post-hoc tests revealed that persons with EarlyHD showed an increased number of errors *per* minute in comparison with CTRL, EOPD and ESPD participants during the preparation of a cup of coffee with milk (Task A) (U= 65.5, p= 0.007, η^2= 0.213; U= 24.5, p= 0.005, η^2= 0.315; and U= 62.5, p= 0.009, η^2= 0.208, respectively) and of toasts with butter (Task B) (U= 80.5, p= 0.029, η^2= 0.140; U= 30, p= 0.012, η^2= 0.255; and U= 71.5, p= 0.021, η^2= 0.161, respectively).

EcoKitchen Time Measures

All clinical groups took longer to finish the tasks than control participants across the different *EcoKitchen* blocks, suggesting that persons with mild HD and PD already present slowed motor and/or cognitive processes that influence their timely performance both in single and multitasking conditions. Moreover, increasing the executive demand of the task had a more detrimental effect in the performance time of persons with ESPD than persons with EOPD, as persons with ESPD were constantly slower in the *EcoKitchen* Block 3. Finally, all clinical groups showed slower reaction times when compared to the control group, taking longer to react to target stimuli while engaged in a primary task, even when prompt action indications were given.

Concretely, we found a statistically significant group effect in Task A and Task B Performance Times in all the *EcoKitchen* Blocks (Figure 3.3 and Table 3.4).

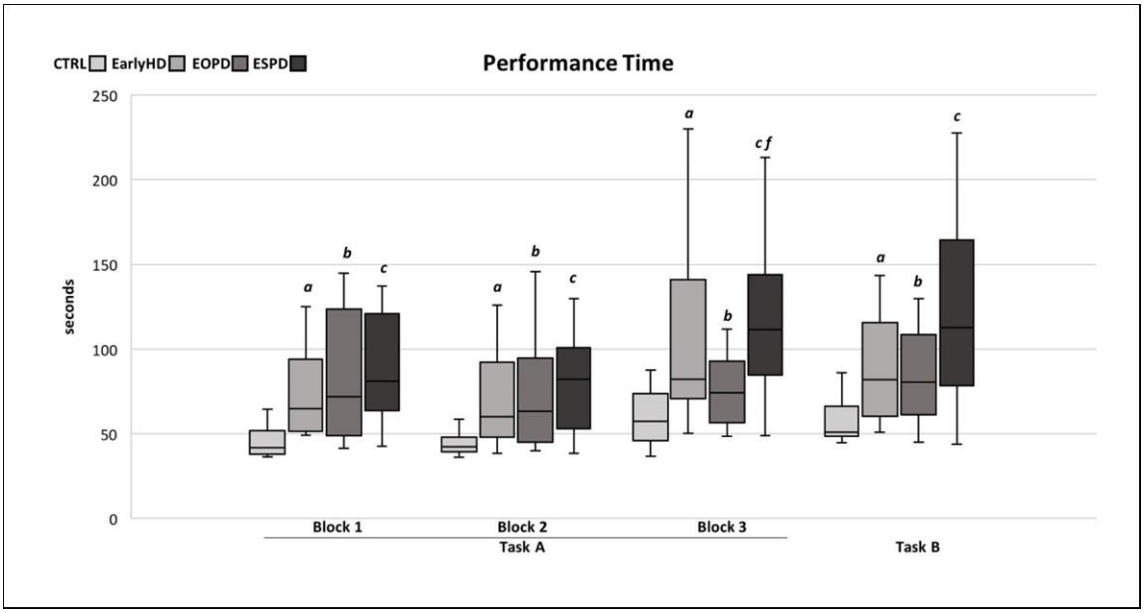

Figure 3.3 *EcoKitchen* Performance Time Task A and Performance Time Task B and significant differences between groups.

Boxplots: central mark - median; edges of box - 25th and 75th percentiles; whiskers - most extreme data points (minimum and maximum). ***a*** *CTRL ≠ EarlyHD;* ***b*** *CTRL ≠ EOPD;* ***c*** *CTRL ≠ ESPD;* ***d*** *EarlyHD ≠ EOPD;* ***e*** *EarlyHD ≠ ESPD;* ***f*** *EOPD ≠ ESPD (Mann-Whitney $p < 0.05$)*

Post-hoc comparisons revealed that the clinical groups were significantly slower than CTRL participants across all the *EcoKitchen* Blocks and Tasks: EarlyHD vs CTRL – Task A: Block 1 – U= 25, p< 0.001, η^2= 0.488; Block 2 – U= 46, p= 0.001, η^2= 0.329; Block 3 – U= 46, p= 0.001, η^2= 0.329; Task B: U= 41, p< 0.001, η^2= 0.365; EOPD vs CTRL – Task A: Block 1 – U= 29, p= 0.002, η^2= 0.316; Block 2 – U= 36, p= 0.007, η^2= 0.253; Block 3 – U= 50, p= 0.039, η^2= 0.147; Task B: U= 36, p= 0.007, η^2= 0.253; and ESPD vs CTRL – Task A: Block 1 – U= 21, p< 0.001, η^2= 0.561; Block 2 – U= 34, p< 0.001, η^2= 0.468; Block 3 – U= 34, p< 0.001, η^2= 0.468; Task B: U= 39, p< 0.001, η^2= 0.435. Interestingly, we found that persons with ESPD spend more time than persons with EOPD to complete Task A in the more cognitively demanding *EcoKitchen* Block 3 (U= 38, p= 0.013, η^2= 0.222), whereas no significant differences were found between the EarlyHD group and both EOPD and ESPD groups in performance time.

A statistically significant group effect was found in the average Reaction Time across the three *EcoKitchen* Blocks (Figure 3.4 and Table 3.4).

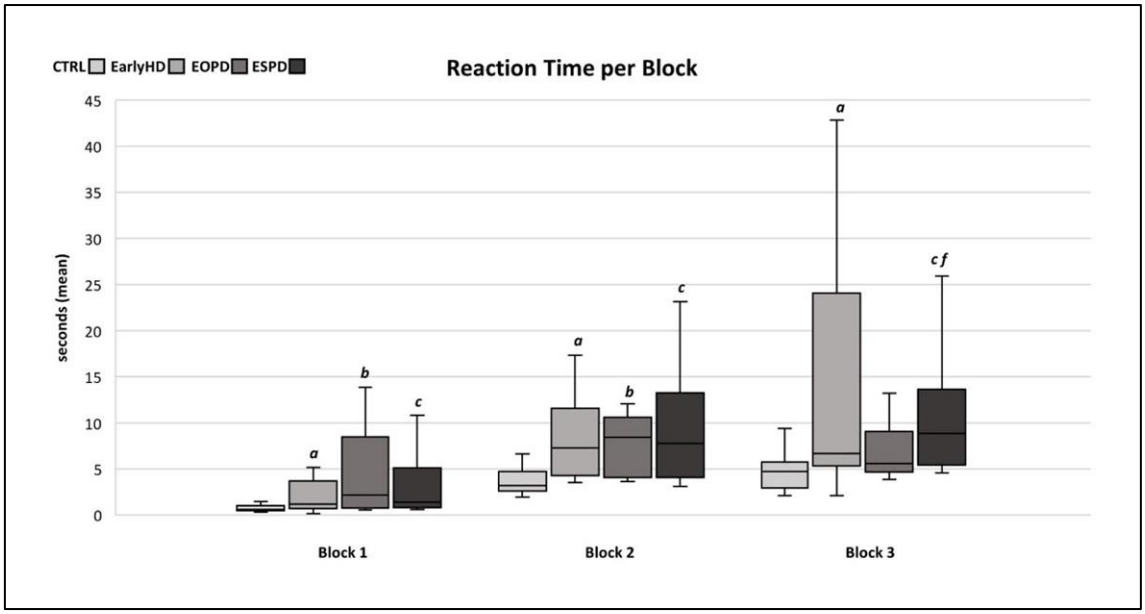

Figure 3.4 *EcoKitchen* Reaction Time per Block and significant differences between groups

Boxplots: central mark - median; edges of box - 25th and 75th percentiles; whiskers - most extreme data points (minimum and maximum). ***a*** *CTRL ≠ EarlyHD;* ***b*** *CTRL ≠ EOPD;* ***c*** *CTRL ≠ ESPD;* ***d*** *EarlyHD ≠ EOPD;* ***e*** *EarlyHD ≠ ESPD;* ***f*** *EOPD ≠ ESPD (Mann-Whitney $p < 0.05$)*

Post-hoc comparisons revealed that the clinical groups were again significantly slower than CTRL participants to react to the different cues: EarlyHD vs CTRL – Block 1: U= 81.5, p= 0.034, η^2= 0.132; Block 2: U= 38.5, p< 0.001, η^2= 0.383; Block 3: U= 68, p= 0.010, η^2= 0.196; EOPD vs CTRL – Block 1: U= 31, p= 0.003, η^2= 0.297; Block 2: U= 22.5, p= 0.001, η^2= 0.382; and ESPD vs CTRL – Block 1: U= 58, p= 0.001, η^2= 0.319; Block 2: U= 47, p< 0.001, η^2= 0.384; Block 3: U= 49, p< 0.001, η^2= 0.371. Persons with ESPD showed an increased reaction time compared to persons with EOPD in the more cognitively demanding Block 3 (U= 47, p= 0.039, η^2= 0.152).

Considering the *EcoKitchen* cues separately, a significant group effect was found in the time the participants took to react and turn off the Stove and the Kettle (Figure 3.5 and Table 3.4).

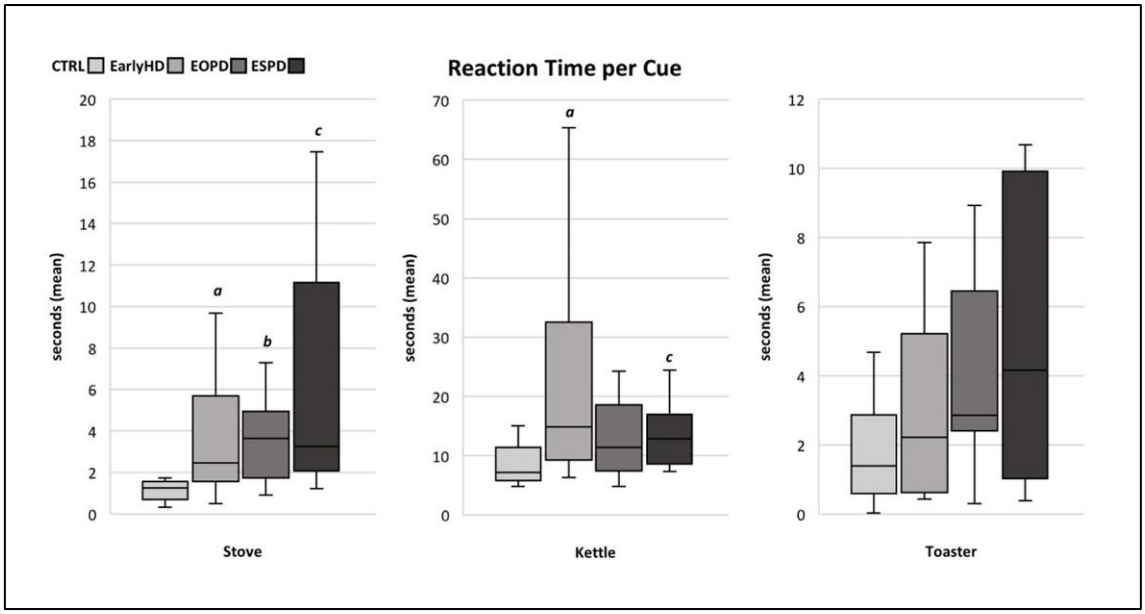

Figure 3.5 *EcoKitchen* Reaction Time per Cue – Stove, Kettle, and Toaster (Mean of the 3 blocks) and significant differences between groups

Boxplots: central mark - median; edges of box - 25th and 75th percentiles; whiskers - most extreme data points (minimum and maximum). ***a*** *CTRL ≠ EarlyHD;* ***b*** *CTRL ≠ EOPD;* ***c*** *CTRL ≠ ESPD;* ***d*** *EarlyHD ≠ EOPD;* ***e*** *EarlyHD ≠ ESPD;* ***f*** *EOPD ≠ ESPD (Mann-Whitney $p < 0.05$)*

The *post-hoc* tests revealed that persons with EarlyHD, EOPD and ESPD took longer than CTRL participants to react to the Stove cue (U= 59, p= 0.004, η^2= 0.247; U= 33, p= 0.004, η^2= 0.279; and U= 44, p< 0.001, η^2= 0.402, respectively). Persons with EarlyHD and ESPD took longer than controls to attend to the Kettle (U= 51, p= 0.002, η^2= 0.296; and U= 55, p< 0.001, η^2= 0.336, respectively).

BADS – the Behavioural Assessment of Dysexecutive Syndrome battery

Testing executive functions using the BADS, a battery of tests that resemble everyday like situations, we observed cognitive deficits in persons with EarlyHD and ESPD but not in persons with EOPD, suggesting that this latter group presents a more preserved cognitive status.

Explicitly, a statistically significant group effect was found for some of the measures computed from BADS, namely the BADS total, the Rule Shift Card test, the Action Program test, and the Zoo Map test scores (Table 3.5).

Table 3.5. BADS (the Behavioural Assessment of Dysexecutive Syndrome battery) results with Kruskal-Wallis and Mann-Whitney comparisons across groups

	CTRL	*EarlyHD*	*EOPD*	*ESPD*	*Kruskal-Wallis*		
BADS	*Median (IQR) [95% CI]*	*Median (IQR) [95% CI]*	*Median (IQR) [95% CI]*	*Median (IQR) [95% CI]*	χ^2	*p-value*	η^2
Total	17 (3) [17-19]	12 (5) a d [10-14.5]	17 (6) [13-19]	13 (6) c [11-15.5]	18.520	<0.001*	0.259
Rule Shift Cards Test	4 (1) [3-4]	3 (2) a [2-3.5]	4 (3) [1-4]	3 (3) c [1-3]	9.463	0.024*	0.108
Action Program Test	4 (0) [4-4]	3 (2) a [2-4]	4 (1) [3-4]	3 (1) c [3-4]	11.831	0.008*	0.147
Key Search Test	3 (2) [2-4]	2 (2) [1-3]	2 (3) [1-4]	1.5 (2) [1-2.5]	7.573	0.056	0.076
Temporal Judgment Test	2 (1) [1-2]	1 (1) [1-2]	2 (1) [1-2]	1.5 (1) [1-2]	2.774	0.428	0.004
Zoo Map Test	2 (2) [2-3]	1 (2) a d [0.5-2]	3 (2) [2.5-4]	1 (3) c f [0-2]	12.016	0.007*	0.150
Modified Six Elements Test	4 (1) [3-4]	3 (2) [2.5-3.5]	3 (1) [2.5-4]	3 (2) [2-4]	4.890	0.180	0.031

CTRL – Controls; EarlyHD – Early Manifest Huntington's Disease; EOPD – Early-Onset Parkinson's Disease; ESPD – Early-Stage Parkinson's Disease
IQR – Interquartile Range [95% Confidence Interval for median]
BADS – The Behavioural Assessment of Dysexecutive Syndrome battery
** Kruskal-Wallis p< 0.05*
a CTRL ≠ EarlyHD; b CTRL≠ EOPD; c CTRL≠ ESPD; d EarlyHD ≠ EOPD; e EarlyHD ≠ ESPD; f EOPD≠ ESPD (Mann-Whitney p < 0.05)

Both persons with EarlyHD and ESPD, but not persons with EOPD, showed significant differences in their BADS performance when compared to controls, specifically in BADS Total score (U= 31, p< 0.001, η^2= 0.440 and U= 76, p= 0.001, η^2= 0.263, respectively), Rule Shift Cards test score (U= 76, p= 0.013, η^2= 0.156 and U= 96.5, p= 0.005, η^2= 0.177, respectively), Action Program test score (U= 69, p= 0.002, η^2= 0.191 and U= 108.5, p= 0.006, η^2= 0.134, respectively), and Zoo Map test score (U= 74, p= 0.014, η^2= 0.166 and U= 117, p= 0.036, η^2= 0.108, respectively). Moreover, we also found that persons with EarlyHD and ESPD showed significant differences compared to persons with EOPD - the EarlyHD group exhibited decreased BADS Total and Zoo Map test scores (U= 34, p= 0.022, η^2= 0.207 and U= 26.5, p= 0.006, η^2= 0.290, respectively) and the ESPD group exhibited a decreased score in the Zoo Map test (U= 49.5, p= 0.022, η^2= 0.165).

IAFAI – the Adults and Older Adults Functional Assessment Inventory

All clinical groups signalled a significantly higher percentage of functional difficulties when compared to control participants, indicating self-awareness of their own impairments. Notably, we found relevant differences in the self-appraisal of functional status of persons with EarlyHD and ESPD, as persons with EarlyHD reported more incapacity due to cognitive factors and persons with ESPD reported more incapacity due to physical factors.

Specifically, we found a significant group effect in all the incapacity percentages computed from IAFAI, namely in the Global Functional Incapacity – GFI, Functional Incapacity in Basic Activities of Daily Living – BADL, Functional Incapacity in Household Instrumental Activities of Daily Living – H-IADL, Functional Incapacity in Advanced Instrumental Activities of Daily Living – A-IADL, Functional incapacity due to Physical Factors – Physical, Functional Incapacity due to Cognitive Factors – Cognitive, and Functional Incapacity due to Emotional Factors – Emotional (Table 3.6).

Table 3.6 Percentage of participants that had a score ≠ 0 in IAFAI (the Adults and Older Adults Functional Assessment Inventory)

	CTRL	*EarlyHD*	*EOPD*	*ESPD*			
					Chi-Square		
IAFAI	% *[95% CI]*	% *[95% CI]*	% *[95% CI]*	% *[95% CI]*	χ^2	*p-value*	*Cramér's V*
GFI	17.6 [3.8-43.4]	93.3 a [68.1-99.8]	90 b [55.5-99.7]	100 c [83.2-100]	39.521	< 0.001*	0.798
BADL	0 [0-19.5]	80 a [51.9-95.7]	90 b [55.5-99.7]	100 c e [83.2-100]	47.267	< 0.001*	0.873
H-IADL	0 [0-19.5]	93.3 a [68.1-99.8]	90 b [55.5-99.7]	70 c [45.7-88.1]	36.927	< 0.001*	0.772
A-IADL	17.6 [3.8-43.4]	80 a [51.9-95.7]	80 b [44.4-97.5]	85 c [62.1-96.8]	22.596	< 0.001*	0.604
Physical	0 [0-19.5]	80 a [51.9-95.7]	90 b [55.5-99.7]	100 c e [83.2-100]	47.267	< 0.001*	0.873
Cognitive	11.8 [1.5-36.4]	93.3 a d e [68.1-99.8]	60 b [26.2-87.8]	60 c [36.1-80.9]	22.034	< 0.001*	0.596
Emotional	11.8 [1.5-36.4]	60 a [32.3-83.7]	40 [12.2-73.8]	50 c [27.2-72.8]	8.954	0.030*	0.380

CTRL – Controls; EarlyHD – Early Manifest Huntington's Disease; EOPD – Early-Onset Parkinson's Disease; ESPD – Early-Stage Parkinson's Disease
IAFAI - the Adults and Older Adults Functional Assessment Inventory; Global Functional Incapacity – GFI, Functional Incapacity in Basic Activities of Daily Living – BADL, Functional Incapacity in Household Instrumental Activities of Daily Living – H-IADL, Functional Incapacity in Advanced Instrumental Activities of Daily Living – A-IADL, Functional incapacity due to Physical Factors – Physical, Functional Incapacity due to Cognitive Factors – Cognitive, and Functional Incapacity due to Emotional Factors – Emotional
[Clopper-Pearson 95% Confidence Intervals]
** Chi-square p< 0.05*
a CTRL ≠ EarlyHD; b CTRL≠ EOPD; c CTRL≠ ESPD; d EarlyHD ≠ EOPD; e EarlyHD ≠ ESPD; f EOPD≠ ESPD (Chi-square test for independence p < 0.05)

Post-hoc tests showed that a higher percentage of persons with EarlyHD, EOPD and ESPD than controls signalled functional difficulties in IAFAI and attributed them to physical, cognitive, and emotional factors: EarlyHD vs CTRL – GFI (χ^2(1)= 18.331, p< 0.001, Cramér's V= 0.757), BADL (χ^2(1)= 21.760, p< 0.001, Cramér's V= 0.825), H-IADL (χ^2(1)= 28.207, p< 0.001, Cramér's V= 0.939), A-IADL (χ^2(1)= 12.441, p< 0.001, Cramér's V= 0.624), Physical (χ^2(1)= 21.760, p< 0.001, Cramér's V= 0.825), Cognitive (χ^2(1)= 21.208, p<0.001, Cramér's V= 0.814), and Emotional (χ^2(1)= 8.219, p= 0.004, Cramér's V= 0.507); EOPD vs CTRL – GFI (χ^2(1)= 13.349, p< 0.001, Cramér's V= 0.703), BADL (χ^2(1)= 22.950, p< 0.001, Cramér's V= 0.922), H-IADL (χ^2(1)= 22.950, p< 0.001, Cramér's V= 0.922), A-IADL (χ^2(1)= 10.139, p= 0.001, Cramér's V= 0.613), Physical (χ^2(1)= 22.950, p< 0.001, Cramér's V= 0.922), and Cognitive (χ^2(1)= 7.026, p= 0.008, Cramér's V= 0.510); and ESPD vs CTRL – GFI (χ^2(1)= 26.496, p< 0.001, Cramér's V= 0.846), BADL (χ^2(1)= 37.000, p< 0.001, Cramér's V= 1.000), H-IADL (χ^2(1)= 19.143, p< 0.001, Cramér's V= 0.719), A-IADL (χ^2(1)= 16.785, p< 0.001, Cramér's V= 0.674), Physical (χ^2(1)= 37.000, p< 0.001, Cramér's V= 1.000), Cognitive (χ^2(1)= 9.090, p= 0.003, Cramér's V= 0.496), and Emotional (χ^2(1)= 6.130, p= 0.013, Cramér's V= 0.407). Interestingly, a higher percentage of persons with

ESPD than persons with EarlyHD reported difficulties in the performance of Basic Activities of Daily Living ($\chi^2(1)= 4.375$, $p= 0.036$, Cramér's $V= 0.354$) and attributed the cause of their functional difficulties to physical factors ($\chi^2(1)= 4.375$, $p< 0.036$, Cramér's $V= 0.354$). Notably, more persons with EarlyHD than persons with EOPD and ESPD reported cognitive factors as the cause of functional difficulties [($\chi^2(1)= 4.167$, $p= 0.041$, Cramér's $V= 0.408$), and ($\chi^2(1)= 4.986$, $p= 0.026$, Cramér's $V= 0.377$), respectively].

Correlational Analyses

The *EcoKitchen* time measures, but not the accuracy measures, seem to give relevant indications about the functional impact of PD clinical phenotype, as they captured some of the disease main features, namely motor symptom severity and disease stage. Specifically, the performance and reaction times of PD participants in the *EcoKitchen* were significantly correlated with their UPDRS and Hoehn and Yahr scale scores (Table 3.7).

Table 3.7 Correlations between the *EcoKitchen*, and Demographical and Clinical data for the clinical groups

	EcoKitchen											
	Performance Time A			*Reaction Time Block*			*Errors/Time A*			*Total Errors*		
Demographics & Clinical data	*EarlyHD*	*EOPD*	*ESPD*	*EarlyHD*	*EOPD*	*ESPD*	*EarlyHD*	*EOPD*	*ESPD*	*EarlyHD*	*EOPD*	*ESPD*
Age	r_s= 0.290 p= 0.295	**r_s= 0.707** **p= 0.022**	r_s= 0.035 p= 0.889	r_s= 0.232 p= 0.404	r_s= 0.488 p= 0.153	r_s= 0.090 p= 0.724	r_s= 0.016 p= 0.954	r_s= -0.254 p= 0.479	r_s= 0.100 p= 0.693	r_s= -0.064 p= 0.820	r_s= -0.062 p= 0.865	r_s= 0.176 p= 0.485
Education	r_s= -0.087 p= 0.759	**r_s= -0.720** **p= 0.019**	r_s= -0.295 p= 0.234	r_s= 0.024 p= 0.932	r_s= -0.462 p= 0.179	r_s= -0.118 p= 0.641	r_s= -0.101 p= 0.720	r_s= 0.219 p= 0.543	r_s= 0.017 p= 0.948	r_s= 0.015 p= 0.958	r_s= 0.085 p= 0.816	r_s= -0.015 p= 0.952
Disease Duration	r_s= 0.504 p= 0.055	r_s= 0.067 p= 0.853	r_s= 0.453 p= 0.059	r_s= 0.486 p= 0.066	r_s= -0.227 p= 0.528	r_s= 0.105 p= 0.678	r_s= 0.123 p= 0.663	r_s= 0.009 p= 0.980	r_s= -0.185 p= 0.463	r_s= 0.381 p= 0.161	r_s= 0.084 p= 0.817	r_s=-0.167 p= 0.507
CAG	r_s= 0.134 p= 0.634	-	-	r_s= 0.211 p= 0.450	-	-	r_s= -0.299 p= 0.279	-	-	r_s= -0.126 p= 0.656	-	-
UHDRS Motor	r_s= 0.402 p= 0.138	-	-	r_s= 0.275 p= 0.322	-	-	r_s= -0.269 p= 0.332	-	-	r_s= 0.064 p= 0.821	-	-
TFC	r_s= -0.228 p= 0.415	-	-	r_s= -0.450 p= 0.092	-	-	r_s= 0.489 p= 0.064	-	-	r_s= 0.362 p= 0.185	-	-
UPDRS	-	r_s= 0.333 p= 0.347	**r_s= 0.694** **p= 0.001**	-	r_s= 0.309 p= 0.385	**r_s= 0.651** **p= 0.003**	-	r_s= 0.067 p= 0.854	r_s= -0.293 p= 0.237	-	r_s= 0.185 p= 0.608	r_s= -0.206 p= 0.411
H & Y	-	r_s= 0.576 p= 0.082	**r_s= 0.515** **p= 0.029**	-	r_s= 0.132 p= 0.717	r_s= 0.374 p= 0.126	-	r_s= -0.059 p= 0.871	r_s= -0.296 p= 0.233	-	r_s= 0.180 p= 0.618	r_s= -0.146 p= 0.564
MoCA	r_s= -0.455 p= 0.088	**r_s= -0.710** **p= 0.021**	r_s= -0.311 p= 0.210	r_s= -0.296 p= 0.284	r_s= -0.549 p= 0.100	r_s= -0.288 p= 0.247	r_s= 0.448 p= 0.094	r_s= -0.124 p= 0.733	r_s= -0.110 p= 0.663	r_s= 0.216 p= 0.440	r_s= -0.204 p= 0.571	r_s= -0.197 p= 0.433
BDI-II	r_s= 0.134 p= 0.633	**r_s= 0.679** **p= 0.031**	r_s= -0.052 p= 0.839	r_s= 0.168 p= 0.551	r_s= 0.196 p= 0.588	r_s= 0.202 p= 0.420	r_s= -0.224 p= 0.423	r_s= -0.080 p= 0.827	r_s= 0.108 p= 0.668	r_s= -0.294 p= 0.287	r_s= 0.044 p= 0.905	r_s= 0.120 p= 0.636
TeLPI QIEC	r_s= 0.023 p= 0.934	**r_s= -0.758** **p= 0.011**	r_s= -0.345 p= 0.161	r_s= 0.151 p= 0.591	r_s= -0.358 p= 0.310	r_s= -0.327 p= 0.185	r_s= 0.071 p= 0.800	r_s= -0.030 p= 0.934	r_s= 0.038 p= 0.880	r_s= 0.167 p= 0.552	r_s= -0.154 p= 0.670	r_s= -0.027 p= 0.915
TeLPI QIV	r_s= 0.027 p= 0.924	**r_s= -0.758** **p= 0.011**	r_s= -0.355 p= 0.148	r_s= 0.199 p= 0.476	r_s= -0.358 p= 0.310	r_s= -0.263 p= 0.291	r_s= 0.071 p= 0.800	r_s= -0.030 p= 0.934	r_s= 0.063 p= 0.804	r_s= 0.176 p= 0.531	r_s= -0.154 p= 0.670	r_s= 0.002 p= 0.993
TeLPI QIR	r_s= 0.005 p= 0.985	**r_s= -0.794** **p= 0.006**	r_s= -0.407 p= 0.094	r_s= 0.165 p= 0.556	r_s= -0.297 p= 0.405	r_s= -0.358 p= 0.144	r_s= 0.107 p= 0.704	r_s= 0.055 p= 0.881	r_s= 0.065 p= 0.798	r_s= 0.169 p= 0.548	r_s= -0.080 p= 0.826	r_s= -0.027 p= 0.915

EarlyHD – Early Manifest Huntington's Disease; EOPD – Early-Onset Parkinson's Disease; ESPD – Early-Stage Parkinson's Disease
CAG – CAG repeat expansion confirmed by an HD genetic test; UHDRS - TFC – Total Functional Capacity scale of the Unified Huntington's Disease Rating Scale; UHDRS - Motor – Motor scale of the Unified Huntington's Disease Rating Scale; UPDRS - Motor – Motor scale of the Unified Parkinson's Disease Rating Scale; H & Y – Hoehn and Yahr scale; MoCA – Montreal Cognitive Assessment; BDI-II – Beck Depression Inventory II; TeLPI – The Irregular Word Reading Test; QIEC – Full Scale Intelligence Quotient; QIV – Verbal Intelligence Quotient; QIR – Performance Intelligence Quotient
Performance Time A, Reaction Time per Block, Errors/Time A and Total Errors variables = mean of the three EcoKitchen blocks
*Correlation is significant at the 0.05 level (2-tailed) - **in bold***

Moreover, the global cognitive status, demographic factors, and neuropsychiatric features of EOPD participants seem to influence their performance time, as demonstrated by the significant correlations found with the MoCA, TeLPI, age, education level, and BDI-II scores. In contrast, no significant correlations were found between any of the *EcoKitchen* parameters and the demographic and clinical data of persons with EarlyHD, nor their results on the cognitive and neuropsychiatric screening measures used.

Discussion

The performance-based results revealed that persons with PD and HD present significant difficulties in the timely completion of executive demanding tasks that replicate everyday routines, the *EcoKitchen*. However, only the EarlyHD group showed diminished accuracy in this task, which suggests higher executive impairment in persons with EarlyHD compared to persons with ESPD and EOPD. Moreover, the BADS results also indicate that cognitive impairment is heterogeneous not only between basal ganglia disorders, but also within the same clinical condition, as persons with early-onset PD present an executive status that parallels the one of control participants and some executive deficits were identified in persons with late-onset PD during the completion of ecologically relevant BADS sub-tests.

The subjective report of daily life incapacities indicated functional deficits' awareness in all clinical groups. Importantly, the distinct IAFAI results of the clinical groups – persons with ESPD signalled more physical deficits and persons with EarlyHD signalled more cognitive deficits as the main cause of their dysfunction – matched their objective *EcoKitchen* performance, considering that persons with ESPD were slower but showed normal accuracy, and persons with EarlyHD were slower and committed more executive errors than the other study groups. The significant associations identified between the *EcoKitchen* time measures and the motor symptoms of the ESPD group further reinforce the notion that persons with early stage PD maintain awareness about the impact of physical/motor abnormalities in their performance of daily life- like tasks.

Thus, we were able to detect distinct functional alterations as a consequence of distinct cognitive profiles in persons with early Parkinson's and Huntington's disease. Moreover, we showed that persons in early disease stages without dementia have

preserved awareness about the underlying causes contributing to their everyday-life deficits.

Objective Assessment of Executive Status

Notably, although the three clinical groups were slower than controls during the completion of both single-task and multi-task executively demanding blocks, only persons with EarlyHD showed diminished accuracy in the *EcoKitchen*. This finding is strongly corroborated by the large effect sizes of the significant differences observed between the time spend by the three clinical groups to perform the tasks and react to the *EcoKitchen* stimuli and the time results of the control group (all $\eta^2 \geq 0.132$) and by the medium and large effect sizes of the significant differences found between the persons with EarlyHD error rate and the error rate of the other study participants (all Cramér's $V \geq 0.346$). It is well accepted that reaction times are prolonged in both persons with PD and HD (Sprengelmeyer et al., 1995), so the *EcoKitchen* time measures were expected to reflect the bradyphrenia that is a hallmark of these diseases (Hanes et al., 1995). Importantly, the differences found in the EOPD, ESPD and EarlyHD task performance might reflect the disparate regional distributions of the neuropathologic changes observed in these disorders – although both have an early effect on the striatum and progressively evolve to more widespread cortical and subcortical dysfunction, there is a greater involvement of the putamen in PD (with its predominantly motor role) and a greater involvement of the caudate nucleus in HD (with its predominantly cognitive role) (Bhatia & Marsden, 1994; Cope et al., 1996; DeLong & Georgopoulos, 1981; Geevarghese et al., 2015; Peinemann et al., 2005; Sprengelmeyer et al., 1995; Starkstein et al., 1992). While cognitive impairment is usually seen as an early HD feature, particularly elicited by tasks that rely on frontostriatal circuits, the cognitive deterioration in idiopathic PD tends to be a relatively late disease manifestation and is thought to evolve according to the progression of dopamine depletion within the striatum, which parallels the motor deficits (Ceravolo et al., 2012; Glosser, 2001; O'Keeffe et al., 2009). Nevertheless, as previously stated, though in the early stages of Parkinson's and Huntington's disease the dichotomy putamen - caudate nucleus is more pronounced, the progressive structural and functional neuropathological changes associated with both conditions are significative, complex, and seldom restricted to specific areas (Andrews & Brooks, 1998; Berti et al., 2012; Huang et al., 2007; Montoya et

al., 2006; Rosas et al., 2003). Thus, we cannot discard the contribution of other brain regions and circuitries to the disparate cognitive and functional deficits observed in persons with PD and HD.

Our performance-based results corroborate previous studies: Hanes et al. (1995) found that persons with HD were impaired in tasks of cognitive flexibility and integration compared to persons with PD, who had standard accuracy and only presented reaction time deficits; Lundervold et al. (1994) showed that persons with HD were more severely impaired on a neuropsychological test battery than persons with PD, that only had mild sensorimotor deficits; Dirnberger and Jahanshahi (2013) pointed out that persons with mild PD usually show longer latencies to initiate correct responses but regular accuracy levels; and Bialystok et al. (2008) compared persons with PD to age-matched and younger controls in a virtual breakfast task and showed that they outperformed same-age controls and also often matched the level of young controls. Interestingly, while the two groups of persons with Parkinson's disease showed an accuracy level similar to healthy participants, significant time differences emerged between persons with ESPD and EOPD, but not between persons with ESPD and EarlyHD, in the most challenging *EcoKitchen* Block 3, where persons with ESPD were slower, both in the time taken to complete the task and in the time taken to react to the cues. This discrepancy between sub-groups of persons with Parkinson's disease reiterates the notion that cognitive impairment can be a distinguishing feature of clinical subgroups of Parkinson's disease (Svenningsson et al., 2012; van Rooden et al., 2011) and that persons with EOPD present a slower rate of cognitive dysfunction and a more preserved executive status than persons with PD (Schrag & Schott, 2006; Tang et al., 2016). Moreover, it suggests that persons with late-onset PD need to slow down in more cognitively demanding conditions to maintain good performance accuracy – the speed-accuracy trade-off often seen in clinical populations (Heitz, 2014).

In one way, the BADS results reinforce this idea of distinct executive profiles between persons with early-onset and late-onset mild PD, as no differences were found between the EOPD and CTRL groups in any of the BADS measures. We have previously shown that BADS was not able to differentiate persons with premanifest HD and healthy participants (Júlio, et al., 2019). The current findings suggest that the EOPD group seems to display subclinical cognitive symptoms that, similarly to persons with premanifest HD, cannot be apprehended by BADS, which might not be sensitive to executive impairments in relatively high functioning individuals (Sohlberg & Mateer, 2001).

In another way, the BADS scores of the EarlyHD and ESPD groups go in line with previous studies that identified executive changes in basal ganglia disorders (Kamei et al., 2008; Koerts et al., 2012; McKinlay et al., 2010; Perfetti et al., 2010; Unmack Larsen et al., 2015). Notably, the BADS sub-tests where persons with EarlyHD and ESPD were significantly different not only from controls, but also from EOPD participants (Rule Shift Card, Action Program, and Zoo Map, all with medium and large significant differences of $\eta^2 \geq 0.108$), have disparate features and tap distinct skills compared to the tasks included in the *EcoKitchen*. The time constraints of the Rule Shift Card and Zoo Map tests imply a score penalization for slower participants; the Action Program and Zoo Map tests involve high-demanding planning, complex problem-solving and logical reasoning skills, as participants must structure an action plan without any assistance or prompting cues (Wilson et al., 1998). These skills might be less important for the execution of simple everyday routines, such as meal preparation. Thus, although the BADS battery has higher ecological validity than classic executive tests and tries to mimic real-world situations (Burgess et al., 2006), its sensitivity to early HD and PD executive changes must be seen with some caution, as it puts at disadvantage persons with bradyphrenia/bradykinesia and involves complex cognitive skills.

Subjective Assessment of Functional Status

A remarkable difference was found between the clinical groups in the IAFAI questionnaire – persons with ESPD reported more functional difficulties due to physical constraints than persons with EarlyHD, and persons with EarlyHD reported more functional difficulties due to cognitive constraints than persons with EOPD and ESPD. These differences observed between the self-report of the clinical groups had moderate effect sizes (Cramér's V between 0.354 and 0.408). Furthermore, all persons with PD and HD indicated a higher number of incapacities in completing basic and instrumental activities of daily living than controls. This finding is strongly supported by the large effect sizes found in our data analysis (Cramér's V between 0.407 and 1). Importantly, this suggests that the subjective appraisal of everyday function is relatively preserved in persons with ESPD and EarlyHD, as it matches their objective performance in simulated everyday tasks. In the *EcoKitchen*, persons with ESPD were slower than controls, which is possibly related to physical factors (bradykinesia), whereas persons with EarlyHD were not only slower than controls, but also committed more errors than all other

participants, which is possibly related to cognitive factors (executive deficits).

On the one hand, our findings challenge the claim of inaccurate self-appraisal as a reflection of prefrontal pathology (Kudlicka et al., 2013; Sitek et al., 2011). Lack of insight has been reported in Parkinson's disease (Kudlicka et al., 2013; Leritz et al., 2004) and Huntington's disease (Andrews et al., 2018; Ho et al., 2006; Nicoll et al., 2014; Sitek et al., 2013). However, most of the existing studies infer the reduced awareness from self-report vs informant report comparisons [e.g., Andrews et al. (2018); Ho et al. (2006)] and are seldom based on the combination of subjective and objective individual measures or comparisons between clinical and healthy participants. Furthermore, many of the studies that found altered awareness in PD and HD included persons in more advanced disease stages and/or that already presented pronounced cognitive deficits, which might play an important role in the ability to recognize one's limitations [e.g., Deck et al. (2019); Ho et al. (2006); Kudlicka et al. (2013)].

On the other hand, the IAFAI data consubstantiate recent findings. Vlagsma et al. (2017) demonstrated that persons with PD have more complaints about time management and initiation skills than their relatives and healthy individuals. Hoth et al. (2007) proved that persons with HD have some degree of self-awareness, rating their own level of functioning as being poorer than their collaterals' level of functioning. Aldaz et al. (2019) showed that persons with HD report higher prevalence of attentional deficits and cognitive problems than persons with PD in a questionnaire of non-motor symptoms. Previous HD studies concluded that in earlier disease stages awareness of functional dysfunction is better preserved than awareness of clinical symptoms *per se* (McCusker & Loy, 2014; Sitek et al., 2011; Snowden et al., 1998).

Finally, the significant correlations found between the *EcoKitchen* time measures and PD clinical features (namely, motor symptom severity and disease stage) also seem to consubstantiate the IAFAI results and the self-appraisal of these persons about the consequence of their physical/motor difficulties upon their daily-life function. This finding goes in line with previous studies that identified significant associations between PD motor symptomatology and disease stage and executive function assessment measures (Domellöf et al., 2011; Pfeiffer et al., 2014; Schneider et al., 2015). Moreover, the lack of significant associations between the *EcoKitchen* performance accuracy and the other measures included in our screening protocol suggests that this assessment tool provides additional information regarding the clinical and cognitive status of study participants that is not conveyed by the other methods. Additionally, the absence of

significant correlations between the *EcoKitchen* results and the demographic, clinical and baseline cognitive features of the EarlyHD group might indicate that this method captures different traits of the disease phenotype and/or that our sample size masked the statistical significance of existing associations (e.g., the marginally significant correlation identified between the *EcoKitchen* Performance Time A and disease duration: r_s= 0.504, p= 0.055).

In sum, our study showed that the disparate objective performance of persons with PD and HD in the *EcoKitchen* corresponded to their distinct subjective report of functional abilities as assessed by the IAFAI, which suggests that persons without dementia and with early-stage Parkinson's and Huntington's disease maintain a preserved awareness regarding the disease impact on their everyday function skills.

Limitations

Some limitations should be considered when interpreting our results.

First, given the exploratory nature of this cross-sectional study and given the relatively small sample of enrolled participants, caution must be taken in the drawing of conclusions and generalization of our results to larger populations, as cross-sectional and longitudinal studies with larger sample sizes and a stricter statistical approach are needed to confirm and expand the current findings.

Second, there was an inevitable age difference across the groups because Parkinson's disease has typically a later onset than Huntington's disease. Thus, when significant differences were observed between groups, prudence is required in the interpretation of these results as age might play a role in the findings. However, this difference did not account for the *EcoKitchen* and IAFAI results – persons with EarlyHD were younger, equally slower, exhibited worse accuracy, reported the same amount of functional problems and more cognitive impairment in relation to persons with ESPD. Moreover, the EOPD and EarlyHD groups were age and education matched and similar findings were obtained. Finally, the absence of significant correlations between the age of persons with EarlyHD and PD and their *EcoKitchen* performance further complements the idea that age does not influence our study results.

Third, all the clinical groups exhibited higher depression rates than healthy participants, which might have played a role in the behavioural performance and awareness status examined in this study. However, as depression is part of the neuropsychiatric features

of both clinical conditions (Galts et al., 2019), and no statistically significant differences emerged between the EarlyHD, EOPD and ESPD groups regarding this symptom, the cognitive and functional inter-group disparities observed cannot be explained by this variable.

Fourth, simulated tasks done in clinical or research settings cannot fully replicate real-world uncertainties, so they are not fully synonymous of everyday life (McGuire, 2014; Moore et al., 2007; Williams et al., 2015). Nevertheless, virtual reality tools are thought to be more affordable, safe, easy for data capturing and scoring, efficient and widely applicable than real-life assessments (Allain et al., 2014; Parsons et al., 2017; Ruse et al., 2014).

Fifth, the IAFAI was only used as a self-report measure, which can lead to an overreporting or underreporting of problems. Still, some authors state that our knowledge about how patients experience their limitations is scarce (Koerts et al., 2012) and that reliance on caregiver reports is also prone to bias and offers only very raw information (Giovannetti et al., 2008). Moreover, our main interest was to compare the patients' subjective perception about their functional status and their objective performance in simulated routine tasks to infer their level of awareness regarding the disease impact on everyday function skills.

Lastly, the clinical groups were tested on their regular medication, which may have interfered on their performance and influenced our findings. Still, this study aimed to compare persons with EarlyHD, EOPD and ESPD on daily life- like executive demanding tasks, and it is expected that persons take their usual medication when they are carrying out their everyday activities.

Conclusion

This study sheds light on the interrelations between cognitive skills, functional ability and awareness in subcortical neurodegenerative movement disorders that damage the basal ganglia and disrupt the frontostriatal circuitry. First, we proved that the *EcoKitchen* can detect and quantify early deficits in everyday-like tasks and is therefore a valuable tool for assessing the effects of rehabilitation strategies on the functional cognition of persons with PD and HD. Second, we have identified distinct cognitive and functional profiles within similar clinical populations, which might reflect the neuropathological differences found in the basal ganglia structures primarily affected early in the course of

Parkinson's and Huntington's disease. Furthermore, we have demonstrated that persons with early-stage PD and HD without dementia maintain awareness regarding the functional impact of their clinical symptoms, as their objective performance of simulated everyday tasks parallels their subjective report of everyday problems. This cross-diagnosis comparison resorting to more sensitive and ecologically valid tools adds critical information about the diverse clinical phenotype of persons with PD and HD and its impact on function – which is crucial to the planning of tailored pharmacological and non-pharmacological interventions. Moreover, our study elucidates about the patients' level of awareness regarding everyday performance. By suggesting that awareness is preserved, we redefine the role of the patient in symptoms report and management, which will have important clinical, research and rehabilitation implications.

From a rehabilitation perspective, our findings provide relevant cues for the design and implementation of diagnosis-specific strategies both in the clinic and at home. Our work suggests that both persons with HD and PD will benefit from an intervention that privileges the motor component involved in the timely performance of everyday chores and appropriate response time to different everyday stimuli – one that is aware of the greater time needs from these persons in task completion. Furthermore, our study indicates that persons with HD will gain from rehabilitation efforts that also target the cognitive component of daily performance – an intervention that enhances the different executive sub-domains (such as planning, psychomotor speed, attention, behaviour monitoring, working memory or inhibitory control skills) implicated in the timely and accurate response to everyday challenges. Finally, by demonstrating that self-awareness is preserved in persons with mild PD and HD without dementia, our study suggests that patients should have a more prominent role in symptoms report and management, and that it will be beneficial to include them in practical decisions about meaningful targets for intervention, vocational choices, quality-of-life issues and/or specific everyday skills to boost.

References

Aarsland, D., Creese, B., Politis, M., Chaudhuri, K. R., Ffytche, D. H., Weintraub, D., & Ballard, C. (2017). Cognitive decline in Parkinson disease. *Nature Reviews Neurology*, *13*(4), 217–231.

https://doi.org/10.1038/nrneurol.2017.27

Albani, G., Raspelli, S., Carelli, L., Morganti, F., Weiss, P. L., Kizony, R., Katz, N., Mauro, A., & Riva, G. (2010). Executive functions in a virtual world: A study in Parkinson's disease. *Studies in Health Technology and Informatics*, *154*, 92–96.

Aldaz, T., Nigro, P., Sánchez-Gómez, A., Painous, C., Planellas, L., Santacruz, P., Cámara, A., Compta, Y., Valldeoriola, F., Martí, M. J., & Muñoz, E. (2019). Non-motor symptoms in Huntington's disease: A comparative study with Parkinson's disease. *Journal of Neurology*, *266*(6), 1340–1350.
https://doi.org/10.1007/s00415-019-09263-7

Allain, P., Foloppe, D. A., Besnard, J., Yamaguchi, T., Etcharry-Bouyx, F., Le Gall, D., Nolin, P., & Richard, P. (2014). Detecting everyday action deficits in Alzheimer's disease using a nonimmersive virtual reality kitchen. *Journal of the International Neuropsychological Society*, *20*(5), 468–477.
https://doi.org/10.1017/S1355617714000344

Althouse A. D. (2016). Adjust for Multiple Comparisons? It's Not That Simple. *The Annals of Thoracic Surgery*, *101*(5), 1644–1645.
https://doi.org/10.1016/j.athoracsur.2015.11.024

Alves, L., Simões, M. R., & Martins, C. (2012). The estimation of premorbid intelligence levels among Portuguese speakers: The Irregular Word Reading Test (TeLPI). *Archives of Clinical Neuropsychology*, *27*(1), 58–68.
https://doi.org/10.1093/arclin/acr103

Andrews, T. C., & Brooks, D. J. (1998). Advances in the understanding of early Huntington's disease using the functional imaging techniques of PET and SPET. *Molecular Medicine Today*, *4*(12), 532–539.
https://doi.org/10.1016/s1357-4310(98)01371-9

Andrews, S. C., Craufurd, D., Durr, A., Leavitt, B. R., Roos, R. A., Tabrizi, S. J., & Stout, J. C. (2018). Executive impairment is associated with unawareness of neuropsychiatric symptoms in premanifest and early Huntington's disease. *Neuropsychology*, *32*(8), 958–965.
https://doi.org/10.1037/neu0000479

Beck, A. T., Steer, R. A., & Brown, G. K. (1996). *Manual for the Beck Depression Inventory-II*. Psychological Corporation.

Beglinger, L. J., O'Rourke, J. J., Wang, C., Langbehn, D. R., Duff, K., Paulsen, J. S., & Huntington Study Group Investigators (2010). Earliest functional declines in Huntington disease. *Psychiatry Research*, *178*(2), 414–418.
https://doi.org/10.1016/j.psychres.2010.04.030

Berti, V., Polito, C., Borghammer, P., Ramat, S., Mosconi, L., Vanzi, E., De Cristofaro, M. T., De Leon, M., Sorbi, S., & Pupi, A. (2012). Alternative normalization methods demonstrate widespread cortical hypometabolism in untreated de novo Parkinson's disease. *The Quarterly Journal of Nuclear Medicine and Molecular Imaging*, *56*(3), 299–308.

Bhatia, K. P., & Marsden, C. D. (1994). The behavioural and motor consequences of focal lesions of the basal ganglia in man. *Brain*, *117 (Pt 4)*, 859–876. https://doi.org/10.1093/brain/117.4.859

Bialystok, E., Craik, F. I., & Stefurak, T. (2008). Planning and task management in Parkinson's disease: Differential emphasis in dual-task performance. *Journal of the International Neuropsychological Society*, *14*(2), 257–265. https://doi.org/10.1017/S1355617708080296

Burgess, P. W., Alderman, N., Evans, J., Emslie, H., & Wilson, B. A. (1998). The ecological validity of tests of executive function. *Journal of the International Neuropsychological Society*, *4*(6), 547–558. https://doi.org/10.1017/s1355617798466037

Burgess, P. W., Alderman, N., Forbes, C., Costello, A., Coates, L. M., Dawson, D. R., Anderson, N. D., Gilbert, S. J., Dumontheil, I., & Channon, S. (2006). The case for the development and use of "ecologically valid" measures of executive function in experimental and clinical neuropsychology. *Journal of the International Neuropsychological Society*, *12*(2), 194–209. https://doi.org/10.1017/S1355617706060310

Caine, E. D., & Shoulson, I. (1983). Psychiatric syndromes in Huntington's disease. *The American Journal of Psychiatry*, *140*(6), 728–733. https://doi.org/10.1176/ajp.140.6.728

Campos, R. C., & Gonçalves, B. (2011). The Portuguese Version of Beck Depression Inventory-II (BDI-II): Preliminary Psychometric Data with Two Non-Clinical Samples. *European Journal of Psychological Assessment, 27*(4), 258–264. http://hdl.handle.net/10174/3952

Ceravolo, R., Pagni, C., Tognoni, G., & Bonuccelli, U. (2012). The epidemiology and clinical manifestations of dysexecutive syndrome in Parkinson's disease. *Frontiers in Neurology*, *3*, 159. https://doi.org/10.3389/fneur.2012.00159

Chaytor, N., Schmitter-Edgecombe, M., & Burr, R. (2006). Improving the ecological validity of executive functioning assessment. *Archives of Clinical Neuropsychology*, *21*(3), 217–227. https://doi.org/10.1016/j.acn.2005.12.002

Cipresso, P., Albani, G., Serino, S., Pedroli, E., Pallavicini, F., Mauro, A., & Riva, G. (2014). Virtual multiple errands test (VMET): A virtual reality-based tool to detect early executive functions deficit in Parkinson's disease. *Frontiers in Behavioral Neuroscience*, *8*, 405. https://doi.org/10.3389/fnbeh.2014.00405

Cohen J. (1988). *Statistical Power Analysis for the Behavioural Sciences.* Routledge.

Cope, M. T., Georgiou, N., Bradshaw, J. L., Iansek, R., & Phillips, J. G. (1996). Simon effect and attention in Parkinson's disease: A comparison with Huntington's disease and Tourette's syndrome. *Journal of Clinical and Experimental Neuropsychology*, *18*(2), 276–290. https://doi.org/10.1080/01688639608408282

Deck, B. L., Xie, S. X., Choi, G., Rick, J., Siderowf, A., Rudovsky, S., Chen-Plotkin, A., Duda, J. E., Morley, J. F., Dahodwala, N., Trojanowski, J. Q., & Weintraub, D. (2019). Cognitive Functional Abilities in Parkinson's Disease: Agreement Between Patients and Informants. *Movement Disorders Clinical Practice*, *6*(6), 440–445. https://doi.org/10.1002/mdc3.12781

DeLong, M.R., & Georgopoulos, A.P. (1981). Motor function of the basal ganglia. In J.M. Brookhart, V.B. Mountcastle, & V.B. Brooks (Eds), *Handbook of physiology: The nervous system. Motor control, part I* (vol.11). American Physiological Society.

Devos, H., Nieuwboer, A., Tant, M., De Weerdt, W., & Vandenberghe, W. (2012). Determinants of fitness to drive in Huntington disease. *Neurology*, *79*(19), 1975–1982. https://doi.org/10.1212/WNL.0b013e3182735d11

Dickson D. W. (2018). Neuropathology of Parkinson disease. *Parkinsonism & Related Disorders*, *46 Suppl 1*(Suppl 1), S30–S33. https://doi.org/10.1016/j.parkreldis.2017.07.033

Dirnberger, G., & Jahanshahi, M. (2013). Executive dysfunction in Parkinson's disease: A review. *Journal of Neuropsychology, 7*(2), 193–224. https://doi.org/10.1111/jnp.12028

Domellöf, M. E., Elgh, E., & Forsgren, L. (2011). The relation between cognition and motor dysfunction in drug-naive newly diagnosed patients with Parkinson's disease. *Movement Disorders*, *26*(12), 2183–2189. https://doi.org/10.1002/mds.23814

Dumas, E. M., van den Bogaard, S. J., Middelkoop, H. A., & Roos, R. A. (2013). A review of cognition in Huntington's disease. *Frontiers in Bioscience*, *5*(1), 1–18. https://doi.org/10.2741/s355

Erro, R., Vitale, C., Amboni, M., Picillo, M., Moccia, M., Longo, K., Santangelo, G., De Rosa, A., Allocca, R., Giordano, F., Orefice, G., De Michele, G., Santoro, L., Pellecchia, M. T., & Barone, P. (2013). The heterogeneity of early Parkinson's disease: A cluster analysis on newly diagnosed untreated patients. *PloS One*, *8*(8), e70244. https://doi.org/10.1371/journal.pone.0070244

Evans, J. J., Chua, S. E., McKenna, P. J., & Wilson, B. A. (1997). Assessment of the dysexecutive syndrome in schizophrenia. *Psychological Medicine*, *27*(3), 635–646. https://doi.org/10.1017/s0033291797004790

Freitas, S., Simões, M. R., Alves, L., & Santana, I. (2011). Montreal Cognitive Assessment (MoCA): Normative study for the Portuguese population. *Journal of Clinical and Experimental Neuropsychology*, *33*(9), 989–996. https://doi.org/10.1080/13803395.2011.589374

Frisch, S., Förstl, S., Legler, A., Schöpe, S., & Goebel, H. (2012). The interleaving of actions in everyday life multitasking demands. *Journal of Neuropsychology*, *6*(2), 257–269. https://doi.org/10.1111/j.1748-6653.2012.02026.x

Fritz, C. O., Morris, P. E., & Richler, J. J. (2012). Effect size estimates: Current use, calculations, and interpretation. *Journal of Experimental Psychology: General*, *141*(1), 2–18. https://doi.org/10.1037/a0024338

Galts, C., Bettio, L., Jewett, D. C., Yang, C. C., Brocardo, P. S., Rodrigues, A., Thacker, J. S., & Gil-Mohapel, J. (2019). Depression in neurodegenerative diseases: Common mechanisms and current treatment options. *Neuroscience and Biobehavioral Reviews*, *102*, 56–84. https://doi.org/10.1016/j.neubiorev.2019.04.002

Geevarghese, R., Lumsden, D. E., Hulse, N., Samuel, M., & Ashkan, K. (2015). Subcortical structure volumes and correlation to clinical variables in Parkinson's disease. *Journal of Neuroimaging*, *25*(2), 275–280. https://doi.org/10.1111/jon.12095

Giovannetti, T., Bettcher, B. M., Brennan, L., Libron, D. J., Kessler, R. K., & Duey, K. (2008). Coffee with jelly or unbuttered toast: Commissions and omissions are dissociable aspects of everyday action impairment in Alzheimer's disease. *Neuropsychology*, *22*(2), 235–245. https://doi.org/10.1037/0894-4105.22.2.235

Glosser G. (2001). Neurobehavioral aspects of movement disorders. *Neurologic Clinics*, *19*(3), 535–551. https://doi.org/10.1016/s0733-8619(05)70033-5

Godefroy, O., Azouvi, P., Robert, P., Roussel, M., LeGall, D., Meulemans, T., & Groupe de Réflexion sur l'Evaluation des Fonctions Exécutives Study Group (2010). Dysexecutive syndrome: Diagnostic criteria and validation study. *Annals of Neurology*, *68*(6), 855–864. https://doi.org/10.1002/ana.22117

Goetz, C. G., Tilley, B. C., Shaftman, S. R., Stebbins, G. T., Fahn, S., Martinez-Martin, P., Poewe, W., Sampaio, C., Stern, M. B., Dodel, R., Dubois, B., Holloway, R., Jankovic, J., Kulisevsky, J., Lang, A. E., Lees, A., Leurgans, S., LeWitt, P. A., Nyenhuis, D., Olanow, C. W., … Movement Disorder Society UPDRS Revision Task Force (2008). Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): Scale presentation and clinimetric testing results. *Movement Disorders*, *23*(15), 2129–2170. https://doi.org/10.1002/mds.22340

Hamilton, J. M., Salmon, D. P., Corey-Bloom, J., Gamst, A., Paulsen, J. S., Jerkins, S., Jacobson, M. W., & Peavy, G. (2003). Behavioural abnormalities contribute to functional decline in Huntington's disease. *Journal of Neurology, Neurosurgery, and Psychiatry*, *74*(1), 120–122. https://doi.org/10.1136/jnnp.74.1.120

Hanes, K. R., Andrewes, D. G., & Pantelis, C. (1995). Cognitive flexibility and complex integration in Parkinson's disease, Huntington's disease, and schizophrenia. *Journal of the International Neuropsychological Society*, *1*(6), 545–553. https://doi.org/10.1017/s1355617700000679

Heitz R. P. (2014). The speed-accuracy tradeoff: History, physiology, methodology, and behavior. *Frontiers in Neuroscience*, *8*, 150.

https://doi.org/10.3389/fnins.2014.00150

Ho, A. K., Robbins, A. O., & Barker, R. A. (2006). Huntington's disease patients have selective problems with insight. *Movement Disorders*, *21*(3), 385–389. https://doi.org/10.1002/mds.20739

Hoehn, M. M., & Yahr, M. D. (1967). Parkinsonism: Onset, progression and mortality. *Neurology*, *17*(5), 427–442. https://doi.org/10.1212/wnl.17.5.427

Hoth, K. F., Paulsen, J. S., Moser, D. J., Tranel, D., Clark, L. A., & Bechara, A. (2007). Patients with Huntington's disease have impaired awareness of cognitive, emotional, and functional abilities. *Journal of Clinical and Experimental Neuropsychology*, *29*(4), 365–376. https://doi.org/10.1080/13803390600718958

Huang, C., Tang, C., Feigin, A., Lesser, M., Ma, Y., Pourfar, M., Dhawan, V., & Eidelberg, D. (2007). Changes in network activity with the progression of Parkinson's disease. *Brain*, *130*(Pt 7), 1834–1846. https://doi.org/10.1093/brain/awm086

Hughes, A. J., Daniel, S. E., Kilford, L., & Lees, A. J. (1992). Accuracy of clinical diagnosis of idiopathic Parkinson's disease: A clinico-pathological study of 100 cases. *Journal of Neurology, Neurosurgery, and Psychiatry*, *55*(3), 181–184. https://doi.org/10.1136/jnnp.55.3.181

Hünerli, D., Emek-Savaş, D. D., Çavuşoğlu, B., Dönmez Çolakoğlu, B., Ada, E., & Yener, G. G. (2019). Mild cognitive impairment in Parkinson's disease is associated with decreased P300 amplitude and reduced putamen volume. *Clinical Neurophysiology*, *130*(8), 1208–1217. https://doi.org/10.1016/j.clinph.2019.04.314

Huntington Study Group (1996). Unified Huntington's Disease Rating Scale: Reliability and consistency. *Movement Disorders*, *11*(2), 136–142. https://doi.org/10.1002/mds.870110204

Jacobs, M., Hart, E. P., & Roos, R. (2018). Cognitive Performance and Apathy Predict Unemployment in Huntington's Disease Mutation Carriers. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *30*(3), 188–193. https://doi.org/10.1176/appi.neuropsych.17070144

Júlio, F., Ribeiro, M. J., Patrício, M., Malhão, A., Pedrosa, F., Gonçalves, H., Simões, M., van Asselen, M., Simões, M. R., Castelo-Branco, M., & Januário, C. (2019). A Novel Ecological Approach Reveals Early Executive Function Impairments in Huntington's Disease. *Frontiers in Psychology*, *10*, 585. https://doi.org/10.3389/fpsyg.2019.00585

Kamei, S., Hara, M., Serizawa, K., Murakami, M., Mizutani, T., Ishiburo, M., Kawahara, R., Takagi, Y., Ogawa, K., Yoshihashi, H., Shinbo, S., Suzuki, Y., Yamaguchi, M., Morita, A., Takeshita, J., & Hirayanagi, K. (2008). Executive dysfunction using behavioral assessment of the dysexecutive syndrome in Parkinson's disease. *Movement Disorders*, *23*(4), 566–573.

https://doi.org/10.1002/mds.21890

Koerts, J., van Beilen, M., Leenders, K. L., Brouwer, W. H., Tucha, L., & Tucha, O. (2012). Complaints about impairments in executive functions in Parkinson's disease: The association with neuropsychological assessment. *Parkinsonism & Related Disorders*, *18*(2), 194–197. https://doi.org/10.1016/j.parkreldis.2011.10.002

Kudlicka, A., Clare, L., & Hindle, J. V. (2013). Awareness of executive deficits in people with Parkinson's disease. *Journal of the International Neuropsychological Society*, *19*(5), 559–570. https://doi.org/10.1017/S1355617713000064

Kudlicka, A., Hindle, J. V., Spencer, L. E., & Clare, L. (2018). Everyday functioning of people with Parkinson's disease and impairments in executive function: A qualitative investigation. *Disability and Rehabilitation*, *40*(20), 2351–2363. https://doi.org/10.1080/09638288.2017.1334240

Lanni, K. E., Ross, J. M., Higginson, C. I., Dressler, E. M., Sigvardt, K. A., Zhang, L., Malhado-Chang, N., & Disbrow, E. A. (2014). Perceived and performance-based executive dysfunction in Parkinson's disease. *Journal of Clinical and Experimental Neuropsychology*, *36*(4), 342–355. https://doi.org/10.1080/13803395.2014.892059

Lee, H. M., Kwon, K. Y., Kim, M. J., Jang, J. W., Suh, S. I., Koh, S. B., & Kim, J. H. (2014). Subcortical grey matter changes in untreated, early stage Parkinson's disease without dementia. *Parkinsonism & Related Disorders*, *20*(6), 622–626. https://doi.org/10.1016/j.parkreldis.2014.03.009

Leritz, E., Loftis, C., Crucian, G., Friedman, W., & Bowers, D. (2004). Self-awareness of deficits in Parkinson disease. *The Clinical Neuropsychologist*, *18*(3), 352–361. https://doi.org/10.1080/1385404049052412

Lezak, M. D., Howieson, D. B., Bigler, E. D., & Tranel, D. (2012). *Neuropsychological Assessment* (5th ed.). Oxford University Press.

Lundervold, A. J., Karlsen, N. R., & Reinvang, I. (1994). Assessment of 'subcortical dementia' in patients with Huntington's disease, Parkinson's disease, multiple sclerosis and AIDS by a neuropsychological screening battery. *Scandinavian Journal of Psychology*, *35*(1), 48–55. https://doi.org/10.1111/j.1467-9450.1994.tb00932.x

McCusker, E., & Loy, C. T. (2014). The many facets of unawareness in Huntington disease. *Tremor and Other Hyperkinetic Movements* , *4*, 257. https://doi.org/10.7916/D8FJ2FD3

McGuire B. E. (2014). Assessing complex executive functions with computerized tests: Is that toast burning?. *Frontiers in Behavioral Neuroscience*, *8*, 362. https://doi.org/10.3389/fnbeh.2014.00362

McIsaac, T. L., Fritz, N. E., Quinn, L., & Muratori, L. M. (2018). Cognitive-Motor Interference in Neurodegenerative Disease: A Narrative Review and Implications for Clinical Management. *Frontiers in Psychology*, *9*, 2061.

https://doi.org/10.3389/fpsyg.2018.02061

McKinlay, A., Grace, R. C., Dalrymple-Alford, J. C., & Roger, D. (2010). Characteristics of executive function impairment in Parkinson's disease patients without dementia. *Journal of the International Neuropsychological Society*, *16*(2), 268–277. https://doi.org/10.1017/S1355617709991299

Mehrabi, N. F., Waldvogel, H. J., Tippett, L. J., Hogg, V. M., Synek, B. J., & Faull, R. L. (2016). Symptom heterogeneity in Huntington's disease correlates with neuronal degeneration in the cerebral cortex. *Neurobiology of Disease*, *96*, 67–74. https://doi.org/10.1016/j.nbd.2016.08.015

Mestre, T. A., Busse, M., Davis, A. M., Quinn, L., Rodrigues, F. B., Burgunder, J. M., Carlozzi, N. E., Walker, F., Ho, A. K., Sampaio, C., Goetz, C. G., Cubo, E., Martinez-Martin, P., Stebbins, G. T., & Members of the MDS Committee on Rating Scales Development (2018). Rating Scales and Performance-based Measures for Assessment of Functional Ability in Huntington's Disease: Critique and Recommendations. *Movement Disorders Clinical Practice*, *5*(4), 361–372. https://doi.org/10.1002/mdc3.12617

Montoya, A., Price, B. H., Menear, M., & Lepage, M. (2006). Brain imaging and cognitive dysfunctions in Huntington's disease. *Journal of Psychiatry & Neuroscience*, *31*(1), 21–29.

Moore, D. J., Palmer, B. W., Patterson, T. L., & Jeste, D. V. (2007). A review of performance-based measures of functional living skills. *Journal of Psychiatric Research*, *41*(1-2), 97–118. https://doi.org/10.1016/j.jpsychires.2005.10.008

Mörkl, S., Müller, N. J., Blesl, C., Wilkinson, L., Tmava, A., Wurm, W., Holl, A. K., & Painold, A. (2016). Problem solving, impulse control and planning in patients with early- and late-stage Huntington's disease. *European Archives of Psychiatry and Clinical Neuroscience*, *266*(7), 663–671. https://doi.org/10.1007/s00406-016-0707-4

Nasreddine, Z. S., Phillips, N. A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., Cummings, J. L., & Chertkow, H. (2005). The Montreal Cognitive Assessment, MoCA: A brief screening tool for mild cognitive impairment. *Journal of the American Geriatrics Society*, *53*(4), 695–699. https://doi.org/10.1111/j.1532-5415.2005.53221.x

Nehl, C., Paulsen, J. S., & Huntington Study Group (2004). Cognitive and psychiatric aspects of Huntington disease contribute to functional capacity. *The Journal of Nervous and Mental Disease*, *192*(1), 72–74. https://doi.org/10.1097/01.nmd.0000106004.67587.57

Nicoll, D. R., Pirogovsky, E., Woods, S. P., Holden, H. M., Filoteo, J. V., Gluhm, S., Corey-Bloom, J., & Gilbert, P. E. (2014). "Forgetting to remember" in Huntington's disease: A study of laboratory, semi-naturalistic, and self-perceptions of prospective memory. *Journal of the International Neuropsychological Society*, *20*(2), 192–199. https://doi.org/10.1017/S1355617713001355

Nimmagadda, S. R., Agrawal, N., Worrall-Davies, A., Markova, I., & Rickards, H. (2011). Determinants of irritability in Huntington's disease. *Acta Neuropsychiatrica, 23*(6), 309–314. https://doi.org/10.1111/j.1601-5215.2011.00563.x

Norris, G., & Tate, R. L. (2000). The Behavioural Assessment of the Dysexecutive Syndrome (BADS): Ecological, Concurrent and Construct Validity. *Neuropsychological Rehabilitation, 10*(1), 33–45. https://doi.org/10.1080/096020100389282

Novak, M. J., & Tabrizi, S. J. (2010). Huntington's disease. *British Medical Journal*, *340*, c3109. https://doi.org/10.1136/bmj.c3109

Novak, M. J., & Tabrizi, S. J. (2011). Huntington's disease: Clinical presentation and treatment. *International Review of Neurobiology*, *98*, 297–323. https://doi.org/10.1016/B978-0-12-381328-2.00013-4

O'Keeffe, G. C., Michell, A. W., & Barker, R. A. (2009). Biomarkers in Huntington's and Parkinson's Disease. *Annals of the New York Academy of Sciences*, *1180*, 97–110. https://doi.org/10.1111/j.1749-6632.2009.04943.x

Oldfield R. C. (1971). The assessment and analysis of handedness: The Edinburgh inventory. *Neuropsychologia*, *9*(1), 97–113. https://doi.org/10.1016/0028-3932(71)90067-4

Parsons, T. D., Carlew, A. R., Magtoto, J., & Stonecipher, K. (2017). The potential of function-led virtual environments for ecologically valid measures of executive function in experimental and clinical neuropsychology. *Neuropsychological Rehabilitation*, *27*(5), 777–807. https://doi.org/10.1080/09602011.2015.1109524

Paulsen J. S. (2011). Cognitive impairment in Huntington disease: Diagnosis and treatment. *Current Neurology and Neuroscience Reports*, *11*(5), 474–483. https://doi.org/10.1007/s11910-011-0215-x

Paulsen, J. S., & Long, J. D. (2014). Onset of Huntington's disease: Can it be purely cognitive?. *Movement Disorders*, *29*(11), 1342–1350. https://doi.org/10.1002/mds.25997

Peinemann, A., Schuller, S., Pohl, C., Jahn, T., Weindl, A., & Kassubek, J. (2005). Executive dysfunction in early stages of Huntington's disease is associated with striatal and insular atrophy: A neuropsychological and voxel-based morphometric study. *Journal of the Neurological Sciences*, *239*(1), 11–19. https://doi.org/10.1016/j.jns.2005.07.007

Perfetti, B., Varanese, S., Mercuri, P., Mancino, E., Saggino, A., & Onofrj, M. (2010). Behavioural assessment of dysexecutive syndrome in Parkinson's disease without dementia: A comparison with other clinical executive tasks. *Parkinsonism & Related Disorders*, *16*(1), 46–50. https://doi.org/10.1016/j.parkreldis.2009.07.011

Petkus, A. J., Filoteo, J. V., Schiehser, D. M., Gomez, M. E., Hui, J. S., Jarrahi, B., McEwen, S., Jakowec, M. W., & Petzinger, G. M. (2020). Mild cognitive impairment, psychiatric symptoms, and executive functioning in patients with Parkinson's disease. *International Journal of Geriatric Psychiatry*, *35*(4), 396–404. https://doi.org/10.1002/gps.5255

Pfeiffer, H. C., Løkkegaard, A., Zoetmulder, M., Friberg, L., & Werdelin, L. (2014). Cognitive impairment in early-stage non-demented Parkinson's disease patients. *Acta Neurologica Scandinavica*, *129*(5), 307–318. https://doi.org/10.1111/ane.12189

Poliakoff, E., & Smith-Spark, J. H. (2008). Everyday cognitive failures and memory problems in Parkinson's patients without dementia. *Brain and Cognition*, *67*(3), 340–350. https://doi.org/10.1016/j.bandc.2008.02.004

Reilmann, R., Leavitt, B. R., & Ross, C. A. (2014). Diagnostic criteria for Huntington's disease based on natural history. *Movement Disorders*, *29*(11), 1335–1341. https://doi.org/10.1002/mds.26011

Rodriguez-Oroz, M. C., Jahanshahi, M., Krack, P., Litvan, I., Macias, R., Bezard, E., & Obeso, J. A. (2009). Initial clinical manifestations of Parkinson's disease: Features and pathophysiological mechanisms. *The Lancet Neurology*, *8*(12), 1128–1139. https://doi.org/10.1016/S1474-4422(09)70293-5

Roman, M. J., Delis, D. C., Filoteo, J. V., Demadura, T. L., Paulsen, J., Swerdlow, N. R., Swenson, M. R., Salmon, D., Butters, N., & Shults, C. (1998). Is there a "subcortical" profile of attentional dysfunction? A comparison of patients with Huntington's and Parkinson's diseases on a global-local focused attention task. *Journal of Clinical and Experimental Neuropsychology*, *20*(6), 873–884. https://doi.org/10.1076/jcen.20.6.873.1111

Rosas, H. D., Koroshetz, W. J., Chen, Y. I., Skeuse, C., Vangel, M., Cudkowicz, M. E., Caplan, K., Marek, K., Seidman, L. J., Makris, N., Jenkins, B. G., & Goldstein, J. M. (2003). Evidence for more widespread cerebral pathology in early HD: An MRI-based morphometric analysis. *Neurology*, *60*(10), 1615–1620. https://doi.org/10.1212/01.wnl.0000065888.88988.6e

Rosenblatt A. (2007). Neuropsychiatry of Huntington's disease. *Dialogues in Clinical Neuroscience*, *9*(2), 191–197. https://doi.org/10.31887/DCNS.2007.9.2/arosenblatt

Ross, C. A., Aylward, E. H., Wild, E. J., Langbehn, D. R., Long, J. D., Warner, J. H., Scahill, R. I., Leavitt, B. R., Stout, J. C., Paulsen, J. S., Reilmann, R., Unschuld, P. G., Wexler, A., Margolis, R. L., & Tabrizi, S. J. (2014). Huntington disease: Natural history, biomarkers and prospects for therapeutics. *Nature Reviews Neurology*, *10*(4), 204–216. https://doi.org/10.1038/nrneurol.2014.24

Rothlind, J. C., Bylsma, F. W., Peyser, C., Folstein, S. E., & Brandt, J. (1993). Cognitive and motor correlates of everyday functioning in early Huntington's disease. *The Journal of Nervous and Mental Disease*, *181*(3), 194–199. https://doi.org/10.1097/00005053-199303000-00008

Rothman K. J. (1990). No adjustments are needed for multiple comparisons. *Epidemiology* , *1*(1), 43–46.

Ruse, S. A., Davis, V. G., Atkins, A. S., Krishnan, K. R., Fox, K. H., Harvey, P. D., & Keefe, R. S. (2014). Development of a virtual reality assessment of everyday living skills. *Journal of Visualized Experiments*, (86), 51405. https://doi.org/10.3791/51405

Saville, D.J. (1990) Multiple Comparison Procedures: The Practical Solution. *The American Statistician, 44*(2), 174-180. https://doi.org/10.1080/00031305.1990.10475712

Schneider, J. S., Sendek, S., & Yang, C. (2015). Relationship between Motor Symptoms, Cognition, and Demographic Characteristics in Treated Mild/Moderate Parkinson's Disease. *PloS One*, *10*(4), e0123231. https://doi.org/10.1371/journal.pone.0123231

Schrag, A., & Schott, J. M. (2006). Epidemiological, clinical, and genetic characteristics of early-onset parkinsonism. *The Lancet Neurology*, *5*(4), 355–363. https://doi.org/10.1016/S1474-4422(06)70411-2

Shallice, T., & Burgess, P. W. (1991). Deficits in strategy application following frontal lobe damage in man. *Brain*, *114(Pt 2)*, 727–741. https://doi.org/10.1093/brain/114.2.727

Shoulson, I., & Fahn, S. (1979). Huntington disease: Clinical care and evaluation. *Neurology*, *29*(1), 1–3. https://doi.org/10.1212/wnl.29.1.1

Shoulson, I., & Young, A. B. (2011). Milestones in Huntington disease. *Movement Disorders*, *26*(6), 1127–1133. https://doi.org/10.1002/mds.23685

Sitek, E. J., Sołtan, W., Wieczorek, D., Schinwelski, M., Robowski, P., Harciarek, M., Guzińska, K., & Sławek, J. (2013). Self-awareness of executive dysfunction in Huntington's disease: Comparison with Parkinson's disease and cervical dystonia. *Psychiatry and Clinical Neurosciences*, *67*(1), 59–62. https://doi.org/10.1111/pcn.12006

Sitek, E. J., Sołtan, W., Wieczorek, D., Schinwelski, M., Robowski, P., Reilmann, R., Guzińska, K., Harciarek, M., Krysa, W., & Sławek, J. (2011). Self-awareness of motor dysfunction in patients with Huntington's disease in comparison to Parkinson's disease and cervical dystonia. *Journal of the International Neuropsychological Society*, *17*(5), 788–795. https://doi.org/10.1017/S1355617711000725

Snowden, J. S., Craufurd, D., Griffiths, H. L., & Neary, D. (1998). Awareness of involuntary movements in Huntington disease. *Archives of Neurology*, *55*(6), 801–805.

https://doi.org/10.1001/archneur.55.6.801

Sohlberg, M. M., & Mateer, C. A. (2001). *Cognitive rehabilitation: An integrative neuropsychological approach*. Guilford Press.

Sousa, L. B., Prieto, G., Vilar, M., Firmino, H., & Simões, M. R. (2015). The Adults and Older Adults Functional Assessment Inventory: A Rasch Model Analysis. *Research on Aging*, *37*(8), 787–814. https://doi.org/10.1177/0164027514564469

Sprengelmeyer, R., Canavan, A. G., Lange, H. W., & Hömberg, V. (1995). Associative learning in degenerative neostriatal disorders: Contrasts in explicit and implicit remembering between Parkinson's and Huntington's diseases. *Movement Disorders*, *10*(1), 51–65. https://doi.org/10.1002/mds.870100110

Starkstein, S. E., Brandt, J., Bylsma, F., Peyser, C., Folstein, M., & Folstein, S. E. (1992). Neuropsychological correlates of brain atrophy in Huntington's disease: A magnetic resonance imaging study. *Neuroradiology*, *34*(6), 487–489. https://doi.org/10.1007/BF00598956

Stout, J. C., & Johnson, S. A. (2005). Cognitive impairment and dementia in basal ganglia disorders. *Current Neurology and Neuroscience Reports*, *5*(5), 355–363. https://doi.org/10.1007/s11910-005-0059-3

Stout, J. C., Paulsen, J. S., Queller, S., Solomon, A. C., Whitlock, K. B., Campbell, J. C., Carlozzi, N., Duff, K., Beglinger, L. J., Langbehn, D. R., Johnson, S. A., Biglan, K. M., & Aylward, E. H. (2011). Neurocognitive signs in prodromal Huntington disease. *Neuropsychology*, *25*(1), 1–14. https://doi.org/10.1037/a0020937

Svenningsson, P., Westman, E., Ballard, C., & Aarsland, D. (2012). Cognitive impairment in patients with Parkinson's disease: Diagnosis, biomarkers, and treatment. *The Lancet Neurology*, *11*(8), 697–707. https://doi.org/10.1016/S1474-4422(12)70152-7

Tabrizi, S. J., Langbehn, D. R., Leavitt, B. R., Roos, R. A., Durr, A., Craufurd, D., Kennard, C., Hicks, S. L., Fox, N. C., Scahill, R. I., Borowsky, B., Tobin, A. J., Rosas, H. D., Johnson, H., Reilmann, R., Landwehrmeyer, B., Stout, J. C., & TRACK-HD investigators (2009). Biological and clinical manifestations of Huntington's disease in the longitudinal TRACK-HD study: Cross-sectional analysis of baseline data. *The Lancet Neurology*, *8*(9), 791–801. https://doi.org/10.1016/S1474-4422(09)70170-X

Tabrizi, S. J., Scahill, R. I., Durr, A., Roos, R. A., Leavitt, B. R., Jones, R., Landwehrmeyer, G. B., Fox, N. C., Johnson, H., Hicks, S. L., Kennard, C., Craufurd, D., Frost, C., Langbehn, D. R., Reilmann, R., Stout, J. C., & TRACK-HD Investigators (2011). Biological and clinical changes in premanifest and early stage Huntington's disease in the TRACK-HD study: The 12-month longitudinal analysis. *The Lancet Neurology*, *10*(1), 31–42. https://doi.org/10.1016/S1474-4422(10)70276-3

Tang, H., Huang, J., Nie, K., Gan, R., Wang, L., Zhao, J., Huang, Z., Zhang, Y., & Wang, L. (2016). Cognitive profile of Parkinson's disease patients: A comparative study between early-onset and late-onset Parkinson's disease. *The International Journal of Neuroscience*, *126*(3), 227–234. https://doi.org/10.3109/00207454.2015.1010646

Unmack Larsen, I., Vinther-Jensen, T., Gade, A., Nielsen, J. E., & Vogel, A. (2015). Assessing impairment of executive function and psychomotor speed in premanifest and manifest Huntington's disease gene-expansion carriers. *Journal of the International Neuropsychological Society*, *21*(3), 193–202. https://doi.org/10.1017/S1355617715000090

van Rooden, S. M., Colas, F., Martínez-Martín, P., Visser, M., Verbaan, D., Marinus, J., Chaudhuri, R. K., Kok, J. N., & van Hilten, J. J. (2011). Clinical subtypes of Parkinson's disease. *Movement Disorders*, *26*(1), 51–58. https://doi.org/10.1002/mds.23346

Vlagsma, T. T., Koerts, J., Tucha, O., Dijkstra, H. T., Duits, A. A., van Laar, T., & Spikman, J. M. (2017). Objective Versus Subjective Measures of Executive Functions: Predictors of Participation and Quality of Life in Parkinson Disease?. *Archives of Physical Medicine and Rehabilitation*, *98*(11), 2181–2187. https://doi.org/10.1016/j.apmr.2017.03.016

Waldvogel, H. J., Kim, E. H., Tippett, L. J., Vonsattel, J. P., & Faull, R. L. (2015). The Neuropathology of Huntington's Disease. *Current Topics in Behavioral Neurosciences*, *22*, 33–80. https://doi.org/10.1007/7854_2014_354

Wichmann, T., & DeLong, M. R. (1993). Pathophysiology of parkinsonian motor abnormalities. *Advances in Neurology*, *60*, 53–61.

Williams, J. K., Kim, J. I., Downing, N., Farias, S., Harrington, D. L., Long, J. D., Mills, J. A., Paulsen, J. S., & PREDICT-HD Investigators and Coordinators of the Huntington Study Group (2015). Everyday cognition in prodromal Huntington disease. *Neuropsychology*, *29*(2), 255–267. https://doi.org/10.1037/neu0000102

Wilson, B., Alderman, N., Burgess, P., Emslie, H., & Evans, J. (1996). *Behavioural assessment of the dysexecutive syndrome.* Thames Valley Test Company.

Wilson, B. A., Evans, J. J., Emslie, H., Alderman, N., & Burgess, P. (1998). The Development of an Ecologically Valid Test for Assessing Patients with a Dysexecutive Syndrome. *Neuropsychological Rehabilitation, 8*(3), 213–228. https://doi.org/10.1080/713755570

Chapter V – Study 4

Preface

Study 4 was designed to test if our novel performance-based tool would be more sensitive than classic neuropsychological tests in depicting the cognitive and functional decline associated with normal ageing – and thus in assessing the functional cognition of older adults. For this, we investigated the impact of healthy ageing on the accuracy and timing features of the *EcoKitchen*. Additionally, this study aimed to establish the cognitive correlates of the *EcoKitchen* task performance, so as to further validate its ability to capture the different executive skills underlying the everyday functioning of healthy adults.

As the global population is ageing, and there is a known impact of age in executive function, it is increasingly important to understand the functional consequences of the cognitive changes exhibited by healthy older adults (Harada et al., 2013; Marcotte et al., 2010; Schmitter-Edgecombe & Parsey, 2014; Tan et al., 2009). Executive functions are more accurate predictors of activities of daily living (ADLs) in normal ageing than are other measures of cognitive function, including memory, language, or visuospatial skills (Cahn-Weiner et al., 2007). Studies using self-report measures and functional questionnaires have shown that healthy cognitive ageing can result in declines in complex functional skills, such as the ability to prepare meals or drive (Harada et al., 2013). However, there is a lack of quantitative, objective measures to assess functional cognition in older adults. In fact, the features of classical standardized EF tests do not replicate the complexity and challenges found in ADLs, and therefore their predictive power for real life performance is limited (Neguț et al., 2016; Schultheis et al., 2002). Thus, the increased ecological validity of the *EcoKitchen* was thought to better reflect the functioning of older adults within the context of daily life and objectively and

quantitively measure the impact of their potential executive deficits on functional status (Alvarez & Emory, 2006; Bogdanova et al., 2016; Neguț et al., 2016).

Lastly, since computerized cognitive programs to train EF have gained popularity in ageing populations as a means to prevent cognitive decline and potentially enhance cognitive functioning (Bogdanova et al., 2016), we believed this work would establish the feasibility of the *EcoKitchen* to be included in these prevention and rehabilitation efforts involving the normal ageing population.

References

Alvarez, J. A., & Emory, E. (2006). Executive function and the frontal lobes: A meta-analytic review. *Neuropsychology Review*, *16*(1), 17–42. https://doi.org/10.1007/s11065-006-9002-x

Bogdanova, Y., Yee, M. K., Ho, V. T., & Cicerone, K. D. (2016). Computerized Cognitive Rehabilitation of Attention and Executive Function in Acquired Brain Injury: A Systematic Review. *The Journal of Head Trauma Rehabilitation*, *31*(6), 419–433. https://doi.org/10.1097/HTR.0000000000000203

Cahn-Weiner, D. A., Farias, S. T., Julian, L., Harvey, D. J., Kramer, J. H., Reed, B. R., Mungas, D., Wetzel, M., & Chui, H. (2007). Cognitive and neuroimaging predictors of instrumental activities of daily living. *Journal of the International Neuropsychological Society*, *13*(5), 747–757. https://doi.org/10.1017/S1355617707070853

Harada, C. N., Natelson Love, M. C., & Triebel, K. L. (2013). Normal cognitive aging. *Clinics in Geriatric Medicine*, *29*(4), 737–752. https://doi.org/10.1016/j.cger.2013.07.002

Marcotte, T. D., Scott, J. C., Kamat, R., & Heaton, R. K. (2010). Neuropsychology and the prediction of everyday functioning. In T. D. Marcotte & I. Grant (Eds.), *Neuropsychology of everyday functioning* (pp. 5–38). The Guilford Press.

Neguț, A., Matu, S-A., Sava, F.A., & David, D. (2016). Task difficulty of virtual reality-based assessment tools compared to classical paper-and-pencil or computerized measures: A meta-analytic approach. *Computers in Human Behavior, 54,* 414-424. https://doi.org/10.1016/j.chb.2015.08.029

Schmitter-Edgecombe, M., & Parsey, C. M. (2014). Assessment of functional change and cognitive correlates in the progression from healthy cognitive aging to dementia. *Neuropsychology*, *28*(6), 881–893. https://doi.org/10.1037/neu0000109

Schultheis, M. T., Himelstein, J., & Rizzo, A. A. (2002). Virtual reality and neuropsychology: Upgrading the current tools. *The Journal of Head Trauma Rehabilitation*, *17*(5), 378–394. https://doi.org/10.1097/00001199-200210000-00002

Tan, J. E., Hultsch, D. F., & Strauss, E. (2009). Cognitive abilities and functional capacity in older adults: Results from the modified Scales of Independent Behavior-Revised. *The Clinical Neuropsychologist, 23*(3), 479–500. https://doi.org/10.1080/13854040802368684

Study 4

Assessing the Impact of Age on Everyday Cognitive Function with Virtual Reality: the *EcoKitchen* task

Adapted from: **Júlio, F.,** Ribeiro, M. J., Simões, M. R., Castelo-Branco, M., & Januário, C. (2022). Assessing the Impact of Age on Everyday Cognitive Function with Virtual Reality: The *EcoKitchen* task. [Manuscript submitted for publication]. University of Coimbra.

Published dataset: **Júlio, F.** (2022, December 18). Assessing the Impact of Age on Everyday Cognitive Function with Virtual Reality: the *EcoKitchen* task_Database. https://doi.org/10.17605/OSF.IO/J26X8

Abstract

Introduction: More realistic assessment tools are imperative for a better understanding of the impact of age-related cognitive deficits on older people's functional status. With this in mind, we probed the ability of the *EcoKitchen*, a non-immersive virtual reality task with increasing executively demanding kitchen chores, to detect the effects of ageing on

the simulated everyday functioning of healthy adults.

Materials and Methods: Fifty-three adults (age between 23 and 77 years) were assessed with the *EcoKitchen* and a set of conventional paper-and-pencil neuropsychological tests. The correlations between the baseline features of study participants and each of the two different assessment methods were examined. The associations between the EcoKitchen variables and an executive composite score were also explored.

Results: Our results showed that older individuals present deficits in the performance of both the *EcoKitchen* task and standard assessment methods. Notably, we found that, unlike conventional tests, the scores of the *EcoKitchen* task were not related to the education and IQ level of participants. Moreover, the *EcoKitchen* time and accuracy measures were significantly correlated with executive tests.

Discussion: We have demonstrated that the *EcoKitchen* task, an ecologically relevant computerized neuropsychological assessment tool, might be more suitable than classic paper-and-pencil tests to capture the impact of ageing on everyday cognitive function, as it proved to be less prone to the influence of confounding factors. Additionally, we have shown that executive function plays an important role in the timely and accurate performance of cognitively challenging virtual reality tasks.

Introduction

The rising number of senior adults in the worldwide population has led to an increasing concern regarding the effects of ageing on independent everyday functioning, given the heavy health care, societal and economic burdens involved (Marcotte et al., 2010; Schmitter-Edgecombe & Parsey, 2014; Tan et al., 2009). The detection of cognitive and functional deficits at early stages of decline is mandatory for developing effective strategies to preserve and rehabilitate everyday cognitive function in older persons.

In this context, we used a non-immersive virtual reality task that involves the completion of increasingly demanding daily life- like kitchen tasks, the *EcoKitchen* (Júlio, Ribeiro, et al., 2019, 2022), to identify the functional implications of the executive deficits associated with ageing in a group of healthy adults.

This task was developed having in mind that the ecological validity of the methods used

to assess cognition and the functional significance of neuropsychological test results are of vital importance. Ecological validity can be defined as the ability of a test to predict everyday function (i.e., the behaviour that occurs in real-world settings) based on the behaviour that occurs in an experimental context (Gioia & Isquith, 2004; Godefroy et al., 2010). As conventional assessment methods fail to predict performance in everyday tasks, we need to find new measures to assess the complex skills underlying daily life activity (Spooner & Pachana, 2006; Vaughan & Giovanello, 2010). First, the same tests created to detect severe cognitive dysfunction arising from gross cerebral pathology are now used to assess subtle alterations related with ageing and estimate functional ability (Burgess et al., 1998; Chaytor & Schmitter-Edgecombe, 2003; Doherty et al., 2015; Titov & Knight, 2005). Second, commonly used tests provide a quantitative measurement of single isolated components of executive functions without considering the multiple cognitive processes required for goal-directed behaviour in everyday multitasking (Diehl et al., 1995; Koerts et al., 2011; Lai et al., 2018; McAlister & Schmitter-Edgecombe, 2013; Scott et al., 2011). Third, persons often perform well in clinical assessments of executive functions but demonstrate disorganized behaviour at home or in less structured environments (Godefroy et al., 2010), as the testing is usually done via paper-and-pencil tasks rather than being presented in a real or simulated context (Rand et al., 2009). Hence, neuropsychological assessment tools designed to capture real life complexity may be more effective at predicting everyday functioning or estimating the functional impact of the person's cognitive status. Importantly, computer simulations and virtual reality tasks seem to provide reliable assessment methods that are standardized, consistent, cost-effective, and that can objectively quantify behaviour in challenging but safe environments, while maintaining strict experimental control over stimulus delivery and measurement (Craik & Bialystok, 2006; Godbout et al., 2005; Rizzo et al., 2000; Zhang et al., 2003).

We have previously demonstrated that the *EcoKitchen* is sensitive to the earliest and subtle functional impairments caused by neurodegenerative disorders with pronounced executive impairments, such as Huntington's disease and Parkinson's disease (Júlio, Ribeiro, et al., 2019, 2022). Importantly, we have shown that the performance on the *EcoKitchen* was associated with a self-report measure of real-world functioning (Júlio, Ribeiro, et al., 2019, 2022; Sousa et al., 2015), which suggests that this assessment tool can serve as a proxy of everyday performance.

Here, our goal was to test if the *EcoKitchen* is sensitive to the effects of ageing and

contrast its ability to capture the impact of age-related cognitive deficits on daily life- like function with that of standard paper-and-pencil tests. A secondary goal was to explore which executive skills underlie the *EcoKitchen* performance of healthy adults. The validation of more ecological testing methods will improve our ability to predict how persons perform in more integrated executively demanding everyday life- like situations and help in the design and implementation of strategies aimed at reducing the cognitive and functional burden associated with the ageing process.

Materials and Methods

Participants

Fifty-three healthy adults (37 women and 16 men, age range between 23 and 77 years old) with no history of dementia, depression, substance abuse, neurological and/or psychiatric condition and no current use of psychotropic medication were recruited from the University of Coimbra (researchers and their relatives working at IBILI - Instituto de Imagem Biomédica e Ciências da Vida, Faculty of Medicine, University of Coimbra, Coimbra, Portugal) and from the Neurogenetics Consultation Service of the Neurological Department of Coimbra University Hospital (healthy relatives of persons with Huntington's disease). All healthy adults recruited at the Hospital were examined by an experienced neurologist to exclude the presence of extrapyramidal signs and any other neurological and/or psychiatric abnormalities. All participants gave written informed consent in accordance with the Helsinki Declaration to participate in the study approved by our Institutional Ethics Committees (University of Coimbra – Faculty of Medicine and Coimbra University Hospital).

We used the "Montreal Cognitive Assessment – MoCA" (Nasreddine et al., 2005), the "Beck Depression Inventory II – BDI-II" (Beck et al., 1996), the "Irregular Word Reading Test - TeLPI" (Alves et al., 2012), and the "Edinburgh Handedness Inventory" (Oldfield, 1971) as screening measures of global cognitive status, depression, intelligence level and handedness of study participants, respectively (Table 4.1).

Table 4.1 Baseline Demographic, Cognitive and Neuropsychiatric Features of Study Participants

	Min – Max	*Mean*	*CI 95% Low – Up*	*SE*
Age	23 - 77	43.92	39.68 - 48.17	2.11
Education	6 - 22	14.85	13.75 - 15.95	0.55
MoCA	20 - 30	26.60	25.88 - 27.33	0.36
BDI-II	0 - 24	5.64	4.09 - 7.20	0.78
TeLPI (FSIQ)	67.44 - 132.34	117.60	114.56 - 120.64	1.51
TeLPI (VIQ)	71.76 - 135.43	119.56	116.50 - 122.62	1.53
TeLPI (PIQ)	70.58 - 122.97	112.32	109.92 - 114.71	1.19

Min – Minimum; Max – Maximum; CI - 95% Confidence Interval for Mean; Low – Lower interval; Up – Upper interval; SE – Standard Error; MoCA – Montreal Cognitive Assessment; BDI-II – Beck Depression Inventory II; TeLPI – The Irregular Word Reading Test; FSIQ – Full Scale Intelligence Quotient; VIQ – Verbal Intelligence Quotient; PIQ – Performance Intelligence Quotient

EcoKitchen

The *EcoKitchen* is a non-immersive virtual reality tool created at our Laboratory that simulates a kitchen setting where individuals must complete different routine tasks as fast and accurately as possible (e.g., preparing a snack or handling kitchen equipment) (Figure 4.1).

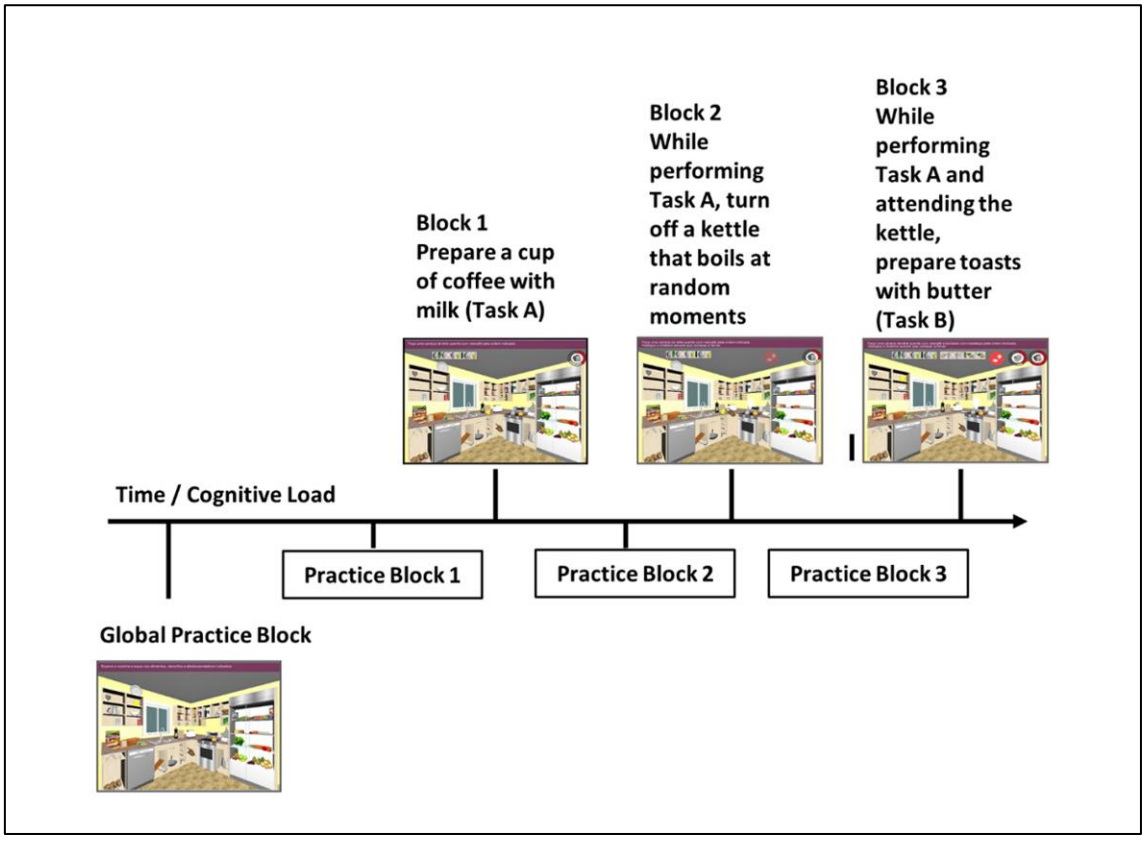

Figure 4.1 *EcoKitchen* Task Design

The task was displayed on a desktop PC, in which participants had a flat-full screen presentation of a kitchen setting in a 23'' monitor and used the computer mouse to navigate around the scenario. The *EcoKitchen* covers several executive skills relevant to everyday function and includes three blocks of increasing cognitive load:

- Block 1, where participants had to collect and use in a sequential order all the items needed to prepare a cup of coffee with milk (Task A);
- Block 2, where participants had to perform Task A, while, simultaneously, paying attention and monitoring a kettle that was on the stove and that boiled at several random moments during the block;
- Block 3, where participants had to perform the tasks described in the first and second blocks (Task A and boiling kettle) and, additionally, were instructed to also prepare toasts with butter (Task B), alternating between Task A and Task B to make sure that both were completed at the same time.

Three main parameters were defined to evaluate the *EcoKitchen* performance:

- Performance Time Task A, that is the time participants were engaged in the preparation of a cup of coffee with milk (counting from the moment the first item of the list was picked to the moment the last item of the list was used); this parameter is thought to reflect psychomotor and processing speed, planning, and motor time;
- Reaction Time, that is the mean of the different reaction times computed from each *EcoKitchen* block, namely Reaction Time Stove (the time participants took to turn off the stove once the clock was completely red), Reaction Time Kettle (the time participants took to turn off the kettle once smoke appeared and a red signal blinked in the computer screen) and Reaction Time Toaster (the time participants took to turn off the toaster once the clock was completely red); this parameter is thought to reflect behaviour monitoring, response initiation, divided attention, set-shifting, task switching, and sustained alertness;
- Total Errors, that is the number of errors committed in each *EcoKitchen* block, namely Sequencing Errors (signaled when participants failed to follow the proper sequence of the task), Item Errors (signaled when participants picked items of the *EcoKitchen* scenario not needed to prepare either Task A or Task B), and Impulsivity Errors Stove and Impulsivity Errors Toaster (signaled when participants tried to turn off the stove or the toaster before the clock being completely red); this parameter is thought to reflect planning, behaviour

monitoring, working memory, attention, response inhibition or inhibitory control, and task switching.

The *EcoKitchen* design, procedures, and data analysis are further detailed somewhere else (Júlio, Ribeiro, et al., 2019, 2022).

Conventional Neuropsychological Test Battery

The participants were tested with paper-and-pencil tests commonly used in neuropsychological assessments to have a standardized representation of the cognitive skills of study participants: the Phonemic Verbal Fluency test – P, M, R (Cavaco et al., 2013) and the Semantic Verbal Fluency test – category animals (Cavaco et al., 2013), as measures of working memory, word generation and inhibition; the Stroop test – Naming, Interference and Reading tasks (Stroop, 1935), to evaluate cognitive flexibility, inhibition and processing speed; the Symbol Digit Modalities test (Smith, 1982), to assess working memory, attention and integration, and processing/psychomotor speed; the Digit Span test (Backward) of the WAIS-III – Wechsler Adult Intelligence Scale (Wechsler, 1997, 2008), to measure attention and working memory; and the Wisconsin Card Sorting Test (Heaton, 1981), to evaluate abstract behaviour, novel problem-solving and set-shifting.

Statistical Analyses

An Executive Composite Score was computed from the following neuropsychological test scores: Phonemic Verbal Fluency – total correct; Semantic Verbal Fluency test – total correct; Stroop Word Reading test – total correct; Stroop Colour Naming test – total correct; Stroop Interference test – total correct; Symbol Digit Modalities test – total correct; Digit Span test – Backward total correct; Wisconsin Card Sorting Test – % correct trials (total number of correct trials/total number of administered trials). This procedure was adapted from one of our previous studies (Júlio, Caetano, et al., 2019). After this step, a reliability analysis was conducted through the calculation of the Cronbach's alpha of our composite score (0.804). A Cronbach's alpha higher than 0.7 indicates that the combination of items has acceptable reliability to represent the variable of interest (George & Mallery, 2016) – in this case, tests of executive function. To reduce the number of comparisons, we decided to use this composite score in the subsequent analysis as a

summary measure of executive function captured by the conventional tests. Pearson product-moment correlation coefficients were calculated to investigate the associations between the demographic, cognitive and neuropsychiatric baseline features of study participants and their performance on the neuropsychological tests and the *EcoKitchen* task. Then, partial correlations with age as covariate were run to determine if the standard executive tests correlated with the *EcoKitchen* measures, whilst controlling for the age-related influences in these associations. An inspection of the *EcoKitchen* outputs suggested the presence of outliers, which were quantitatively checked using the logical conditions ($x_i \geq Q_3 + 1.5 * IQR$) and ($x_i \leq Q_1 - 1.5 * IQR$); based on these conditions, we discarded four participants in the data analysis of the *EcoKitchen* Performance Time A (final $n = 49$), three participants in the *EcoKitchen* Reaction Time (final $n = 50$), and two participants in the *EcoKitchen* Total Errors (final $n = 51$). Moreover, the *EcoKitchen* variables included in the correlation matrices were averaged across the three blocks to obtain a more concise representation of the data derived from this tool. The level of significance was adjusted using Benjamini–Hochberg corrections with false positive rate established at 0.05 when dealing with multiple comparisons, and only the correlations that survived these corrections were further examined. All calculations were performed with IBM SPSS Statistics (Version 24) with an alpha set at 0.05.

Results

The *EcoKitchen* performance time and number of errors presented a gradual increase with increasing age, indicating that this task is sensitive to the cognitive decline associated with ageing (Figure 4.2).

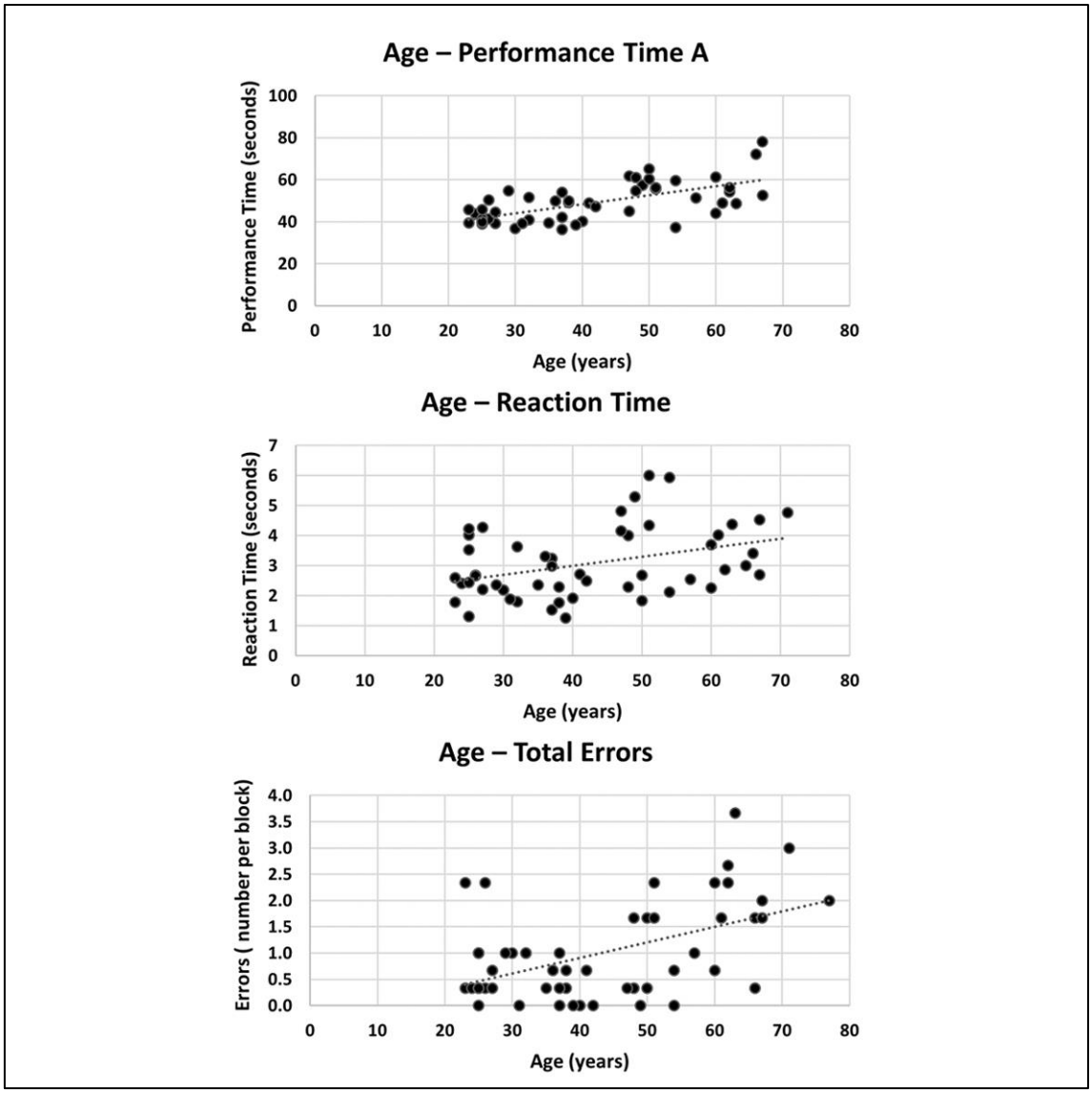

Figure 4.2 Scatter-Plots between *EcoKitchen* Parameters and Age with Best Linear Fitting Line

In fact, correlation analyses revealed an effect of age on the performance of study participants across the two components of our assessment protocol, as older age was associated with slower performance and reduced accuracy on the *EcoKichen* and the executive function tests. Specifically, age was positively correlated with *EcoKitchen* performance and reaction times and the number of errors and was negatively correlated with the Executive Composite Score (Table 4.2).

Table 4.2 Pearson Correlations between Baseline Features and Test Performance

	EcoKitchen							
	Performance Time A		*Reaction Time*		*Total Errors*		*Executive Composite Score **	
Baseline Features	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*
Age	0.635	<0.001 [a]	0.374	0.008 [a]	0.499	<0.001 [a]	-0.467	<0.001 [a]
Education	-0.279	0.052	-0.163	0.258	0.029	0.839	0.477	<0.001 [a]
MoCA	-0.553	<0.001 [a]	-0.492	<0.001 [a]	-0.392	0.004 [a]	0.600	<0.001 [a]
BDI-II	0.130	0.373	0.136	0.345	0.132	0.355	-0.155	0.267
TeLPI-FS	-0.210	0.148	-0.217	0.130	0.074	0.607	0.474	<0.001 [a]
TeLPI-V	-0.223	0.123	-0.213	0.138	0.069	0.632	0.483	<0.001 [a]
TeLPI-P	-0.193	0.184	-0.220	0.125	0.079	0.581	0.461	0.001 [a]

[a] Correlation significant after Benjamini-Hochberg corrections; [b] Correlation significant at p≤ 0.05
MoCA – Montreal Cognitive Assessment; BDI-II – Beck Depression Inventory II; TeLPI – The Irregular Word Reading Test; FSIQ – Full Scale Intelligence Quotient; VIQ – Verbal Intelligence Quotient; PIQ – Performance Intelligence Quotient
** Phonemic Verbal Fluency – total correct + Semantic Verbal Fluency test – total correct + Stroop Word Reading test – total correct + Stroop Color Naming test – total correct + Stroop Interference test – total correct + Symbol Digit Modalities test – total correct + Digit Span test – Backward total correct + Wisconsin Card Sorting Test % Correct Trials (total number of correct trials/total number of administered trials)*

Notably, education and IQ level had a significant effect on paper-and-pencil test results, but not on the *EcoKitchen* task. The *EcoKitchen* time and accuracy parameters were associated with age and global cognitive status as measured by the MoCA, but showed no relation to other variables, whereas the standard tests were influenced by several demographic and cognitive features.

Concretely, we found that age and global cognition showed robust correlations with the *EcoKitchen* Performance Time A, Reaction Time and Total Errors results: all significant correlations $|r| \geq 0.374$, $p \leq 0.008$. Furthermore, we found that the composite score computed from the conventional executive tests showed significant correlations with almost all the demographic and cognitive screening variables (all significant correlations $|r| \geq 0.461$, $p \leq 0.001$), except for the Beck Depression Inventory score.

When we partialled out the influence of age, we found significant correlations between all the *EcoKitchen* variables and the performance on standard neuropsychological tests (Table 4.3). The Executive Composite Score was particularly associated with the *EcoKitchen* performance time ($r = -0.385$, $p < 0.005$).

Table 4.3 Partial Correlations (controlling for Age) between the *EcoKitchen* and the Executive Composite Score

	EcoKitchen					
	Performance Time A		Reaction Time		Total Errors	
Neuropsychological Tests	*r*	*p*	*r*	*p*	*r*	*p*
Executive Composite Score *	-0.385	0.005 [b]	-0.299	0.031 [b]	0.288	0.038 [b]

[b] *Correlation significant at p≤ 0.05*
** Phonemic Verbal Fluency – total correct + Semantic Verbal Fluency test – total correct + Stroop Word Reading test – total correct + Stroop Color Naming test – total correct + Stroop Interference test – total correct + Symbol Digit Modalities test – total correct + Digit Span test – Backward total correct + Wisconsin Card Sorting Test % Correct Trials (total number of correct trials/total number of administered trials)*

Discussion

Our study demonstrated that a quantitative non-immersive virtual reality task, the *EcoKitchen*, can detect and detail age-related decrements in the performance of cognitively demanding everyday-like routines by healthy adults. Moreover, we found that this task was more impermeable to confounding factors in probing the age influence on the executive skills underlying everyday function than conventional neuropsychological assessment tests. Finally, our study indicated that the features of everyday cognitive function assessed by the *EcoKitchen*, particularly the performance time, are associated with the cognitive domains addressed by the traditional executive tests commonly used to study cognition and predict function. This strongly suggests that working memory, inhibition, attention, set-shifting and psychomotor/processing speed skills are pertinent for the timely and accurate performance of everyday-like tasks by healthy adults. Importantly, these cognitive skills seem to be more purely apprehended by assessment tools with higher ecological validity, such as the *EcoKitchen* task, as these seem to be less prone to the influence of demographic factors such as education level or IQ.

Previous studies showed that the *EcoKitchen* is sensitive to subtle cognitive and functional alterations in preclinical populations that exhibited a similar performance to healthy individuals in standard cognitive assessment methods (Júlio, Ribeiro, et al., 2019, 2022). Here, in a cross-sectional cohort of healthy adults, both the *EcoKitchen* parameters and the standardized test measures were sensitive to the age-induced alterations on

cognitive function. These findings are in line with the study of McAlister and Schmitter-Edgecombe (2016), that found an ageing effect in both experimental and classic executive function measures, and with the study of Allaire and Marsiske (1999), that showed that everyday cognitive tests and basic traditional measures were similarly associated with age.

Notably, while the *EcoKitchen* performance was significantly correlated with age and global cognitive status, it did not depend on education or IQ. In contrast, the classic tests correlated with the years of education and the IQ level of study participants. These results reinforce Royall et al. (2007) criticism about conventional cognitive testing having educational, linguistic, or cultural biases and low ecological validity – and seem to favor the use of more impartial and closer to real life assessment tools, such as the *EcoKitchen*.

Furthermore, our observation that an increase in age is paralleled by an increase in performance time and in the number of errors committed during task completion validates earlier work: Craik and Bialystok (2006) found that older adults were slower and more inaccurate than younger adults using a simulated "cooking breakfast" task; Schmitter-Edgecombe and Parsey (2014) noted that the ease and efficiency with which older adults complete everyday tasks is compromised; and McAlister and Schmitter-Edgecombe (2013) demonstrated that older adults took longer and failed to correctly sequence naturalistic executively demanding tasks.

A secondary aim of this study was to check the convergent validity of the *EcoKitchen* task with executive measures. In other words, we aimed to clarify if a more realistic measure of everyday cognitive function would capture the same cognitive sub-domains as conventional neuropsyhological tests. Normal ageing was found to alter different executive sub-skills strongly related to functional status, such as mental flexibility (Bell-McGinty et al., 2002), task switching (Kramer et al., 1999; Kray & Lindenberger, 2000; Mayr, 2001; Vaughan & Giovanello, 2010; Verhaeghen & Cerella, 2002), planning (Lewis & Miller, 2007), multitasking (McAlister & Schmitter-Edgecombe, 2013), inhibition (Murman, 2015), processing and psychomotor speed (Murman, 2015; Ylikoski et al., 1998), sustained attention (Ylikoski et al., 1998), complex sequencing ability (Cahn-Weiner et al., 2002), and novel problem solving (Heaton et al., 1986). Accordingly, significant associations were found between the three *EcoKitchen* parameters and the executive composite score computed from standardized neuropsychological tests after adjusting for the effect of ageing. This result fits in previous observations. Schmitter-Edgecombe et al. (2011) showed that processing/psychomotor speed, as assessed by

tests such as the Symbol Digit Modalities test, was a relevant cognitive predictor of performance on tasks like the *EcoKitchen*, after adjusting for age. Several authors also indicated that conventional paper-and pencil executive tests, such as the Wisconsin Card Sorting Test or the Trail Making Test, significantly predict performance-based instrumental activities of daily living (Aretouli & Brandt, 2010; Bell-McGinty et al., 2002; Cahn-Weiner et al., 2002; Gold, 2012). Additionally, this result further substantiates the convergent validity of the *EcoKitchen* task in the assessment of executive skills.

Nevertheless, there are some limitations to the current study that deserve to be mentioned. First, larger studies are mandatory to confirm and build upon our results, as the relatively small sample size hampers the generalization of the findings. Second, given the cross-sectional, exploratory and correlational nature of this study, the identification of the mechanisms mediating the age differences in performance has some interpretative difficulty and thus there is the need for a broader, multimodal, longitudinal study to validate our findings. Finally, virtual reality or performance-based assessment tools applied in clinical or research settings are not the same as real-life tasks, which might prevent us from drawing robust conclusions about the functional status of study participants based on this kind of measures. However, these methods are thought to have several benefits compared to real-world tasks, as they involve quantitative and safe environments, and have many positive attributes, namely safety, objectivity, efficiency, affordability, and wider applicability (Allain et al., 2014; Parsons et al., 2017; Ruse et al., 2014) – features of capital importance to evaluate the feasibility of potential interventions. Importantly, as stated before, the *EcoKitchen* task has previously proven to be associated with a self-report measure of real-world functioning, The Adults and Older Adults Functional Assessment Inventory - IAFAI (Júlio, Ribeiro, et al., 2019, 2022; Sousa et al., 2015), which suggests that it can serve as a surrogate of everyday performance.

To conclude, our study demonstrated that the *EcoKitchen*, a non-immersive virtual reality task, is sensitive to the effect of ageing on everyday cognitive function and probes executive skills similar to the ones assessed with standard paper-and-pencil tests. Importantly, the *EcoKitchen* time and accuracy measures may be able to deliver a more impartial portrait of everyday cognition since they seem to be less influenced by demographic factors like education level and IQ than the conventional tests. Additionally, our findings strongly suggest that executive functions are implicated *per se* in the timely and accurate completion of simulated daily-life tasks. These observations highlight the importance of taking advantage of current technology to develop more

ecological assessment tests. Notably, the use of more realistic assessment tools such as the *EcoKitchen* will help identify specific routines and settings where difficulties are more probable to occur thereby contributing towards the development of tailored interventions aimed at delaying potential functional decline and promoting individual safety and welfare in the ageing population.

References

Allain, P., Foloppe, D. A., Besnard, J., Yamaguchi, T., Etcharry-Bouyx, F., Le Gall, D., Nolin, P., & Richard, P. (2014). Detecting everyday action deficits in Alzheimer's disease using a nonimmersive virtual reality kitchen. *Journal of the International Neuropsychological Society*, *20*(5), 468–477. https://doi.org/10.1017/S1355617714000344

Allaire, J. C., & Marsiske, M. (1999). Everyday cognition: Age and intellectual ability correlates. *Psychology and Aging*, *14*(4), 627–644. https://doi.org/10.1037//0882-7974.14.4.627

Alves, L., Simões, M. R., & Martins, C. (2012). The estimation of premorbid intelligence levels among Portuguese speakers: The Irregular Word Reading Test (TeLPI). *Archives of Clinical Neuropsychology*, *27*(1), 58–68. https://doi.org/10.1093/arclin/acr103

Aretouli, E., & Brandt, J. (2010). Everyday functioning in mild cognitive impairment and its relationship with executive cognition. *International Journal of Geriatric Psychiatry*, *25*(3), 224–233. https://doi.org/10.1002/gps.2325

Beck, A. T., Steer, R. A., & Brown, G. K. (1996). *Manual for the Beck Depression Inventory-II.* Psychological Corporation.

Bell-McGinty, S., Podell, K., Franzen, M., Baird, A. D., & Williams, M. J. (2002). Standard measures of executive function in predicting instrumental activities of daily living in older adults. *International Journal of Geriatric Psychiatry*, *17*(9), 828–834. https://doi.org/10.1002/gps.646

Burgess, P. W., Alderman, N., Evans, J., Emslie, H., & Wilson, B. A. (1998). The ecological validity of tests of executive function. *Journal of the International Neuropsychological Society*, *4*(6), 547–558. https://doi.org/10.1017/s1355617798466037

Cahn-Weiner, D. A., Boyle, P. A., & Malloy, P. F. (2002). Tests of executive function predict instrumental activities of daily living in community-dwelling older individuals. *Applied*

Neuropsychology, *9*(3), 187–191.
https://doi.org/10.1207/S15324826AN0903_8

Cavaco, S., Gonçalves, A., Pinto, C., Almeida, E., Gomes, F., Moreira, I., Fernandes, J., & Teixeira-Pinto, A. (2013). Semantic fluency and phonemic fluency: Regression-based norms for the Portuguese population. *Archives of Clinical Neuropsychology*, *28*(3), 262–271.
https://doi.org/10.1093/arclin/act001

Chaytor, N., & Schmitter-Edgecombe, M. (2003). The ecological validity of neuropsychological tests: A review of the literature on everyday cognitive skills. *Neuropsychology Review*, *13*(4), 181–197.
https://doi.org/10.1023/b:nerv.0000009483.91468.fb

Craik, F. I., & Bialystok, E. (2006). Planning and task management in older adults: Cooking breakfast. *Memory & Cognition*, *34*(6), 1236–1249.
https://doi.org/10.3758/bf03193268

Diehl, M., Willis, S. L., & Schaie, K. W. (1995). Everyday problem solving in older adults: Observational assessment and cognitive correlates. *Psychology and Aging*, *10*(3), 478–491.
https://doi.org/10.1037//0882-7974.10.3.478

Doherty, T. A., Barker, L. A., Denniss, R., Jalil, A., & Beer, M. D. (2015). The cooking task: Making a meal of executive functions. *Frontiers in Behavioral Neuroscience*, *9*, 22.
https://doi.org/10.3389/fnbeh.2015.00022

George, D., & Mallery, P. (2016). IBM SPSS Statistics 23 Step by Step: A Simple Guide and Reference (14th ed.). Routledge.
https://doi.org/10.4324/9781315545899

Gioia, G. A., & Isquith, P. K. (2004). Ecological assessment of executive function in traumatic brain injury. *Developmental Neuropsychology*, *25*(1-2), 135–158.
https://doi.org/10.1080/87565641.2004.9651925

Godbout, L., Grenier, M. C., Braun, C. M., & Gagnon, S. (2005). Cognitive structure of executive deficits in patients with frontal lesions performing activities of daily living. *Brain Injury*, *19*(5), 337–348.
https://doi.org/10.1080/02699050400005093

Godefroy, O., Azouvi, P., Robert, P., Roussel, M., LeGall, D., Meulemans, T., & Groupe de Réflexion sur l'Evaluation des Fonctions Exécutives Study Group (2010). Dysexecutive syndrome: Diagnostic criteria and validation study. *Annals of Neurology*, *68*(6), 855–864.
https://doi.org/10.1002/ana.22117

Gold D. A. (2012). An examination of instrumental activities of daily living assessment in older adults and mild cognitive impairment. *Journal of Clinical and Experimental Neuropsychology*, *34*(1), 11–34.
https://doi.org/10.1080/13803395.2011.614598

Heaton, R. K. (1981). *A Manual for the Wisconsin Card Sorting Test.* Psychological Assessment Resources.

Heaton, R. K., Grant, I., & Matthews, C. G. (1986). Differences in neuropsychological test

performance associated with age, education, and sex. In I. Grant, K. M. Adams, (Eds.), *Neuropsychological assessment of neuropsychiatric disorders*. Oxford University Press.

Júlio, F., Caetano, G., Januário, C., & Castelo-Branco, M. (2019). The effect of impulsivity and inhibitory control deficits in the saccadic behavior of premanifest Huntington's disease individuals. *Orphanet Journal of Rare Diseases, 14(*1), 246. https://doi.org/10.1186/s13023-019-1218-y

Júlio, F., Ribeiro, M. J., Morgadinho, A., Sousa, M., van Asselen, M., Simões, M. R., Castelo-Branco, M., & Januário, C. (2022). Cognition, function and awareness of disease impact in early Parkinson's and Huntington's disease. *Disability and Rehabilitation*, *44*(6), 921–939. https://doi.org/10.1080/09638288.2020.1783001

Júlio, F., Ribeiro, M. J., Patrício, M., Malhão, A., Pedrosa, F., Gonçalves, H., Simões, M., van Asselen, M., Simões, M. R., Castelo-Branco, M., & Januário, C. (2019). A Novel Ecological Approach Reveals Early Executive Function Impairments in Huntington's Disease. *Frontiers in Psychology*, *10*, 585. https://doi.org/10.3389/fpsyg.2019.00585

Koerts, J., Van Beilen, M., Tucha, O., Leenders, K. L., & Brouwer, W. H. (2011). Executive functioning in daily life in Parkinson's disease: Initiative, planning and multi-task performance. *PloS One*, *6*(12), e29254. https://doi.org/10.1371/journal.pone.0029254

Kramer, A. F., Hahn, S., & Gopher, D. (1999). Task coordination and aging: Explorations of executive control processes in the task switching paradigm. *Acta Psychologica*, *101*(2-3), 339–378. https://doi.org/10.1016/s0001-6918(99)00011-6

Kray, J., & Lindenberger, U. (2000). Adult age differences in task switching. *Psychology and Aging*, *15*(1), 126–147. https://doi.org/10.1037//0882-7974.15.1.126

Lai, J. S., Goodnight, S., Downing, N. R., Ready, R. E., Paulsen, J. S., Kratz, A. L., Stout, J. C., McCormack, M. K., Cella, D., Ross, C., Russell, J., & Carlozzi, N. E. (2018). Evaluating cognition in individuals with Huntington disease: Neuro-QoL cognitive functioning measures. *Quality of Life Research*, *27*(3), 811–822. https://doi.org/10.1007/s11136-017-1755-6

Lewis, M. S., & Miller, L. S. (2007). Executive control functioning and functional ability in older adults. *The Clinical Neuropsychologist*, *21*(2), 274–285. https://doi.org/10.1080/13854040500519752

Marcotte, T. D., Scott, J. C., Kamat, R., & Heaton, R. K. (2010). Neuropsychology and the prediction of everyday functioning. In T. D. Marcotte & I. Grant (Eds.), *Neuropsychology of everyday functioning* (pp. 5–38). The Guilford Press.

Mayr U. (2001). Age differences in the selection of mental sets: The role of inhibition, stimulus ambiguity, and response-set overlap. *Psychology and Aging*, *16*(1), 96–109. https://doi.org/10.1037/0882-7974.16.1.96

McAlister, C., & Schmitter-Edgecombe, M. (2013). Naturalistic assessment of executive function and everyday multitasking in healthy older adults. *Neuropsychology, development, and cognition. Section B, Aging, neuropsychology and cognition*, *20*(6), 735–756. https://doi.org/10.1080/13825585.2013.781990

McAlister, C., & Schmitter-Edgecombe, M. (2016). Executive function subcomponents and their relations to everyday functioning in healthy older adults. *Journal of Clinical and Experimental Neuropsychology*, *38*(8), 925–940. https://doi.org/10.1080/13803395.2016.1177490

Murman D. L. (2015). The Impact of Age on Cognition. *Seminars in Hearing*, *36*(3), 111–121. https://doi.org/10.1055/s-0035-1555115

Nasreddine, Z. S., Phillips, N. A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., Cummings, J. L., & Chertkow, H. (2005). The Montreal Cognitive Assessment, MoCA: A brief screening tool for mild cognitive impairment. *Journal of the American Geriatrics Society*, *53*(4), 695–699. https://doi.org/10.1111/j.1532-5415.2005.53221.x

Oldfield R. C. (1971). The assessment and analysis of handedness: The Edinburgh inventory. *Neuropsychologia, 9*(1), 97–113. https://doi.org/10.1016/0028-3932(71)90067-4

Parsons, T. D., Carlew, A. R., Magtoto, J., & Stonecipher, K. (2017). The potential of function-led virtual environments for ecologically valid measures of executive function in experimental and clinical neuropsychology. *Neuropsychological Rehabilitation*, *27*(5), 777–807. https://doi.org/10.1080/09602011.2015.1109524

Rand, D., Basha-Abu Rukan, S., Weiss, P. L., & Katz, N. (2009). Validation of the Virtual MET as an assessment tool for executive functions. *Neuropsychological Rehabilitation*, *19*(4), 583–602. https://doi.org/10.1080/09602010802469074

Rizzo, A., Buckwalter, J. G. , Van der Zaag, Neumann, C. U., Thiebaux, M., Chua, C., Van Rooyen, A., Larson, P., & and Humphrey, L.. (2000). Virtual Environment Applications in Clinical Neuropsychology. *Proceedings of the IEEE Virtual Reality 2000 Conference (VR '00)*. IEEE Computer Society: USA. http://doi.org/10.1109/VR.2000.840364

Royall, D. R., Lauterbach, E. C., Kaufer, D., Malloy, P., Coburn, K. L., Black, K. J., & Committee on Research of the American Neuropsychiatric Association (2007). The cognitive correlates of functional status: A review from the Committee on Research of the American Neuropsychiatric Association. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *19*(3), 249–265. https://doi.org/10.1176/jnp.2007.19.3.249

Ruse, S. A., Davis, V. G., Atkins, A. S., Krishnan, K. R., Fox, K. H., Harvey, P. D., & Keefe, R. S. (2014). Development of a virtual reality assessment of everyday living skills. *Journal of*

Visualized Experiments, (86), 51405.
https://doi.org/10.3791/51405

Schmitter-Edgecombe, M., & Parsey, C. M. (2014). Assessment of functional change and cognitive correlates in the progression from healthy cognitive aging to dementia. *Neuropsychology*, *28*(6), 881–893.
https://doi.org/10.1037/neu0000109

Schmitter-Edgecombe, M., Parsey, C., & Cook, D. J. (2011). Cognitive correlates of functional performance in older adults: Comparison of self-report, direct observation, and performance-based measures. *Journal of the International Neuropsychological Society*, *17*(5), 853–864.
https://doi.org/10.1017/S1355617711000865

Scott, J. C., Woods, S. P., Vigil, O., Heaton, R. K., Schweinsburg, B. C., Ellis, R. J., Grant, I., Marcotte, T. D., & San Diego HIV Neurobehavioral Research Center (HNRC) Group (2011). A neuropsychological investigation of multitasking in HIV infection: Implications for everyday functioning. *Neuropsychology*, *25*(4), 511–519.
https://doi.org/10.1037/a0022491

Smith, A. (1982). *Symbol Digits Modalities Test (SDMT) Manual.* (Revised). Western Psychological Services.

Sousa, L. B., Prieto, G., Vilar, M., Firmino, H., & Simões, M. R. (2015). The Adults and Older Adults Functional Assessment Inventory: A Rasch Model Analysis. *Research on Aging*, *37*(8), 787–814.
https://doi.org/10.1177/0164027514564469

Spooner, D. M., & Pachana, N. A. (2006). Ecological validity in neuropsychological assessment: A case for greater consideration in research with neurologically intact populations. *Archives of Clinical Neuropsychology*, *21*(4), 327–337.
https://doi.org/10.1016/j.acn.2006.04.004

Stroop, J. R. (1935). Studies of interference in serial verbal reactions. *Journal of Experimental Psychology: General, 18*, 643–662.
https://doi.org/10.1037/0096-3445.121.1.15

Tan, J. E., Hultsch, D. F., & Strauss, E. (2009). Cognitive abilities and functional capacity in older adults: Results from the modified Scales of Independent Behavior-Revised. *The Clinical Neuropsychologist, 23*(3), 479–500.
https://doi.org/10.1080/13854040802368684

Titov, N., & Knight, R. G. (2005). A computer-based procedure for assessing functional cognitive skills in patients with neurological injuries: The virtual street. *Brain Injury*, *19*(5), 315–322.
https://doi.org/10.1080/02699050400013725

Vaughan, L., & Giovanello, K. (2010). Executive function in daily life: Age-related influences of executive processes on instrumental activities of daily living. *Psychology and Aging*, *25*(2), 343–355.
https://doi.org/10.1037/a0017729

Verhaeghen, P., & Cerella, J. (2002). Aging, executive control, and attention: A review of meta-analyses. *Neuroscience and Biobehavioral Reviews*, *26*(7), 849–857. https://doi.org/10.1016/s0149-7634(02)00071-4

Wechsler D. (1997). *WAIS-III administration and scoring manual* (3rd ed.) The Psychological Corporation.

Wechsler D. (2008). *WAIS-III: Escala de Inteligência de Wechsler para adultos – Manual (*3rd ed.)Portuguese Version [Wechsler Adult Intelligence Scale - WAIS-III]. Cegoc.

Ylikoski, R., Ylikoski, A., Erkinjuntti, T., Sulkava, R., Keskivaara, P., Raininko, R., & Tilvis, R. (1998). Differences in neuropsychological functioning associated with age, education, neurological status, and magnetic resonance imaging findings in neurologically healthy elderly individuals. *Applied Neuropsychology*, *5*(1), 1–14. https://doi.org/10.1207/s15324826an0501_1

Zhang, L., Abreu, B. C., Seale, G. S., Masel, B., Christiansen, C. H., & Ottenbacher, K. J. (2003). A virtual reality environment for evaluation of a daily living skill in brain injury rehabilitation: Reliability and validity. *Archives of Physical Medicine and Rehabilitation*, *84*(8), 1118–1124. https://doi.org/10.1016/s0003-9993(03)00203-x

Chapter VI - General Discussion

This body of work has demonstrated that novel computer-based assessment methods can identify impairments in terms of performance time and accuracy in persons that show a regular response to more conventional neuropsychological measures. Taken together, our findings underline the importance of designing and testing objective, quantitative neuropsychological assessment methods that can effectively distinguish between preclinical, clinical, and non-clinical populations and can accurately portray the impact of subtle cognitive changes on functional status and daily life- like tasks. This more refined assessment approach is thought to be vital to customize and evaluate the effects of any intervention that targets cognition and function according to the idiosyncrasies of disease stages, nosological entities and age categories.

More complex assessment tools are needed to detect subtle cognitive and functional deficits.

The 4-block saccadic paradigm with increasing executive and memory demands was able to capture cognitive and behavioural deficits presented by persons with premanifest HD during oculomotor performance (Júlio, Caetano, et al., 2019). We demonstrated impulsivity and inhibition abnormalities not only in early manifest patients (Júlio et al., 2013) but also in highly functioning persons with PreHD. These abnormalities were found only in the saccadic accuracy and trajectory parameters computed from the eye-tracking measures, since none of the several classic executive and memory tests employed in the cognitive assessment of study participants was able to capture the changes that occur in preclinical HD.

The *EcoKitchen*, a non-immersive virtual reality measure with cumulative cognitive load that simulates meal preparation tasks, was able to capture the changes in cognition and function underlying preclinical HD (Júlio, Ribeiro, et al., 2019). We showed impairments

in the performance accuracy of persons with PreHD during the completion of executively demanding simulated meal preparation tasks but not in their responses to a set of classic EF tests and to BADS (Júlio, Ribeiro, et al., 2019). These results reinforce the claims that specific deficits in executive control (Maurage et al., 2017), multi-tasking (Snowden, 2017) and cognitive slowing as captured by timed tasks (Eddy & Rickards, 2015) are among the earliest HD-related cognitive changes, namely in persons with premanifest HD who often show an intact functional capacity. Additionally, these findings indicate that timed and fractionable EF tasks are highly sensitive to disease course (Alvarez & Emory, 2006; Snowden, 2017; Stout et al., 2011; Tabrizi et al., 2012).

Virtual reality measures can mimic daily life function and detect functionally significant deficits.

Our findings support the idea that computer-based measures might be superior to more conventional neuropsychological tests in detecting tangible impairments in IADL performance (Stout et al., 2016), as they are able to mimic the complexity of everyday cognition. In fact, measures that can detect and monitor impairments in skills essential for daily life might prove relevant to evaluate the functional state, disease progression, and response to therapy of patients with neurodegenerative disorders (Artusi et al., 2018). Moreover, these objective assessment tools can help to overcome the challenges posed by the patients' poor insight, their lack of mental flexibility and impoverished planning abilities (Bogdanova et al., 2016). High demanding performance-based assessment tools with increased level of complexity and requiring additional cognitive resources, might be the most sensitive method to defeat the caveats and limitations of conventional cognitive and functional assessments (Neguț et al., 2016).

Several technological assets are currently available to measure clinically relevant parameters in these disorders, particularly those targeting motor symptoms (Bogdanova et al., 2016; Maetzler et al., 2016; Maggio et al., 2018; Reilmann & Schubert, 2017). The inclusion of validated, treatment-related and symptom-specific data collected with digital tools will create a new era in the management of these conditions: it will provide valid and accurate information that is clinically relevant, it will contribute to ecologically effective therapeutic decisions, it will offer a target range for treatment response or disease course, and it will allow an easy and repetitive use by healthcare professionals and/or patients (Maetzler et al., 2016). Additionally, computerized individually tailored "game-like" tasks or artificial environments with which the person can interact may

improve the motivation and enjoyment of those being assessed, influencing their quality of life and the ability to get high quality information to be used in future treatment or rehabilitation efforts (Maggio et al., 2018). Hence, the computerized tools created for our work may facilitate not only the assessment, but also the rehabilitation of the cognitive skills of persons with clinical and non-clinical conditions that have a relevant impact on functional status but who show a standard performance in commonly used neuropsychological assessment methods (Bogdanova et al., 2016; Maggio et al., 2018).

Virtual reality measures can identify the cognitive and functional specificities of persons with HD and PD.

Our work has captured differences in the timing and accuracy of the task performance of persons with early manifest HD, early-stage PD and early-onset PD. Notably, these differences were identified by the *EcoKitchen* but not by BADS (Júlio, Ribeiro, et al., 2022). We have shown that persons with HD display more pronounced executive deficits than medicated persons with PD in everyday routine simulation (Bialystok, et al., 2008; Hanes et al., 1995; Lundervold et al., 1994; Roman et al., 1998). These differences are thought to reflect the neuropathological features of each condition within the same subcortical degenerative category (Lundervold et al., 1994): the primary involvement of the caudate nucleus and its links to frontal lobe areas in persons with early manifest HD, which are related to impairments on tasks that rely on executive functions (Aylward et al., 1996; Berent et al., 1988; Grahn et al., 2009; Hasselbalch et al., 1992; Lawrence et al., 1998; Rosas et al., 2001; Snowden, 2017; Vonsattel & DiFiglia, 1998); the primary involvement of the putamen and its links to more basic sensorimotor regions in early stage idiopathic PD, which are associated with decreased psychomotor speed, movement poverty and slowness, or bradyphrenia (Brown & Marsden, 1990; Darweesh et al., 2017; Dirnberger & Jahanshahi, 2013; Grahn et al., 2009; Hanes et al., 1995; Kish et al., 1988; Koerts et al., 2011).

Persons with HD and PD maintain awareness regarding their cognitive and functional status.

The comparison of subjective and objective measures of functional cognition has revealed that the clinical populations involved in our work keep a preserved insight about their condition. The *EcoKitchen* performance was found to be closely related to the

self-appraisal of functional status in persons with HD and PD – decreased *EcoKitchen* performance accuracy corresponding to more cognitive complaints in the HD group and slower *EcoKitchen* performance time corresponding to more physical complaints in the PD group. Additionally, these results underscore that motor function, but not cognitive function is a predictor of activities of daily living in persons with early PD (Cahn et al., 1998) and that persons with early HD present more cognitive complaints than physical complaints (Helder et al., 2001).

The performance on virtual reality measures is less influenced by demographic factors than performance on standard neuropsychological tests.

The age effect on the EF skills of older healthy adults as captured by the *EcoKitchen* was less biased compared to conventional executive tests – which were correlated with the education and IQ level of study participants (Júlio, Ribeiro, Simões, et al., 2022). Since response inhibition and executive abilities requiring a speeded motor component are particularly susceptible to age effects (Alvarez & Emory, 2006; Harada et al., 2013), the increasing cognitive demanding *EcoKitchen* tasks were effective at identifying age-related decline on these skills. Thus, our novel tool allowed us to determine how functional status decreases with ageing and how this relates to executive function, which is vital to identify everyday functioning alterations, point out early safety issues and help distinguish healthy states from disease states (Harada et al., 2013). Furthermore, the *EcoKitchen* can be a useful method for the functional rehabilitation of older adults, by improving their participation in certain activities, building their cognitive reserve, and promoting their cognitive retraining – all approaches to achieve a successful cognitive ageing (Harada et al., 2013).

In sum, we believe that the knowledge derived from our work offers new insights into the complex and diverse phenotype of basal ganglia disorders (Glidden et al., 2020). Additionally, it offers valuable tips for those who care for these populations, develop experimental therapeutics, and deal with the symptomatic burden of these disorders to plan tailored and more effective interventions to address the EF problems shown by these patients (Glidden et al., 2020). Specifically, in HD, as no effective treatments to ameliorate cognitive decline and its consequences on function exist (Shoulson & Young, 2011), even though this is considered one of the most impactful disease symptoms by patients and families (Simpson et al., 2016), it seems crucial to develop new ways to

minimize the functional consequences of EF changes (Glidden et al., 2020; Pollard, 2008; Snowden, 2017). Notably, the *EcoKitchen* presents itself as an affordable and sensitive tool to assess the functional cognition of both clinical and healthy populations in an ecologically relevant way and can be used in the training/rehabilitation work with persons exhibiting functionally impactful EF deficits.

Future work

An important extension of the current work will be to explore and document more comprehensively the existing relations between performance on the computer-based simulation tasks and performance in real-life settings. When attempting to answer ecological questions about the impact of EF deficits on everyday function it is relevant to take other factors into account, as neuropsychological measures can only go so far. Personality measures, informant or clinician ratings, behavioural observations, and demographic variables should all be considered along with the test/task results (Chaytor & Schmitter-Edgecombe, 2003). Thus, future research should focus on the predictive validity of ecologically relevant EF assessment tasks in relationship to real-life performance and other objective criteria and to investigate the advantages and disadvantages of each measure (Neguț et al., 2016). Furthermore, as previously mentioned, the potential utility of these novel tasks in rehabilitation efforts should also be tested. Since the early detection of altered cognitive sub-domains is thought to be extremely relevant for the planning and implementation of neuropsychological and neuromodulation therapeutic interventions to improve EF (Maurage et al., 2017), our computer-based tasks might be valuable methods to include in this endeavour. Having in mind the profound negative impact of executive impairments on function (Alvarez & Emory, 2006), future studies may try to look at the daily-life repercussions of repeated training on these digital tasks. Concretely, the *EcoKitchen* task can be adapted to train more integrated behavioural repertoires in rehabilitation settings (Schultheis et al., 2002). Additionally, as we have shown that both persons with HD and PD maintain a relatively preserved self-awareness about the functional impact of their clinical condition, future work can investigate the level of insight that these groups have into their cognitive/executive deficits. As the link between cognitive and motor functions in HD

and PD can be so intricate that sometimes it proves impossible to separate (Eddy & Rickards, 2015) and because persons with suspected cognitive changes may be more impaired than they admit on self-report measures (Albert et al., 1999), it would be relevant to further clarify to what extent persons with HD and PD are aware of executive dysfunction symptoms *per se* and develop a more refined assessment of self-appraisal of cognitive deficits.

Lastly, two caution notes should be made when discussing our work. First, some of the conventional neuropsychological tests included in our standard assessment protocol lack proper validation in the Portuguese population, which could have limited their efficacy to detect any deviations from the norm. Second, we need to acknowledge that despite the efficacy of our computer-based assessment tools in detecting the functional impact of EF deficits, we cannot neglect that technological familiarity might have influenced the scores on these digital assessments (Porffy et al., 2022). Nevertheless, we strongly believe that with the growing computerization of society, virtual game-like tasks create broader possibilities for the assessment and rehabilitation of functionally relevant cognitive skills compared to conventional neuropsychological assessment tests.

Concluding Remarks

This PhD work was set up to improve the detection of functionally significant deficits associated with the cognitive and behavioural changes caused by Huntington's disease and related conditions. Many years of close contact with persons with HD and their families, both as a professional and as a volunteer for HD national and international organizations, have made me greatly aware of the tremendous impact that the HD clinical phenotype has on the daily life of those affected by this complex disease and everyone around them. Moreover, it made me realize that this impact can be very subtle but still impose an extremely heavy burden not only in the individual but also in the family and even in the society. Therefore, having more realistic assessment tools to measure the functional consequences of HD symptoms is imperative to properly plan effective prevention and remediation strategies for this condition, as well as to design and promote reliable research aimed at finding personalised treatments or interventions for HD.

During the implementation of the different studies with HD clinical and preclinical populations, patients with PD and healthy adults, we were able to test the efficacy of novel computer-based assessment methods to detect the earliest impairments in performance time and accuracy caused by EF deficits. Specifically, the *EcoKitchen* was able to capture the functionally significant changes associated with the cognitive impairments of the different populations tested. Importantly, several years after the groundwork of this PhD project, the use of digital technology and computer-based assessment tools in movement disorders like HD or PD is still limited and often bounded to the evaluation of motor features, such as balance, gait or tremor; thus, more investment in the use of digital tools to grasp the cognitive and behavioural alterations of clinical and non-clinical populations is needed.

Particularly the *EcoKitchen* task has proven to be a relevant contribution to reach this goal.

On the one hand, our results indicate that it was able to fill the existing gaps in the ecological assessment of executively impaired but still relatively high functioning persons who presented a standard performance in conventional assessment tools.

On the other hand, the HD families that participated in these studies and the ones that attended the oral presentations about our work thought that the *EcoKitchen* was a user-friendly assessment tool that could lead to tangible positive changes minimizing their daily life challenges.

By detecting the early and subtle functional deficits related to cognitive alterations, we believe we are giving an important contribution to improve the management of these deficits – which, in turn, will foster the independence and promote the well-being of these populations.

By establishing that patients are self-aware of their functional deficits, we are giving them a more prominent role in symptom report and management. This will hopefully contribute to a more patient-centred approach to neurological diseases with extremely high societal costs.

I would like to end this work by quoting Álvaro Lapa, a fabulous Portuguese painter and writer, who wrote in one of his paintings from the 90's:

"Temos o Trilho, Falta-nos o Mapa" ["We Have the Trail, We Lack the Map"].

This makes perfect sense when we think about the road that still lies ahead for Huntington's disease and similar conditions.

Actually, this makes perfect sense if we think of life itself.

References

Albert, S. M., Michaels, K., Padilla, M., Pelton, G., Bell, K., Marder, K., Stern, Y., & Devanand, D. P. (1999). Functional significance of mild cognitive impairment in elderly patients without a dementia diagnosis. *The American Journal of Geriatric Psychiatry, 7*(3), 213–220. https://doi.org/10.1097/00019442-199908000-00005

Alvarez, J. A., & Emory, E. (2006). Executive function and the frontal lobes: A meta-analytic review. *Neuropsychology Review*, *16*(1), 17–42. https://doi.org/10.1007/s11065-006-9002-x

Artusi, C. A., Mishra, M., Latimer, P., Vizcarra, J. A., Lopiano, L., Maetzler, W., Merola, A., & Espay, A. J. (2018). Integration of technology-based outcome measures in clinical trials of Parkinson and other neurodegenerative diseases. *Parkinsonism & Related Disorders*, *46 Suppl 1*(Suppl 1), S53–S56. https://doi.org/10.1016/j.parkreldis.2017.07.022

Aylward, E. H., Codori, A. M., Barta, P. E., Pearlson, G. D., Harris, G. J., & Brandt, J. (1996). Basal ganglia volume and proximity to onset in presymptomatic Huntington disease. *Archives of Neurology*, *53*(12), 1293–1296. https://doi.org/10.1001/archneur.1996.00550120105023

Berent, S., Giordani, B., Lehtinen, S., Markel, D., Penney, J. B., Buchtel, H. A., Starosta-Rubinstein, S., Hichwa, R., & Young, A. B. (1988). Positron emission tomographic scan investigations of Huntington's disease: Cerebral metabolic correlates of cognitive function. *Annals of Neurology*, *23*(6), 541–546. https://doi.org/10.1002/ana.410230603

Bialystok, E., Craik, F. I., & Stefurak, T. (2008). Planning and task management in Parkinson's disease: Differential emphasis in dual-task performance. *Journal of the International Neuropsychological Society*, *14*(2), 257–265. https://doi.org/10.1017/S1355617708080296

Bogdanova, Y., Yee, M. K., Ho, V. T., & Cicerone, K. D. (2016). Computerized Cognitive Rehabilitation of Attention and Executive Function in Acquired Brain Injury: A Systematic Review. *The Journal of Head Trauma Rehabilitation*, *31*(6), 419–433. https://doi.org/10.1097/HTR.0000000000000203

Brown, R. G., & Marsden, C. D. (1990). Cognitive function in Parkinson's disease: From description to theory. *Trends in Neurosciences*, *13*(1), 21–29. https://doi.org/10.1016/0166-2236(90)90058-i

Cahn, D. A., Sullivan, E. V., Shear, P. K., Pfefferbaum, A., Heit, G., & Silverberg, G. (1998). Differential contributions of cognitive and motor component processes to physical and instrumental activities of daily living in Parkinson's disease. *Archives of Clinical Neuropsychology*, *13*(7), 575–583.

Chaytor, N., & Schmitter-Edgecombe, M. (2003). The ecological validity of neuropsychological

tests: A review of the literature on everyday cognitive skills. *Neuropsychology Review*, *13*(4), 181–197. https://doi.org/10.1023/b:nerv.0000009483.91468.fb

Darweesh, S. K., Verlinden, V. J., Stricker, B. H., Hofman, A., Koudstaal, P. J., & Ikram, M. A. (2017). Trajectories of prediagnostic functioning in Parkinson's disease. *Brain*, *140*(2), 429–441. https://doi.org/10.1093/brain/aww291

Dirnberger, G., & Jahanshahi, M. (2013). Executive dysfunction in Parkinson's disease: A review. *Journal of Neuropsychology*, *7*(2), 193–224. https://doi.org/10.1111/jnp.12028

Eddy, C. M., & Rickards, H. E. (2015). Cognitive deficits predict poorer functional capacity in Huntington's disease: But what is being measured?. *Neuropsychology*, *29*(2), 268–273. https://doi.org/10.1037/neu0000134

Glidden, A. M., Luebbe, E. A., Elson, M. J., Goldenthal, S. B., Snyder, C. W., Zizzi, C. E., Dorsey, E. R., & Heatwole, C. R. (2020). Patient-reported impact of symptoms in Huntington disease: PRISM-HD. *Neurology*, *94*(19), e2045–e2053. https://doi.org/10.1212/WNL.0000000000008906

Grahn, J. A., Parkinson, J. A., & Owen, A. M. (2009). The role of the basal ganglia in learning and memory: Neuropsychological studies. *Behavioural Brain Research*, *199*(1), 53–60. https://doi.org/10.1016/j.bbr.2008.11.020

Hanes, K. R., Andrewes, D. G., & Pantelis, C. (1995). Cognitive flexibility and complex integration in Parkinson's disease, Huntington's disease, and schizophrenia. *Journal of the International Neuropsychological Society*, *1*(6), 545–553. https://doi.org/10.1017/s1355617700000679

Harada, C. N., Natelson Love, M. C., & Triebel, K. L. (2013). Normal cognitive aging. *Clinics in Geriatric Medicine*, *29*(4), 737–752. https://doi.org/10.1016/j.cger.2013.07.002

Hasselbalch, S. G., Oberg, G., Sørensen, S. A., Andersen, A. R., Waldemar, G., Schmidt, J. F., Fenger, K., & Paulson, O. B. (1992). Reduced regional cerebral blood flow in Huntington's disease studied by SPECT. *Journal of Neurology, Neurosurgery, and Psychiatry*, *55*(11), 1018–1023. https://doi.org/10.1136/jnnp.55.11.1018

Helder, D. I., Kaptein, A. A., van Kempen, G. M., van Houwelingen, J. C., & Roos, R. A. (2001). Impact of Huntington's disease on quality of life. *Movement Disorders*, *16*(2), 325–330. https://doi.org/10.1002/mds.1056

Júlio, F., Caetano, G., Januário, C., & Castelo-Branco, M. (2013). The potential role of neuropsychological and saccadic measures in defining disease progression and severity in Huntington's disease. *Journal of Huntington's Disease* 2(3), 57.

Júlio, F., Caetano, G., Januário, C., & Castelo-Branco, M. (2019). The effect of impulsivity and inhibitory control deficits in the saccadic behavior of premanifest Huntington's disease

individuals. *Orphanet Journal of Rare Diseases*, *14*(1), 246. https://doi.org/10.1186/s13023-019-1218-y

Júlio, F., Ribeiro, M. J., Morgadinho, A., Sousa, M., van Asselen, M., Simões, M. R., Castelo-Branco, M., & Januário, C. (2022). Cognition, function and awareness of disease impact in early Parkinson's and Huntington's disease. *Disability and Rehabilitation*, *44*(6), 921–939. https://doi.org/10.1080/09638288.2020.1783001

Júlio, F., Ribeiro, M. J., Patrício, M., Malhão, A., Pedrosa, F., Gonçalves, H., Simões, M., van Asselen, M., Simões, M. R., Castelo-Branco, M., & Januário, C. (2019). A Novel Ecological Approach Reveals Early Executive Function Impairments in Huntington's Disease. *Frontiers in Psychology*, *10*, 585. https://doi.org/10.3389/fpsyg.2019.00585

Júlio, F., Ribeiro, M. J., Simões, M. R., Castelo-Branco, M., & Januário, C. (2022). Assessing the Impact of Age on Everyday Cognitive Function with Virtual Reality: The *EcoKitchen* task. [Manuscript submitted for publication]. University of Coimbra. Published dataset: https://doi.org/10.17605/OSF.IO/J26X8

Kish, S. J., Shannak, K., & Hornykiewicz, O. (1988). Uneven pattern of dopamine loss in the striatum of patients with idiopathic Parkinson's disease. Pathophysiologic and clinical implications. *The New England Journal of Medicine*, *318*(14), 876–880. https://doi.org/10.1056/NEJM198804073181402

Koerts, J., Van Beilen, M., Tucha, O., Leenders, K. L., & Brouwer, W. H. (2011). Executive functioning in daily life in Parkinson's disease: Initiative, planning and multi-task performance. *PloS One*, *6*(12), e29254. https://doi.org/10.1371/journal.pone.0029254

Lawrence, A. D., Sahakian, B. J., & Robbins, T. W. (1998). Cognitive functions and corticostriatal circuits: Insights from Huntington's disease. *Trends in Cognitive Sciences*, *2*(10), 379–388. https://doi.org/10.1016/s1364-6613(98)01231-5

Lundervold, A. J., Karlsen, N. R., & Reinvang, I. (1994). Assessment of 'subcortical dementia' in patients with Huntington's disease, Parkinson's disease, multiple sclerosis and AIDS by a neuropsychological screening battery. *Scandinavian Journal of Psychology*, *35*(1), 48–55. https://doi.org/10.1111/j.1467-9450.1994.tb00932.x

Maetzler, W., Klucken, J., & Horne, M. (2016). A clinical view on the development of technology-based tools in managing Parkinson's disease. *Movement Disorders*, *31*(9), 1263–1271. https://doi.org/10.1002/mds.26673

Maggio, M. G., De Cola, M. C., Latella, D., Maresca, G., Finocchiaro, C., La Rosa, G., Cimino, V., Sorbera, C., Bramanti, P., De Luca, R., & Calabrò, R. S. (2018). What About the Role of Virtual Reality in Parkinson Disease's Cognitive Rehabilitation? Preliminary Findings from a Randomized Clinical Trial. *Journal of Geriatric Psychiatry and Neurology*, *31*(6), 312–318. https://doi.org/10.1177/0891988718807973

Maurage, P., Heeren, A., Lahaye, M., Jeanjean, A., Guettat, L., Verellen-Dumoulin, C., Halkin, S.,

Billieux, J., & Constant, E. (2017). Attentional impairments in Huntington's disease: A specific deficit for the executive conflict. *Neuropsychology*, *31*(4), 424–436. https://doi.org/10.1037/neu0000321

Neguț, A., Matu, S.-A., Sava, F. A., & David, D. (2016). Task difficulty of virtual reality-based assessment tools compared to classical paper-and-pencil or computerized measures: A meta-analytic approach. *Computers in Human Behavior, 54,* 414–424. https://doi.org/10.1016/j.chb.2015.08.029

Pollard, J. (2008). *Hurry Up and Wait: A Cognitive Care Companion: Huntington's Disease in the Middle and More Advanced Years*. Lulu.com

Porffy, L. A., Mehta, M. A., Patchitt, J., Boussebaa, C., Brett, J., D'Oliveira, T., Mouchlianitis, E., & Shergill, S. S. (2022). A Novel Virtual Reality Assessment of Functional Cognition: Validation Study. *Journal of Medical Internet Research*, *24*(1), e27641. https://doi.org/10.2196/27641

Reilmann, R., & Schubert, R. (2017). Motor outcome measures in Huntington disease clinical trials. *Handbook of clinical neurology*, *144*, 209–225. https://doi.org/10.1016/B978-0-12-801893-4.00018-3

Roman, M. J., Delis, D. C., Filoteo, J. V., Demadura, T. L., Paulsen, J., Swerdlow, N. R., Swenson, M. R., Salmon, D., Butters, N., & Shults, C. (1998). Is there a "subcortical" profile of attentional dysfunction? A comparison of patients with Huntington's and Parkinson's diseases on a global-local focused attention task. *Journal of Clinical and Experimental Neuropsychology*, *20*(6), 873–884. https://doi.org/10.1076/jcen.20.6.873.1111

Rosas, H. D., Goodman, J., Chen, Y. I., Jenkins, B. G., Kennedy, D. N., Makris, N., Patti, M., Seidman, L. J., Beal, M. F., & Koroshetz, W. J. (2001). Striatal volume loss in HD as measured by MRI and the influence of CAG repeat. *Neurology*, *57*(6), 1025–1028. https://doi.org/10.1212/wnl.57.6.1025

Schultheis, M. T., Himelstein, J., & Rizzo, A. A. (2002). Virtual reality and neuropsychology: Upgrading the current tools. *The Journal of Head Trauma Rehabilitation*, *17*(5), 378–394. https://doi.org/10.1097/00001199-200210000-00002

Shoulson, I., & Young, A. B. (2011). Milestones in Huntington disease. *Movement Disorders*, *26*(6), 1127–1133. https://doi.org/10.1002/mds.23685

Simpson, J. A., Lovecky, D., Kogan, J., Vetter, L. A., & Yohrling, G. J. (2016). Survey of the Huntington's Disease Patient and Caregiver Community Reveals Most Impactful Symptoms and Treatment Needs. *Journal of Huntington's Disease*, *5*(4), 395–403. https://doi.org/10.3233/JHD-160228

Snowden J. S. (2017). The Neuropsychology of Huntington's Disease. *Archives of Clinical Neuropsychology*, *32*(7), 876–887. https://doi.org/10.1093/arclin/acx086

Stout, J. C., Glikmann-Johnston, Y., & Andrews, S. C. (2016). Cognitive assessment strategies in

Huntington's disease research. *Journal of Neuroscience Methods*, *265*, 19–24. https://doi.org/10.1016/j.jneumeth.2015.12.007

Stout, J. C., Paulsen, J. S., Queller, S., Solomon, A. C., Whitlock, K. B., Campbell, J. C., Carlozzi, N., Duff, K., Beglinger, L. J., Langbehn, D. R., Johnson, S. A., Biglan, K. M., & Aylward, E. H. (2011). Neurocognitive signs in prodromal Huntington disease. *Neuropsychology*, *25*(1), 1–14. https://doi.org/10.1037/a0020937

Tabrizi, S. J., Reilmann, R., Roos, R. A., Durr, A., Leavitt, B., Owen, G., Jones, R., Johnson, H., Craufurd, D., Hicks, S. L., Kennard, C., Landwehrmeyer, B., Stout, J. C., Borowsky, B., Scahill, R. I., Frost, C., Langbehn, D. R., & TRACK-HD investigators (2012). Potential endpoints for clinical trials in premanifest and early Huntington's disease in the TRACK-HD study: Analysis of 24-month observational data. *The Lancet Neurology*, *11*(1), 42–53. https://doi.org/10.1016/S1474-4422(11)70263-0

Vonsattel, J. P., & DiFiglia, M. (1998). Huntington disease. *Journal of Neuropathology and Experimental Neurology*, *57*(5), 369–384. https://doi.org/10.1097/00005072-199805000-00001

List of Publications

Papers in international journals with referees

Júlio, F., Caetano, G., Januário, C., & Castelo-Branco, M. (2019). The effect of impulsivity and inhibitory control deficits in the saccadic behavior of premanifest Huntington's disease individuals. *Orphanet Journal of Rare Diseases*, *14*(1), 246. https://doi.org/10.1186/s13023-019-1218-y

Júlio, F., Ribeiro, M. J., Morgadinho, A., Sousa, M., van Asselen, M., Simões, M. R., Castelo-Branco, M., & Januário, C. (2022). Cognition, function and awareness of disease impact in early Parkinson's and Huntington's disease. *Disability and Rehabilitation*, *44*(6), 921–939. https://doi.org/10.1080/09638288.2020.1783001

Júlio, F., Ribeiro, M. J., Patrício, M., Malhão, A., Pedrosa, F., Gonçalves, H., Simões, M., van Asselen, M., Simões, M. R., Castelo-Branco, M., & Januário, C. (2019). A Novel Ecological Approach Reveals Early Executive Function Impairments in Huntington's Disease. *Frontiers in Psychology*, *10*, 585. https://doi.org/10.3389/fpsyg.2019.00585

Júlio, F., Ribeiro, M. J., Simões, M. R., Castelo-Branco, M., & Januário, C. (2022). Assessing the Impact of Age on Everyday Cognitive Function with Virtual Reality: The *EcoKitchen* task. [Manuscript submitted for publication]. University of Coimbra.
Published dataset: **Júlio, F.** (2022, December 18). Assessing the Impact of Age on Everyday Cognitive Function with Virtual Reality: the *EcoKitchen* task_Database. https://doi.org/10.17605/OSF.IO/J26X8

Lavrador, R., **Júlio, F**., Januário, C., Castelo-Branco, M., & Caetano, G. (2022). Classification of Huntington's Disease Stage with Features Derived from Structural and Diffusion-Weighted Imaging. *Journal of Personalized Medicine, 12*(5), 704. https://doi.org/10.3390/jpm12050704

Miranda, Â., Lavrador, R., **Júlio, F.,** Januário, C., Castelo-Branco, M., & Caetano, G. (2016). Classification of Huntington's disease stage with support vector machines: A study on oculomotor performance. *Behavior Research Methods*, *48*(4), 1667–1677. https://doi.org/10.3758/s13428-015-0683-z

Papers in international conference proceedings

Caetano, G., **Júlio, F.,** Cunha, G., & Januário, C. (2013). Cortical Thickness and Basal Ganglia Volume alterations in Huntington's disease: Relation to Oculomotor Function. *Journal of Huntington's Disease 2*(3): 331-391.
https://doi.org/10.3233/JHD-139005

Caetano, G., **Júlio, F.,** Januário, C., & Castelo-Branco, M. (2013). Oculomotor and Executive Function in Huntington's Disease: An fMRI study. *Journal of Huntington's Disease 2*(3): 331-391.
https://doi.org/10.3233/JHD-139005

Júlio, F., Caetano, G., Januário, C., & Castelo-Branco, M. (2013). The potential role of neuropsychological and saccadic measures in defining disease progression and severity in Huntington's disease. *Journal of Huntington's Disease 2*(3), 331-391.
https://doi.org/10.3233/JHD-139005

Júlio, F., Malhão, A., Pedrosa, F., Gonçalves, H., Simões, M., Simões, M.R., van Asselen, M., Casteolo-Branco, M., & Januário, C. (2016). Everyday Executive Function in Huntington's Disease: Early Deficits Assessed by a Virtual Reality Task. *Journal of Neurology Neurosurgery & Psychiatry, 87*(Suppl 1): A1–A120.
https://doi.org/10.1136/jnnp-2016-314597.144

Júlio,F., Malhão, A., Pedrosa, F., Gonçalves, H., Simões, M., Patrício, M., Simões, M.R., van Asselen, M., Castelo-Branco, M., & Januário, C. (2017). Assessing Executive Function in Huntington's Disease: A Comparison Between a Virtual Reality Task and Conventional Neuropsychological Tests. *Neurotherapeutics, 15*(1), 249-250.
https://doi.org/10.1007/s13311-017-0579-y

Júlio, F., Patrício, M., Malhão, A., Pedrosa, F., Gonçalves, H., Simões, M., Morgadinho, AS., Sousa, M., Simões, MR., van Asselen, M., Castelo-Branco, M., & Januário, C. (2018). Assessment of Functional Cognition in Huntington's and Parkinson's disease - A comparison study. *Journal of Neurology Neurosurgery & Psychiatry, 89* (Suppl 1): A53.
https://doi.org/10.1136/jnnp-2018-EHDN.142

List of Communications

Oral Communications

Caetano, G., **Júlio, F.,** Miranda, Â., Lavrador, R., Januário, C., & Castelo-Branco, M. (2015, December 3). Alterations in Huntington's disease: from cognition and oculomotor performance to brain structure and function [Conference Session]. VII Annual Meeting of IBILI - Instituto Biomédico de Investigação em Luz e Imagem. Coimbra, Portugal.

Júlio, F. (2016, May 21). Alterações comportamentais e cognitivas nas doenças do movimento: doença de Parkinson/doença de Huntington: Que baterias usar? [Conference Session – Invited Speaker]. Fórum de Neurologia 2016 - Curso de Doenças do Movimento. Sociedade Portuguesa de Neurologia. Monte Real, Portugal. https://www.spneurologia.com/edition_download.php?id=81

Júlio, F., Caetano, G., Miranda, Â., Lavrador, R., Januário, C., & Castelo-Branco, M. (2015, October). Neuropsychological and Oculomotor features of Manifest and Premanifest Huntington's Disease [Conference Session]. EHDN Investigator Meeting. Madrid, Spain.

Júlio, F. & Duarte, I. C. (2016, November 9). Função executiva na doença de Huntington: novas perspetivas sobre resultados de comportamento e de imagem [Conference Session]. 2ª Edição das Conferências Santa Casa Neurociências: Doenças Neurodegenerativas Associadas ao Envelhecimento. Santa Casa da Misericórdia de Lisboa. Lisboa, Portugal. http://www.app.com.pt/wp-content/uploads/2016/10/Programa_conferencia_santacasa_neurociencias_vf.pdf

Júlio, F., Januário, C., Rego, A. C. (2015, March). Doenças de Poliglutaminas - Parte I: Doença de Huntington [Conference Session]. Seminário de Neurociências. FMUC- Faculdade de Medicina da Universidade de Coimbra e IBILI - Instituto Biomédico de Investigação em Luz e Imagem. Casa da Cultura de Coimbra, Coimbra, Portugal.

Júlio, F., Malhão, A., Pedrosa, F., Gonçalves, H., Simões, M., Simões, M.R., van Asselen, M., Castelo-Branco, M., & Januário, C. (2017, July 6-7). *EcoKitchen* - a virtual reality assessment task of daily executive functioning in basal ganglia disorders [Conference Session]. 7th Iberian Congress on Perception. ICNAS - Institute for Nuclear Sciences Applied to Health. Coimbra, Portugal.

https://www.uc.pt/en/icnas/CIP2017

Júlio, F., Malhão, A., Pedrosa, F., Gonçalves, H., Simões, M., Simões, M.R., van Asselen, M., Castelo-Branco, M., & Januário, C. (2017, September 22-24). Clinical trials – how to measure if treatments work: *EcoKitchen*, a new assessment task of daily executive functioning in Huntington's Disease [Conference Session – Invited Speaker]. The 2nd European Huntington Association Conference. Sofia – Bulgaria.
http://eurohuntington.org/wp-content/uploads/2017/05/Sofia-program-pub2.pdf

Júlio, F., Malhão, A., Pedrosa, F., Gonçalves, H., Simões, M., Simões, M.R., van Asselen, M., Castelo-Branco, M., & Januário, C. (2017, November). Assessment and Rehabilitation Programs in Adults and Elderly [Academic Class of Clinical Psychogerontology] Master in Psychology - Faculty of Psychology and Education Sciences, University of Coimbra. Coimbra – Portugal.

Júlio, F., Malhão, A., Pedrosa, F., Gonçalves, H., Simões, M., Simões, M.R., van Asselen, M., Castelo-Branco, M., & Januário, C. (2020, February 13-14). Virtual Reality as a Tool to Predict the Functional Impact of Executive Deficits [Conference Session - Invited Speaker]. The European Conference on Controversies in Huntington's Disease. Vienna, Austria.
https://www.emedevents.com/c/medical-conferences-2020/the-european-conference-on-controversies-in-huntington-s-disease-ecch2020

Júlio, F., Simões, M.R., van Asselen, M., & Januário, C. (2015, November 17-21). Everyday Executive Function: a Novel Ecological Approach [Conference Session]. III International Congress of The Cognitive and Behavioural Centre for Research and Intervention - CINEICC/III Portuguese Association for Behavioural Therapy (APTC). Coimbra, Portugal.
https://congressocineicc2015.wordpress.com/

Simões, M.R., Moura, O. Freitas, S., Lemos, R., Gonçalves, M.M., Gonçalves-Montera, M., Lopes, A.F., Alves, L., Pires, L., Ferreira, I., **Júlio, F.,** Sousa, L.B. (2017, Setembro, 14). O (importante) papel dos testes no processo de avaliação neuropsicológica: Investigações portuguesas e implicações para a prática profissional [Conference Session – Invited Speaker]. Neuropsicologia: Novos Desafios. Ordem dos Psicólogos Portugueses. Lisboa, Portugal.
https://www.ordemdospsicologos.pt/pt/eventosoppespecialidades/neuropsicologia

Poster Communications

Caetano, G., **Júlio, F.,** Cunha, G., & Januário, C. (2013, September 15-18). Cortical Thickness and Basal Ganglia Volume alterations in Huntington's disease: Relation to Oculomotor Function [Poster presentation]. 2013 World Congress on Huntington's Disease, Rio de Janeiro, Brazil.
https://content.iospress.com/articles/journal-of-huntingtons-disease/jhd139005

Caetano, G., **Júlio, F.,** Januário, C., & Castelo-Branco, M. (2012, December 6-7). Oculomotor function in Huntington's disease: an fMRI study [Poster presentation] IV Annual Meeting of IBILI - Instituto Biomédico de Investigação em Luz e Imagem, Coimbra, Portugal.

Caetano, G., **Júlio, F.,** Januário, C., & Castelo-Branco, M. (2013, May 30-June 1). Oculomotor and Executive Function in Huntington's Disease: an fMRI study [Poster presentation]. XIII Meeting of the Portuguese Society for Neuroscience (SPN), Luso, Portugal.
http://www.spn.org.pt/about/meetings.asp

Caetano, G., **Júlio, F**., Januário, C., & Castelo-Branco, M. (2013, September 15-18).Oculomotor and Executive Function in Huntington's Disease: an fMRI study [Poster presentation]. 2013 World Congress on Huntington's Disease, Rio de Janeiro, Brazil.
https://content.iospress.com/articles/journal-of-huntingtons-disease/jhd139005

Caetano, G., **Júlio, F.,** Januário, C., & Castelo-Branco, M. (2013, December 12-13). Cross-sectional assessment of alterations in Huntington's disease: on brain function and structure [Poster presentation]. V Annual Meeting of IBILI - Instituto Biomédico de Investigação em Luz e Imagem, Coimbra, Portugal.

Caetano, G., **Júlio, F.,** Januário, C., & Castelo-Branco, M. (2015, June 4-5). Cross-Sectional Assessment of Alterations in Huntington's Disease: from cognition and oculomotor performance to brain structure and function [Poster presentation]. XIV Meeting of the Portuguese Society for Neurociences, Póvoa do Varzim, Portugal.
http://www.ibmc.up.pt/spn2015/index.html

Caetano, G., **Júlio, F.,** Lavrador, R., Januário, C., & Castelo-Branco, M. (2015, July 7-11). Cross-Sectional Assessment of Alterations in Huntington's Disease: on cognition, oculomotor performance, brain function, and brain anatomy [Poster presentation]. 9th World Congress of the International Brain Research Association, Rio de Janeiro, Brasil.
https://ibro.org/world-congress/

Caetano, G., Leitão, R., **Júlio, F.,** Cunha, G., Januário, C., & Castelo-Branco, M. (2013, May 30-June 1). Underpinning alterations in Cortical thickness and Basal Ganglia Volumetric measures in Huntington's Disease [Poster presentation]. XIII Meeting of the Portuguese Society for Neuroscience (SPN), Luso, Portugal.
http://www.spn.org.pt/about/meetings.asp

Caetano, G., Lavrador, R., **Júlio, F.,** Januário, C., & Castelo-Branco, M. (2014, June 8-12). NeuroImaging in Huntington's Disease: On brain function, and on brain structure from

classical approaches to application of multivoxel pattern analysis. [Poster presentation]. Organization for Human Brain Mapping Annual Meeting, Hamburg, Germany. https://www.humanbrainmapping.org/i4a/pages/index.cfm?pageID=3565

Júlio, F., Caetano, G., Januário, C., & Castelo-Branco, M. (2013, May 30-June 1). Neuropsychological and Saccadic Measures in Premanifest and Manifest Huntington's Disease [Poster presentation]. XIII Meeting of the Portuguese Society for Neuroscience (SPN), Luso, Portugal. http://www.spn.org.pt/about/meetings.asp

Júlio, F., Caetano, G., Januário, C., & Castelo-Branco, M. (2013, September 15-18). The potential role of neuropsychological and saccadic measures in defining disease progression and severity in Huntington's disease [Poster presentation]. 2013 World Congress on Huntington's Disease, Rio de Janeiro, Brazil. https://content.iospress.com/articles/journal-of-huntingtons-disease/jhd139005

Júlio, F., Caetano, G., Januário, C., & Castelo-Branco, M. (2013, October 25). Neuropsychological and saccadic markers of progression and severity in Huntington's Disease [Poster presentation]. 4th PF2MUC Symposium – Faculdade de Medicina da Universidade de Coimbra, Coimbra, Portugal. https://www.researchgate.net/publication/283505118_Personalized_Periodontal_Treatment_-_The_role_of_Genetic_test

Júlio, F., Caetano, G., Januário, C., & Castelo-Branco, M. (2014, September 19-21). Cognitive and Oculomotor Performance in Premanifest Huntington Disease: One-Year Follow-Up [Poster presentation]. European Huntington's Disease Network Conference 2014, Barcelona, Spain. http://www.euro-hd.net/html/network/events/ehdn2014

Júlio, F., Caetano, G., Januário, C., & Castelo-Branco, M. (2014, December 11–12). One-year follow-up examination of cognitive and oculomotor performance in premanifest Huntington disease [Poster presentation]. VI Annual Meeting of IBILI - Instituto Biomédico de Investigação em Luz e Imagem, Coimbra, Portugal.

Júlio, F., Malhão, A., Pedrosa, F., Gonçalves, H., Abreu, R., Simões, M., Patrício, M., Duarte, C., van Asselen, M., Simões, M.R., Castelo-Branco, M., & Januário, C. (2017, November 6). A novel ecological assessment of executive function in Huntington's disease [Poster presentation]. Mostra PsihD – 1ª Mostra de Doutoramento em Psicologia. Faculdade de Psicologia e Ciências da Educação da Universidade de Coimbra, Coimbra, Portugal.

Júlio, F., Malhão, A., Pedrosa, F., Gonçalves, H., Simões, M., Morgadinho, A.S., Sousa, M., Simões, M.R., van Asselen, M., Castelo-Branco, M., &Januário, C. (2018, September 14-16). Assessment of Functional Cognition in Huntington's and Parkinson's disease - a comparison study [Poster presentation]. European Huntington's Disease Network 2018 Conference. Vienna, Austria

Júlio, F., Malhão, A., Pedrosa, F., Gonçalves, H., Simões, M., Simões, M.R., van Asselen, M., Castelo-Branco, M., & Januário, C. (2016, September 16-18). Everyday Executive Function

in Huntington's Disease: Early Deficits Assessed by a Virtual Reality Task [Poster presentation]. 9th European Huntington's Disease Network (EHDN) Plenary Meeting 2016. The Hague, The Netherlands.
http://www.euro-hd.net/html/network/events/ehdn2016/announcement?clps63119_5959020=1

Júlio, F., Patrício, M., Malhão, A., Pedrosa, F., Gonçalves, H., Simões, M., Rego, A.C., Simões, M.R., van Asselen, M., Castelo-Branco, M., & Januário, C. (2017, May 25-26). A novel ecological assessment of executive function in Huntington's disease [Poster presentation]. XV Meeting of the Portuguese Society for Neuroscience. Braga, Portugal.
http://meetingspn.weebly.com/

Júlio, F., Simões, M.R., Malhão, A., Pedrosa, F., Simões, M., Gonçalves, H., van Asselen, M., Castelo-Branco, M., & Januário, C. (2015, December 3-4). Everyday Executive Function: a Novel Ecological Approach [Poster presentation]. VII Annual Meeting of IBILI - Instituto Biomédico de Investigação em Luz e Imagem, Coimbra, Portugal.
https://www.uc.pt/icnas/investigacao/Meetings/IBILImeeting15

Lavrador, R., **Júlio, F**., Januário, C., Castelo-Branco, M., & Caetano, G. (2014, June 8-12). Classification of MRI Data in Huntington's Disease: Grey Matter Tissue and Fractional Anisotropy [Poster presentation]. Organization for Human Brain Mapping Annual Meeting, Hamburg, Germany.
https://www.humanbrainmapping.org/i4a/pages/index.cfm?pageID=3565

Lavrador, R., **Júlio, F**., Januário, C., Castelo-Branco, M., & Caetano, G. (2014, December 11–12). Support vector machine classification in Huntington's disease using MRI data: grey matter tissue and fractional anisotropy maps [Poster presentation]. VI Annual Meeting of IBILI - - Instituto Biomédico de Investigação em Luz e Imagem, Coimbra, Portugal.

Lavrador, R., **Júlio, F.,** Januário, C., Castelo-Branco, M., & Caetano, G. (2015, June 4-5). Classification of Huntington's Disease stage using segmented grey matter tissue and diffusion weighted derived features [Poster presentation]. XIV Meeting of the Portuguese Society for Neurociences, Póvoa do Varzim, Portugal.
http://www.ibmc.up.pt/spn2015/index.html

Miranda, A., Lavrador, R., **Júlio, F.,** Januário, C., Castelo-Branco, M., & Caetano G. (2014, December 11–12). Support Vector Machine Classification in Huntington's disease using eye-tracking psychophysics derived features. [Poster presentation]. VI Annual Meeting of IBILI - - Instituto Biomédico de Investigação em Luz e Imagem, Coimbra, Portugal.

Miranda, A., Lavrador, R., **Júlio**, F., Januário, C., Castelo-Branco, M., & Caetano, G. (2015, June 4-5). Support Vector Machine Classification in Huntington's Disease using eye-tracking psychophysics derived features [Poster presentation]. XIV Meeting of the Portuguese Society for Neurociences, Póvoa do Varzim, Portugal.
http://www.ibmc.up.pt/spn2015/index.html

Curriculum Vitae

Filipa Lima Ramos Santos Júlio was born on December 2, 1976, in Coimbra, Portugal.
In 1994, she concluded her high school education at Escola Secundária José Falcão in Coimbra. She got a BSc in Psychology (Clinical and Health Psychology – 5 years) at the Faculty of Psychology and Education Sciences – Universidade do Minho in 2000. In 1998, she received an Academic Achievement Award from Universidade do Minho.
She worked as a clinical psychologist between 2001 and 2005, and, in 2007, she started to work as a research assistant at IBILI – Instituto de Imagem Biomédica e Ciências da Vida (Faculty of Medicine – Universidade de Coimbra). She was co-investigator of the Registry study from the EHDN - European Huntington's Disease Network between 2009 and 2017, at the Neurology Department of CHUC - Centro Hospitalar e Universitário de Coimbra. She is a EHDN regular member since 2010.
In 2013, she started her PhD in Neuropsychology at the Faculty of Psychology and Educational Sciences – Universidade de Coimbra, under the supervision of Professor Cristina Januário and the co-supervision of Professors Mário Rodrigues Simões and Marieke Van Asselen, who later was replaced by Doctor Maria Ribeiro. She received a PhD grant from the Fundação para a Ciência e Tecnologia – Portugal between 2013 and 2017. In 2016, she received the Best Clinical Poster Award at the 9th EHDN Plenary Meeting in The Hague, The Netherlands.
She is a full member of the Ordem dos Psicólogos Portugueses since 2010 (professional card number 1427). In 2016, she got her Clinical and Health Psychology Expert Certificate and her Neuropsychology Expert Certificate from the Ordem dos Psicólogos Portugueses.
As a volunteer, Filipa joined the Associação Portuguesa dos Doentes de Huntington in 2008 and served as President of the Board from 2009 to 2014. She is since then the Vice-President. She also volunteered for several other HD global organizations, such as HDYO - Huntington's Disease Youth Organization and HDBuzz. From 2011 to 2018, she

was Member at Large of the Board of the International Huntington Association. Since 2012, she is the Secretary of the Board of the European Huntington Association. Since 2018, she is member of the Ethics Committee of the i3S – Instituto de Investigação e Inovação em Saúde at the Universidade do Porto.

In 2020, she started working as a Project Manager for the European Huntington Association.

A much more comprehensive Curriculum Vitae of Filipa Júlio can be found in the CiênciaVitae Platform - Ciência ID: 5B1F-FB8F-E7BE