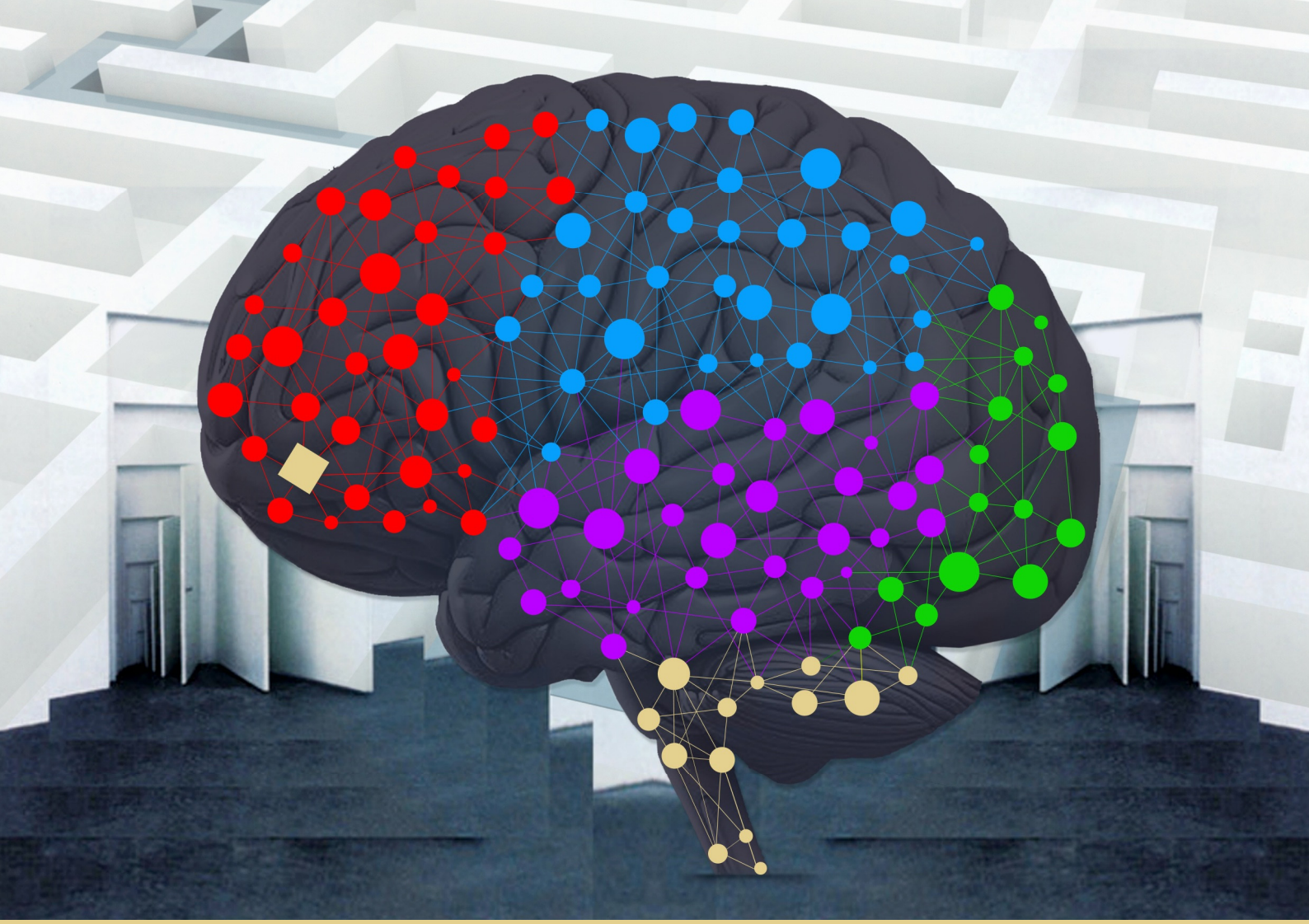

**Paula Micaela de Oliveira Banca**

# The neural correlates of impaired cognitive control in Obsessive-Compulsive Disorder

Tese do Programa de Doutoramento em Ciências da Saúde, ramo de Ciências Biomédicas, orientada por Prof. Doutor Miguel Castelo-Branco, Prof. Doutor João Relvas e Prof. Doutora Valerie Voon e apresentada à Faculdade de Medicina da Universidade de Coimbra.

**2014**

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UNIVERSIDADE DE COIMBRA

# The neural correlates of impaired cognitive control in Obsessive-Compulsive Disorder

**Paula Micaela de Oliveira Banca**

2014

The studies presented in this thesis were carried out at the Visual Neuroscience Laboratory at IBILI (Institute for Biomedical Imaging and Life Sciences), Faculty of Medicine, University of Coimbra, Portugal, and at Department of Psychiatry, University of Cambridge, United Kingdom. This work was supported by a personal scholarship from the Portuguese Foundation for Science and Technology (SFRH/BD/33889/2009), attributed by the PhD Program in Experimental Biology and Biomedicine (BEB), Center for Neuroscience and Cell Biology, Coimbra, Portugal, and by the following grants: Compete, PEst- C/SAU/UI3282/2013, CENTRO-07-ST24-FEDER-00205, Bial Foundation 132 and 133/13 and Wellcome Trust.

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**Universidade de Coimbra**

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# The neural correlates of impaired cognitive control in Obsessive-Compulsive Disorder

Thesis presented to obtain a Ph.D. degree in Biomedical Sciences at the Faculty of Medicine of the University of Coimbra

Tese do Programa de Doutoramento apresentada à Faculdade de Medicina da Universidade de Coimbra para prestação de provas de Doutoramento em Ciências da Saúde, ramo de Ciências Biomédicas

**Paula Micaela de Oliveira Banca**

**2014**

Supervised by: Miguel Castelo-Branco, M.D., Ph.D.

Co-Superviser by: Valerie Voon, M.D., Ph.D. and João Relvas, M.D., Ph.D.

*Para a Clara*

*"Every passing minute is another chance to turn it all around"*

In *Vanilla Sky*

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# ABBREVIATIONS

| | |
|---|---|
| **ACC** | Anterior cingulate cortex |
| **ADIS-IV** | Anxiety disorders interview schedule for diagnostic and statistical manual of mental disorders – 4th edition |
| **BA** | Brodmann area |
| **BDI** | Beck depression inventory |
| **BOLD** | Blood-oxygen-level dependent |
| **CANTAB** | Cambridge neuropsychological test automated battery |
| **CBT** | Cognitive behaviour therapy |
| **CGT** | Cambridge gambling task |
| **Cl** | Coherence levels |
| **COR** | Coronal |
| **CT** | Cognitive therapy |
| **CSF** | Cerebrospinal fluid |
| **CSTC** | Cortico-striatal-thalamo-cortical |
| **DBS** | Deep brain stimulation |
| **dlPFC** | Dorsolateral prefrontal cortex |
| **DSM** | Diagnostic and statistical manual of mental disorders |
| **DSM-V** | Diagnostic and statistical manual of mental disorders – 5th edition |
| **DTI** | Diffusion tensor imaging |
| **EPI** | Echo planar imaging |
| **ERP** | Exposure and response prevention |
| **ERPs** | Event-related brain potentials |
| **FA** | Flip angle |
| **FDA** | Food and drug administration |
| **FOV** | Field of view |
| **fMRI** | Functional magnetic resonance imaging |
| **GCM** | Granger causality mapping |

| | |
|---|---|
| **GLM** | General linear model |
| **HC** | High conflict |
| **HCLL** | High conflict lose-lose |
| **HCWW** | High conflict win-win |
| **HU** | High uncertainty |
| **HU-CF** | High uncertainty following correct feedback |
| **HU-IF** | High uncertainty following incorrect feedback |
| **HV** | Healthy volunteers |
| **HDDM** | Hierarchical drift diffusion modelling |
| **ICD** | International statistical classification of diseases |
| **ICD-11** | International statistical classification of diseases – 11th edition |
| **IGT** | Iowa gambling task |
| **IQ** | Intelligence quotient |
| **LC** | Low conflict |
| **LH** | Left hemisphere |
| **LL** | Lose-lose |
| **LU** | Low uncertainty |
| **LU-CF** | Low uncertainty following correct feedback |
| **LU-IF** | Low uncertainty following incorrect feedback |
| **mCPP** | Meta-chlorophenylpiperazine |
| **NART** | National adult reading test |
| **OCD** | Obsessive-compulsive disorder |
| **OC** | Obsessive-compulsive |
| **OFC** | Orbitofrontal cortex |
| **PD** | Parkinson disease |
| **PET** | Positron emission tomography |
| **PFC** | Prefrontal cortex |
| **RDMT** | Random dot motion task |
| **RFX** | Random effects |
| **LH** | Left hemisphere |

| | |
|---|---|
| **RT** | Reaction time |
| **RTb** | Baseline reaction time |
| **rTMS** | Repetitive transcranial magnetic stimulation |
| **SAG** | Sagital |
| **SAPAP3** | SAP90/PSD-95-associated protein-3 |
| **SB** | Stimulation blocks |
| **SD** | Standard deviation |
| **SEM** | Standard error of the mean |
| **SERT** | Serotonin receptor and transporter |
| **SRIs** | Serotonin reuptake inhibitors |
| **SSAI** | Trait anxiety inventory |
| **SSRIs** | Selective serotonin reuptake inhibitors |
| **SSRT** | Stop-signal reaction time |
| **STAI** | State anxiety inventory |
| **STN** | Subthalamic nucleus |
| **STN DBS** | Deep brain stimulation of the subthalamic nucleus |
| **TE** | Echo time |
| **TR** | Repetition time |
| **TRA** | Transversal |
| **vmPFC** | Ventromedial prefrontal cortex |
| **WL** | Win-lose |
| **WW** | Win-win |
| **Y-BOCS** | Yale-Brown obsessive-compulsive scale |
| **Ycomp** | Yale-Brown obsessive-compulsive scale - compulsive subscale |
| **Yobs** | Yale-Brown obsessive-compulsive scale - obsessive subscale |
| **Ytotal** | Yale-Brown obsessive-compulsive scale - total score |

# SUMMARY

Obsessive-compulsive disorder (OCD) is a very severe and lifelong psychiatric illness that is typically manifested by intrusive thoughts and compulsive urges to perform stereotypic and ritualistic behaviours. Patients experience these intense urges and compulsive actions despite having full insight into how senseless, irrational and excessive they are. This ego-dystonic nature of the disease is striking and has been an intriguing question for the scientific community.

Compulsivity, a maladaptive perseveration of behaviour, arises from irrational decisions. Considering that decision-making is characterized by a parallel and flexible engagement between goal-directed and habitual systems, a recent account has suggested that a bias in favour of the latter might underlie compulsivity in OCD. In other words, compulsivity might result from excessive stimulus-response habit formation, rendering behaviour insensitive to goal value.

The main focus of this thesis was the investigation of the mechanisms underlying compulsivity in OCD. We used a multimodal approach, combining standard behavioural, computational analysis and functional neuroimaging methods to provide an in-depth investigation of the decision-making abnormalities that may underlie the urge to perform compulsive acts. As compulsive acts may be conceptualized as a means to accumulate sufficient evidence for a decision' commitment, the first study of this thesis investigated potential abnormalities in the cognitive process of weighing and evaluating evidence prior to a decision in OCD patients. This cognitive process is intrinsic to all decisions and is often abnormal in psychiatric disorders, varying from an impulsive to a cautious style of decision-making. We hypothesized that compared to healthy volunteers, OCD patients would need to accumulate more evidence, particularly under uncertainty situations. We indeed showed impairments in evidence accumulation processes for decisions of a perceptual nature in OCD, an impairment that was more evident in patients with higher compulsivity scores. We

highlight the utility of behavioural, including computational, approaches by demonstrating a differential influence of high and low uncertainty contexts on evidence accumulation (decision threshold) and on the quality of evidence gathered (drift rates). Patients required more evidence under high uncertainty contexts. Nevertheless under low uncertainty ones, despite normative accumulation, the strength or quality of evidence from the stimulus entering the decision process was poorer compared to healthy volunteers. These findings suggest impaired decision-making processes in dissociated mechanisms underlying the encoding of perceptual uncertainty as function of its level. We further emphasize that OCD patients are sensitive to monetary incentives in heightening speed in the speed-accuracy tradeoff. In this manner, they improve evidence accumulation without sacrificing accuracy and shift away from a pathological internal monitoring. These results suggest a differential role of implicit incentives and external feedback in decision-making processes in OCD.

In the second study of this thesis we developed a novel individualized ecologically-valid symptom provocation design: a live provocation functional magnetic resonance imaging paradigm with synchronous video-recording of behavioural avoidance responses. By pairing symptom provocation with online avoidance responses on a trial-by-trial basis, we sought to investigate the neural mechanisms leading to the compulsive responses and to explore the recent habit account of OCD whereby compulsivity might arise from excessive avoidance habit formation. During symptom provocation, participants could choose to reject or terminate the provoking stimuli resulting in cessation of the provocation. This design allowed us to separately assess the neural correlates of symptom provocation, urge to avoid, rejection and relief. We identified a dichotomous pattern of activation/deactivation during exposure to symptoms characterized by a decreased activity of caudate-prefrontal circuits accompanied by hyperactivation of putaminal regions, suggesting a dissociation between regions engaged in goal-directed and habitual behaviours. The putaminal hyperactivity during symptom provocation preceded subsequent deactivation during

avoidance and relief events, indicating a pivotal role of putamen in regulation of behaviour and habit formation in OCD. Effective connectivity analysis further allowed us to propose a causal model for compulsivity in OCD, in which two main structures causally influence the aforementioned corticostriatal dissociation: ventromedial prefrontal cortex and putamen. By suggesting an imbalance in circuitry underlying habitual and goal-directed action control as a fundamental mechanism underlying compulsivity in OCD, our findings and consequent proposed model provide a direct explanation for the impaired cognitive control observed in OCD patients as well as their ego-dystonic experience. Our results complement current models of symptom generation in OCD, corroborate the habit account of OCD and may enable the development of future therapeutic approaches that aim to alleviate this imbalance and suppress habits.

The work presented in this thesis improves our knowledge concerning the mechanisms underlying compulsivity in OCD by demonstrating impaired decision-making and cognitive control in these patients. It further corroborates the recent habit based account of OCD and provides new insights on the neural basis of compulsive habits, explaining how they emerge and how they relate with the other core features of OCD: obsessions and anxiety.

# SUMÁRIO

A perturbação obsessivo-compulsiva (POC) é uma doença psiquiátrica crónica e severa, que se manifesta pela presença de pensamentos intrusivos e uma necessidade compulsiva de executar acções estereotipadas e ritualísticas. Estes impulsos e comportamentos compulsivos são vividos de forma intensa pelos doentes, mesmo quando estão cientes do irrealismo e irracionalidade que eles comportam. Esta natureza egodistónica da doença é marcante e continua a ser uma questão controversa no seio da comunidade científica.

As compulsões, preservação maladaptativa do comportamento, surgem de decisões irracionais. A tomada de decisão é caracterizada pelo envolvimento paralelo, balanceado e flexível entre um sistema neuronal orientado por objectivos e um sistema que dá suporte a comportamentos repetitivos baseados em hábitos. Levantou-se recentemente a hipótese de que um desiquilíbrio que favoreça o sistema de hábitos poderá estar na base dos comportamentos compulsivos. Por outras palavras, a compulsividade poderá resultar de uma excessiva formação de hábitos, tornando o comportamento insensível a objectivos que mudam consoante o contexto.

Esta tese teve com foco principal a investigação dos mecanismos que estão na origem da compulsividade na POC. Usámos uma abordagem multimodal, que combinou análises comportamentais padrão, computacionais e métodos de neuroimagem funcional, com vista a uma investigação exaustiva de eventuais disfunções no processo de tomada de decisão que poderão estar na origem dos impulsos para executar acções compulsivas. Como os comportamentos compulsivos podem ser conceptualizados como uma forma de acumular informação antes de tomar uma decisão, o primeiro estudo investigou eventuais anomalias no processo cognitivo de avaliação da evidência precedente a uma decisão em doentes com POC. Este processo cognitivo, que pode variar de um estilo de decisão mais impulsivo a

um estilo mais cauteloso, é intrínseco a todas as decisões e é frequentemente disfuncional em doenças psiquiátricas. Levantámos a hipótese de que os doentes com POC, comparativamente a indivíduos saudáveis, necessitariam de acumular mais evidência, em particular em contextos de grande incerteza. De facto identificámos perturbações no processo de acumulação de evidência relativo a decisões de natureza perceptual em doentes com POC, mais evidentes em doentes com níveis de compulsividade mais elevados. Demonstrámos uma influência diferencial de contextos de maior ou menor incerteza no processo de acumulação de evidência, incluindo na forma qualitativa com que essa evidência é codificada. Os doentes necessitaram de reter mais informação em condições de maior incerteza. No entanto, em condições de menor incerteza, apesar de terem um tempo de reacção normal, a qualidade com que essa evidência é codificada é mais pobre (acumulação mais lenta) em comparação com indivíduos saudáveis. Estes resultados sugerem anomalias no processo de tomada de decisão em diferentes mecanismos que estão na base da codificação da percepção de incerteza, que variam consoante o nível de incerteza. Realçámos também que os doentes são mais sensíveis a incentivos monetários que promovam rapidez de resposta, melhorando a forma como acumulam evidência sem sacrificar a sua performance e conseguindo desviar-se de uma monitorização interna patológica. Estes resultados sugerem um papel diferencial entre incentivos implícitos e feedback externo em processos de decisão na POC.

No segundo estudo desenvolvemos um novo método de provocação de sintomas, individualizado e mais ecológico que os habitualmente usados: um paradigma de provocação em tempo real, aplicado em ressonância magnética funcional, acompanhado de filmagem simultânea e devidamente sincronizada das respostas de evitamento dos participantes. Ao emparelhar a provocação de sintomas com respostas de evitamento, procurámos investigar os mecanismos neuronais que estão na base das compulsões e explorar a recente teoria de rigidez de hábitos, que considera que os comportamentos compulsivos nascem de uma excessiva formação de hábitos de evitamento. Durante a provocação de sintomas, os participantes puderam escolher rejeitar a estimulação, terminando assim a exposição aos sintomas.

Este desenho experimental permitiu-nos avaliar separadamente os correlatos neuronais da provocação de sintomas, do impulso para execução de respostas de evitamento, da rejeição do estímulo e sensação de alívio. Identificámos um padrão dicotómico de activação/inibição durante a exposição aos sintomas, caracterizado por uma inibição da actividade dos circuitos que ligam o caudado às regiões prefrontais e por uma hiperativação do putamen. Este padrão dicotómico sugere que, na base da POC, existe uma dissociação entre regiões cerebrais que estão envolvidas em comportamentos habituais e comportamentos orientados por objectivos. A hiperatividade do putamen durante a provocação de sintomas precedeu uma subsequente inibição durante eventos de evitamento e alívio, o que é indicativo do papel fulcral do putamen na regulação do comportamento e formação de hábitos na POC. Análises de conectividade funcional permitiram-nos propor um modelo causal para a compulsividade na POC, no qual duas importantes estruturas cerebrais exercem uma influencia causal na dissociação cortico-estriada acima mencionada: o córtex prefrontal ventromedial e o putamen. Ao sugerir um desequilíbrio dos circuitos que estão na base do controlo de acções habituais e acções orientadas por objectivos como mecanismo fundamental da compulsividade na POC, as nossas descobertas permitiram construir um modelo explicativo para a incapacidade de controlo cognitivo e experiência egodistónica observada nestes doentes. Assim sendo, os resultados aqui apresentados complementam modelos actuais que visam explicar a geração de sintomas na POC, corroboram a teoria de hábitos e estimulam o desenvolvimento de estratégias terapêuticas futuras que visem aliviar este desequilíbrio e suprimir hábitos.

O trabalho apresentado nesta tese amplia o actual conhecimento científico no que concerne aos mecanismos neuronais subjacentes à compulsividade na POC ao demonstrar anomalias no processos de tomada de decisão e no controlo cognitivo nestes doentes. Este trabalho corrobora a recente teoria de hábitos e identifica as bases neuronais dos hábitos compulsivos, explicando como surgem e como se relacionam com outras características da doença, tais como as obsessões e a ansiedade.

# Chapter 1

## General Introduction

Obsessive-compulsive disorder (OCD) is a severe and disabling psychiatric condition, characterized by the occurrence of either obsessions, compulsions or most commonly both. Obsessions are persistent and recurrent thoughts, impulses or images that are experienced as intrusive and cause marked anxiety and distress (e.g. did I hurt my child?). Compulsions are repetitive behaviours (e.g. organizing knifes and other devices that may cause harm or inspecting a child's body to be sure no harm has been caused by the OCD patient) or mental acts (e.g. repetitive praying), which are carried out in an effort to prevent or alleviate intense anxiety caused by obsessions. These behaviours are clearly excessive, not realistically connected to what they are designed to neutralise or prevent, and interfere substantially with the normal life functioning of the affected individuals and their family.

Although standard nomenclatures (Diagnostic and Statistical Manual of Mental Disorders (DSM) and International Statistical Classification of Diseases (ICD)) regard OCD as a unitary entity, the symptoms are remarkably heterogeneous and different kinds of obsessions and compulsions can exist and even co-exist. Research has consistently identified symptom dimensions in which obsessions and compulsions tend to co-occur from childhood through adulthood: i) obsessions about bearing responsibility for causing or failing to prevent harm; checking compulsions and reassurance-seeking; ii) symmetry obsessions, ordering and counting rituals; iii) contamination obsessions, and washing and cleaning rituals and iv) repugnant obsessions concerning sex, violence, and religion (Abramowitz, Taylor, & McKay, 2009). This contemporary multidimensional conceptualization of OCD, despite some limitations, has been successful in explaining significant part of the variance of OCD studies and has provided a more complete picture of the disorder (Mataix-Cols, Rosario-Campos, & Leckman, 2005).

People with this disorder are aware of the senselessness of their symptoms. They recognize that their obsessions are somewhat unrealistic, irrational and excessive and that their compulsions are absolutely unnecessary and only further exacerbate

feelings of distress and anxiety due to an inability to prevent such symptoms. However, despite this insight, patients are unable to control mind intrusions and to act in coherence with their awareness and will. This ego-dystonic feature of the disease has been a big challenge to scientific community, an intriguing question with no explanation until now. Why do patients keep performing ritualistic behaviours despite being aware that they serve no real purpose?

## EPIDEMIOLOGY

Obsessive-compulsive disorder is the fourth most frequent psychiatric condition following phobias, substance abuse and major depression (Karno, Golding, Sorenson, & Burnam, 1988; Kessler et al., 2005; Robins et al., 1984). It afflicts 2-3% of the world population and the male to female ratio is approximately the same (Karno et al., 1988; Lochner et al., 2004; Robins et al., 1984). It usually arises in early adulthood or late adolescence, and if left untreated has a chronic course. Males typically have an earlier age of onset than females, often during childhood (Heyman et al., 2003; Lochner et al., 2004). Cross-national studies show that the prevalence, age of onset and core features of OCD do not differ by much across many different populations or different ethnic groups (Horwath & Weissman, 2000; Weissman et al., 1994). The only exception to this cross-cultural homogeneity is the content of the obsessions, in which cultural factors may play a significant role (Fontenelle, Mendlowicz, Marques, & Versiani, 2004).

OCD tend to co-exist with several other mental disorders. Epidemiological studies consistently report rates of comorbidity ranging from 50 to 60 percent of OCD patients also presenting at least one other psychological illness, most commonly an Axis I disorder (Denys, Tenney, van Megen, de Geus, & Westenberg, 2004; Pigott, L'Heureux, Dubbert, Bernstein, & Murphy, 1994; Torres et al., 2006). The disorders that more frequently co-occur with OCD are mood disorders (especially depression),

anxiety disorders (generalized anxiety disorder, specific phobias, social phobia), Tourette's syndrome, tic disorders, somatoform disorders (hypochondriasis and body dysmorphic disorder) and grooming disorders (especially trichotillomania and pathological skin picking) (Bienvenu et al., 2012; Denys et al., 2004; Rasmussen & Eisen, 1992; Torres et al., 2006). Although associations between OCD and eating disorders, substance dependence (alcohol or drug) and impulse-control disorders such as pathological gambling, pyromania and kleptomania are also observed, these findings are less consistent (Bienvenu et al., 2012; Denys et al., 2004; Torres et al., 2006). Whether comorbid disorders affect the clinical severity of obsessive-compulsive symptoms is still debatable due to contradictory findings (Denys et al., 2004; Tukel, Polat, Ozdemir, Aksut, & Turksoy, 2002).

Evidence from family aggregation studies suggests that OCD is familial and results from twin studies demonstrate that the familial co-segregation is due in part to genetic factors. The concordance rate for OCD is greater among pairs of monozygotic twins (80-87%) than among pairs of dizygotic twins (47-50%) (D. Bolton, Rijsdijk, O'Connor, Perrin, & Eley, 2007; van Grootheest, Cath, Beekman, & Boomsma, 2005). Moreover, OCD first-degree relatives not only appear to have 3 to 12 times higher risk to develop the disorder comparing to the general population (Grados, Walkup, & Walford, 2003) but also show similar deficits on specific cognitive tasks that have been observed in patients (Chamberlain, Fineberg, Menzies, et al., 2007). A recently published study showed that the risk for OCD among relatives of OCD probands increase proportionally to the degree of genetic relatedness, which convincingly highlights the familial risk for OCD (Mataix-Cols et al., 2013). It is estimated that genetic factors influence OCD symptoms by approximately 27-47%, being the remaining variance attributed to environmental factors (Pauls, 2010). There are no reported sex differences in heritability. However, there might be a stronger familiarity in childhood-onset OCD than in cases in which the disorder develops later in life (do Rosario-Campos et al., 2005; Nestadt et al., 2000). More than 80 candidate gene studies, focusing on genes in the serotonergic,

dopaminergic and glutamatergic pathways, have been published during the last decade (Pauls, 2010). Although they may truly be associated with the onset, severity, or persistence of OCD symptoms, it is questionable whether they may be involved in the aetiology of a disorder. Given the complexity of the OCD phenotype, it is highly likely that this disease has a polygenic basis (Ting & Feng, 2008).

Over the past decade, a wide variety of psychiatric and medical conditions has progressively come to be considered as OCD spectrum disorders due to its similarities with OCD regarding clinical symptomatology, demographic, comorbidity, familial and course patterns and responses to therapeutic strategies (Aouizerate, Guehl, et al., 2004). These include somatoform, tic, grooming disorders and Tourette's syndrome. Consequently, it has been highly discussed and it remains controversial whether the classification of OCD in new diagnostic manuals (DSM-V (American Psychiatric Association, 2013) and ICD-11 (under revision)) should be kept into the anxiety group disorders or as part of a larger spectrum comprising these aforementioned obsessive-compulsive related disorders (Abramowitz et al., 2009; Robbins, Gillan, Smith, de Wit, & Ersche, 2012). Although this reclassification took place in the DSM-V, released last year (2013), further research is needed to determine whether this paradigm shift in the conceptualization of the disorder will improve the understanding of its causes and treatment.

## NEUROBIOLOGY OF OCD

### Neuroanatomical basis of OCD

Convergence findings in neuroscientific research point to the involvement of cortico-striatal-thalamo-cortical (CSTC) pathways in the pathophysiology of OCD. Thus, OCD implicates abnormalities within pathways (loops) that run from specific territories in frontal lobes to the striatum, and via direct and indirect pathways to the thalamus and back to the frontal site where each loop starts (Alexander, DeLong, &

Strick, 1986; Menzies et al., 2008; Milad & Rauch, 2012; Tekin & Cummings, 2002). Each loop is thought to play a relatively specific functional role, determined by the specific frontocortical area involved. This organization may account for the symptom specificity of OCD and OC-spectrum disorders (Graybiel & Rauch, 2000). It has been hypothesised that three major networks underlie OCD: (i) the limbic circuits, comprising the orbitofrontal cortex (OFC), which includes the ventromedial prefrontal cortex (vmPFC), the anterior cingulate cortex (ACC) and the ventral striatum; (ii) the motor circuit, which includes the sensorimotor cortices and the putamen; and (iii) the associative circuit comprising the dorsolateral prefrontal cortex (dlPFC), parietal cortices and the caudate (Graybiel & Rauch, 2000; Milad & Rauch, 2012). Instead of largely segregated as initially thought, it is known now that these cortico-striatal pathways are integrated within the striatum and the thalamus and are interconnected in parallel and in spiral, with information cascading from one loop to the next (Haber & Knutson, 2010).

Early work on brain injury comprising focal lesions of the basal ganglia reported the emergence of striking obsessive-compulsive behaviours in some patients as well as some symptoms of frontal lobe syndrome. These observations suggest that the basal ganglia and its connections to the frontal lobes might be involved in OCD, forming the basis for the fronto-striatal hypothesis (Laplane et al., 1989). The emergence and evolution of modern brain imaging methods provided an opportunity to establish the role of basal ganglia in OCD and refine the understanding of the involvement of fronto-striatal circuits in the aetiology of the disease. Functional imaging studies have consistently showed an abnormal metabolic activity in the OFC, the ACC and the caudate nucleus (Graybiel & Rauch, 2000; Saxena, Brody, Schwartz, & Baxter, 1998; Whiteside, Port, & Abramowitz, 2004). During approximately two decades, it was believed that activity within these nodes of the CSTC network was increased at rest in patients relative to healthy controls, accentuated during symptom provocation and attenuated following successful treatment with both serotonin reuptake inhibitors (SRIs) and cognitive behaviour therapy (CBT) (Saxena et al., 1998; Saxena & Rauch,

2000). Moreover, increased functional connectivity between the OFC, ACC and caudate was observed in OCD patients, a hyper-connectivity that was also seemingly remediated following successful treatment, suggesting that over-activity in this circuit, as opposed to one core region, could be responsible for OCD symptoms (Schwartz, Stoessel, Baxter, Martin, & Phelps, 1996). However, this knowledge has been recently questioned due to the emergence of studies in fear conditioning (Milad et al., 2013) and symptom provocation in children (Gilbert et al., 2009), showing decreased activity in frontal areas such as vmPFC (and OFC in general) and dlPFC. Recent functional connectivity studies using resting state functional magnetic resonance imaging (fMRI) have also shown reduced connectivity within the limbic CSTC circuit (Posner et al., 2014), insula and other parts of the frontal cortex (Jang et al., 2010; Meunier et al., 2012; Stern, Fitzgerald, Welsh, Abelson, & Taylor, 2012), which contradict previous findings of increased connectivity between the OFC and PFC and the ventral and dorsal striatum, thalamus, and motor regions (Harrison et al., 2009; Sakai et al., 2011). These inconsistent results are difficult to interpret, given the differences in directionality that have been observed across studies, as well as the wide range of regions whose aberrant connectivity has been implicated. Nonetheless, these results are broadly consistent with a fronto-striatal account of OCD.

Symptom provocation studies in OCD have largely contributed to the CSTC model of OCD by consistently showing hyperactivity in the same aforementioned areas. However, some of these studies (Breiter et al., 1996; Mataix-Cols et al., 2004; Simon, Kaufmann, Musch, Kischkel, & Kathmann, 2010) have also reported metabolic abnormalities in insula and amygdala suggesting that limbic structures may also play a role in the aetiology of the disease, in addition to the CSTC main circuitry. Moreover, whereas the early CSTC model of OCD placed deep emphasis on the role of the OFC generically, it is now known that different sub-regions of the OFC play distinct roles in processing reward, negative affect, and specifically fear and anxiety (Kringelbach & Rolls, 2004; Milad & Rauch, 2007). This evidence has led several OCD researchers to currently consider the CSTC account an oversimplified and

insufficient model of OCD. New accounts should take into consideration the functional subdivisions of the OFC and the role of the insula, amygdala and the hippocampus and their interaction with the frontal cortex in mediating fear and anxiety in patients with OCD (Milad & Rauch, 2012).

Structural imaging studies, some focusing on gray matter volume or thickness and others focusing on the white matter and fiber tracts connecting the different brain regions, also converge to identify abnormalities within the fronto-striatal circuitry in OCD. A recent meta-analysis shows consistent findings in the dorsal ACC, with significantly reduced grey matter volume in patients with OCD (Radua, van den Heuvel, Surguladze, & Mataix-Cols, 2010). Less consistent are the grey matter density findings in the OFC, thalamus, putamen and parietal regions, with results often differing in the directionality of the effect (J. J. Kim et al., 2001; Menzies et al., 2008; Pujol et al., 2004; Radua & Mataix-Cols, 2009; Radua et al., 2010). With respect to white matter integrity investigations in patients with OCD, studies using diffusion tensor imaging (DTI) report abnormalities in terms of decreased fractional anisotropy compared to healthy volunteers (Koch, Reess, Rus, Zimmer, & Zaudig, 2014). Although findings are heterogeneous, the cingulate bundle, the corpus callosum (Nakamae et al., 2011; Saito et al., 2008) and the anterior limb of the internal capsule (Cannistraro et al., 2007; Nakamae et al., 2011) are most commonly affected by decreased white matter integrity in adult OCD patients.

To conclude, despite a consensus regarding the involvement of the CSTC circuitry in the aetiology of OCD, the specific role of the numerous parallel distributed loops that compose this circuitry and how they integrate cognitive-affective brain regions is still unknown. A host of inconsistencies have been reported in neurobiological studies of OCD, which suggest that the neural underpinnings of the disorder may vary as a function of patient heterogeneity.

**Neurochemical basis of OCD**

As reviewed in the previous section, dysfunctional nodes within the fronto-striatal circuitry, possibly mediated by glutamate neurotransmission, under modulation by altered dopaminergic or serotoninergic influences, are thought to underlie obsessive-compulsive symptoms. Despite the well-established efficacy of drugs targeting the serotoninergic, dopaminergic or glutamatergic systems for the treatment of OCD, the role of serotonin, dopamine or glutamate in the pathogenesis of this disease remains a mystery. The earliest evidence for a possible disruption in the brain's serotonin system of patients with OCD was the finding that positive therapeutic effects of clomipramine were correlated with a decrease in concentrations of the serotonin metabolite 5-hydroxyindoleacetic acid in the cerebrospinal fluid (CSF) (Thoren, Asberg, Bertilsson, et al., 1980). This suggested that selective serotonin reuptake inhibitors (SSRIs) might have their anti-obsessive effect in OCD by serotonin reuptake blockade. However, studies measuring pre-treatment baseline levels of serotonin have failed to detect consistent evidence of significant differences in serotonin concentrations in patients with OCD in comparison with controls (Insel, Mueller, Alterman, Linnoila, & Murphy, 1985; Leckman et al., 1995; Thoren, Asberg, Bertilsson, et al., 1980). Other work, more focused on dynamic measures of serotoninergic function in OCD, has shown that the administration of the serotonin agonist meta-chlorophenylpiperazine (mCPP) exacerbated obsessive symptoms in OCD patients (Zohar, Mueller, Insel, Zohar-Kadouch, & Murphy, 1987), an effect that was remediated after treatment with serotonin reuptake inhibitors (SRIs) (Hollander et al., 1991; Zohar, Insel, Zohar-Kadouch, Hill, & Murphy, 1988). These findings led to questions about the role of serotonin receptors in OCD, but the studies investigating serotonin receptor and transporter (SERT) followed the same trend of inconsistency. Some studies using positron emission tomography (PET) have observed decreased SERT and serotonin receptor binding potential in OCD patients (Matsumoto et al., 2010; Perani et al., 2008), while others have reported no differences (Simpson et al., 2003; Simpson et al., 2011). These inconsistencies may reflect the use of different methodologies in the studies, different inclusion criteria

and also the heterogeneity of the OCD population. For example, two recent studies provided evidence that suggests physiological differences between early and late onset patients within the OCD population, in which only late-onset patients were associated with abnormally low levels of SERT availability (Hesse et al., 2011; Simpson et al., 2011). In sum, no specific abnormality in the serotoninergic system has been identified to date as a cause for OCD, although some promising work on this topic has been done.

Dysfunctions on the dopaminergic and glutamatergic systems have also been hypothesized to underlie the pathology of OCD, but studies focusing on these systems are mixed and scarce. A frontocortical hyper-glutamatergic function has been proposed to account for the CSTC abnormalities observed in imaging studies of OCD (Saxena & Rauch, 2000), and in support of this, a study showed elevated CSF glutamate levels in OCD patients compared to healthy controls (Chakrabarty, Bhattacharyya, Christopher, & Khanna, 2005). Some genes involved in glutamatergic neurotransmission have also been found to be associated with OCD (for review see (Ting & Feng, 2008) and (Pittenger, Bloch, & Williams, 2011)). For example, genetically engineered mice lacking the gene encoding for the signaling complex protein SAP90/PSD-95-associated protein-3 (SAPAP3) – a protein that plays a key role in glutamatergic synaptic signaling and is strongly expressed in the striatum (Ting & Feng, 2008) – exhibited increased anxiety and compulsive self-grooming, which decreases following chronic treatment with fluoxetine (SSRI) (Welch et al., 2007). Futhermore, proton magnetic resonance spectroscopy studies have also found glutamatergic abnormalities in OCD patients: reduced concentration in ACC (Yucel et al., 2008) and increased concentration in caudate (Rosenberg et al., 2000), which declined in response to paroxetine (SSRI) (J. Bolton, Moore, MacMillan, Stewart, & Rosenberg, 2001; Moore, MacMaster, Stewart, & Rosenberg, 1998; Rosenberg et al., 2000). However, these results must be interpreted cautiously because other studies failed to replicate them (Brennan, Rauch, Jensen, & Pope, 2013).

Phenotypic similarities between OCD and Tourette's Syndrome, a disorder that involves striatal dopaminergic dysfunction (Leckman, 2002), suggested that dopamine neurotransmission could also be affected in OCD. This hypothesis was further reinforced by the observation that augmentation of SSRIs with dopamine antagonists is an effective treatment for some refractory OCD patients (Stein, Bouwer, Hawkridge, & Emsley, 1997). In preclinical studies, the administration of dopamine agonists leads to stereotypic behaviour (Szechtman, Sulis, & Eilam, 1998). In humans, these agents can exacerbate obsessive-compulsive symptoms (Koizumi, 1985; Rosse et al., 1993). Based on this evidence, it might be expected that dopamine levels would be enhanced in OCD patients. However, several studies failed to identify differences in the concentration of the dopamine metabolites in CSF of OCD patients and matched controls (Leckman et al., 1995; Swedo et al., 1992; Thoren, Asberg, Bertilsson, et al., 1980). Moreover, treatment with acute d-amphetamine has been shown to bring benefits to OCD patients' symptoms, which is contradictory (Insel, Hamilton, Guttmacher, & Murphy, 1983). In summary, like serotonin, the dopamine and glutamate possible hypothesis of OCD lack consistent empirical support beyond the positive benefits of the pharmacological treatment. It should nevertheless be noted that, although empirical data are limited, they do not contradict the prevailing account of OCD pathogenesis as resulting from a dysmodulation of frontal-striatal circuits via glutamatergic, serotoninergic and dopaminergic mechanisms (Fineberg, Chamberlain, Hollander, Boulougouris, & Robbins, 2011).

**Animal models**

Different animal research approaches, which run from genetic and pharmacological to neurobehavioural models, have provided insight to several aspects and in particular the aetiology of OCD. Evidence yielded by these models is convergent with current pharmacological and neurobiological models in humans (Fineberg et al., 2011).

Animal models commonly investigate associations between genetic, pharmacological, anatomical lesions and other types of manipulations in animals and behaviours that resemble OCD. These behaviours typically consist of stereotypies such as excessive grooming in rodents (Sahakian, Robbins, Morgan, & Iversen, 1975) or perseverative operant responding for food that rats do not eat (Robbins & Sahakian, 1979), paw licking in dogs (Rapoport, Ryland, & Kriete, 1992) or feather-picking in birds (Grindlinger & Ramsay, 1991). It is possible, however, that these models relate more to anxiety, stress or other disorders of the OCD spectrum like trichotillomania, than to OCD per se (Fineberg et al., 2011).

Pharmacological models of OCD in rodents tend to use high doses of stimulant drugs such as d-amphetamine and cocaine to produce dopamine-induced stereotypy. However, more recently, clinical studies showed that single doses of d-amphetamine have, in fact, ameliorated OCD symptoms (Insel et al., 1983; Joffe, Swinson, & Levitt, 1991). Quinpirole, a D2/D3 dopamine receptor agonist, also led to repetitive checking in rats, a behaviour that was reduced following a treatment with clomipramine (Szechtman et al., 1998). Therefore, the role of dopamine remains questionable due to these mixed results. In another model of OCD, rewarded spatial alternation, the administration of mCPP, a serotonin agonist previously mentioned, increased perseverative behaviour in rodents, showing a dysfunctional persistence towards one path in a T-maze (Tsaltas et al., 2005). This effect was abolished following treatment with an SSRI (fluoxetine), but not a benzodiazepine or desipramine. These results mirror those reported in the previous section, where symptom exacerbation in OCD patients resulting from mCPP could be ameliorated with fluoxetine (Hollander et al., 1991) and clomipramine (Zohar et al., 1988) pre-treatments, suggesting that this particular rat model may represent a possible proxy for OCD.

Reversal learning is a similar model, in which reinforcement contingencies of a two-choice discrimination paradigm is, at some point during the experiment, reversed so

that the response to a previously rewarded stimulus is then punished or vice versa. Marmoset monkeys showed reversal learning impairments, reflecting perseveration in responding to a formerly reinforced stimulus even though the contingencies have changed. These deficits were consequence of OFC (Dias, Robbins, & Roberts, 1996) and medial striatum (Clarke, Robbins, & Roberts, 2008) lesions and serotonin depletion within the prefrontal cortex (PFC) (Clarke et al., 2005) and OFC (Clarke, Walker, Dalley, Robbins, & Roberts, 2007). These results are consistent with a human study that shows reduced activation in OFC, dlPFC and anterior PFC during a reversal learning task in OCD patients and their unaffected relatives, as compared with healthy controls (Chamberlain et al., 2008; Remijnse et al., 2006; Remijnse et al., 2009).

Another neurobehavioural model tested in animals is the signal attenuation paradigm, which considers that a deficient response feedback mechanism underlies compulsivity. Here, rodents are trained to lever press for food, whose delivery is signalled by the presentation of a compound stimulus (light+tone). Subsequently, the classical contingency between the stimulus and food is extinguished (extinction phase). This manipulation produced increased lever pressing during extinction, an effect that was attenuated by drugs currently used therapeutically in OCD (SSRIs), and not affected by anxiolytics (diazepam) and tricyclic antidepressants (desipramine), a treatment that is known to be ineffective for this disorder (Joel & Avisar, 2001).

The recent development of optogenetics, a highly selective method to control brain circuits, has deepened our understanding of the neural basis of OCD and other disorders that include compulsivity as a clinical feature (Rauch & Carlezon, 2013). This method allows temporally and spatially precise manipulation of electrical and biochemical events in the brain using fiber-optic light in living organisms. Using this technique, two studies identified a specific circuitry involved in regulating repetitive behaviour (excessive grooming) in mice. Ahmari et al. found that hyper-stimulation of an excitatory circuit between glutamatergic neurons in the OFC and the

ventromedial striatum triggered compulsive behaviours (Ahmari et al., 2013). Burguiere et al. discovered that in a genetic mouse model of OCD, excessive grooming was caused by an impaired pathway in the ventromedial striatum (the inhibition of medium spiny neurons by fast-spiking striatal interneurons) within this same neural circuit (Burguiere, Monteiro, Feng, & Graybiel, 2013).

Animal models constitute, undoubtedly, an important vehicle for elucidating the neurobiological substrates of OCD, specially its compulsive behaviour nature that is easier to address. However, we should be aware of their limited capacity to model the full phenotype of OCD, particularly due to their inability to investigate obsessive thoughts, which is a core feature of the disease. To date, there is no ideal and universally accepted animal model that can account for simulating OCD in its entirety, given the heterogeneity and aetiological complexity of the disease.

## TREATMENT

The current first-line psychological and pharmacological treatments for OCD are cognitive behaviour therapy (CBT) and selective serotonin reuptake inhibitors (SSRIs) (Pallanti & Hollander, 2014). These treatments have been developed despite the lack of understanding about the precise neurobiological mechanisms underlying OCD, and have been proving to be partially effective in the management of the symptoms. They are widely used worldwide for the sole purpose of alleviating symptoms, not as a cure. None of these treatments are wholly effective and a significant proportion of patients remain partially symptomatic or completely treatment resistant. In these cases, much more complex pharmacological interventions, or even neurosurgical treatments, may be warranted. This section presents a brief review of each of these therapeutic approaches.

**Psychological treatment**

Cognitive-behavioural therapy involving exposure and response prevention (ERP) is an established and effective treatment for OCD. ERP involves a systematic, repeated and prolonged exposure to stimuli that provoke anxiety followed by response prevention of compulsive rituals that would have been performed in this instance (Meyer, 1966). The exposure, either in vivo or imagination, typically proceeds from stimuli that produce moderate distress to stimuli that produce greater distress. The aim of this technique is to allow patients to learn that the decreasing obsessional anxiety experienced with repeated exposure is not linked to the completion of compulsion acts (Abramowitz, 2006). A large number of studies have shown that ERP is highly effective in reducing not only the urge to respond but also the obsessive thoughts (Foa & Goldstein, 1978). Marks and colleagues reported a profound reduction in OCD symptom severity after 3–7 weeks of ERP treatment while no change occurred during the control condition (Marks, Hodgson, & Rachman, 1975). Other studies have highlighted the superiority of this treatment as compared to isolated pharmacological interventions both in terms of effectiveness in treating OCD symptoms (Foa et al., 2005; Kobak, Greist, Jefferson, Katzelnick, & Henk, 1998) and relapses following cessation of treatment (Simpson et al., 2004). ERP is usually delivered as part of a CBT programme that involves cognitive therapy (CT). CT focuses on challenging obsessions, contrary to ERP, which targets compulsions. It is designed to help patients identify and re-appraise intrusive unrealistic thoughts, such as their probability of occurrence, or the misconception of thought-action fusion (that thinking something is the same as doing it) (Foa, 2010). By doing this, CT helps reducing the distress associated with obsessions and work as a perfect complement to ERP.

It is estimated that 60-90% of patients benefit from CBT, experiencing a reduction of 50-80% of symptoms, with long term remission seen in 45% of patients (Warren & Thomas, 2001). Moreover, evidence shows that psychotherapeutic interventions induce changes in cerebral metabolism, leading to a normalization of functional brain

activity at a global level (Beauregard, 2014). CBT is therefore considered essential and, given the side-effects of medication and high rates of relapse after pharmacological discontinuation, the preferable type of intervention for OCD. One of the limitations of this therapeutic intervention is the lack of motivation and engagement sometimes seen in patients, who refuse CBT or drop out early because they are not willing to expose themselves to situations that provoke anxiety. Furthermore, the lack of CBT availability often results in long waiting lists, causing patients to turn to pharmacotherapy.

**Pharmacological treatment**

Pharmacological agents classified as selective serotonin reuptake inhibitors are the leading pharmacological treatment option for OCD, approved by the Food and Drug Administration (FDA) (Ting & Feng, 2008). Their primary mechanism of action is to block the serotonin transporter located in the plasma membranes of presynaptic nerve terminals, thereby inhibiting the neurotransmitter reuptake, allowing serotonin to remain in the synaptic cleft longer to exert its effects.

Clomipramine, a tricyclic antidepressant and non-selective serotonin reuptake inhibitor, was the first drug to demonstrate beneficial effects on OCD symptoms. The first double-blind, placebo-controlled pharmacological studies of clomipramine in OCD were published in the 1980s (Thoren, Asberg, Cronholm, Jornestedt, & Traskman, 1980). This discovery led to the subsequently investigation of other antidepressants, a more pharmacologically selective class of drugs – SSRIs – that later equally proved their efficacy in reducing OCD symptoms and became the treatment of choice for OCD due to their fewer side-effects, better safety and tolerability profile (Koran, Hackett, Rubin, Wolkow, & Robinson, 2002; Ravizza, Barzega, Bellino, Bogetto, & Maina, 1996; Zohar & Judge, 1996).

All of the currently available SSRIs that have been investigated and that are commonly prescribed (fluoxetine, fluvoxamine, sertraline, paroxetine, escitalopram and citalopram) seem to exhibit similar efficacy in treating OCD symptoms. The treatment effect develops slowly and gradually over weeks and months, and higher SSRI doses and extended treatment duration appear to produce greater effect sizes (Fineberg & Gale, 2005). A number of placebo controlled trials show that these drugs can reduce symptoms by 30-60% in a long-term and continued treatment (Koran et al., 2002; Pigott & Seay, 1999; Ravizza et al., 1996) and are associated to significant relapse rates when discontinued (if pharmacotherapy is the only type of treatment) (Abramowitz et al., 2009).

Even though SSRIs have been shown to be effective, approximately 40-60% patients with OCD do not gain significant benefits and are classified as treatment resistant (for review see (Goodman, McDougle, & Price, 1992; Kaplan & Hollander, 2003)). Early age of onset, longer illness duration, high comorbidity and greater illness severity are common predictors for the lack of pharmacological response (Mataix-Cols, Rauch, Manzo, Jenike, & Baer, 1999). These patients often need more complex interventions, such as augmentation of ongoing serotonergic treatment in combination with an antipsychotic, dopaminergic or glutamatergic agents and CBT (Pallanti & Hollander, 2014). Double-blind randomised controlled studies have shown that some patients who fail to respond to the maximum tolerated dose of SSRIs significantly improve by adding an antipsychotic medication (e.g. risperidone or haloperidol) (Bloch et al., 2006b) or a dopaminergic agent (e.g. d-amphetamine) (Koran, Aboujaoude, & Gamel, 2009). Recently, a controlled trial study has given further evidence for the involvement of the glutamatergic system in OCD by showing positive effects of an antiglutamatergic agent (ketamine) in reducing OCD symptoms (Rodriguez et al., 2013).

In conclusion, and as previously mentioned, the available treatments for OCD (psychological or pharmacological) are not wholly effective and are mainly used to

provide a better quality of life for patients, alleviating symptoms. The recommended treatment for adults (and most commonly used) includes a combination of CBT and SSRI pharmacotherapy (with or without augmentation strategies) because studies have been indicating the superiority of combination strategies in comparison to either ERP or drug therapy in isolation (Foa et al., 2005; Marks, Stern, Mawson, Cobb, & McDonald, 1980). For children and adolescents, due to concerns about the potential adverse effects associated with SSRIs, the recommendation is that CBT should be used as first-line treatment. Many patients, however, remain partially symptomatic or completely treatment refractory. In the latter cases, when patients suffer from a severely debilitating OCD and have failed to respond to all available conventional treatments (psychological and pharmacological), neurosurgical interventions may be an option.

**Neurosurgical interventions and brain stimulation**

Current surgical interventions involve making a small lesion (10-20 mm), often using radio-frequency heated electrodes or gamma knife techniques, to interrupt specific brain tracks linking structures that have been implicated in the pathophysiology of OCD (Pato, 2003). These procedures include anterior capsulotomy, anterior cingulotomy, subcaudate tractotomy, and limbic leucotomy and all aim to interrupt the connections between the cortex, the basal ganglia and related structures (Abramowitz et al., 2009). Data compiled from several small studies have yielded success rates of 25-84% with these treatments (Cosgrove & Rauch, 2003; Jenike, 1998; Mindus & Jenike, 1992). However, due to safety concerns, there has been a growing interest in alternative, non-ablative surgical procedures, such as deep brain stimulation (DBS) or even non-surgical brain stimulation methods such as repetitive transcranial magnetic stimulation (rTMS). These alternative procedures are reversible, adjustable, and offer new opportunities in terms of targeting brain regions that the ablative techniques cannot reach (Aouizerate et al., 2006). DBS, which uses electrical stimulation rather than ablation of nerve cells, has been shown to be highly effective

in treating advanced forms of Parkinson's disease (Kleiner-Fisman et al., 2006). Therefore it has also been proposed as a therapeutic alternative for intractable OCD. When applied bilaterally in the anterior limb of the internal capsule instead of anterior capsulotomy, DBS produced a sustained improvement in symptomatology, as defined by a 35% or more reduction in Y-BOCS scores during the 33-month period of follow-up (Gabriels, Cosyns, Nuttin, Demeulemeester, & Gybels, 2003; Nuttin, Cosyns, Demeulemeester, Gybels, & Meyerson, 1999). Another study showed a profound improvement in obsessive–compulsive symptoms (more than 60% reduction in Y-BOCS scores) in two Parkinsonian patients with comorbid OCD after being treated with DBS of the subthalamic nucleus (Mallet et al., 2002). Other pilot patient studies have reported beneficial reductions in OCD symptoms when electrodes have been implanted into caudate (Aouizerate, Cuny, et al., 2004), subthalamic nucleus (Mallet et al., 2008) or the nucleus accumbens (Denys et al., 2010), all regions that have been implicated in the neurobiology of OCD. With rTMS, electrical activity in the brain is altered by placing an external electromagnet over certain brain regions. The interest for the potential use of rTMS in OCD is very recent and the literature on its therapeutic efficacy for this condition is very scarce. Until now, three target areas have been selected of which the supplementary motor area (SMA) and the orbitofrontal cortex (OFC) seem to be the most promising in terms of potential efficacy and could more accurately be targeted with the help of neuronavigational techniques (Jaafari et al., 2012b). The stimulation of the dlPFC does not appear to be so effective (Alonso et al., 2001; Prasko et al., 2006; Sachdev, Loo, Mitchell, McFarquhar, & Malhi, 2007). The existing results do not yet support the inclusion of rTMS in the therapeutic toolbox for OCD, but they do appear to be promising.

Nowadays, DBS seems to be the first-line surgical technique since it is the least invasive and, compared to rTMS, better empirically supported. Although both DBS and rTMS appear to be very promising, there are still unknown factors. On one hand, the definition of the optimal targets for stimulation, both in terms of their possible

efficacy and their risks and benefits, is still a critical concern. Moreover, target areas for rTMS in particular, are still unexplored. Searching for new devices and coils would help to reach new targets, for example the ACC or the insula (Jaafari et al., 2012b). On the other hand, the efficacy and safety of both neurostimulation methods remain to be confirmed by further randomized controlled trials employing standard clinical outcome assessment and standard criteria for the selection of severely OCD patients in larger samples (Aouizerate et al., 2006).

## OCD: A MULTIFACETED DISORDER

### Neurocognitive endophenotypes: basis for a cognitive approach

Recent cognitive models of OCD have been focusing on the search for endophenotypes. Neurocognitive endophenotypes consist of behavioural or cognitive abnormalities, associated with discrete deficits in defined neural systems, which are present in first-degree relatives of patients who do not have the diagnosis, and therefore serve as a link between the disease phenotype and the underlying genotype that confers vulnerability to the disease (Gottesman & Gould, 2003). Psychiatric diagnoses and their neurobiological underpinnings have always been challenging due to the broad complexity and heterogeneity of the symptoms that may occur in a particular disorder and the confusing array of comorbidities with other psychiatric disorders. The concept of neurocognitive endophenotypes was therefore developed to provide more quantitative measures of the deficits and more accurate descriptions of the phenotypes by avoiding the exclusive use of clinical rating scales. Defining such endophenotypes facilitates translational research across species and allows discerning possible neural commonalities across disorders that may highlight new genetic or therapeutic avenues (Robbins et al., 2012).

Several forms of cognitive flexibility and behavioural inhibition have been intensively investigated on the search for OCD endophenotypes, such as reversal learning, extra-

dimensional attentional set-shifting and motor impulsivity (Fineberg et al., 2011). Consistent animal and human findings on reversal learning, a cognitive function described above, highlight the possible involvement of OFC and PFC in this cognitive function and suggest its potential role as an endophenotype of OCD (for detailed description of the findings see animal models section). Concerning extra-dimensional set-shift paradigms, OCD patients and their unaffected first-degree relatives show impairments shifting attention from one perceptual dimension of a complex stimulus to another (Chamberlain, Fineberg, Menzies, et al., 2007). Extra-dimensional attentional set-shifting appears to be more dependent on dlPFC and reversal learning more dependent on OFC (Dias et al., 1996).

Motor response inhibition has also been consistently observed in OCD patients. In the stop-signal reaction time (SSRT) task, in which it is necessary to stop an already initiated response on presentation of a stop-signal, patients and their unaffected first-degree relatives showed delayed response inhibition compared with healthy controls (Menzies et al., 2007). Evidence from human studies implicates the right inferior frontal gyrus (Aron, Fletcher, Bullmore, Sahakian, & Robbins, 2003), the striatum and subthalamic nucleus (Aron, Behrens, Smith, Frank, & Poldrack, 2007) in the underlying inhibitory process of this task. Homologous structures, the lateral OFC and medial striatum, were implicated in rodent versions of SSRT (Eagle & Robbins, 2003; Eagle, Tufft, Goodchild, & Robbins, 2007). Although investigation of these particular features of cognitive inflexibility and behavioural inhibition have given relevant insight into the underlying behavioural control mechanisms implicated in OCD, it should be emphasized that it is still unclear how these deficits relate to recurrent intrusive thoughts that are very typical in OCD.

In addition to inhibitory deficits, impairments in other executive functions such as planning and decision-making have also been reported in OCD (Cavedini, Zorzi, Piccinni, Cavallini, & Bellodi, 2010; Chamberlain, Blackwell, Fineberg, Robbins, & Sahakian, 2005). Cognitive planning has been tested with different versions of the

original Tower of London task from the Cambridge neuropsychological test automated battery (CANTAB) (Purcell, Maruff, Kyrios, & Pantelis, 1998b). In this task, subjects need to rearrange a set of snooker balls in pockets on a computer screen to match the appearance of another set determined by the computer, within the confines of the game rules. The aim is to solve each problem in the minimum possible number of moves. Although the support for pure planning deficits in OCD is limited due to inconsistent findings in the number of moves used to solve the task, there is strong evidence for abnormal psycho-motor slowing, as indexed by lengthened latency times compared to controls (Cavedini et al., 2010; Nielen & Den Boer, 2003; Purcell, Maruff, Kyrios, & Pantelis, 1998a; Veale, Sahakian, Owen, & Marks, 1996; Watkins et al., 2005). The nature of this slowing phenomenon remains unknown and attentional problems, strategy failures or chronic doubting after negative feedback have been hypothesized as possible explanations for this result.

Decision-making in OCD has been studied primarily using gambling tasks. Using the Iowa Gambling Task (IGT), which assesses the ability to acquire a preference through reward and punishment as represented by gains and losses of play money, OCD patients, as opposing to healthy controls, do not show a preference for advantageous choices (Cavedini et al., 2010). Moreover, patients with greater severity of symptoms demonstrate poorer risk adjustment over time (Nielen, Veltman, de Jong, Mulder, & den Boer, 2002). Cavedini and his colleagues further found that poor performers on this task were less likely to respond to treatment with SSRI's alone, while responsiveness in this group improved only with the introduction of risperidone, suggesting an additive dopaminergic contribution (Cavedini et al., 2002). This study also suggested that decision-making impairments on this task may represent a marker for treatment resistant forms of the disorder. OCD findings using this task are not consistently positive though (Lawrence et al., 2006; Nielen et al., 2002). By employing the Cambridge Gambling Task (CGT), which requires subjects to gamble points over a range of probabilities of winning, no deficits were found in OCD patients (Chamberlain, Fineberg, Menzies, et al., 2007; Watkins et al., 2005).

These inconsistent findings in the OCD decision-making literature may be related with task differences. IGT has an implicit learning component, which is not present in the CGT, and therefore possible deficits may reflect failures in associative feedback learning, which was proven to be an issue in OCD (Nielen, den Boer, & Smid, 2009).

Decision-making is a broad construct, which includes several aspects such as selective attention, risk, reward sensitivity, associative learning or working memory. Therefore we should be aware of its limitations to provide clear information about specific impairments linked to the OCD pathogenesis, or in other words, to play a role as a neurocognitive endophenotype. There are a few studies, however, which have tried to focus on particular aspects of the decision-making process in OCD. A good example is a study by Foa and colleagues who, by being aware of the influence that discrepancies in risk perception might exert in the decisional process, developed a task to specifically examine decision-making in OCD under high and low-risk scenarios, in addition to scenarios relevant to specific OCD symptoms (Foa et al., 2003). This study showed that OCD subjects are more risk averse under low risk (defined as variance with a lower difference between the positive and negative OCD-relevant outcomes) as compared to high risk (defined as greater difference between outcomes). The authors consider that patients' desire for additional information under low risk and OCD-relevant situations may be associated with an elevated (relative to healthy subjects) perception of risk.

The complexity that underlies typical gambling paradigms used to investigate the decision-making process in OCD has led to mixed findings, which are difficult to interpret, and has prevented the generation of new insights into specific aspects of decision-making, as well as its neural correlates. The first part of this thesis aims to fulfil this gap in the OCD literature by considering that it is crucial to parcel the broad process of decision-making into narrow measurable constructs.

**Habit account of OCD: basis for a behaviour approach**

As mentioned in the introductory note of this thesis, the irrational and ego-dystonic nature of compulsive urges in OCD is puzzling, hard to understand not only for the patients and general community, but also for scientists who still struggle to find an elucidation for this intriguing clinical neuroscience question. How can a patient perform 'endless' rituals, reaching exhaustion, and at the same time be completely aware of the senseless and contra-productive nature of these behaviours? One possible explanation is that the pathological obsessions and compulsions might result from abnormal or maladaptive habits over which patients are unable to exert sufficient high-level control. Underlying this might be a disruption or an imbalance between goal-directed and habitual control and an abnormal habit formation mechanism (Graybiel & Rauch, 2000).

Action performance, habit formation mechanisms and the dichotomy between goal-directed and habitual behaviours have been extensively studied in rodents during the past decades (B. W. Balleine, Delgado, & Hikosaka, 2007; Dias-Ferreira et al., 2009; Dickinson, 1985; Dickinson & Balleine, 1993; Yin, Knowlton, & Balleine, 2006). According to this dual-system account, different behavioural strategies are used to respond to environmental demands and it is the ability to shift between them that enables successful decisions (B. W. Balleine, 2007). The goal-directed system encodes actions that are performed to achieve specific outcomes, whereas the habitual-system drives action selection based on stimulus-response associations (Dickinson & Balleine, 1993). The goal-directed system is vital for responding to permanent changes in the environment but it is effortful to sustain its activity because it demands continuous monitoring of the environment. The habitual system is more efficient but can lead to behavioural inflexibility in case of over-learned stimulus associations (Adams, 1982). Reliance on the habitual system, however, only becomes apparent when our environment or desires change and our behaviour does not adapt.

It has been suggested that rodent cortico-striatal circuits involving prelimbic cortex (B. W. Balleine & Dickinson, 1998; Corbit & Balleine, 2003; Killcross & Coutureau, 2003; Yin, Ostlund, Knowlton, & Balleine, 2005) and dorsomedial striatum (B. W. Balleine et al., 2007) are implicated in goal-directed actions whereas the dorsolateral striatum (Yin et al., 2006) is involved in habit formation. More recently, human fMRI studies have provided convergent support for this dissociation in homologous brain regions (B. Balleine & O'Doherty, 2010; de Wit, Corlett, Aitken, Dickinson, & Fletcher, 2009; E. Tricomi, Balleine, & O'Doherty, 2009a; E. M. Tricomi, Delgado, & Fiez, 2004; Valentin, Dickinson, & O'Doherty, 2007). Valentin et al. showed, by using a selective devaluation procedure in extinction, that activity in OFC was sensitive to the choice of actions that led to valued or devalued outcomes, therefore playing an important role in determining the incentive value of outcomes in goal-directed decisions (Valentin et al., 2007). Another study used incongruent associations to create conflict in the goal-directed system, forcing subjects to solely rely on the habit system. By contrasting these trials with congruent and unrelated (control) trials, that are supported by both the goal-directed and habitual system, they demonstrated that goal-directed, as opposed to habitual actions, is reflected in increased activity of the vmPFC (which is part of the OFC) (de Wit et al., 2009). Other studies using computational analysis have similarly revealed that the vmPFC and the caudate nucleus track changes in contingency levels between actions and outcomes (Liljeholm, Tricomi, O'Doherty, & Balleine, 2011; E. M. Tricomi et al., 2004). In addition, by comparing groups who received brief versus extended (two days) training on a free-operant habit task for food outcomes and by using a selective satiety method of outcome devaluation, Tricomi and colleagues observed that activity in the putamen increases when behaviour becomes autonomous from outcome value following over-training (E. Tricomi et al., 2009a).

Neurochemical evidence of habit formation and goal-directed behaviour is also consistent with the notion that an imbalance between these functions may contribute to a dysfunctional regulation of action control, which is possibly critical in OCD. It

has been proven that changes in dopamine signal the transition from goal-directed to habit-based instrumental performance (Wickens, Horvitz, Costa, & Killcross, 2007). Lesions to the nigrostriatal dopamine pathway (Faure, Haberland, Conde, & El Massioui, 2005) and dopaminergic neuron-specific NMDA receptor knock-out rats (Wang et al., 2011) result in a failure to develop habits after over-training whereas repeated injections of amphetamine in rats enhanced habit formation (A. Nelson & Killcross, 2006). Accordingly, stimulants have shown to provoke stereotypic behaviour (Szechtman et al., 1998) and exacerbate obsessive-compulsive symptoms (Koizumi, 1985; Rosse et al., 1993) in humans, as previously described in an earlier section.

In sum, a host of studies in rodents and humans have reached consensus that fronto-striatal circuits mediate the transition from goal-directed to habitual control over behaviour. This empirical knowledge is very consistent with the consensual neurobiological findings of fronto-striatal abnormalities in OCD and with the neurocognitive profile of motor inhibition failures observed in these patients following repetition of behaviour. Thus, it seems obvious to consider a habit account of OCD, hypothesising that an anomalous shift from goal-directed to habitual control over action may mediate compulsivity in this disease. Although this hypothesis was raised, for the first time, in 2000 by Graybiel and Rauch (Graybiel & Rauch, 2000), to date only one study has tested it in patients (Gillan et al., 2011). This study used an appetitive instrumental learning task to test if OCD patients would favour habits over goal-directed action selection. Participants were trained to perform responses to different stimuli in order to gain rewarding outcomes. In subsequent outcome devaluation and 'slips of action' tests, they assessed whether participants were able to flexibly adjust their behaviour to changes in the desirability of the outcomes. The authors also used a post-experiment questionnaire to elucidate whether subjects had acquired the contingency information necessary to make goal-directed actions during training, or if they had instead learned via the stimulus-response habit system. They found no deficits in OCD patients' ability to use

feedback to respond appropriately to stimuli during the training stage, but their knowledge of the outcomes of these responses was impaired relative to healthy controls, indicating a deficit in goal-directed control and an overreliance on habits (Gillan et al., 2011).

In order to extend the investigation of a habit account of OCD, the second part of this thesis focuses on the investigation of this possible disruption in the balance between goal-directed behaviour and habit learning using a potentially more ecological paradigm to OCD. With the same aim, Gillan and colleagues (Gillan et al., 2011) used a cognitive procedure unrelated to the disease, which we consider a limitation. We believe that a symptom provocation task, in which subjects are exposed to individually tailored stimuli in real-time and further paired with a measure of the avoidance responses modelling compulsive actions, will capture such imbalances.

## GENERAL OUTLINE OF THE THESIS: AIMS AND HYPOTHESIS

This thesis is a result of a 4-year project that focused in an extremely disabling and prevalent psychiatric condition: OCD. The neurobiology of this condition remains a mystery and scientific progresses are still far to provide efficient treatments to sufferers. This project aimed to provide new insights to the pathophysiology of this disorder. It specifically focused on the mechanisms underlying the urge to perform the compulsive act, which has been understudied. One of our concerns was to investigate not only how compulsive habits emerge but also explore how this maladaptive behaviour relates to the other core symptoms of OCD: obsessions and anxiety. Bearing this in mind, the project was organized in two components, whereby we studied the same construct – decision-making - using a cognitive approach (*Chapter 2*), focusing in the mechanism *per se* (with a symptom-unrelated methodological paradigm), and a behavioural integrative approach (with an OCD

symptom-related methodological paradigm) (*Chapter 3*). Understanding how the symptoms (obsessions, compulsions) interact with one another, as well as their neural correlates, is of critical importance to advance scientific understanding of how the disorder develops over time, its pathogenesis and to find adequate treatments.

*Chapter 1* presents the current knowledge on the neurocognitive, neuroanatomical and neurophysiological functioning of the disorder. It also puts into perspective all the current available treatments as well as their degree of efficacy. A review of the existing literature addressing the specific topics of decision-making and habit formation in OCD is further presented in order to better understand the hypothesis that inspired this project.

*Chapter 2 and 3* present the methodology used for the clinical assessment of the patients and the body of results obtained from the experimental work conducted to test the hypotheses of this thesis. A multimodal approach, combining behavioural, computational and functional neuroimaging methods was used to investigate the mechanisms underlying compulsivity in OCD.

*Chapter 2* describes a study that test the general hypothesis that abnormalities in the decision-making process may account for the prominence of doubts and indecision clinically observed in OCD patients. In this chapter, the cognitive process of weighing and evaluating evidence prior to a decision is thoroughly investigated. The inability to commit to a final decision is a critical feature in OCD and compulsive behaviours may be conceptualized as pathological means to accumulate sufficient evidence to commit to a decision. In the repetitive act of washing or checking, the available sensory-perceptual evidence appears insufficient to commit to a solid decision: patients are unable to decide whether their hands are sufficiently clean or the door is properly locked. Instead, the compulsive behaviour itself appears to reflect the need for continuous 'evidence gathering', possibly to reduce uncertainty. This process of accumulating evidence has been assessed in OCD using probabilistic

reasoning tasks with inconsistent findings. Decisions are commonly based on sensory ambiguity rather than probabilistic evaluations. Therefore we investigate evidence accumulation in OCD using both probabilistic and perceptual tasks, in order to extend the OCD literature to perceptual decisions. We apply behavioural and computational approaches to characterize response strategies using both logistic regression analysis and hierarchical drift diffusion modelling. We test the hypothesis that OCD patients, compared to healthy controls, would accumulate more evidence in both the perceptual and probabilistic tasks, particularly during high relative to low uncertainty.

*Chapter 3* describes an fMRI study that directly tested, using a realistic symptom provocation paradigm, the interesting possibility that the neural circuits that normally mediate habits and automated behaviors become hyperactive or inaccessible to a stop signal in OCD: a possible disruption of the interplay between goal-direct and habit circuits. Regardless of the variability of phenotypes, we search for the common mechanisms underlying the compulsive avoidance responses in OCD by pairing the tailored symptom provocation with online avoidance responses on a trial-by-trial basis. Inspired by the animal model of habit formation in OCD, we hypothesize that the compulsive urges to avoidance responses observed by OCD patients would be associated with lower activity in regions implicated in goal-directed behaviours and higher activity in regions implicated in habitual behaviours.

Finally, the overall results are discussed in *Chapter 4,* in order to provide a comprehensive and integrative view of the main findings of the present work. Clinical implications and future directions are also addressed.

# Chapter 2

## Evidence accumulation in Obsessive-Compulsive Disorder: the role of perceptual uncertainty and implicit incentive

**ABSTRACT**

Compulsive behaviours are typical symptoms of Obsessive-Compulsive Disorder that reflect difficulties to commit to ultimate decisions. They may be conceptualized as a means to accumulate sufficient evidence prior to a decision. Here we investigate the process of evidence accumulation in OCD in perceptual discrimination and probabilistic reasoning, hypothesizing impairments in both decision types. Twenty-eight OCD patients and 35 healthy control subjects were tested with a low-level visual perceptual task (random dot motion task), whereby different coherent levels for motion were defined to measure high and low uncertainty, a probabilistic reasoning task (jumping to conclusions task) and two response conflict tasks as control tasks (flanker task and probabilistic selection task). Logistic regression analysis across all coherence levels (which accounted for visual detection threshold) and hierarchical drift diffusion modelling (HDDM) were used to characterize response strategies between patients with OCD and healthy controls in the random dot motion task. Patients compared to healthy volunteers were more cautious in weighing the alternatives and accumulated more evidence particularly during high uncertainty in the visual perceptual but not in the probabilistic task. This behaviour was consistent across different analyses and was more evident in patients with higher compulsivity scores. HDDM analysis further showed higher decision threshold, or evidence needed to make a decision, in patients under high uncertainty and slower drift rate, reflecting poorer quality of evidence, under low uncertainty. With incentives to emphasize speed, patients decreased the decision boundary threshold relative to healthy volunteers, accumulating less evidence in low uncertainty. These findings were unrelated to visual perceptual deficits and response conflict. In sum, this study extends the assessment of evidence gathering in OCD from probabilistic to perceptual decisions. Using both behavioural and computational approaches we highlight impairments in evidence accumulation in OCD and an influence of uncertainty. We further emphasize that OCD patients are sensitive to salient incentives on the speed-accuracy tradeoff, improving evidence accumulation

and shifting away from pathological internal monitoring. These findings may have relevance for therapeutic approaches.

*Keywords*: Obsessive-compulsive disorder, evidence accumulation, decision threshold, drift rate, cost-benefit ratio, uncertainty, implicit incentives, external feedback.

## INTRODUCTION

The weighting of evidence prior to a decision can be trivial or can require careful deliberation. The amount of evidence required has much inter-individual variability and can be abnormal in psychiatric disorders. The inability to commit to a final decision is a critical feature in Obsessive-Compulsive Disorder. In the repetitive act of washing or checking, the available sensory-perceptual evidence appears insufficient to commit to a solid decision: patients appear unable to decide whether their hands are sufficiently clean or the door is properly locked (Sachdev & Malhi, 2005). Instead, the compulsive behaviour itself appears to reflect the need for continuous 'evidence gathering', possibly to reduce uncertainty (Rotge et al., 2008; Stern et al., 2013).

This process of accumulating and evaluating evidence prior to a decision can be assessed using probabilistic reasoning tasks. In the Beads-in-a-Jar task (Beads task) participants judge from which of two jars, containing equal but opposite ratios of colour beads, the beads are being selected (Volans, 1976). In patients with schizophrenia, lower evidence accumulation is consistently observed (Fine, Gardner, Craigie, & Gold, 2007; Moutoussis, Bentall, El-Deredy, & Dayan, 2011). In the Information Sampling Task participants decide which of two colours is predominant in a 5 x 5 matrix by opening boxes to make a decision (Clark, Robbins, Ersche, & Sahakian, 2006). Although both behavioural measures are conceptually similar, recent studies in schizophrenia (Huddy et al., 2013) and binge drinking (Banca et al., submitted) show impairments in the Beads task but not the Information Sampling Task suggesting important task differences. These differences are deeply discussed in a binge drinking study we recently carried out (Banca et al., submitted) and include the following topics: i) how information is presented by the tasks (more or less explicitly); ii) the use of differing known probabilities for sampling evidence; iii) the different formats used by both tasks to visually display the amount of information acquired, which can differently affects working memory, iv) eventually differences in monetary rewards, which can affect the evidence accumulation process. Evidence

accumulation in OCD has focused on probabilistic reasoning but the results are mixed. Using the Beads task, two studies (Fear & Healy, 1997; Pelissier & O'Connor, 2002) showed that OCD patients gather more evidence compared to healthy controls although a third study (Volans, 1976) showed similar findings only after controlling for neuroticism as a confounder. In contrast, a recent study did not replicate this difference (Jacobsen, Freeman, & Salkovskis, 2012). Using the Information Sampling Task, there were also no differences in evidence accumulation between OCD patients and controls (Chamberlain, Fineberg, Blackwell, et al., 2007).

In this study, we assess evidence gathering in OCD in the perceptual domain. Decisions in daily life are commonly perceptual (e.g. do my hands look or feel clean?) rather than probabilistic (e.g. are my hands likely to be clean?), or a mix of the two. Typical experimental approaches using sensory discrimination in vibrotactile (Romo & Salinas, 2003), auditory (Kaiser, Lennert, & Lutzenberger, 2007), and visual (e.g. using the 'random dot motion' task (RDMT)) (Newsome, Britten, & Movshon, 1989) domains have been widely used to investigate perceptual decision making in primates and healthy humans (for review see (Gold & Shadlen, 2007; Heekeren, Marrett, & Ungerleider, 2008)). The analysis separates transient sensory integration and decision formation (Gold & Shadlen, 2007). Drift diffusion models, which define a decision when accumulated noisy evidence reaches a criterion level (a decision boundary), have been particularly successful in explaining response-time and accuracy data in these binary choice tasks (Ratcliff & McKoon, 2008).

We compared OCD subjects and healthy volunteers using the RDMT, a low-level visual perceptual task in which participants decide whether a net of randomly moving dots is predominantly moving right or left. We tested decision thresholds across a range of coherence levels to control for visual processing and compared high and low uncertainty conditions, thus linking decision making to perceptual uncertainty. The data were analyzed with conventional behavioural analyses, including mathematical models. Deep brain stimulation of the subthalamic nucleus (STN DBS)

in Parkinson's patients has recently been shown to decrease the influence of task difficulty on perceptual decisions using the RDMT (Green et al., 2013). STN DBS has also been shown to be effective in the treatment of OCD (Mallet et al., 2008) but whether OCD patients are affected on the RDMT is not known. We also tested subjects using a probabilistic reasoning task (Speechley, Whitman, & Woodward, 2010). We hypothesized that compared to healthy volunteers, OCD subjects would accumulate more evidence in both the perceptual and probabilistic tasks, particularly during high relative to low uncertainty.

The RDMT has features possibly relevant to response conflict as lower coherence motion may invoke competing responses. In event-related brain potentials (ERPs) studies OCD patients have consistently shown enhanced error related negativity relative to healthy controls (Gehring, Himle, & Nisenson, 2000; Johannes et al., 2001) in response conflict tasks although variability in behavioural differences has been observed (Fitzgerald et al., 2005; Kashyap, Kumar, Kandavel, & Reddy, 2013; Marsh et al., 2013; Najmi, Hindash, & Amir, 2010; Page et al., 2009a; Ursu, Stenger, Shear, Jones, & Carter, 2003). This error-processing enhancement is localized within the rostral ACC (Fitzgerald et al., 2005; Kiehl, Liddle, & Hopfinger, 2000) with similar enhanced activity also during correct high conflict trials, suggesting abnormalities in conflict detection in OCD (Endrass, Klawohn, Schuster, & Kathmann, 2008; Ursu et al., 2003). Here we use two different tasks assessing response conflict to act as control tasks: a variation of the Flanker task (Eriksen & Eriksen, 1974), a motor response competition task, modified to enhance task difficulty and a probabilistic selection task (Frank, Samanta, Moustafa, & Sherman, 2007). In this latter task, participants learn 3 stimulus-pair contingencies during training and are tested on high conflict (HC) and low conflict (LC) decisions by varying the stimulus reinforcement values using different pairings.

## MATERIALS AND METHODS

### Participants

Sixty-three participants, 28 OCD patients and 35 healthy volunteers (HV), took part in the study. Recruitment was done through community settings and clinicians in East Anglia and advertisements to local support groups. All patients were screened by a psychiatrist, using a structured clinical interview (the Mini International Neuropsychiatric Inventory (Sheehan et al., 1998)), to confirm the OCD diagnosis (DSM-IV-TR criteria) (American Psychiatric Association, 2000) and exclude any comorbid psychiatric disorders. General exclusion criteria for both groups were substance dependence, current major depression of moderate severity, serious neurological, medical or psychiatric illnesses, or head injury. Patients for whom hoarding was the primary complaint were also excluded because hoarding has been recently considered a discrete diagnostic entity due to its significantly different epidemiological, phenomenological, and neurobiological characteristics (Marchand & Phillips McEnany, 2012). Healthy controls were medication free. Groups were matched for gender, age and verbal IQ using the National Adult Reading Test (H. E. Nelson, 1982).

Nineteen of the 28 patients with OCD were taking SSRIs medication. Four of them were also taking antipsychotic medication. To assess the severity and characteristics of OCD symptoms, each patient completed the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) (Goodman et al., 1989). Healthy controls were free from medication or neurological, medical or psychiatric conditions. All participants completed the Beck Depression Inventory (BDI) (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961) and the State and Trait Anxiety Inventory (SSAI/STAI) (Spielberger, 1985).

Participants completed 4 behavioural tasks in a counterbalanced order and were compensated for their time and performance. This study was approved by the

University of Cambridge Research Ethics Committee and written informed consent was obtained.

**Behavioural procedures**

*Random-dot motion task (RDMT)*

Participants viewed a cloud of dots moving within a borderless circle in the screen centre (Figure 1). The goal was to decide whether the dots cloud appeared to be moving right or left. Subjects pressed 'S' for left and 'K' for right using their index fingers. Two sets of 500 dots (dot size: 3 pixels) were created: the 'coherent set' (dots moving coherently) and the 'random set' (dots moving randomly). From the first 50 ms frame to the next, the 'coherent set' moved 1 pixel towards the target direction whereas the 'random set' was randomly reallocated. In the subsequent frame the sets switched, with the 'coherent set' displayed randomly and the 'random set' displayed coherently. This strategy prevented tracking of a specific dot and ensured the cloud remained centred while maintaining the global perception of movement towards one direction (Forstmann et al., 2010). Nine different motion coherence levels (*Cl*) were defined by varying the proportion of dots in the 'coherent set'. *Cl* were selected following extensive piloting to ensure coverage of a wide range of individual visual detection thresholds (*Cl*: 0 (random control condition), 0.025, 0.05, 0.1, 0.15, 0.25, 0.35, 0.45 and 0.7) and to ensure representation of high and low uncertainty. Each trial was followed by an inter-trial fixation cross, centred in the middle of the screen, varying between 0.5 to 1 second duration. The stimulus was displayed for a maximum duration of 10 seconds and ceased following a response. Monetary feedback (+£1 or -£1) indicated whether the response was correct or incorrect.

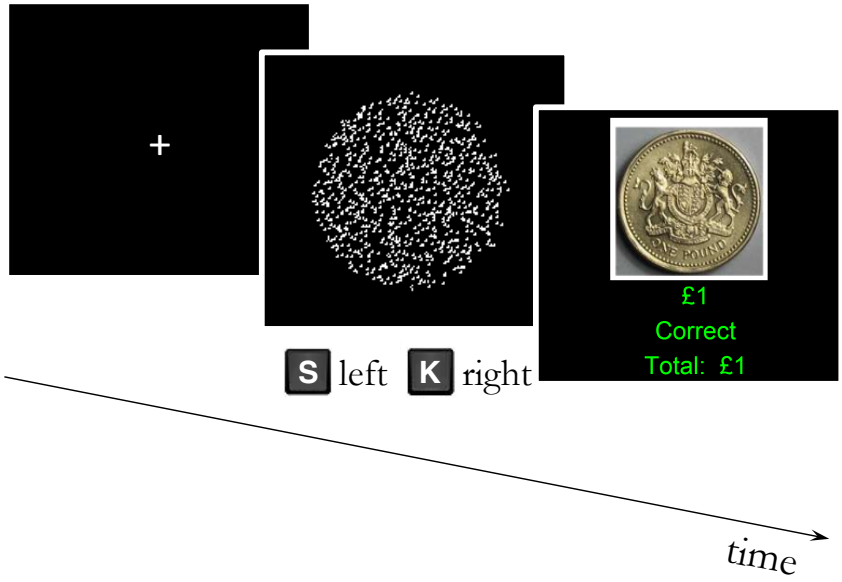



**Figure 1.** Random-dot motion task (RDMT). Participants viewed a net of dots randomly moving within a borderless circle in the centre of the screen. The goal was to decide whether the net of dots appeared to be moving to the right (s) or left (k) direction.

The task consisted of a practice session and 3 separate condition blocks. The first block comprised 180 trials, 20 trials for each level of coherence, randomly interleaved, and included 9 *Cl* (to assess individual visual detection thresholds) with monetary feedback. Responses were immediately followed by 1 sec-feedback: 'correct' associated with winning 1£ or 'incorrect' associated with losing 1£. It lasted approximately 20 min.

Blocks 2 and 3 included 6 *Cl* : 0, 0.05, 0.15, 0.25, 0.45 and 0.7. The second block assessed subjective confidence following the decision without monetary incentives. After each decision, participants rated their degree of confidence that their answer was correct on a visual analogue line anchored from 'Not confident' (0) to 'Very confident' (6). Participants responded using a mouse indicating their response on the continuous scoring line. Block 2 comprised 5 trials for each *Cl* and the duration was approximately 5 min.

The third block introduced a monetary penalty (Cost) for slow responses individualized for reaction time (RT) to measure the speed-accuracy tradeoff. Participants were told they would be penalized for incorrect or slow responses and rewarded for fast and accurate responses. Feedback was individualized for baseline RT (RTb) of the first session: if RT was more than 1SDb above RTb, the feedback was 'too slow, 2£ loss';; if RTb - 1SDb < RT < RTb + 1SD the feedback was 'speed OK, 0.50£ earned';; if RT < RTb - 1SDb the feedback was 'FAST, 1£ earned'; if RT < RTb - 2SDb the feedback 'VERY FAST, 2£ earned'. Block 3 comprised 20 trials for each *CI* and lasted approximately 10 min.

Participants were instructed to make their decision as quickly and accurately as they could. Stimulus delivery was coded using Cogent toolbox in MATLAB (Math-Works).

Primary outcome measures were accuracy, response time and confidence rates.

*Probabilistic reasoning task*

Participants were shown two lakes with fish (Speechley et al., 2010) containing opposite ratios of black and gold fish (e.g. Gold lake: *P*=0.70 gold fish/*P*=0.30 black fish, with the opposite ratio in the Black lake) (Figure 2). Participants were informed of the fish ratio. They were told a series of fish would be 'caught' from one of the lakes and presented sequentially. The same sequence of fish colour for each trial was used in all the participants. The goal was to infer from which lake the fish were caught. Participants viewed as many fish as necessary (maximum 10) before their decision.

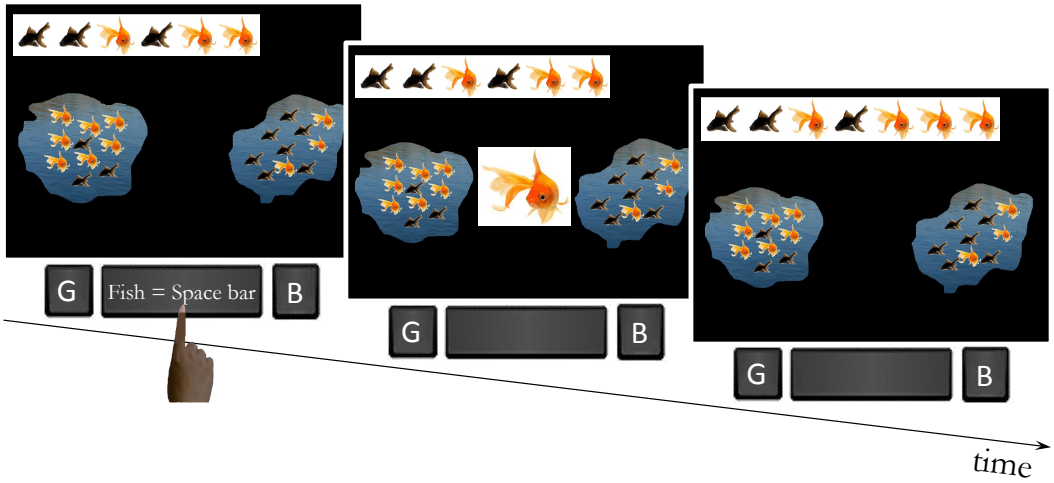



**Figure 2**. Probabilistic task. Participants were shown two lakes containing opposite ratios of gold and black fish (Gold Lake: P=0.70 gold fish; P=0.30 black fish / Black Lake: P=0.70 black fish; P=0.30 gold fish). Fish were caught from one of the lakes and shown sequentially. The goal was to infer from which lake the fish were caught. Participants either chose additional evidence (space bar) or made a decision (G=Gold Lake; B=Black Lake). Fish caught were displayed at the top of the screen.

Participants completed 10 trials with monetary feedback (+/-£1) for decision accuracy (session 1). In the Cost condition (session 2), they were penalized 10 pence for each fish viewed, which was subtracted from the possible win of 1£ for a correct response. An incorrect response resulted in a loss of 1£ plus the cost per fish accumulated during the trial. This second session also consisted of 10 trials.

The task controlled for working memory by showing the caught fish at the top of screen. The fish remained on screen until the subject chose another fish or made a decision. There was no time limit to the task and subjects took approximately 8 min. The task was coded in Visual Basics.

Primary outcome measures were the number of fish sampled (evidence accumulated) and decision accuracy.

*Control tasks*

Two tasks were administered to control for response conflict.

*Probabilistic selection task*

The Probabilistic selection task (Frank, Seeberger, & O'Reilly R, 2004) (Figure 3B) consisted of a training session followed by a testing session. The training session was composed by 3 different stimulus pairs presented randomly: AB, CD, EF pairs (only named for illustrative purposes). Participants chose between the two stimuli, using the left or right arrow key. Visual feedback indicated whether the response was correct (£1) or incorrect (-£1). Each stimulus pair was associated with different contingencies. In AB trials, A was associated with P=0.85 correct / P=0.15 incorrect and B the opposite contingency. The CD and EF trials had the following contingencies: P (C)=0.75; P (D)=0.25 and P (E)=0.65; P (F)=0.35. The patterns assigned to each stimulus (A to F) were counterbalanced across all the participants.

During training, participants learned the 3 stimulus-pair contingencies and advanced to the testing session only if they reached criterion level. We followed the performance assessment criteria developed by Frank and colleagues (Frank et al., 2007): minimum 65% A choices in AB, 60% C in CD, 50% E in EF. Up to 3 blocks of training (180 trials) were used to acquire the required learning to proceed to the next session.

The testing session used the same stimuli, but with different pairings. No feedback was provided. In 72 trials, 24 trials consisted of win-win (WW) stimuli that were both previously associated with high winning probabilities (e.g. AC), 28 lose-lose trials (LL), in which both stimuli were previously associated with low winning probabilities (e.g. DF), and win-lose trials (WL), in which only one pattern was associated with high winning probabilities (excluding the combinations used during training). Thus, WW and LL trials measured high conflict (HC) decisions (in which participants choose between similar reinforcement values), whereas WL measured low conflict

(LC) decisions (with more easily discriminable values). Stimuli were presented for a maximum of 10s, and disappeared when the choice was made. This task was coded in E-Prime 2.0 software.

Outcome measures included accuracy and RT between high conflict (represented by a choice between stimuli both previously associated with high or low winning probabilities) and low conflict choices (choice between similar reinforcement values).

*Flanker task*

The Flanker task (Eriksen & Eriksen, 1974) (Figure 3A) was modified to enhance task difficulty. We used letters and arrows as visual stimuli. Participants were required to identify the target character in the centre of a 5-characters string, which could be the same as the flankers (congruent: e.g. MMMMM or > > > > >) or different (incongruent: e.g. MMSMM or > > < > >). Participants responded using a thumb-response button box that they were holding with both hands. Participants pressed the left button (left thumb) for target arrow pointing left or target letter S and right button (right thumb) for target arrow pointing right or target letter M.

The visual stimuli were presented in white on a black screen, using E-Prime 2.0 software. In order to increase task difficulty, stimuli was coded in order to randomly appear in 4 different quadrants of the screen (top left, top right, bottom left or bottom right). For each trial, the centre target letter/arrow appeared 50 ms after the onset of the flankers, thus leaving the full stimulus string (flanker + target) displayed for 150 ms. Then participants had 1000 ms to respond. If the response was incorrect or if participants did not respond within the time limit, feedback 'WRONG' was displayed for 500 ms. No feedback was given to the correct responses. Participants were instructed to respond as quickly and accurately as possible.

In total 288 trials, excluding 10 practice trials, were randomly presented. Half of the trials were congruent and the other half incongruent. Primary outcome measures were response time and accuracy.

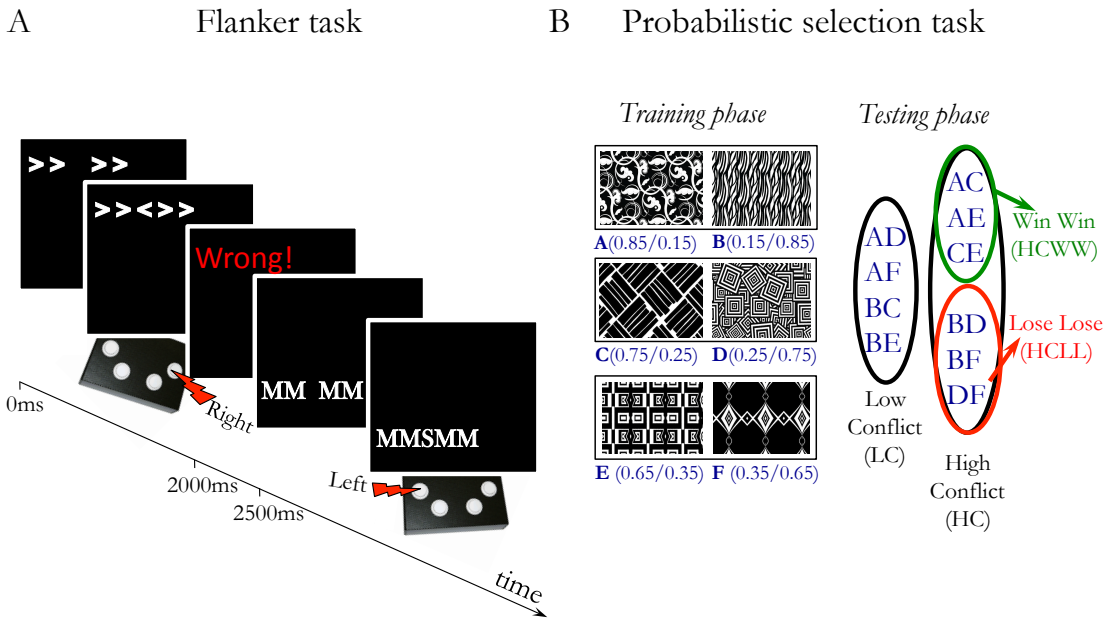



**Figure 3**. Flanker task and probabilistic selection task. **Panel A**. Flanker task. Subjects viewed a string of arrows or letters varying in screen position. The goal was to indicate the direction of the central character flanked by either the same (congruent) or different (incongruent) flankers, using the left (for left arrow or S) or right (for right arrow or M) button. **Panel B**. Probabilistic selection task. During training, subjects learned stimulus contingencies from randomly presented stimulus pairs from 3 probability configurations followed by monetary feedback for correct and incorrect choices. Correct choices were determined probabilistically (ratio of positive/negative monetary feedback is shown in parentheses for each stimulus). In the testing phase novel combinations were presented to assess high and low conflict decisions. This schematic illustration was adapted from (Frank et al., 2007).

**Data Analysis**

Subject characteristics and primary outcomes of the behavioural tasks were analysed using Chi-square, independent t-tests and mixed-measures ANOVA. The relationship between primary outcome measures and clinical measures were compared using Pearson correlation.

*Random Dot Motion Task*

The RDMT was analysed in detail by using 3 different approaches focusing on different concepts. A simple mixed-measures ANOVA was used to specifically assess the influence of uncertainty, directly comparing high and low uncertainty conditions. A regression analysis further accounted for individual visual detection thresholds and assessed performance across all coherence levels. A hierarchical drift diffusion modelling analysis was used to investigate in-depth mechanisms underlying the different response strategies between patients and healthy controls.

*ANOVA*

Considering that the higher the proportion of dots in the 'coherent set', the lower the uncertainty, we defined high uncertainty by merging trials from 0.025 and 0.05 *Cl* and low uncertainty by merging trials from 0.45 and 0.7 *Cl* conditions. Group was used as a between-subjects factor and high uncertainty versus low uncertainty as a within-subjects factor. For the main hypothesis, we assumed $p<0.05$ was significant. We also used a mixed measures ANOVA design to study the effect of Cost, Feedback (negative and positive) and Confidence in OCD.

*Regression analysis*

We conducted regression analyses on accuracy and response time (RT) assuming *Cl* represents the available evidence for detecting motion direction. By only analyzing correctly identified trials, log(RT) can be interpreted as an index of the cognitive demand required for successful recognition of the motion direction.

*Accuracy*: Using accuracy as the primary outcome, we computed a logistic discrimination, $\log\left(\frac{p-0.5}{1-p}\right) = B_S\left(Cl - T_{75}\right)$ to model the identification of coherent motion $(p)$ and characterized behaviour with 2 parameters, *visual detection threshold* $(T_{75})$ and *sensitivity* $(B_S)$. Visual detection threshold is the *Cl* at which 75% correct identification occurs (assuming chance performance is 50%). $B_S$ measures sensitivity to variation in *Cl*. Logistic discrimination assumes binomial distribution of the correct motion direction identification $(p)$.

*Reaction time*: Using successful RT as a primary outcome, we then used logarithmic regression, $\log(RT) = B_C Cl + B_0$ to predict response time ($RT$) in correctly identified trials, and characterized behaviour using *RT intercept* ($B_0$) and *decay* ($B_C$). The intercept represents the adjusted response for $Cl = 0$ (i.e. the response time for zero evidence is $RT_0 = \exp(B_0)$). The negative decay score indicates the steepness of the *RT* exponential reduction and represents the release of cognitive demand with increasing *Cl* or increasing certainty for motion direction. This regression assumes Poisson distribution of *RT*. We excluded the random condition ($Cl = 0$). The generative models were fitted to the behavioural data for each participant.

*Hierarchical drift diffusion modelling*

We also used Hierarchical Drift Diffusion Model (HDDM) to further explore the mechanisms underlying decisions in the RDMT analysis. This software package (http://ski.clps.brown.edu/hddm_docs/) (Wiecki, Sofer, & Frank, 2013) allows a fast and flexible estimation of the drift-diffusion model (the most widely used mathematical model of two-alternative forced-choice decision-making tasks (Ratcliff & McKoon, 2008)) and the related linear ballistic accumulator model (Wiecki et al., 2013). In this model each choice is represented as a diffusion towards an upper and lower decision boundary. When the accumulated noisy evidence reaches one of these two boundaries over time, the decision is made and the respective response initiated.

HDDM simultaneously accounts for the proportion of correct and incorrect trials and its respective RT distributions across conditions, considering the latter a result of underlying latent parameters of a decision-making model. It further estimates the posterior probability density of the diffusion model parameters, by using Markov chain Monte Carlo simulation, generating group data, while accounting for individual differences (for details about the model see (Wiecki et al., 2013)). These parameters estimates include: *drift rate (v)* - the speed of the evidence accumulation process toward either boundary or the quality of the accumulated evidence; *decision threshold (a)* - the distance between the two boundaries or amount of evidence accumulated; and *non-decision time* - perceptual encoding and motor execution. The model also allows for a prepotent bias affecting the starting point of the drift process relative to the two boundaries. It then uses analytic integration of the likelihood function for variability in drift-rate and numerical integration for variability in non-decision time and bias.

In this framework, we fit participants' RT and accuracy measures into the model. We compared *drift rate (v)* and *decision threshold (a)* for high and low uncertainty between groups separately for no cost and cost conditions by directly comparing the distribution overlap between posteriors assuming the probability of overlap ($P$) < 5% is significantly reduced (Wiecki et al., 2013). We compared the mean difference and standard deviation of the decision threshold posteriors between groups for high versus low uncertainty in the no cost condition using a t-test. For the main hypothesis, we assumed $p<0.05$ was significant.

We tested the hypothesis that OCD patients would show a more cautious style of responding represented by a higher *decision threshold* and/or a slower *drift rate*.

*Probabilistic Reasoning Task*

The probabilistic reasoning task was assessed using a mixed-measures ANOVA to investigate the role of Cost on the evidence accumulated (number of the fish

sampled) and accuracy, with Group (OCD vs HV) as a between-subjects factor and Cost as a within-subjects factor.

*Control Tasks*

*Probabilistic selection task*

For the training phase, we assessed both accuracy and learning consistency. Consistency was defined for individual performance in terms of how well the actual performance reflected the performance of an optimal learner taking into account the actual evidence observed. The accuracy score is based on the prior probability of the options whereas the consistency score is based on the posterior probability of the options. Thus, the consistency score is a more accurate score of performance as an index of learning. We also assessed measures of win-stay or lose-switch. Group differences were analysed using independent t-tests.

For the testing phase we used a mixed measures ANOVA with Group as a between-subjects factor and Conflict as a within-subjects factor, to assess accuracy and response time on correct trials.

*Flanker Task*

In the Flanker task, the mean response time for correct trials and accuracy were computed for each visual context (congruent and incongruent) and each stimulus type (arrow and letters). These measures were analysed using an ANOVA with the following factors: group, visual context and stimulus type, in which the last 2 were specified as repeated measures.

## RESULTS

Twenty-eight OCD subjects and 35 HV were assessed. Table 1 summarizes the groups' demographic and clinical characteristics.

**Table 1.** Demographic and clinical characteristics of the participants

| | OCD (n=28) | HV (n=35) | Statistics | | |
|---|---|---|---|---|---|
| | | | t | df | p |
| Gender (female/male) | 16/12 | 20/15 | | | |
| Age | 37.5 (13.5) | 37.9 (14.7) | 0.141 | 61 | ns |
| Verbal IQ | 115.4 (5.8) | 118.4 (6.0) | 1.705 | 45 | ns |
| Y-BOCS Total | 24.3 (6.9) | - | | | |
| Obsessions | 12.6 (3.8) | - | | | |
| Compulsions | 12.1 (3.2) | - | | | |
| OCS | - | 9.88 (3.31) | | | |
| OCI-R | - | 9.76 (8.91) | | | |
| BDI | 18.0 (10.1) | 4.4 (4.7) | -6.498 | 60 | <0.001 |
| STAI-S | 46.9 (12.5) | 32.7 (10.4) | -4.826 | 59 | <0.001 |
| STAI-T | 54.4 (11.7) | 35.2 (10.8) | -6.581 | 58 | <0.001 |

Standard deviations are in parentheses: Mean (SD)

The different degrees of freedom (df) resulted from missing data in the dataset.

OCD, patient group; HV, healthy volunteers; NART, National Adult Reading Test; Y-BOCS, Yale-Brown Obsessive Compulsive Scale (total, obsession and compulsion scores); BDI, Beck Depression Inventory; STAI-S, State component of State-Trait Anxiety Inventory; STAI-T, Trait component of State-Trait Anxiety Inventory.

### Random-Dot Motion Task

The data from 2 OCD participants were excluded as their performance was at chance level throughout the task.

*ANOVA*

First, we performed a simple mixed measures ANOVA analysis based on successful RT with Uncertainty (high uncertainty: 0.025/0.05 *CI* and low uncertainty: 0.45/0.70 *CI*) as a within-subjects factor and Group (OCD and HV) as a between-subjects factor. There was a main effect of Uncertainty ($F(1,59)=179.7$, $p<0.0001$), Group ($F(1,59)=4.88$, $p<0.031$) and a Group by Uncertainty interaction ($F(1,59)=4.46$, $p<0.039$). OCD patients were significantly slower than HV in the high uncertainty condition (Figure 4A).

We further analyzed successful RT using mixed measures ANOVA with Cost (Cost and No Cost) and Uncertainty as a within-subjects factor and Group (OCD and HV) as a between-subjects factor. There was a main effect of Cost ($F(1,59)=229.3$, $p<0.0001$), Uncertainty ($F(1,59)=177.7$, $p<0.0001$) and Group by Cost ($F(1,59)=6.9$, $p=0.01$), Cost by Uncertainty ($F(1,59)=133.8$, $p<0.0001$) and a Cost by Uncertainty by Group ($F(1,59)=7.03$, $p=0.01$) interactions but no Group effect ($p=0.08$) or Group by Uncertainty interaction ($p=0.14$) (Figure 4A). Thus, both groups reduced RT as a function of cost. The Uncertainty effect between groups in the Cost condition was lost.

Finally, we assessed confidence ratings and the mean post-feedback reaction time (RT). There was a main effect of Confidence ($F(1,59)=101.2$, $p<0.0001$) but no Confidence by Group interaction ($p=0.62$) (Figure 4B). Analysis of successful RT after positive or negative feedback (1£ loss or 1£ win) showed a main effect of Uncertainty (high and low) ($F(1,59)=127.2$, $p<0.0001$) and of Feedback type (correct and incorrect) ($F(1,59)=8.90$, $p<0.004$) in post-feedback RT. However, no Group effect ($p=0.06$), Group by Uncertainty ($p=0.14$), Group by Feedback ($p=0.42$) or Feedback by Uncertainty ($p=0.25$) interactions were observed (Figure 4C). Thus, feedback has an equal effect between groups meaning that OCD subjects were as sensitive as HV to positive and negative external feedback.

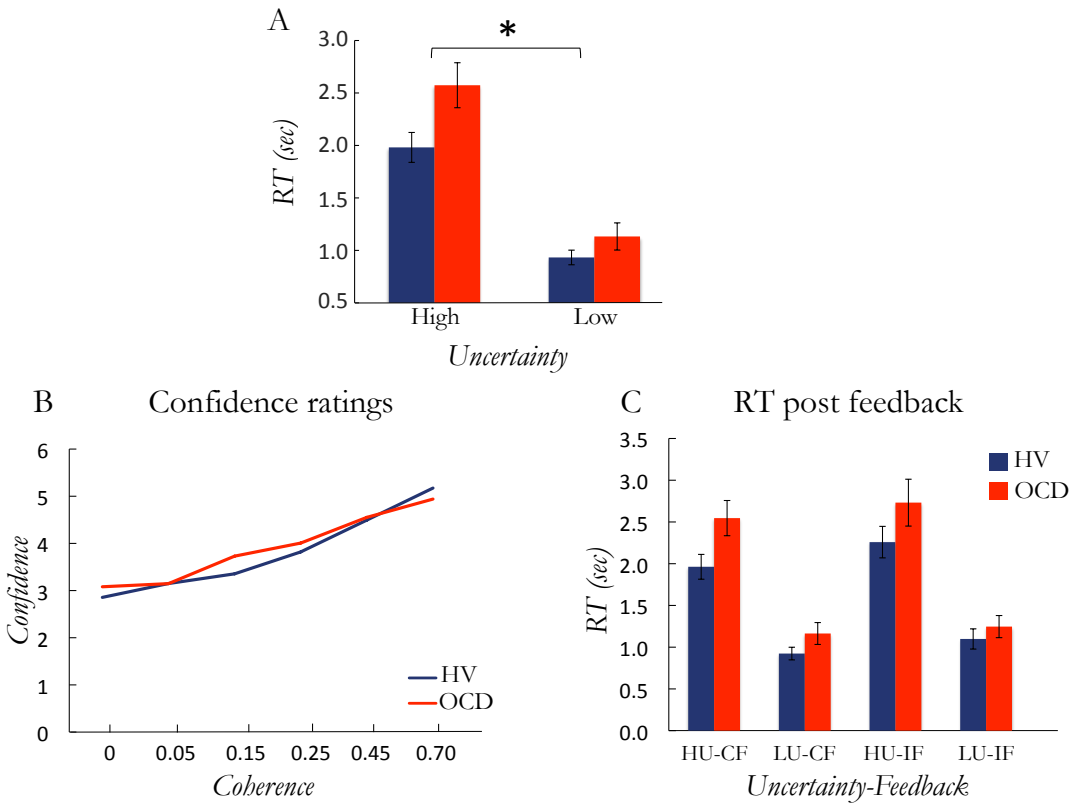



**Figure 4**. ANOVA analyses. **Panel A**. RT in correctly identified trials for high (0.025 and 0.05 coherence levels) and low uncertainty trials (0.45 and 0.7 coherence levels). *Group x Uncertainty interaction: $p<0.05$. **Panel B.** Mean confidence ratings across motion coherence levels. **Panel C.** Mean RT in the subsequent trial following positive or negative feedback: high uncertainty following correct feedback (HU-CF), low uncertainty following correct feedback (LU-CF), high uncertainty following incorrect feedback (HU-IF), low uncertainty following incorrect feedback (LU-IF). Error bars represent SEMs.

*Logarithmic regression*

Both groups showed a negative correlation between visual detection threshold and sensitivity (OCD: r=-0.4349, p=0.0298; HV: r=-0.3793, p=0.0323) indicating that participants that were good at the task (low threshold) were also more sensitive to variation in coherence level. There was also a strong positive correlation between the decay (release of cognitive demand) and visual detection threshold (OCD: r=0.6419, p=0.0005; HV: r=0.5171, p=0.0024), and a strong negative correlation between

decay and sensitivity to variation in coherence level (OCD: r=- 0.4070, p=0.0435; HV: r=-0.5009, p=0.0035). Thus, participants who became faster with increasing coherence level had lower visual detection threshold and higher sensitivity to variation in evidence (bearing in mind that the decay parameter is negative, so good performance is indicated by a high negative value).

*RT* intercept differed between groups (t=2.37, df=59, p=0.021) but not visual detection threshold, sensitivity, and decay (Figure 1B and C; Table 2). As the RT intercept occurs at low *CI*, this result is consistent with OCD patients being slower than HV at low *CI* or higher uncertainty. The regression analysis in the Cost condition showed no group differences (Table 2).

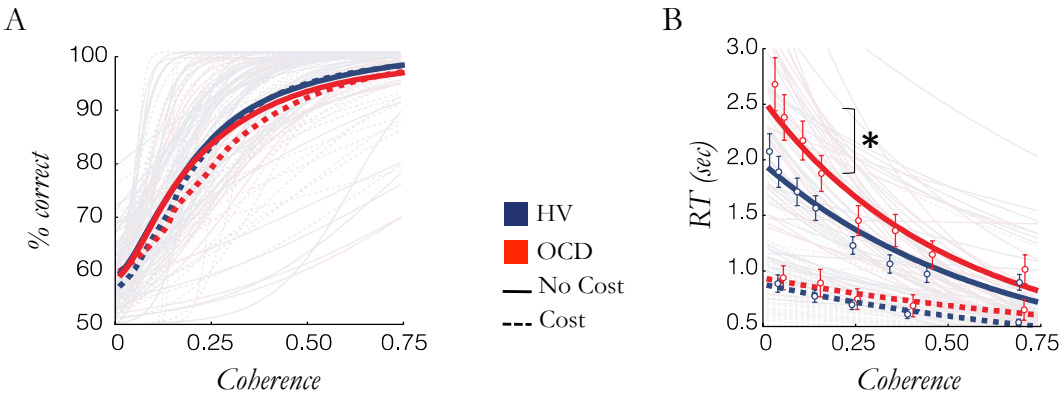



**Figure 5. Panel A.** Logistic discrimination of coherent motion across the 9 coherence levels for patients with obsessive compulsive disorder (OCD: red) or healthy volunteers (HV: blue). **Panel B**. Logarithmic regression for reaction time (RT) in correctly identified trials across the 9 coherence levels. *RT intercept, p<0.05; Open circle: mean average; solid (no cost) and dotted (cost) lines: estimated group averages.

**Table 2**. Random-Dot Motion Task statistics for the regression analysis.

| | Parameters | OCD | HV | Statistics | |
|---|---|---|---|---|---|
| | | | | t | p |
| **No Cost** | **Visual detection threshold ($T_{75}$)** | 0.22 (0.21) | 0.19 (0.17) | 0.583 | 0.56 |
| | **Sensitivity ($B_S$)** | 13.35 (12.19) | 13.64 (11.39) | -0.095 | 0.92 |
| | **RT intercept ($RT_0$)** | 2.53 (1.07) | 1.96 (0.82) | 2.365 | 0.02 |
| | **Decay ($B_C$)** | -1.61 (0.83) | -1.36 (0.60) | -1.368 | 0.18 |
| **Cost** | **Visual detection threshold ($T_{75}$)** | 0.23 (0.12) | 0.21 (0.14) | 0.649 | 0.52 |
| | **Sensitivity ($B_S$)** | 17.62 (39.63) | 21.07 (37.13) | -0.343 | 0.73 |
| | **RT intercept ($RT_0$)** | 0.96 (0.68) | 0.88 (0.43) | 0.540 | 0.59 |
| | **Decay ($B_C$)** | 0.60 (0.44) | -0.69 (0.45) | 0.715 | 0.48 |

Standard deviations are in parentheses: Mean (SD)

OCD, patient group; HV, healthy volunteers.

There was no correlation between visual detection threshold and RT intercept (HV: p=0.68; OCD: p=0.33), suggesting that visual detection threshold was unrelated to these findings.

A positive correlation was found between the Y-BOCS compulsive subscale scores and the *visual detection threshold* ($r$=0.48, p= 0.015) and the *decay* ($r$=0.40, p= 0.047). Thus, more severe compulsive symptoms correlated with higher motion detection thresholds and lower release of cognitive demand with increasing evidence. There were no other significant correlations between the RDMT parameters and clinical measures (Table 3) or the outcome measures from other tasks (Table 4).

**Table 3**. Correlations between the parameters estimated with regression analysis of the Random-Dot Motion Task (no cost condition) and clinical measures.

| Correlations: r (p-value) | | | | | |
|---|---|---|---|---|---|
| **Parameters** | **Ycomp** | **Yobs** | **Ytotal** | **BDI** | **STAI-S** |
| **Vis. detection threshold ($T_{75}$)** | 0.48 (0.015) | 0.38 (0.06) | 0.45 (0.022) | OCD: 0.29 (0.17) HV: -0.004 (0.98) | OCD: 0.24 (0.25) HV: 0.05 (0.76) |
| **Sensitivity ($B_S$)** | -0.01 (0.95) | -0.15 (0.47) | -0.11 (0.59) | OCD: -0.15 (0.46) HV: -0.04 (0.82) | OCD: 0.12 (0.58) HV: 0.05 (0.77) |
| **RT intercept ($B_0$)** | -0.25 (0.22) | -0.02 (0.89) | -0.14 (0.51) | OCD: 0.14 (0.51) HV: 0.13 (0.46) | OCD: 0.27 (0.19) HV: 0.10 (0.57) |
| **Decay ($B_C$)** | 0.40 (0.047) | 0.18 (0.38) | 0.34 (0.09) | OCD: -0.009 (0.96) HV: -0.04 (0.80) | OCD:-0.10 (0.62) HV: -0.07 (0.69) |

OCD, patient group; HV, healthy volunteers; Ycomp: Y-BOCS compulsive subscale, Yobs: Y-BOCS obsessive subscale; Ytotal: Y-BOCS total score; BDI, Beck Depression Inventory; STAI-S, State component of State-Trait Anxiety Inventory.

**Table 4**. Correlations between the parameters estimated with regression analysis of the Random-Dot Motion Task (no cost condition) and behavioural outputs from other tasks.

| Correlations: r (p-value) | | | |
|---|---|---|---|
| **Parameters** | **Probabilistic Reasoning Task** | **Flanker Task** | **Probabilistic Selection Task** |
| **Vis. detection threshold ($T_{75}$)** | OCD: 0.15 (0.47) HV: -0.18 (0.31) | OCD: -0.21 (0.34) HV: 0.15 (0.39) | OCD: -0.18 (0.47) HV: 0.18 (0.43) |
| **Sensitivity ($B_S$)** | OCD: -0.28 (0.16) HV: -0.11 (0.53) | OCD: -0.12 (0.57) HV: -0.001 (0.99) | OCD: -0.21 (0.39) HV: -0.12 (0.59) |
| **RT intercept ($B_0$)** | OCD: -0.34 (0.09) HV: -0.11 (0.53) | OCD: -0.06 (0.78) HV: -0.19 (0.28) | OCD:-0.006 (0.82) HV: -0.16 (0.46) |
| **Decay ($B_C$)** | OCD: 0.24 (0.24) HV: -0.04 (0.84) | OCD: -0.03 (0.89) HV: 0.32 (0.07) | OCD: -0.07 (0.79) HV: 0.12 (0.58) |

*Hierarchical drift diffusion modelling*

In the HDDM analysis, decision threshold was higher in OCD patients than in HV, (high uncertainty: *P*=<0.0001; low uncertainty: *P*=0.021) with a greater difference in high compared to low uncertainty (mean difference: high M=0.34 SD=0.046; low M=0.1 SD=0.052; t=19.355 p=0.0001) (Figure 6). However, the drift rate was slower in OCD patients as compared to HV only in low uncertainty (*P*=0.0002) but not in high uncertainty (*P*=0.13).

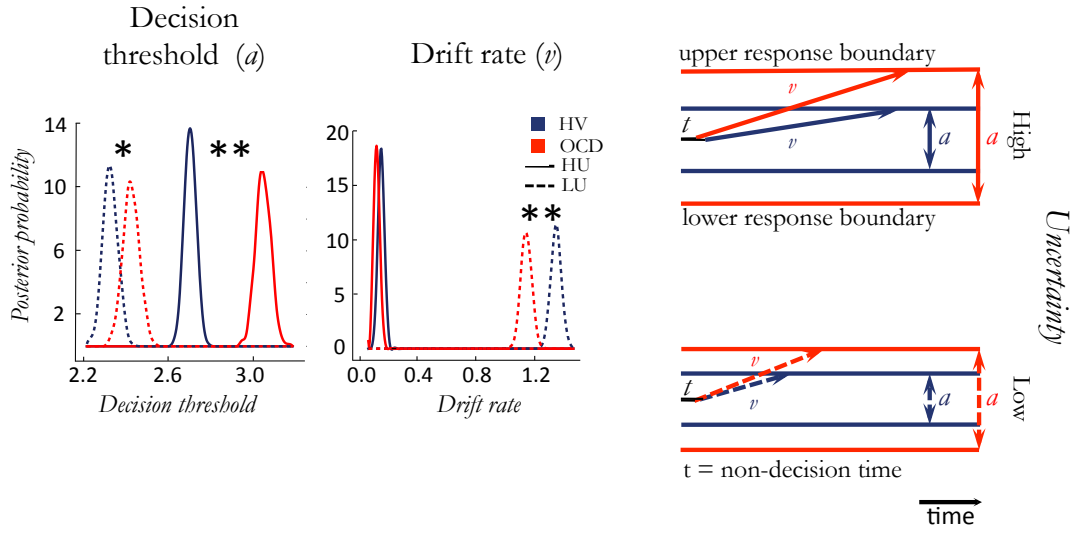



**Figure 6**. Hierarchical drift diffusion modelling of random dot motion task. Posterior density plots of the group means of the decision thresholds and drift-rates for No Cost condition and their schematic representation (on the right). Red lines: Obsessive compulsive disorder (OCD); blue lines: healthy volunteers (HV); solid lines: high uncertainty (HU); Dashed lines: low uncertainty (LU); *p<0.05; **p<0.001.

There was an effect of cost on decision threshold and drift rate. Both groups significantly decreased decision thresholds ($P$<0.0001) and increased drift rate ($P$<0.0001) as a function of cost (Figure 2B). In the Cost condition, OCD subjects had similar thresholds to HV in high uncertainty ($P$=0.80) and *lower* thresholds in low uncertainty ($P$=0.04). With cost, OCD patients continued to show slower drift rates compared to HV in low uncertainty ($P$<0.0001) but not high uncertainty ($P$= 0.26).

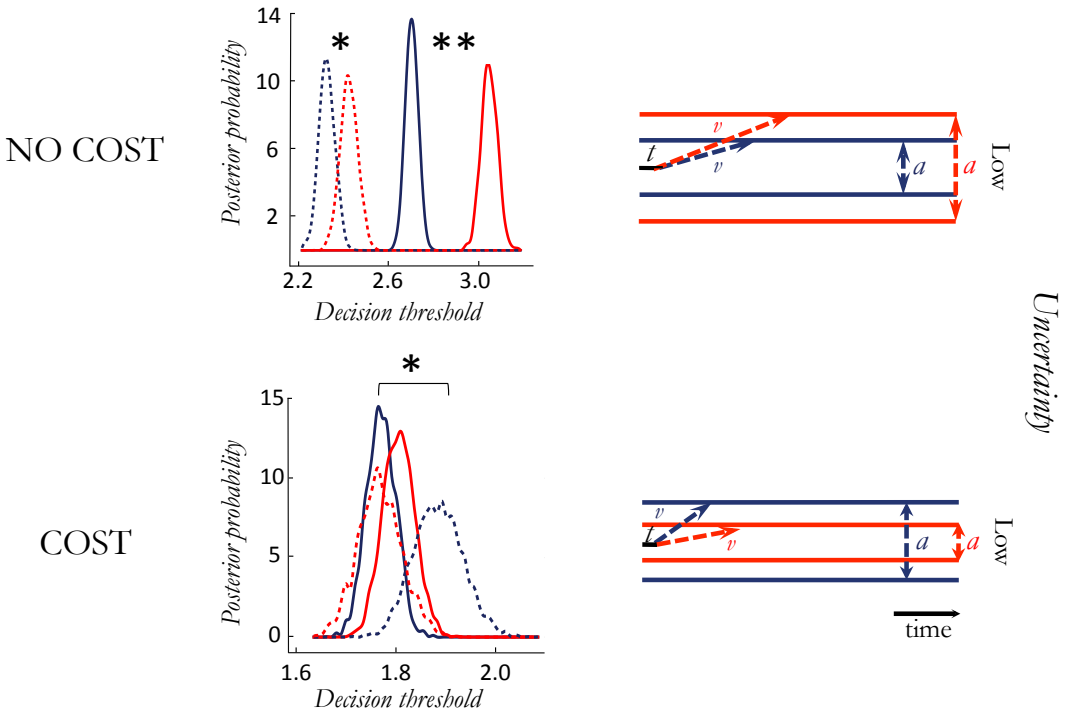



**Figure 7**. Hierarchical drift diffusion modelling of random dot motion task. Posterior density plots of the group means for decision thresholds comparing Cost and No Cost conditions. Schematic representation is on the right. Red lines: Obsessive compulsive disorder (OCD); blue lines: healthy volunteers (HV); Dashed lines: low uncertainty (LU); *p<0.05; **p<0.001.

### Probabilistic reasoning task

Groups did not differ in evidence accumulated ($F(1,61)=0.217$, $p=0.643$) or accuracy ($F(1,61)=0.961$, $p=0.331$). There was a main effect of Cost on evidence accumulated ($F(1,61)=69.8$, $p<0.0001$) and accuracy ($F(1,61)=109.9$, $p<0.0001$) and no Group by Cost interaction on evidence accumulated ($F(1,61)=0.001$, $p=0.978$) or accuracy ($F(1,61)=0.014$, $p=0.907$) (Figure 8).

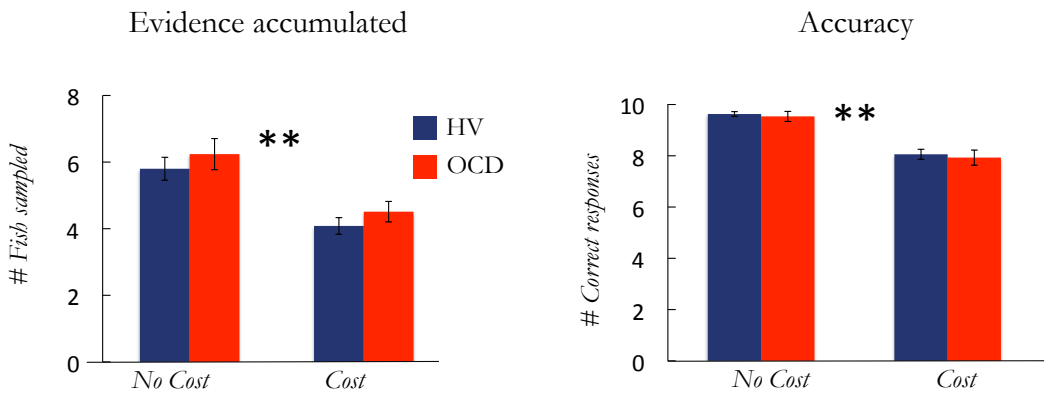



**Figure 8.** Mean number of fish sampled (evidence accumulated) and mean accuracy for Obsessive-compulsive disorder (OCD) and healthy volunteers (HV). Error bars represent SEM; **p<0.0001.

### Control Tasks

*Probabilistic Selection Task*

In the training phase, there were no differences between groups in the consistency score (p=0.636) or in RT (p=0.888). There were also no differences in the number of win-stay (p=0.722) or lose-switch measures (p=0.827).

In the testing phase, there was a main effect of conflict on accuracy (F=73.08 (1,43), p=<0.0001) and on RT (F=77.21 (1,43), p=<0.0001). However, there was no Group

by Conflict interaction or Group main effect, either in accuracy (Group x Conflict: p=0.489 and Group effect: p=0.229) or RT (Group x Conflict: p=0.682 and Group effect: p=0.839). There was a main effect of the Type of conflict (WW or LL) within the high conflict condition (HC) on RT (F=34.12 (1,43), p=<0.0001), although not on accuracy (p=0.366). Within the high conflict condition, there were no Group by Type of conflict interaction or a Group effect, either in accuracy (Group by Conflict: p=0.637 and Group effect: p=0.692) or RT (Group by Conflict: p=0.789 and Group effect: p=0.745). These results are shown in Figure 9A.

*Flanker task*

Three participants were not tested on this task due to time constraints. Thus, the following results are from 26 OCD participants and 34 HV.

Both groups showed an effect of flankers on RT and accuracy, indexed by a main effect of visual context (congruent or incongruent) on RT ($F(1,58)=408.2$, $p<0.0001$) and accuracy ($F(1,58)=108.7$, $p<0.0001$). There was a main effect of stimulus type (arrows or letters) on RT ($F(1,58)=9.2$, $p<0.004$) and a Visual context by Stimulus type interaction on RT ($F(1,58)=66.5$, $p<0.0001$) and on accuracy ($F(1,58)=45.5$, $p<0.0001$).

The OCD group made slightly more errors (% accuracy for congruent: M=90.3%, SD=10.8; incongruent: M=80.4%, SD=10.9) than the HV group (congruent: M=94.2%, SD=4.7; incongruent: M=81.8%, SD=9.7). They were also slightly faster (RT for congruent: M=416.8ms, SD= 78.8; incongruent: M=541.1ms, SD=102.5) than HV (congruent: M=434.3ms, SD=79.0; incongruent: M=548.5, SD=95.6). However, these differences were not significant: there was no Group effect (p=0.582 for RT and p=0.240 for accuracy) or Group by Visual context interaction (p=0.400 for RT and p=0.266 for accuracy) or Group by Stimulus type interaction (p=0.590 for RT and p=0.928 for accuracy). These results are shown in Figure 9B.

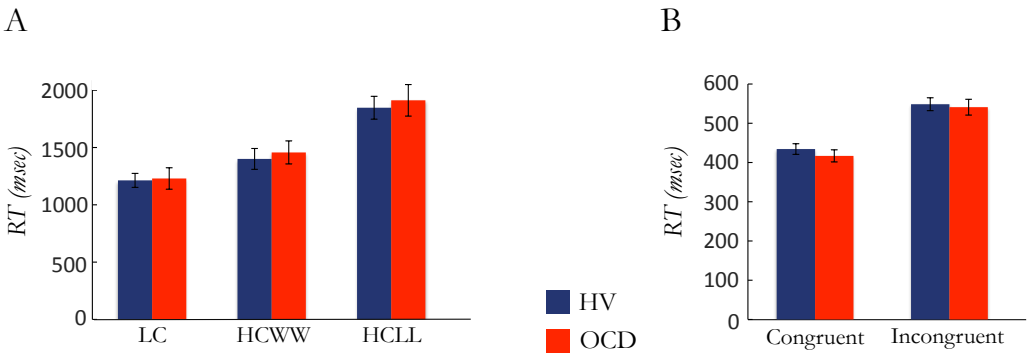



**Figure 9.** Control tasks results. **Panel A.** Probabilistic selection task. Mean response time for low conflict (LC), high conflict win-win (HCWW) and high conflict lose-lose (HCLL) conditions in OCD and HV. **Panel B.** Flanker task. Mean response time (RT) for congruent and incongruent conditions for OCD and HV. Error bars represent SEM.

*Relationship between behavioural tasks*

There were no correlations between the parameter estimates of the four behavioural tasks (p-values are reported in Table 4).

## DISCUSSION

We show that patients with OCD compared to healthy volunteers were more cautious in weighing the alternatives with enhanced evidence accumulation for the visual perceptual task but not the probabilistic decision task. The standard behavioural analyses emphasized a role for slower decisions for higher perceptual uncertainty in OCD subjects compared to healthy volunteers. Similarly, higher severity of compulsivity scores was associated with greater impairments in evidence accumulation with higher motion detection thresholds, slower performance and higher cognitive investment in ambiguous trials. In the HDDM analysis, OCD subjects had higher decision boundaries, or evidence needed to make a decision,

particularly in high uncertainty. However, the HDDM analysis also emphasized a slower drift rate in OCD patients particularly under low uncertainty. The drift rate is a measure of the speed of accumulation of evidence over time and represents the strength or quality of evidence from the stimulus entering the decision process (Ratcliff & McKoon, 2008). These findings emphasize the compatibility and added value of the standard behavioural and computational model analyses. Our findings further highlight that by emphasizing speed (in the Cost condition of the RDMT), OCD subjects normalized their decision reaction time and reversed the difference in decision boundaries, thus improving evidence accumulation and speed and shifting away from a pathological internal monitoring without compromising accuracy.

*Random dots motion task*

Several features make this low-level perceptual task an optimal paradigm to study evidence accumulation in OCD. First it has been extensively investigated in primate studies and healthy humans (Gold & Shadlen, 2007; Heekeren et al., 2008; Newsome et al., 1989). Second, by using neutral and non-threatening stimuli, decision accumulation is assessed without confounding OCD-relevant stimuli. Third, in studies manipulating dot motion viewing time, decision accuracy improved as a function of motion-viewing duration (Burr & Santoro, 2001; Gold & Shadlen, 2007), contrary to other perceptual tasks in which the two were unrelated (Uchida, Kepecs, & Mainen, 2006). Thus, RDMT reaction time is representative of decision making (Gold & Shadlen, 2007). Fourth, patients with OCD have reported difficulties with high-level perceptual tasks (Rey-Osterrieth Complex Figure Test (Savage et al., 1999), and biological motion or body perception impairments (Jung et al., 2009; J. Kim et al., 2008; Shin et al., 2013)) but no differences in low-level visual processing (RDMT) have been observed (J. Kim et al., 2008). We further confirm that visual detection thresholds were similar between groups. Finally, this task controls for working memory by using a single stimulus presentation. Other perceptual paradigms assessed in OCD have studied working memory (Lambrecq et al., 2013), perceptual visual deficits (J. Kim et al., 2008) and uncertainty (Rotge et al., 2008; Rotge et al., 2012;

Toffolo, Van den Hout, Hooge, Engelhard, & Cath, 2013; M. A. van den Hout et al., 2009) without specifically focusing on the degree of uncertainty or evaluating decision formation. Many of these tasks did not control for working memory which maybe particularly relevant in OCD given reported working memory (Chamberlain, Fineberg, Blackwell, et al., 2007; Morein-Zamir et al., 2010) and memory confidence or distrust impairments (Dar, 2004; Hermans et al., 2008; M. A. van den Hout et al., 2009). Thus, the RDMT measures cognitive evidence accumulation without the relevant confounders of working memory or high-level visual perception.

Probabilistic reasoning studies in OCD have previously shown inconsistent results (Fear & Healy, 1997; Jacobsen et al., 2012; Pelissier & O'Connor, 2002; Volans, 1976). Perceptual decision tasks may be more ecologically valid as many daily decisions are based on sensory ambiguity rather than probabilistic evaluations. Perceptual tasks have been applied to healthy volunteers with high OC scores (a visual search task focusing on absent targets with presumably greater uncertainty (Toffolo et al., 2013) and a perceptual colour judgement task), showing prolonged RT and increased indecisiveness along with greater feedback requests (Sarig, Dar, & Liberman, 2012). Here we focused specifically on OCD patients. Our study also controlled for possible related explanations related to conflict monitoring, by considering both perceptual and probabilistic types of conflict. We did not find any group differences in the Flanker task or probabilistic selection task or any correlations between conflict outcome measures and the RDMT. Healthy individuals with high compared to low OC scores tested with the probabilistic selection task have shown diminished error related negativity in dACC activity whereas motor response competition errors tested with the Flanker task were associated with greater rostral ACC reactivity (Grundler, Cavanagh, Figueroa, Frank, & Allen, 2009). We did not study the neural role for response conflict as it was out of the scope of our study.

*The role of uncertainty*

The standard behavioural and HDDM analyses were highly consistent. Our findings suggest that situations of high uncertainty (e.g. exposure to biological fluids from an ill individual) may induce OCD subjects with contamination fears to gather excessive evidence (e.g. compulsive hand washing) to support their decision (e.g. that their hands are no longer contaminated). The HDDM analysis further extend these findings showing that under low uncertainty, OCD subjects had slower drift rates towards the decision boundary, or poorer quality of evidence from the stimulus. The context of low uncertainty is perhaps more reflective of OCD in which the objective uncertainty (e.g. exposure to household items or after repeated hand washing) is indeed very low. Using a delayed matching-to-sample task with unrestricted choice verification, poor insight triggered greater checking behaviours in OCD patients, which indexed uncertainty (Jaafari et al., 2011; Rotge et al., 2008). However, these studies did not manipulate levels of uncertainty. OCD subjects have also shown greater explicit subjective ratings of uncertainty for low but not higher uncertainty evidence in a probabilistic reasoning task (Stern et al., 2013). In this task, participants viewed two decks containing equal but opposite ratios of red and blue cards and had to decide, by observing four draws with fixed evidence, from which of the two decks a sequence of cards was being selected. The subjective levels of certainty were assessed during intermediate levels of evidence. We measured subjective decision confidence at all levels and did not find any differences. Some (Dar, 2004; Stern, Welsh, et al., 2012) but not all studies (Sarig et al., 2012) have shown impairments in subjective certainty in OCD. Patients have also been shown to be more risk averse under low risk (defined as variance with a lower difference between positive and negative OCD-relevant outcomes) as compared to high risk situations (defined as greater difference between outcomes). Although our current study has broad similarities on the role of low uncertainty, we focused on neutral stimuli under uncertainty (in which probabilities are unknown) as compared to OCD-relevant outcomes of risk (in which the probabilities are known).

Although OCD checking may be motivated by the wish to reduce uncertainty, checking compulsions appear to have the opposite effect, fostering doubt, greater uncertainty and meta-memory problems (Boschen & Vuksanovic, 2007; Coles, Radomsky, & Horng, 2006; Hermans et al., 2008; Radomsky, Gilchrist, & Dussault, 2006; M. van den Hout & Kindt, 2003a, 2003b). This paradoxical effect might be a consequence of deficits in memory confidence, which ironically appears to result from the checking behaviour itself (Constans, Foa, Franklin, & Mathews, 1995; Dar, 2004; Hermans et al., 2008; Hermans, Martens, De Cort, Pieters, & Eelen, 2003; Lambrecq et al., 2013; Rotge et al., 2012; M. A. van den Hout et al., 2009). OC-like perseveration itself has been suggested to impair memory and perception distrust (Hermans et al., 2008; M. A. van den Hout, Engelhard, de Boer, du Bois, & Dek, 2008; M. A. van den Hout et al., 2009). For instance, prolonged visual attention to stimuli provokes feelings of dissociation and uncertainty about perception (M. A. van den Hout et al., 2008; M. A. van den Hout et al., 2009). Thus, shifting the attentional focus may secondarily improve perceptual uncertainty and may have therapeutic relevance.

*Speed-accuracy tradeoff*

Here we show that by emphasizing speed over accuracy we eliminate and indeed reverse differences in evidence accumulation with no differences in accuracy between groups. The drift rate hastens and decision boundaries decrease across all subjects. However, although OCD subjects still have slower drift rates under low uncertainty conditions, they markedly improve the evidence accumulation with *lower* decision boundaries compared to healthy volunteers. In other words, although patients still implicitly experienced the quality of the evidence poorer and were slower to reach the decision boundary, despite this, they required less evidence to make a decision and did not sacrifice accuracy. Similarly, we show that OCD subjects and healthy volunteers were equally sensitive to monetary cost on evidence accumulation in the probabilistic task. Thus, patients are sensitive to a monetary penalty on information sampling in both the perceptual and probabilistic domains. Our results contrasts with

a study with the Information Sampling Task showing that patients with OCD were not sensitive to points penalty for evidence accumulation (Chamberlain, Fineberg, Blackwell, et al., 2007) which may be less salient than monetary penalty. There are also other reported differences between the Information Sampling Task and other probabilistic reasoning tasks (Huddy et al., 2013).

Our results suggest that in OCD subjects, explicit salient incentives on evidence accumulation (speed or information sampling) may be implicitly incorporated into and shift the internal cost-benefit signals during the evidence accumulation process presumably shifting away from pathological internal monitoring. The cost condition of the RDMT had both penalties and incentives for speed although sensitivity to penalty for evidence accumulation was demonstrated in the probabilistic reasoning task. We also did not find an influence on outcome parameters following positive or negative feedback further emphasizing a reliance on internal signals rather than external feedback. These findings dovetail with Rotge *et al* who show decreased sensitivity to external feedback in OCD subjects (Rotge et al., 2012).

*Standard behavioural and computational analyses*

We emphasize the compatibility and added value of the standard behavioural and computational analyses. The former, which conventionally focus on successful trials, highlighted a role for high uncertainty. This was seen in a logarithmic regression analysis commonly used in visual processing studies, which accounts for visual detection thresholds and fit across all coherence levels for successful trials. Similarly, HDDM which models both successful and unsuccessful trials, showed greater decision boundaries, or evidence needed to make a decision, which was particularly enhanced under high uncertainty. Drift diffusion models of decision-making suggest that a speeded choice between two options is made when the accumulated evidence reaches a critical decision boundary (Ratcliff & McKoon, 2008; Ratcliff, Van Zandt, & McKoon, 1999; Usher & McClelland, 2001). HDDM has the potential to characterize the mechanism underlying these results by estimating the latent

parameters, drift rate and decision boundaries based on the distributions of RT for both correct and incorrect trials (Wiecki et al., 2013).

The inclusion of incorrect trials in the HDDM analyses may also be relevant. In OCD subjects, incorrect trials as assessed in conflict tasks using ERP measures are associated with a robust enhancement in error related negativity whereas correct trials are associated with a weaker increase in correct related negativity (Endrass et al., 2008). This enhanced monitoring of incorrect responses may also be reflected in the implicit assessment of the evidence quality, which may be more relevant in ambiguous or low uncertainty situations.

*Conclusion*

Compulsive behaviours in OCD may be an attempt to accumulate sufficient evidence to commit to a decision and may be influenced by the degree of uncertainty. Indecisiveness in OCD may also be more related to perceptual distrust rather than memory distrust. Our results highlight the differential role of implicit incentives and external feedback in decision formation in OCD. We emphasize that OCD subjects are sensitive to monetary incentives emphasizing speed in evidence accumulation, shifting the speed-accuracy tradeoff away from the pathological internal monitoring without sacrificing accuracy. This capacity to shift may reflect mechanisms underlying cognitive behavioural therapeutic approaches. That STN DBS has been shown to influence this task in patients with Parkinson's disease (Green et al., 2013) suggests a potential mechanism by which STN stimulation may improve symptoms in OCD subjects.

# Chapter 3

## Corticostriatal dissociation during symptom provocation in Obsessive Compulsive Disorder

**ABSTRACT**

Intrusive thoughts and compulsive urges to perform stereotyped behaviours are typical symptoms of Obsessive Compulsive Disorder. Emerging evidence implicates a cognitive bias towards habit formation at the expense of goal-directed performance in OCD. In this study, we developed a novel individualized ecologically valid symptom provocation design: a live provocation fMRI paradigm with synchronous video-recording of behavioural avoidance responses. By pairing symptom provocation with online avoidance responses on a trial-by-trial basis, we sought to investigate the neural mechanisms leading to the compulsive avoidance response. In keeping with the model of habit formation in OCD, we hypothesized that OCD would be associated with lower activity in regions implicated in goal-directed behaviours and higher activity in regions implicated in habitual behaviours. Fifteen OCD patients and fifteen healthy control subjects participated in an fMRI task. Online stimuli were individually tailored to achieve effective symptom provocation at neutral, intermediate and strong intensity levels. During the symptom provocation block, the participant could choose to reject or terminate the provoking stimuli resulting in cessation of the symptom provocation. We thus separately analysed the neural correlates of symptom provocation, the urge to avoid, rejection and relief. Strongly symptom-provoking conditions evoked a dichotomous pattern of deactivation/activation in patients, a brain pattern not observed in healthy subjects: a deactivation of caudate-prefrontal circuits accompanied by hyperactivation of putaminal regions. This finding suggests a dissociation between regions engaged in goal-directed and habitual behaviours. The putaminal hyperactivity during patients' symptom provocation preceded subsequent deactivation during avoidance and relief events, indicating a pivotal role of putamen in regulation of behaviour and habit formation in OCD. Effective connectivity analysis identified the ventromedial prefrontal cortex/orbitofrontal cortex as the main structure underlying this circuitry confirming its role in modulating compulsivity in OCD. These findings suggest an imbalance in circuitry underlying habitual and goal-directed action control that may

represent a fundamental mechanism underlying compulsivity in OCD. Our results complement current models of symptom generation in OCD and may enable the development of future therapeutic approaches that aim to alleviate this imbalance.

*Keywords*: Live symptom provocation, Obsessive-Compulsive Disorder, Causality, Imbalanced circuitry, Caudate/Putamen.

## INTRODUCTION

A prominent feature of Obsessive Compulsive Disorder is the propensity to perform compulsive behaviours despite negative consequences. OCD has been conceptualized as a disorder of self-control and behavioural inhibition (Milad & Rauch, 2012; Robbins et al., 2012). Data from symptom evocation and provocation studies in OCD show hyperactivity of the orbitofrontal, dorsolateral prefrontal, anterior cingulate cortices, caudate, insula and amygdala (Adler et al., 2000; Baioui et al., 2013; Breiter et al., 1996; Hendler et al., 2003; Mataix-Cols et al., 2004; McGuire et al., 1994; Nakao et al., 2005; Rauch et al., 1994; Schienle, Schafer, Stark, Walter, & Vaitl, 2005; Simon, Kaufmann, Kniesche, Kischkel, & Kathmann, 2013; Simon et al., 2010). These studies support a neurobiological model of OCD suggesting an important role for dysfunctional loops in cortico-striato-thalamo-cortical circuits (Graybiel, 2008; Milad & Rauch, 2012) as well as the involvement of limbic structures to the aetiology of this disease (Admon et al., 2012; Simon et al., 2013; Simon et al., 2010; Stern, Welsh, et al., 2012). Symptom provocation studies commonly use exposure to words or images related to the symptoms and ask patients to recognize or recall contexts related to past symptoms (Baioui et al., 2013; Gilbert et al., 2009; Mataix-Cols et al., 2004; Nakao et al., 2005; Schienle et al., 2005; Simon et al., 2010). Some studies employed mental imagery and others exposed patients to a direct provocation, using real sensory stimulation (e.g. tactile exposure to triggers such as contaminated objects). However, these evocation and provocation studies have been studied separately from the compulsive avoidance behaviour. In this study we used a real-time tailored provocation task paired with online behavioural avoidance responses. Using a clearly defined chain of symptomatic events on a trial-by-trial basis we aimed to investigate the common neural correlates of symptom generation and mechanisms leading to the compulsive avoidance behaviour.

Studies of OCD point towards hyperactive regions implicated in action monitoring and response conflict such as the anterior cingulate cortex (ACC) (Menzies et al.,

2008; Milad & Rauch, 2012) and a shift from goal-directed to habitual behaviours implicating cortico-striatal circuitry (Gillan et al., 2011). Deficits in error monitoring (Melcher, Falkai, & Gruber, 2008; Page et al., 2009b; Rao, Arasappa, Reddy, Venkatasubramanian, & Reddy, 2010; Schlosser et al., 2010), response inhibition (Bannon, Gonsalvez, Croft, & Boyce, 2002; Morein-Zamir et al., 2013; Page et al., 2009b), task switching (Chamberlain, Fineberg, Menzies, et al., 2007) and reversal learning (Chamberlain et al., 2008) indexed by cognitive tasks such as Stroop, Go/No Go, Stop-Signal, Reversal Learning Intra/Extradimensional Shift tasks, have been consistently shown in OCD. This behavioural inflexibility, which has been associated with abnormal activity of a subregion likely within the rostral part of dACC and OFC (Fitzgerald et al., 2010; Fitzgerald et al., 2005; Maltby, Tolin, Worhunsky, O'Keefe, & Kiehl, 2005), may be closely related with difficulties to quickly shift between goal-directed and habitual behaviour strategies (Shenhav, Botvinick, & Cohen, 2013). An incongruent or conflicting stimulus context requires inevitably more cognitive monitoring than a congruent one, which can easily be processed automatically, because no conflict is involved (Shenhav et al., 2013). The studies by Gillan and colleagues suggesting a bias towards habit formation at the expense of goal-directed performance in OCD patients provide good evidence for this duality between controlled and automatic processes (Gillan et al., 2013; Gillan et al., 2011).

The dichotomy between goal-directed and habitual behaviours has been extensively studied in rodents (B. W. Balleine et al., 2007; Dias-Ferreira et al., 2009; Dickinson, 1985; Dickinson & Balleine, 1993; Yin et al., 2006). According to this dual-system model, different behavioural strategies are used to respond to environmental demands and it is the ability to shift between them that enables successful decisions (B. W. Balleine, 2007). The goal-directed system encodes actions that are performed to achieve specific outcomes, whereas the habitual-system drives action selection based on stimulus-response associations (Dickinson & Balleine, 1993). The goal-directed system is vital for responding to permanent changes in the environment but

it is effortful to sustain its activity because it demands continuous monitoring of the environment. The habitual system is more efficient but can lead to behavioural inflexibility in case of over-learned stimulus associations (Adams, 1982). It has been suggested that rodent cortico-striatal circuits involving prelimbic cortex (B. W. Balleine & Dickinson, 1998) and dorsomedial (B. W. Balleine et al., 2007) striatum are implicated in goal-directed actions whereas dorsolateral striatum (Yin et al., 2006) is involved in habit formation. Recent studies have highlighted the homologies between animal and human physiology of action control (B. Balleine & O'Doherty, 2010; de Wit & Dickinson, 2009; E. Tricomi, Balleine, & O'Doherty, 2009b).

Here we used a novel symptom provocation design focusing on individualized real-time multisensory exposure with greater ecological validity to provoke compulsive behaviours. We measured, on a trial-by-trial basis, patient's avoidance responses thus linking the provocation to the compulsive avoidance behaviour. We compared the effects of healthy controls and OCD patients' provocation at variable levels of intensity, using baseline control blocks with silent counting. We then carried out a functional connectivity analyses with seed regions chosen for Granger causality analysis to identify direction of interactions in the network implicated in impairment in response control and habit formation.

In line with the goal-directed/habitual behaviour dichotomy account and with the recent suggestion that compulsivity in OCD might arise from excessive avoidance habit formation that is related to a subjective urge to respond (Gillan et al., 2013), we hypothesize that OCD would be associated with a decrease in caudate activity implicated in goal-directed behaviours and an increase in putaminal activity implicated in habitual behaviours. This simple dichotomy is well known in the motor and action control domains in neurological conditions such as Parkinson disease (PD). A recent study (Hadj-Bouziane et al., 2012) addressed the idea that goal-directed behaviours are predominantly caudate-dependent whereas habitual responses are primarily putamen-dependent, at advanced PD stages, where dopamine

depletion is greater in the putamen than in the caudate nucleus. The emergence of habitual responses was more vulnerable to the disease than the early phase of learning dominated by goal-directed actions, in line with the hypothesis. Our symptom provocation paradigm was designed to capture such imbalances using direct measures of avoidance responses modelled as compulsive actions.

## MATERIALS AND METHODS

### Participants

Fifteen OCD patients and 15 healthy control (HC) subjects matched for gender, age and years of education (OCD: 8M/7F; mean age = 32.3, SD ± 9.02; mean years of education = 13.7, SD ± 3.7; HC: 8M/7F; mean age = 31.0 SD ± 8.9; mean years of education = 15.0, SD ± 3.4) participated in this study. Control subjects were recruited from the community, were unmedicated and had never suffered from a psychiatric illness. OCD patients were recruited from the Hospital of University of Coimbra. Diagnoses were established by a psychiatrist and clinical psychologists using the Structured Clinical Interview for the Diagnosis of DSM IV psychiatric disorders and the Anxiety Disorders Interview Schedule for DSM-IV (ADIS-IV) (DiNardo, Brown, Barlow, & Psychological, 1994). To assess the severity and characteristics of OCD symptoms, each patient completed the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS). All patients scored >18 indicating at least moderate severity (mean score = 26, SD ± 6.20). Depression scores were obtained with the Beck Depression Inventory (BDI) (Beck et al., 1961) (mean score = 13.8, SD ± 8.7). Anxiety was measured using the Hamilton Anxiety Rating Scale (Hamilton, 1959) (mean score = 7.2, SD ± 3.51). Exclusion criteria included the presence of comorbidity with other Axis I diagnoses, neurological disorders, history of drug, alcohol addiction and any serious medical condition. Although 5 of our patients scored higher than 16 in the BDI scale, this was not sufficient, based on the clinical interview, to establish a diagnosis. Nevertheless, we used this measure as a

covariate in the analysis. All patients had initiated Cognitive Behavioural Therapy, and fourteen patients were on antidepressant and/or anxiolytic medication. A handedness inventory (Oldfield, 1971) was administered and average laterality quotient was 95.

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Commissions of the Faculty of Medicine of the University of Coimbra. Written informed consent was obtained after a detailed explanation of the study and after a pre-experimental interview to tailor the experimental conditions to each participant.

**Experimental paradigm: symptom provocation task**

We used a repeated-measures crossover design and provided in addition a comparisons of the patterns generated by both groups (OCD patients and healthy subjects). This design is an optimal approach to assess the effects of an intervention within the same population (Hedayat & Yang, 2005) (e.g. symptom provocation versus neutral provocation). We used individually tailored stimulation, which has been shown to be effective for symptom provocation (Baioui et al., 2013). For patients, the choice of stimuli resulted from a pre-experimental interview between the patient, two members of the experimental team (PB and MCB), a clinician (JR) and a psychotherapist (FP), to identify the maximum degree of natural symptom provocation acceptable to each patient. Thus, the online stimulation was individually tailored both in the type of stimuli and the degree of stimulation. For healthy controls, the stimuli included the most salient patients' set of stimuli (also likely to perturb healthy subjects due to their generic intrusive nature, and new ones designed to cause similar intrusive thoughts (such as contamination fears). This strategy was preferred to a complete patient-control matched experiment because many stimuli identified to trigger symptoms in patients would not have any impact in healthy controls.

The experiment consisted of 30-second blocks of provocation of variable intensity, then 30 seconds of a silent counting baseline followed by a 6-second inter-trial interval for the control motor response (Figure 1C). This sequence was repeated 12 times per session, for a total of four sessions in each participant. The provocation stimuli were delivered at three intensity levels (neutral, intermediate or strong) in pseudo-randomized order. The pseudo-randomization was based on predefined session lists prescribing an arbitrary order of stimulation by balanced perturbation of the three intensity levels (four neutral, four intermediate and four strong provocation blocks) with the restriction that no two adjacent stimulation blocks offered the same intensity level. Thus, a total of 48 blocks of provocation were delivered to each participant, 16 at each intensity level. Within a session, the stimuli at each intensity level were held constant, but between the four sessions, four different stimuli per intensity level were used to avoid habituation over sessions.

The silent counting task baseline between the provocation blocks was intended to allow the patients to shift their focus of attention away from the previous provocation stimuli. By engaging in a neutral task the patients were distracted from any ruminative or obsessive thoughts triggered by previous stimuli. In the counting task, participants observed a random sequence of two numbers (1 and 2) over a 30-second period and were instructed to count the number of times the number 1 appeared. Subjects then reported the answer from one of two options presented on the screen during the 6-second inter-trial interval.

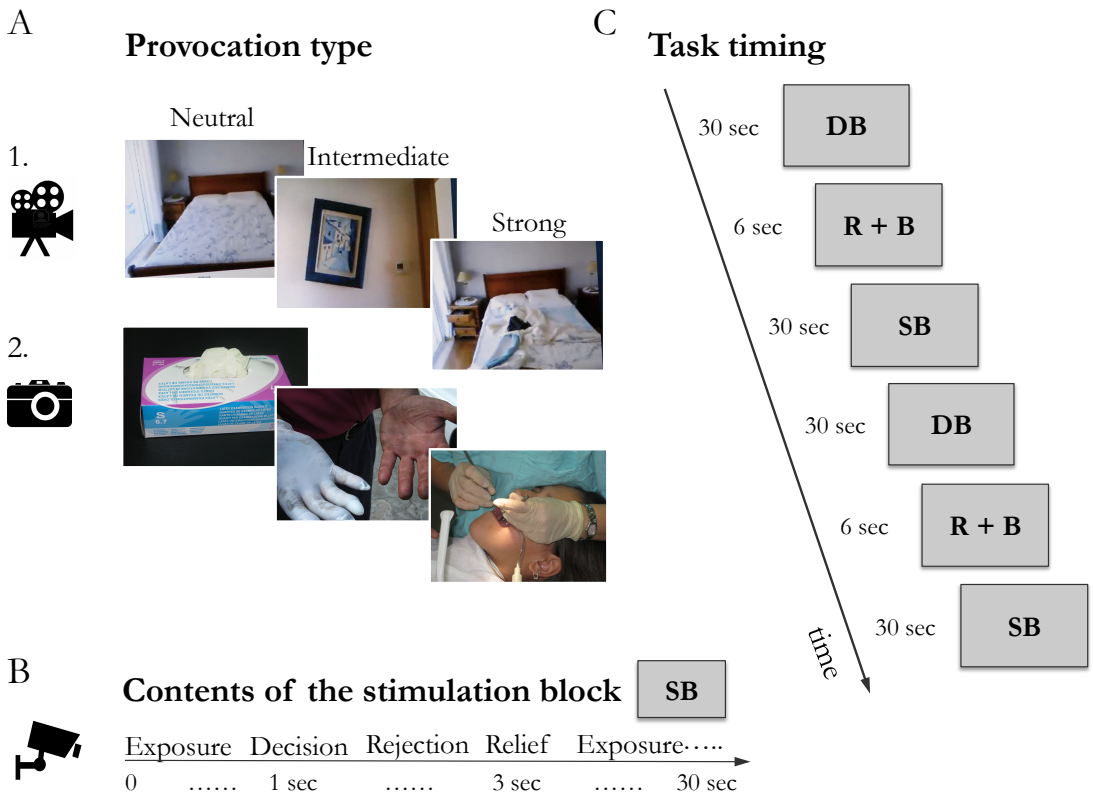



**Figure 1**. **Panel A.** Examples of the two different modalities used for the symptom provocation task. **1.** Online video-streaming of scenarios from the patients' homes (remote provocation). Strong blocks were live videos capturing the experimenter disorganizing the patients' homes while neutral videos showed the rooms like the patients had left them. **2.** shows the tactile modality in which the experimenter directly delivered the provoking stimuli to the patient's hand. In this case, the patient would see an image of a glove that she would touch. The visual presentation was intended to inform the patient about the type of stimuli delivered to the hand. **Panel B.** Contents of the stimulation block. Both modalities used a video-recording system to record and timestamp the exposure, decision to reject, rejection and relief events within the stimulation blocks. **Panel C**. Task timing. The experiment comprised 30 sec of provocation blocks of variable intensity (SB – stimulation blocks), 30 sec of a baseline-counting task (DB – distractive baseline) and 6 sec of response plus baseline block (R+B – response plus baseline). This sequence was repeated 12 times per run, for a total of 4 runs in each patient.

During the provocation blocks, participants were instructed to spontaneously signal if they were no longer able to tolerate the provocation stimulus. Using a single hand gesture, participants would signal to the experimenter to cease the exposure. The provocation would then cease for a 3-second period of relief, as described below, after which exposure would return. When the exposure continued, participants were allowed to reject it again (Figure 1B). Thus, depending on the number and duration of rejections, the number of provocation events presented within the 30-sec provocation blocks would vary between sessions and subjects (for details, see Results section). The timing of these rejection events was synchronously acquired using a MRI compatible video recording system. We explicitly discussed with the participant before the study to use this hand gesture only when they were no longer able to tolerate the provocation. As expected, rejection events did not occur in healthy controls and in patients during neutral blocks. They occurred mainly in patients during the strong provocation blocks**.** In patients, some of the provocation events in the intermediate condition had to be re-labelled after the exposure. This happened occasionally when a stimulus was rejected during a planned intermediate provocation block. In the subsequent analyses, the stimulation in that block was labelled as strong to reflect the real experience of the patient during the provocation. No strong or neutral blocks were relabelled. Rejection events therefore indicated that symptom provocation was effective, and the number of rejections inside a provocation block indexed how effective the provocation was perceived by the patient. Given that the number of events and its impact on the neural response is taken into account in the statistical model of the event related analysis, this added additional information to the block design analysis.

In healthy controls, the 3 intensity levels were defined based on the scores collected from a stimuli-rating scale.

There were two types of tailored provocation stimuli: tactile provocation near bore and visual provocation online (Figure 1A). In the near-bore provocation, for

example, a patient with biological contamination obsession and washing compulsions would touch with their left hand three different provocation stimuli of varying provocation intensity. During these provocations, the participant experienced live provocation with their left hand while visual stimuli were presented to indicate the level of provocation while in the scanner. The live provocation for this participant was as follows: Neutral - the patient touched clean and untouched gloves; Intermediate - the patient touched gloves, which had been categorized by the participant as potentially contaminated because they had been used by known individuals (e.g. the experimenter or the psychotherapist); Strong - the participant touched gloves that they believed to be biologically contaminated because they had been used by individuals who were ill or by unknown individuals in high risk jobs (e.g. dentists, nurses). The stimuli were placed in the participant's hand by the experimenter (PB) during the scanning session. A rejection hand gesture was accommodated by removal of the glove from the participant's hand followed by 3 seconds relief and disinfecting of the hand with an antibacterial wipe.

In other participants, to achieve a realistic and efficient provocation, we streamed online videos in real-time from the patients' homes. For example, for a patient with obsessions for symmetry, organization and cleanliness, they watched real-time videos from within their homes in which the experimenter (PB) would disorganize and litter the home. For this procedure, custom Matlab software was used to capture online footage using Internet and synchronous Skype connection. Such real-time video exposure also allowed online rejection requests. Rejection hand gestures followed the same design as near bore provocation. For details about the type of provocation used for each patient, see Table 1. Healthy subjects underwent the tactile provocation near bore type.

The visual stimulation consisted of natural scenes of similar complexity for all subjects. Visual provocation stimuli always contained a scene with at most one

provoking agent. All visual stimuli were presented at high contrast levels and had identical durations.

In summary, participants were exposed to individualized provocation stimuli of differing intensity (neutral, intermediate and strong) in a mixed block-event related design in which individual rejection events were video-recorded and time-stamped. Rejection events occurred when participants could no longer tolerate the provocation and modelled the compulsive or avoidance behavioural response. This allowed the analysis of the provocation stimuli, the decision to reject, the rejection event and the relief period. This design involved intensive patient interviewing and preparation, and it required strict control for recording artefacts caused by movement inside the scanner.

**Table 1.** Symptom manifestation and experimental design for each subject.

| Patient # | Symptom manifestation | Individually Tailored Provocative Task[1] |
|---|---|---|
| 1 | Contamination | Direct touch by a videorecorded intervening person with removal upon request. |
| 2 | Contamination | Direct touch with an object placed by a videorecorded intervening person with removal/cleaning upon request. |
| 3 | Checking, symmetry & ordering | Visual and tactile exposure with objects placed by an intervening videorecorded person. |
| 4 | Contamination | Direct touch with an object placed by a videorecorded intervening person with removal/cleaning upon request. |
| 5 | Contamination | Visualization of real time videos (online) of own home with online contamination by remote experimenter with possibility for rejection/correction of exposure. |
| 6 | Checking, symmetry & ordering | Visualization of real time (online) videos of patient's home, with remote experimenter changing order and correcting upon request |
| 7 | Checking, symmetry & ordering; pathological doubts | Visualization of real time (online) videos of patient's home, with remote experimenter changing order and correcting upon request |
| 8 | Contamination | Visualization of real time videos (online) of own home with online contamination by remote experimenter with possibility for rejection/correction of exposure. |
| 9 | Contamination | Direct touch with an object placed by a videorecorded intervening person with removal/cleaning upon request |
| 10 | Obsessive ruminations, magical thinking, propitiatory rituals | Visualization of recent (same day) bad/catastrophic images/news related to patient's specific concerns. News were created by the researcher, to maximize tailoring to patient's concerns. |
| 11 | Obsessive ruminations, magical thinking, propitiatory rituals | Visualization of videos related to bad/catastrophic events with audio "counting down" numbers (from 10 to 0) to enhance symptoms. |
| 12 | Contamination | Direct touch with an object placed by a videorecorded intervening person with removal/cleaning upon request. |
| 13 | Contamination | Direct touch with an object placed by a videorecorded intervening person with removal/cleaning upon request. |
| 14 | Contamination | Direct touch with an object placed by a videorecorded intervening person with removal/cleaning upon request. |
| 15 | Contamination | Direct touch with an object placed by a videorecorded intervening person with removal/cleaning upon request. |

[1] Three levels, from neutral to strong, were used - behavioral avoidance possible for each event

**Data acquisition**

Visual stimuli were presented using Presentation software (Neurobehavioural Systems, Inc., Albany, CA, USA) and natural tactile stimuli were used with simultaneous videorecording. Custom Matlab software was used for synchronization with remote and local videorecording.

Participants were scanned in a 3T Siemens Magnetom TimTrio scanner, at the Portuguese Brain Imaging Network, using a 12-channel head coil. For each participant, and prior to functional runs, 160 anatomical slices were acquired with the following parameters: one T1-weighted (T1w) MPRAGE sequence, TR (repetition time)=2.3s, TE (echo time)=2.98ms, voxel size=1x1x1mm$^3$, FA (flip angle)=9º, FOV (field of view)=256x256. To minimize the motion of the subject's head during the study, foam padding was employed. fMRI data were acquired using BOLD contrast whole brain echo planar imaging (EPI). We used two slightly different protocols 1. (n = 5), TR=3s, TE=39ms, voxel size=2x2x3mm$^3$, 3mm-thick-slices with no inter-slice gap, with an in-plane matrix of 128x128 voxels, flip angle=90º, FOV=256x256, 39 interleaved axial slices, 295/run. 2. (n=10), TR=2s, TE=39ms, voxel size=3x3x4mm$^3$, 4mm-thick-slices with no inter-slice gap, with an in-plane matrix of 84x84 voxels, flip angle = 90º, FOV=256x256, 29 interleaved axial slices per volume, in a total of 420 volumes per run). The acquisition protocol was changed to improve connectivity analyses, for which a lower TR is advantageous.

**Image processing and data analysis**

Analyses were carried out using BrainVoyager QX 2.6 (Brain Innovation, Maastricht, The Netherlands). Pre-processing included intensity inhomogeneity correction, slice-scan-time correction, temporal high-pass filtering to remove low frequency drifts, realignment, and rigid-body transformation of data to the first image to correct for motion. Functional data were coregistered to anatomical data and subsequently transformed into Talairach space. A spatial smoothing using a Gaussian filter

(FWHM 4 mm) was performed. Four sessions were excluded from further analysis due to motion artefacts.

Statistical analyses were performed on individual and group data using a random effects (RFX) general linear model (GLM) to implement between and within subjects ANOVA. The design matrix was based on regressors separately created for each type of blocked conditions (baseline and neutral, intermediate and strong provocation) and event onset times derived from video recordings from each scan session. The time-stamped video recorded events were rejection onset time, rejection duration and relief periods. Additionally, decision to reject was defined as an event 1 sec before initiation of the hand gesture signalling rejection. In this way, block onset times were predetermined by the experimental design (Figure. 1C), whereas event onset times were based on the behavioural response of the participants during the stimulation (Figure. 1B). In order to account for hemodynamic delay and dispersion, each of the predictors was convolved with a double-gamma hemodynamic response function as implemented in BrainVoyager. Statistical maps were corrected for multiple comparisons using FDR correction and the cluster threshold estimator plug-in for BrainVoyager QX (Forman et al., 1995). Each map was first thresholded at $p < 0.05$ and then submitted to cluster threshold estimation based on a Monte Carlo simulation with 1000 iterations, which yields a value of $p < 0.05$ corrected for multiple comparisons.

Time course analysis was performed for patient's putamen due to its surprising results at event level. We first extracted the time varying BOLD response for left and right putamen based on the clusters found on the statistical GLM maps (Contrast: decision to reject>rejection events). To estimate the underlying neuronal signal, we deconvolved the hemodynamic response from the BOLD signal using the PPI module in SPM8. This procedure also removes confounds such as the DC component. We then characterized the individual event-related response as the average of sequences of estimated neuronal signal time-locked to the rejection event.

The plots show the average neuronal signal relative to rejection normalized across patients +/- SEM (Fig. 3B).

Finally, after localising the brain regions directly involved in OCD symptomatology, we ran an effective connectivity analysis by applying the Granger Causality Mapping (GCM) method (Roebroeck, Formisano, & Goebel, 2005). The purpose was to get information about the functional interactions between those brain areas, as well as information about the direction of these interactions in order to infer their causal relationship. Since GCM requires the specification of seed regions, after which measures of effective connectivity for all voxels in the brain are calculated in reference to the time course in the seeded clusters, several seed regions were individually created. These seeds were spheres of 3mm centred at the peaks of activation clusters obtained from the GLM analysis. The seed regions were selected based on their direct involvement in OCD symptomatology observed consistently in our block and event-related analyses, and consistent with previous studies in OCD reporting abnormal activation in these regions (Del Casale et al., 2011; Milad & Rauch, 2012). The resulting seed regions were: dorsal ACC (BA 24), vmPFC/OFC, Amygdala, Caudate head, and Putamen. RFX GCMs were first calculated for each individual patient. Statistical thresholds for these maps were computed using a bootstrap method (Roebroeck et al., 2005) with corrections for multiple comparisons based on false discovery rate ($q<0.05$) (Genovese, Lazar, & Nichols, 2002). A mean group GCM was then created, using t-tests, yielding effective connectivity information to the seed regions throughout the entire brain. The obtained granger causality maps pointed up which areas in the brain are influenced by activity in each seed and which areas whose activity influences the activation in the specified seed region.

## RESULTS

OCD patients performed rejection events during the strong provocation blocks. As expected, the neutral blocks did not evoke any rejection response confirming their role as control conditions. Healthy subjects did not perform rejection events. The presence of rejection events in patients allowed to divide the 30 sec Strong rejection blocks into Exposure, Rejection events and Relief periods. The Exposure event was further subdivided by separately assessing the 1 sec duration prior to the Rejection event, modelling the Decision to reject. The mean (SD) number of rejection events (submitted to random effects analysis) was 25.33 (6.20) and their mean (SD) duration was 2.14 (1.64) sec. Their coefficient of variation of 0.24 implies low variability in symptom provocation across subjects. It was expected that some subjects would exhibit higher number of rejection episodes than others, but our patients showed a sufficient number of rejections for statistical analysis, and across-subject variability was useful for random-effects analysis. The mean (SD) duration of the strong exposure (submitted to the event-related analysis) was 9.56 (5.83).

Brain activity was modelled both as a function of strong *blocks* containing symptomatic provocation as well as a function of the real-time presence of effective symptom evoking stimuli (*event* related analysis) (see Methods). Both approaches yielded converging results.

We first conducted a random effects block analysis of all 30 seconds of the strong>neutral blocks in both groups (healthy controls and OCD patients). The brain pattern was clearly different across groups. In patients, we identified hyperactivity of bilateral putamen, a caudal subregion of dorsal cingulate cortex (dACC in BA 24), insula, amygdala, parahipocampal gyrus and presupplementary motor area (preSMA) and a deactivation of vmPFC, *pregenual* cingulate cortex, dorsolateral prefrontal cortex and the head of the caudate nucleus (Figure 2A and

Table 2). In healthy subjects we only found insula activity and a deactivation of parietal areas and precuneus (see Figure 2B).

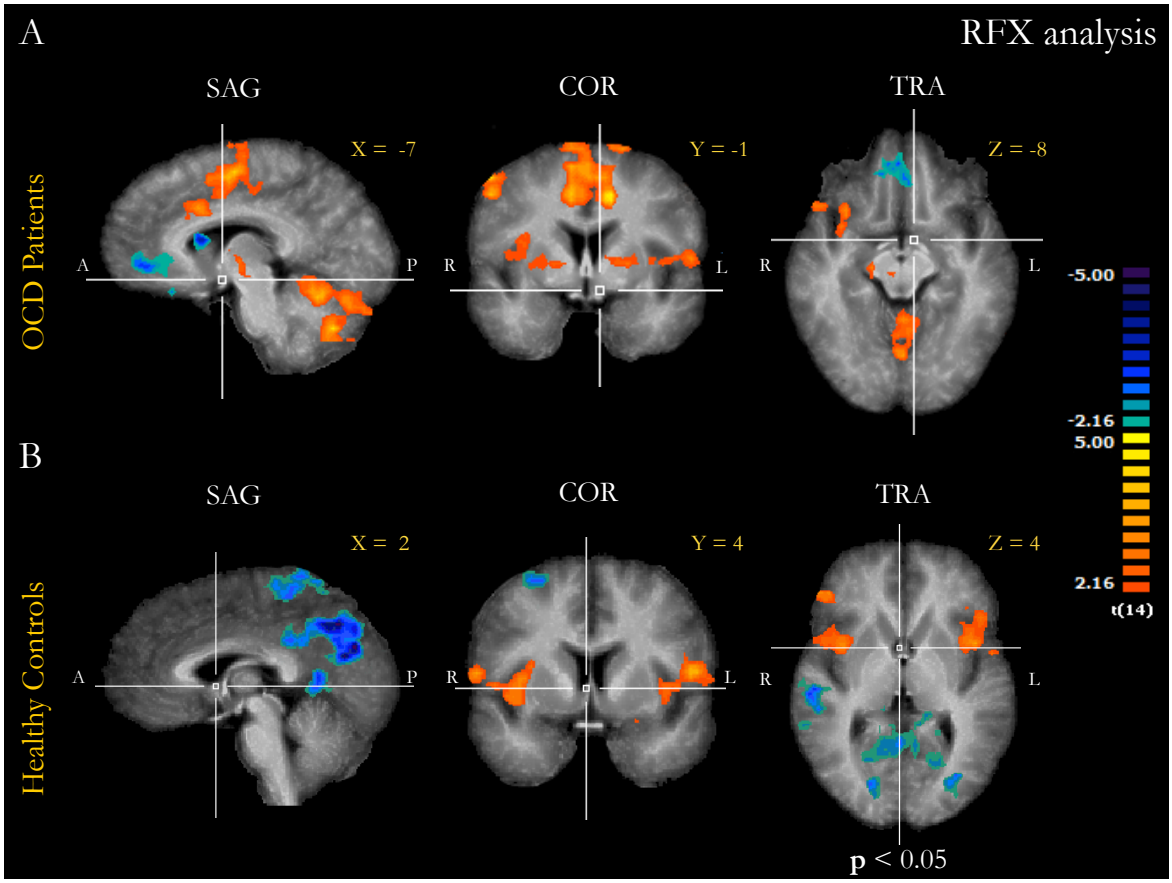



**Figure 2.** Random effects GLM analyses. Contrast: strong>neutral provocation blocks. **Panel A.** Patient group. Deactivation of ventromedial and medial frontal cortex and caudate structures, and hyper-activation of putaminal, caudal dorsal cingulate cortex and pre-supplementary motor cortex structures ($p < 0.05$, corrected for multiple comparisons using cluster threshold correction, minimum cluster size = 113 voxels). Peak deactivation coordinates (X,Y,Z): (**SAG**) left caudate (-7,10,15), left medial frontal cortex (-10,43,-3) and (**TRA**) right vmPFC/OFC (14,42,-4); Peak activation coordinates: (**SAG**) left caudal dACC, BA24 (-13,1,39), (**COR)** left pre-SMA (-7,-8,54), right pre-SMA (3,-5,54), right putamen (26,7,15) and left putamen (-22,-2,6). See Table 2 for details regarding peak voxel coordinates, cluster size, t and p values for random-effects analysis. **Panel B.** Healthy control group. Activation of insula and deactivation of parietal areas and precuneus ($p < 0.05$, corrected for multiple comparisons using cluster threshold correction, minimum cluster size = 87 voxels). Peak deactivation coordinates (X,Y,Z): (**SAG**) right precuneus (2,-74,27) and (**TRA**) right insula (37,7,-3) and left insula (-43,7,3).

**Table 2.** Peak voxel coordinates, cluster size and t and p values associated to several regions of the brain (RFX analysis) in the OCD patient group. Analyzed contrast: strong condition VS neutral condition ($p < 0.05$, corrected for multiple comparisons using cluster threshold correction, minimum cluster size = 113 voxels).

| Regions | Peak X | Peak Y | Peak Z | t | p | # voxels |
|---|---|---|---|---|---|---|
| Caudate LH | -7 | 10 | 15 | -3.963 | 0.001 | 476 |
| Caudate RH | 2 | 9 | 15 | -2.926 | 0.011 | 156 |
| Putamen (+ Globus Pallidus) LH | -22 | -2 | 6 | 3.019 | 0.009 | 223 |
| Putamen (+ Globus Pallidus) RH | 26 | 7 | 15 | 3.693 | 0.002 | 235 |
| Pregenual ACC LH | -10 | 34 | 3 | -3.435 | 0.004 | 276 |
| ACC BA24 LH | -13 | 1 | 39 | 5.267 | 0.000 | 601 |
| ACC BA24 RH | 5 | -8 | 45 | 4.462 | 0.001 | 1625 |
| vmPFC LH | -7 | 28 | -15 | -3.011 | 0.009 | 2764 |
| vmPFC RH | 14 | 42 | -4 | -3.729 | 0.002 | 3127 |
| Insula LH | -34 | 13 | 9 | 4.992 | 0.000 | 1804 |
| Insula RH | 32 | 16 | 12 | 3.301 | 0.005 | 849 |
| Thalamus LH | -13 | -14 | 3 | 3.258 | 0.006 | 453 |
| Thalamus RH | 5 | -11 | 3 | 4.871 | 0.000 | 913 |
| Supplementary motor area LH | -7 | -8 | 54 | 4.383 | 0.001 | 1964 |
| Supplementary motor area RH | 3 | -5 | 54 | 4.804 | 0.000 | 4274 |

We then performed an event related GLM analysis in the OCD group focusing on the Strong blocks separately modelling the following: (i) Exposure events (excluding Decision, Rejection and Relief events); (ii) the Decision to reject (modelled as one second prior to the rejection event); (iii) Rejection events modelling the avoidance behavioural response; and (iv) the Relief periods. These separate events are represented graphically in Figure 1B. Strong Exposure>neutral condition showed deactivation of the vmPFC, pregenual ACC, dorsolateral prefrontal cortex (dlPFC) and the head of the caudate, and hyperactivation of the caudal subregion of dACC (in BA24) and preSMA similarly found in the GLM block analysis. In contrast, the bilateral putamen, amygdala and insula activity seen in the GLM analysis above appeared to be involved only in the Decision to rejection, Rejection and Relief phases. During both the Decision to reject and Rejection events, patients showed

hyperactivation of the caudal (near to preSMA) part of dACC, amygdala, insula, putamen, globus pallidus and right caudate while vmPFC remained deactivated (Decision to reject+Reject events>neutral condition) (all p<0.05 corrected) (Figure3).

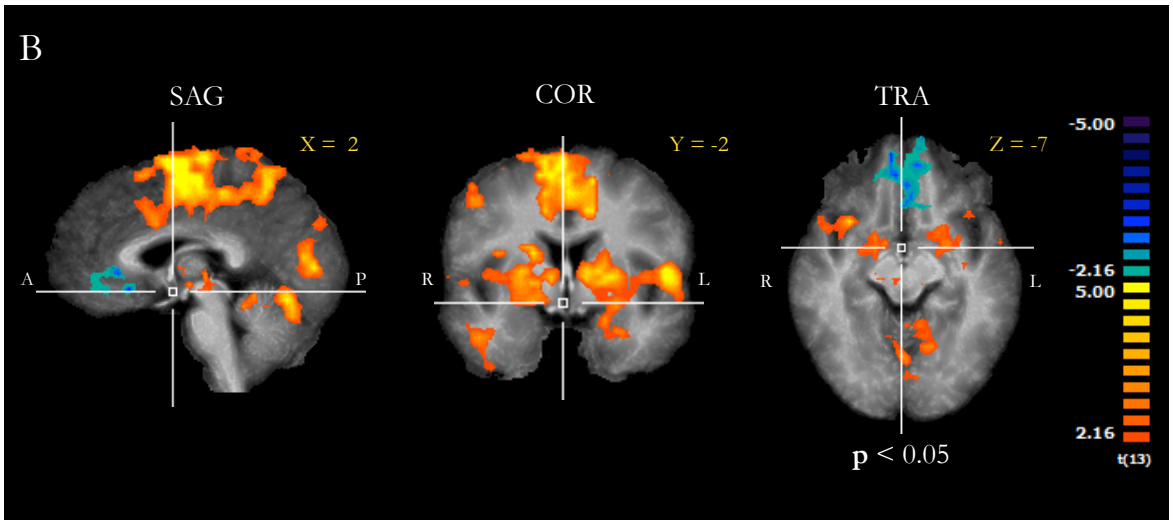



**Figure 3**. Random effects analysis at the event level in the OCD patient group. Hyper-activation of caudal dorsal cingulate cortex, amygdala, insula, putamen, globus pallidus and right caudate and deactivation of ventromedial prefrontal cortex. Peak de/activation coordinates (X,Y,Z): (**SAG**) left caudal dACC, BA24, (-10,19,30), right caudal dACC, BA 24, (2,7,30); (**TRA**) right amygdala (23,-8,-9), left amygdala (-22,-3,-10), right vmPFC/OFC (8,52,-6), left vmPFC/OFC (-7,46,-6): (**COR)** left putamen (-19,-2,6), right putamen (23,1,2), right caudate (17,1,18), right palidum (12,1,6), left palidum (-16,-2,9), left insula (-34,19,9) right insula (31,13,18). Contrast: decision to reject+reject events>neutral condition, p<0.05, corrected for multiple comparisons using cluster threshold correction, minimum cluster size = 104 voxels.

When these phases were considered separately, bilateral putaminal hyper-activation was only found in the Decision to reject phase (Figure 4, left panel A), deactivating immediately after the stimuli withdrawal (contrast: Decision to reject>Reject event) (p<0.05 corrected) (Figure 4, right panel A). During Relief periods (Relief>Neutral), patients showed activation in bilateral amygdala and deactivation in bilateral caudate and putamen (all p<0.05 corrected) (Figure 4C).

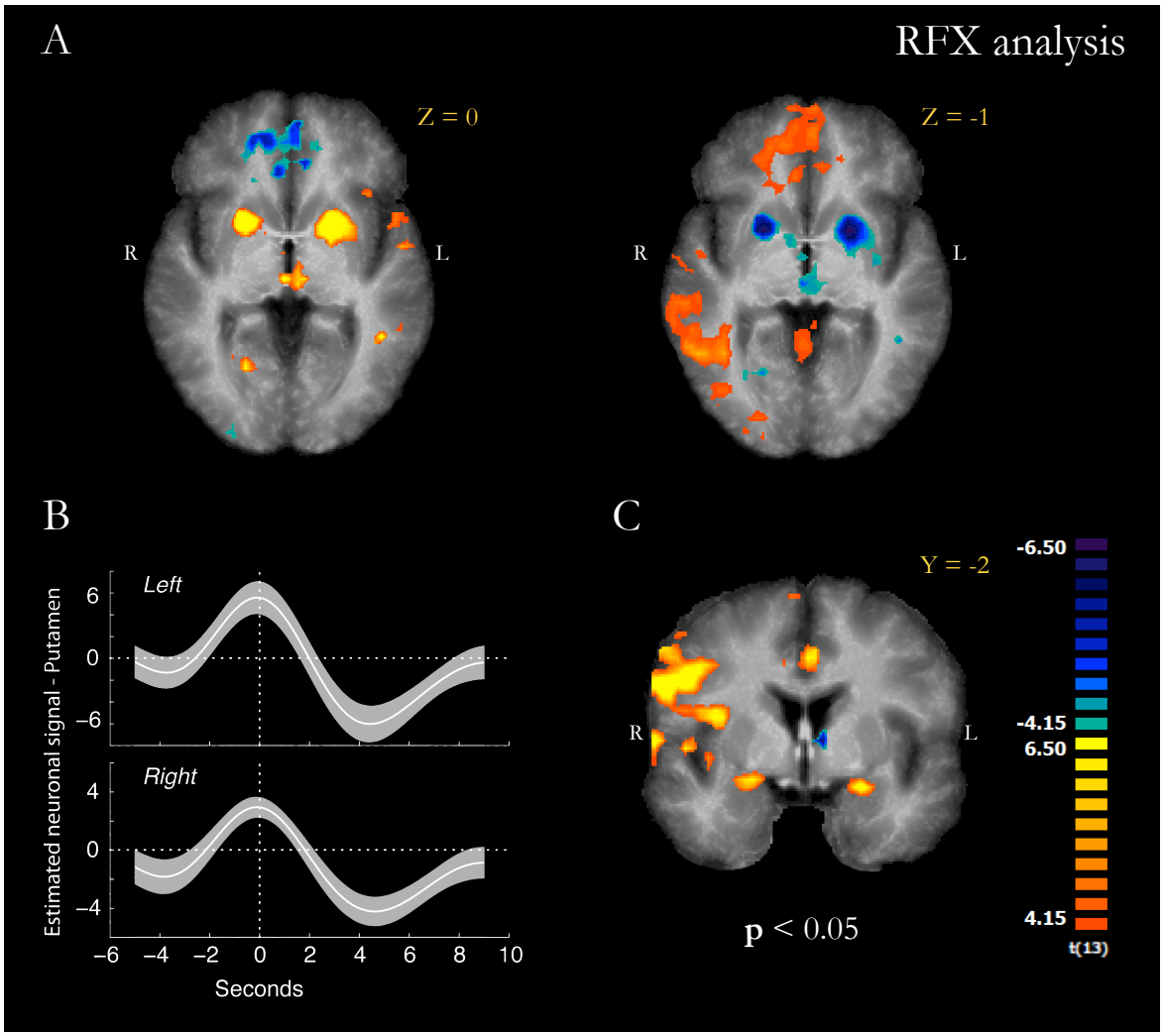
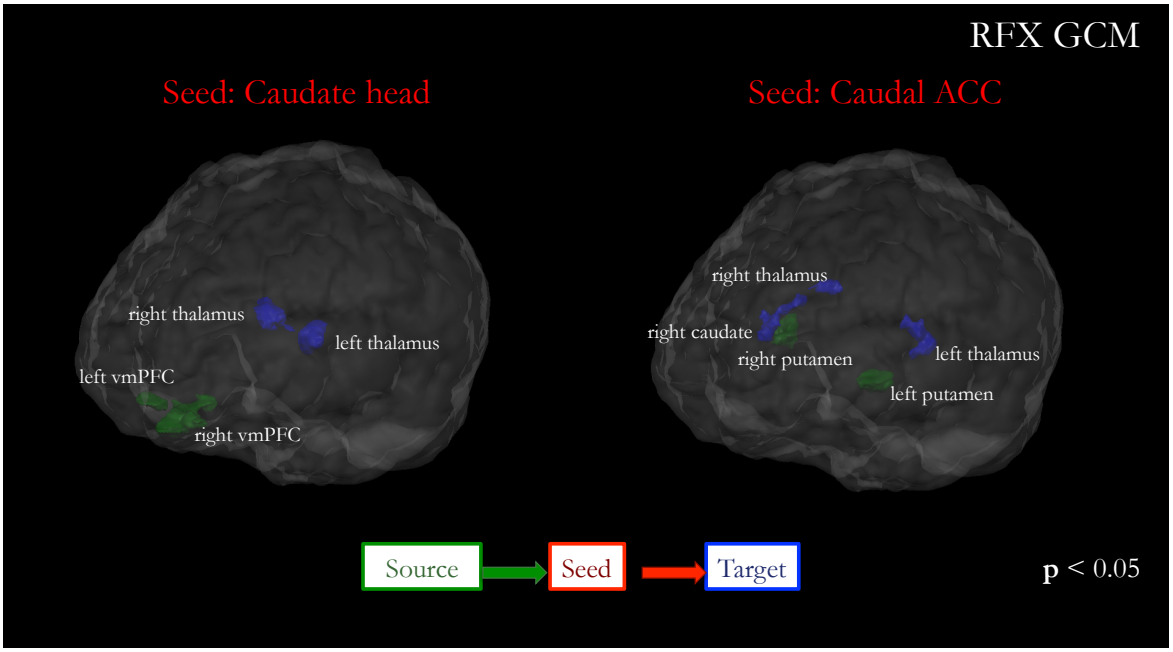



**Figure 4. Panel A (left)**. hyperactivation of bilateral putamen just prior to rejection events in the OCD patient group. Contrast: decision to reject >reject events, p<0.05, corrected for multiple comparisons using cluster threshold correction, minimum cluster size = 17 voxels. Peak activation coordinates (X,Y,Z): left putamen (-19,4,0), right putamen (20,4,3). **Panel A (right).** hypoactivation of bilateral putamen during stimulus withdrawal, p<0.05, corrected for multiple comparisons using cluster threshold correction, minimum cluster size = 8 voxels. Peak activation coordinates (X,Y,Z): left putamen (-19,4,0), right putamen (20,4,3). **Panel B.** Estimated neuronal signal from the putamen (left and right) obtained by hemodynamic deconvolution of the BOLD response. Zero represents the timing in which the rejection event started. **Panel C.** Activation of amygdala during relief periods. Peak activation coordinates (X,Y,Z): left amygdala (-25,1,-12) and right amygdala (17,-5,-9). Deactivation in bilateral caudate and putamen is not shown in this slice. Contrast: relief events >baseline, FFX GLM, p<0.05 FDR corrected, minimum cluster size = 103 voxels.

There were no correlations between the imaging results and the BDI and anxiety scores, suggesting that these covariates were not explaining our results.

Our random-effects analysis in the OCD group highlighted hyperactivity and deactivations of specific networks in response to Strong Exposure: 1) deactivation of ventromedial/orbitofrontal, pregenual frontal cortex and caudate structures, and 2) hyperactivation of putamen, amygdala, insula and dorsal caudal cingulate (BA24) and their neighbouring preSMA structures. Given the identification of this dichotomous circuitry, we ran a Granger causality analysis (Roebroeck et al., 2005). We selected seed regions based on the regions identified in the random-effects analysis to analyze a data-driven search for causal network activation: caudate head, vmPFC/ OFC (deactivated areas) putamen, amygdala and the posterior subregion of dACC (BA 24) (hyper-activated areas). The effective connectivity analysis identified two main structures causally influencing the circuitry shown in our provocation paradigm: the vmPFC causally influenced caudate head, amygdala and putamen and the putamen causally influenced the caudal part of ACC, that is near preSMA (Figure 5A).



◄ **Figure 5.** Connectivity analysis in the OCD group. Granger causality analysis shows that the head of the caudate (seed region from RFX GLM analysis) is causally influenced by ventromedial prefrontal cortex (vmPFC) and that the caudal dorsal cingulate cortex (seed region for analysis) is influenced by the putamen. Putamen and amygdala seed regions analyses are not shown in this figure but are referred in the results section.

## DISCUSSION

In this study we focused on the neural correlates of symptom generation in OCD, by using a novel symptom provocation stimulation task in which subjects were exposed to individually tailored stimuli in real-time and further paired with a measure of the avoidance response. We presumed this avoidance or rejection responses modelled the compulsive behaviour and that our task design would allow us to examine their neural correlates as well as their preceding and subsequent phases. Our study design thus allowed the dissociation of neural correlates underlying phases of exposure, the decision to perform the compulsive action, rejection and relief.

We identified a dichotomous pattern of activation/deactivation during exposure to symptom provocation specifically in patients with OCD: 1) decreased activity in ventromedial and dorsolateral prefrontal cortex and caudate head, and 2) hyperactivity of bilateral putamen, caudal cingulate cortex (BA24), pre-supplementary motor area and supplementary motor area and limbic regions such as amygdala, parahippocampal gyrus and insular cortex. Hyperactivity of bilateral putamen in particular was localized to the decision phase prior to a rejection event. Effective connectivity analysis using Granger Causality Modelling identified two main structures causally influencing this circuitry shown in OCD symptom provocation: vmPFC and putamen. The former may underlie the integration of affective meaning and behaviour regulation, whereas the latter may be critically involved in habit formation and repetitive response selection.

This dichotomous circuitry contrasts with patterns of fronto-striato-limbic hyperactivation shown in previous OCD studies, which is likely related to differences in task design. For instance, several studies in OCD show increased activity in frontal areas using different behavioural tasks; however, these studies focus on testing different cognitive processes and tasks rather that symptom generation (Chamberlain et al., 2008; Fitzgerald et al., 2005; Maltby et al., 2005). Moreover, some symptom evocation and provocation studies asked patients to imagine, recognize or recall contexts related to past symptoms using exposure to images or words (Baioui et al., 2013; Gilbert et al., 2009; Mataix-Cols et al., 2004; Nakao et al., 2005; Schienle et al., 2005; Simon et al., 2010) or using real sensory stimulation (physical objects) (Adler et al., 2000; Breiter et al., 1996; Hendler et al., 2003; McGuire et al., 1994; Rauch et al., 1994). However, these previous studies did not include subject driven feedback, and were not designed to address the link between symptom provocation and compulsive behaviour. This novel feature used in our task may be one of the main reasons for the identification of differential involvement of frontal areas known to be related to executive control and behaviour regulation (Hare, Camerer, & Rangel, 2009; Roy, Shohamy, & Wager, 2012). Another possible reason may be related with differences in the efficacy of the symptom provocation across the studies. A study in children (Gilbert et al., 2009) showed a deactivation pattern similar to that observed in our study although this study did not assess efficacy of symptom provocation or specifically test avoidance events at the event level.

Our results are consistent with the account that vmPFC gates activity of regions involved in goal-oriented behaviour such as the caudate nucleus and inter-connected regions such as the dlPFC. Additionally, activation of the putamen, a critical structure in repetitive, habitual behaviour, leads in turn to overactivation of other structures such as the caudal part of dACC known to be involved in conflict monitoring and response selection (BA24) and preSMA (Graybiel, 2008; Robbins et al., 2012). These latter regions may mediate repeated-action patterns and action control under conflict. Our findings thus dovetail with animal models of compulsivity (Dias-Ferreira et al.,

2009; Gremel & Costa, 2013) and are corroborated by human structural connectivity data, suggesting a duality that predicts differences in the balance between habitual and goal directed action control (de Wit et al., 2012; Meunier et al., 2012). This duality is also present in diseases with impaired action control such as Parkinson disease, with differential effects on goal-directed and habitual processes (Hadj-Bouziane et al., 2012).

The vmPFC is suggested to be a key structure in the integration of value-guided stimulation and in mediating affective behavioural and physiological responses (Roy et al., 2012). Alternatively, the vmPFC may also be related to impairments in conditioned fear extinction. Milad *et al* have recently shown that patients with OCD show deficits in conditioned fear extinction, particularly in recalling extinction memory, an effect associated with reduced activation in vmPFC (Milad et al., 2013). Lesions in the vmPFC in rodents are also associated with increased recovery of fear a day after extinction training, demonstrating the role of the vmPFC in consolidation of extinction learning and consequent inhibition of inappropriate behaviours (Quirk, Russo, Barron, & Lebron, 2000). Recall of a fearful memory and consequent vmPFC deactivation triggered by the provocation stimuli may also play a role in the provocation aspect of our study. Thus, deficits in affective integration of stimuli that trigger OCD-related fears, which in turn result in failure to activate the vmPFC/OFC and consequent impairment of activity in the network involved in goal-directed behaviours shifting instead to salient stimuli, might induce pathological habitual behaviours.

We showed a crucial role for the putamen in OCD subjects with greater bilateral putaminal hyperactivation during the decision phase, in the course of stimuli exposure, prior to the rejection event (Figure 4). Our findings are consistent with a model in which the provocation stimuli are encoded as a potential threat or activation of a fearful memory via a vmPFC-putamen-caudal ACC and pre-SMA network involved in repetitive behaviours. With sufficient exposure, the urge for the

compulsive avoidance behaviour is then mediated via putaminal activation, which biases the OCD cognitive system towards the potential threat stimuli, activating the habitual-system and producing automatic responses. Previous studies have dorsal ACC involvement in conflict monitoring (Shackman et al., 2011). The dACC is a wide structure containing several areas and the subdivisions that seem to be hyperactive in our paradigm are related to response selection and conflict monitoring. Accordingly, a notable meta-analysis that performed a connectivity-based parcellation of the human cingulate cortex, focusing on its relations to functional specialization, suggested that a more anterior part of the dACC (anterior cingulate sulcus and paracingulate cortex) monitors action errors and conflict whereas a more posterior zone underlies response selection (Beckmann, Johansen-Berg, & Rushworth, 2009). We found hyperactivity in mid cingulate and caudal dorsal cingulate regions that mediate both cognitive components in conflict monitoring and response selection components. Two theories predominate about the overall function of this region of cortex: 'conflict monitoring' and 'attention/ selection for action' (M. Botvinick, Nystrom, Fissell, Carter, & Cohen, 1999). A role for cognitive evaluation appears to be relevant. This is also consistent with the activation of preSMA, which has a more cognitive function than SMA proper and is involved in monitoring of action switching (Picard & Strick, 2001). This view is supported by the results of Pardo et al. (1990), who found activation in the pre-SMA during the Stroop conflict task (Pardo, Pardo, Janer, & Raichle, 1990). Overall pre-SMA function is more closely related to maintenance of relevant sensory information than response selection or production.

As expected, we observed increased activity in paralimbic regions such as amygdala (in particular during post rejection appraisal), parahippocampal gyrus and insular cortex, similarly to other studies on symptom provocation and fear (Admon et al., 2012; Schienle et al., 2005; Shapira et al., 2003; Simon et al., 2013; Simon et al., 2010; Stern, Welsh, et al., 2012). These structures have consistently been associated with emotional processing, especially in detecting and appraising potential threats

(amygdala) (Fiddick, 2011) and pain perception (insula) (Apkarian, Bushnell, Treede, & Zubieta, 2005; Mutschler, Ball, Wankerl, & Strigo, 2012).

There were several limitations to this study. First, the majority of our OCD patients were taking SSRIs and/or anxiolytic medication, which might potentially influence the neuronal and behavioural responses. However, as we used a within-patient repeated-measures design with each subject acting as their own control, in addition to the comparison with an healthy control group, we could control for confounding variables and within subject variability (Hedayat & Yang, 2005). Second, our study sample size does not allow for a neuronal differentiation of OCD subtypes. OCD is a clinically heterogeneous disorder characterized by different symptom dimensions (Katerberg et al., 2010; Mataix-Cols, Pertusa, & Leckman, 2007). Investigations aiming to differentiate neuronal indices symptomatically may therefore be interesting to pursue in follow-up work and should also address the direct influence of comorbidities in different OCD subtypes.

The existence of a dichotomous pattern of deactivation/hyperactivation may provide evidence for a novel functional parcellation of the neural circuitry involved in OCD at the event level and possibly other neuropsychiatric disorders of impulse control and/or compulsive behaviour. This is consistent with behavioural and anatomical data from an animal model (Dias-Ferreira et al., 2009; Gremel & Costa, 2013) and human connectivity findings (de Wit et al., 2012; Meunier et al., 2012). Our results also put in a new context previous studies that failed to show activation of vmPFC/mOFC in OCD, albeit in tasks not directly related to symptom generation (Rauch et al., 2007). Our results favour the perspective that this dichotomy represents a generic phenomenon, and are consistent with the recent anatomical data in animals (Dias-Ferreira et al., 2009; Gremel & Costa, 2013) and humans (de Wit et al., 2012), supporting the existence of a circuit underlying habitual behaviour that is over-activated in impulse control disorders. Dias-Ferreira et al (Dias-Ferreira et al., 2009) have proposed that stress can cause compulsive behaviours in the rat due to

abnormal cortico-striatal activation, and Gremel and Costa (Gremel & Costa, 2013) have shown that inhibition of OFC disrupts goal-directed actions, whereas activation of this structure specifically increases goal-directed performance. These results are compatible with our findings.

Our results also support the recent suggestion that dysfunction in the goal-directed response system and increased reliance on the habitual-response system are fundamental mechanisms that may underlie the urge to perform compulsive acts (Gillan et al., 2011). The vmPFC-putaminal-dACC (BA24) pathway points towards abnormal affective integration of stimuli, conflict monitoring and decision making, favouring repetitive actions based on increased error signalling (M. M. Botvinick, Cohen, & Carter, 2004; Robinson, Overstreet, Charney, Vytal, & Grillon, 2013). Cingulotomy has been shown to significantly reduce OCD (Dougherty et al., 2002; Richter et al., 2008) in line with this model. Finally, our findings corroborate results using transcranial magnetic stimulation on frontal regions and supplementary motor area and deep brain stimulation focusing on the caudate nucleus (Bourne, Eckhardt, Sheth, & Eskandar, 2012; Jaafari et al., 2012a). They are also in agreement with the view that exogenous stimulation may restore behavioural control from the striatum back to PFC regions, thereby reversing the state of pathological imbalance (Mian, Campos, Sheth, & Eskandar, 2010).

Taken together, our findings may inform the development of therapeutic interventions, for instance using rTMS, aiming to target regions specifically involved in action control or repetitive behaviour in order to enhance or down-regulate the brain activity that specifically characterizes the experienced symptoms.

# Chapter 4

## General Discussion and Conclusions

This thesis constitutes an in-depth investigation of the mechanisms underlying decision-making and compulsivity in OCD. When one thoroughly thinks about the OCD symptoms, it becomes clear that this disorder is characterized by two different decision-making abnormalities, possibly associated to distinct neural mechanisms – indecisiveness and compulsiveness – which seem to stand in two opposite ends of the same continuum. On one hand, pathological doubts, reflecting an inability to settle on a verdict and truly commit to a decision, maintain OCD patients in an 'indecisive limbo'. Washers and checkers are good examples of this: instead of committing to an immediate decision, stick to it and accept its consequences, they are unable to decide whether their hands are clean or the door is properly locked. The available sensory-perceptual evidence seems to be simply not enough for these patients to commit to a solid decision. On the other hand, compulsive acts appear to be automatic, impulsive and represent irrational decisions. Following the theory raised by Sachdev and Malhi, which conceptualizes OCD as a disorder of decision-making (Sachdev & Malhi, 2005), this thesis separately assessed these two branches of decision-making using two specific approaches. Indecisiveness, indexed by the amount of evidence accumulated and evaluated prior to a decision, was investigated in *Chapter 2* using neutral tasks that covered two different decision types: perceptual discrimination and probabilistic reasoning. We applied standard behavioural and computational analysis to characterize response strategies between patients with OCD and healthy controls using both logistic regression analysis and hierarchical drift diffusion modelling. Compulsiveness was studied in *Chapter 3* using functional magnetic resonance imaging and a tailored symptom provocation task paired with online avoidance responses on a trial-by-trial basis. By implementing a novel paradigm that brings together real provocation (resulting from an online direct stimulation) and the possibility to measure directly online behavioural avoidance responses, modelling compulsive actions, we sought to pursue an integrative study linking real obsessions and compulsions. Hence, the study presented in *Chapter 3* aimed to unroll the mechanism underlying symptom generation, particularly the urge to perform the compulsive avoidance act.

Although we studied these two different decision-making abnormalities (indecisiveness and compulsiveness) separately, we were aware that they may lie in the same continuum and somehow interact with each other to account for the complete OCD phenotype. Therefore, this final chapter integrates the findings from both studies, place them in the actual context of OCD research by discussing these abnormalities in reference to the results from other studies and provides suggestions for future studies. In addition, we propose a new and relatively simple neural causal model for compulsivity in OCD, which provides a possible explanation for the impairments in cognitive and executive control observed by these patients.

## MECHANISMS UNDERLYING EVIDENCE ACCUMULATION IN OCD: A FOCUS ON INDECISIVENESS

Decision formation, including the cognitive process of weighing and accumulating evidence prior to a decision, is critical to be investigated in OCD given that compulsive acts implicitly involve decisional processes. Experimental approaches using sensory discrimination in several domains have been widely used to investigate the mechanisms of perceptual decision-making in primates and healthy humans due to their ability to precisely control the quantity and quality of sensory evidence (Gold & Shadlen, 2007; Heekeren et al., 2008). The vibrotactile frequency-discrimination task requires the subject to decide which of two sequentially tactile stimuli has higher frequency of vibration (Romo & Salinas, 2003). The auditory discrimination task asks participants to decide whether two sounds presented sequentially were the same or different (Kaiser et al., 2007). In the random-dot motion task (RDMT) participants must decide whether a net of randomly moving dots is predominantly moving in one direction or the opposite direction (right or left, for instance) (Newsome et al., 1989). These approaches often ask participants to choose between two possible stimulus categories and have been particularly useful to separate the neural mechanisms underlying sensory discrimination, which is transiently encoded from the senses, and

decision formation, which results from an accumulation of evidence over time until the final commitment is reached (Heekeren et al., 2008). Besides, recent computational models of behavioural results based on drift diffusion models have been successful in explaining response-time and accuracy data in these binary choice tasks and in potentially providing deeper explanations about the cognitive strategies that underlie decision-making (Ratcliff & McKoon, 2008).

These paradigms used both in monkey physiology and human neuroimaging have been showing that the neural mechanisms of perceptual decision-making are remarkably similar in both species. Low-level sensory neurons encode sensory discrimination evidence that is used in the decision-making process (for instance visual motion is represented in hMT+/V5 neurons (Newsome et al., 1989) and tactile stimulation in primary somatosensory cortex (Salinas, Hernandez, Zainos, & Romo, 2000)). This causal link between the representation of sensory evidence in sensory regions and perceptual decisions is also observed for higher-level perceptual categories, such as object or face processing (Afraz, Kiani, & Esteky, 2006; Heekeren, Marrett, Bandettini, & Ungerleider, 2004). The decisions are then formed by a downstream cortical regions, including areas such as the lateral intraparietal area (presumably the intraparietal sulcus in humans) and the dorsolateral prefrontal cortex, by accumulating and comparing sensory evidence (Heekeren et al., 2004; Sereno, Pitzalis, & Martinez, 2001; Shadlen & Newsome, 2001). This was possible to observe due to a gradually increase in the neuronal activity of these areas while gathering evidence, which was slower during difficult trials and faster during easier trials. Furthermore, this system that represents decision variables extends not only to motor and premotor structures but also to other structures involved in detecting perceptual uncertainty or difficulty (such as anterior insula and the inferior frontal gyrus) (Rebola, Castelhano, Ferreira, & Castelo-Branco, 2012) and performance monitoring (such as posterior medial prefrontal cortex and anterior cingulate cortex) (Heekeren et al., 2008). Some models consider that these networks act in a hierarchical manner with a serial progression from perception to action (Opris &

Bruce, 2005) and others with serial but also parallel processing (Heekeren et al., 2008).

The neural basis of decision-making in healthy humans (generally described in the previous paragraph) has been slowly unveiled. However, this has been less investigated in psychiatric disorders, especially in OCD. We explored OCD decision-making in *Chapter 2,* investigating the cognitive process of gathering evidence prior to a decision by looking for possible decision formation abnormalities in OCD patients. The previous successful use of perceptual tasks in disentangling the decision formation processes led us to consider the RDMT an optimal paradigm to investigate indecisiveness in patients with OCD. The advantages of using this paradigm in this particular study were detailed discussed in *Chapter 2* (discussion section). Only probabilistic decisions have been previously assessed in OCD, even though the symptomatic doubts often observed in patients have a more perceptual nature (e.g. do my hands look or feel clean?) than a probabilistic one (e.g. are my hands likely to be clean?). Therefore, our study extends the OCD literature to the perceptual decision domain, which may be more closely linked to the disease itself. However, probabilistic decisions were also assessed in order to solve inconsistencies in previous findings (Fear & Healy, 1997; Jacobsen et al., 2012; Pelissier & O'Connor, 2002; Volans, 1976).

Our study demonstrated that patients, compared to healthy volunteers, are more cautious in weighing the alternatives and require more evidence in perceptual decisions but not in probabilistic decisions. It further highlighted the convergence and divergence of standard behavioural and computational modelling approaches to decision demonstrating a differential influence of high and low uncertainty contexts on evidence accumulation and on the quality of evidence. Patients required more evidence under high uncertainty contexts, as indexed by longer reaction times (RTs), response time intercepts and higher decision boundaries. Moreover, patients also demonstrated impairments under low uncertainty contexts: despite normal

behavioural RTs, the strength or quality of evidence from the stimulus entering the decision process was poorer in patients, compared to healthy volunteers, as indexed by slower drift rates towards the decision boundary. These results suggest that patients' intolerance to uncertainty in contexts in which objective uncertainty is very low may be explained by a poorer encoding of the evidence in the decision-making process. On the other hand, the strength or quality of evidence entering in the decisional processing in contexts of objective high uncertainty is not impaired but the evidence required by patients to commit to a decision is dysfunctionally higher. Hence, our study provided evidence for dissociated mechanisms underlying the encoding of perceptual uncertainty as function of its level.

The influence of implicit incentives and external feedback in OCD decision formation was also explored in this study. OCD patients were sensitive to implicit salient incentives on the speed-accuracy tradeoff, possibly by influencing internal cost-benefit ratios, improving evidence accumulation and shifting away from pathological internal monitoring. However, this effect was not observed for explicit external feedback. Therefore, our findings also emphasize a differential role of implicit cost and external feedback in decision formation in OCD.

The study presented in *Chapter 2* reported findings that may be relevant for the development of therapeutic approaches. We provided evidence for decision-making impairments in OCD patients specifically under perceptual contexts. Although we hypothesized impairments in both types of decisions, it is highly compatible with clinical observations that only perceptual contexts lead to a more cautious style of decision-making. Indeed, the contexts that commonly trigger obsessions are those related with sensory ambiguity. Importantly, due to the possibility of confounding variables, our tasks controlled for working memory factors. Therefore we suggest that the observed impairments may be particularly related to perceptual rather than memory distrust. Several studies have indeed showed that the decay in feelings of uncertainty after OCD checking rituals is unreal and that these acts only supply

further doubts, triggering more uncertainty and meta-memory problems (Boschen & Vuksanovic, 2007; Coles et al., 2006; Hermans et al., 2008; Radomsky et al., 2006; M. van den Hout & Kindt, 2003a, 2003b). Two previous studies on perceptual uncertainty in OCD showed that prolonged visual attention itself might provoke feelings of dissociation and enhanced uncertainty about the perception (M. A. van den Hout et al., 2008; M. A. van den Hout et al., 2009). Thus, the prolonged attentional focus and repeated checking may itself invoke subjective feelings of dissociation or uncertainty, which may then drive further compulsive behaviours. These findings, together with the sensitiveness to implicit salient incentives on the speed-accuracy tradeoff observed in our study, suggest that training patients to shift their attention from their problematic perceptual focus using implicit incentives may be a good therapeutic approach. This would likely improve the cognitive processing of perceptual uncertainty and consequently avoid pathological monitoring and the need to compulsive actions. This strategy may be useful to train in addition to the ERP therapeutic approach, delivered as part of a CBT programme discussed in *Chapter 1*, providing patients with skills to suppress compulsions, which is a common difficulty experienced by patients in therapy and a prominent reason for CBT drop outs.

### NEURAL CORRELATES OF IMPAIRED COGNITIVE CONTROL IN OCD: A FOCUS ON COMPULSIVENESS

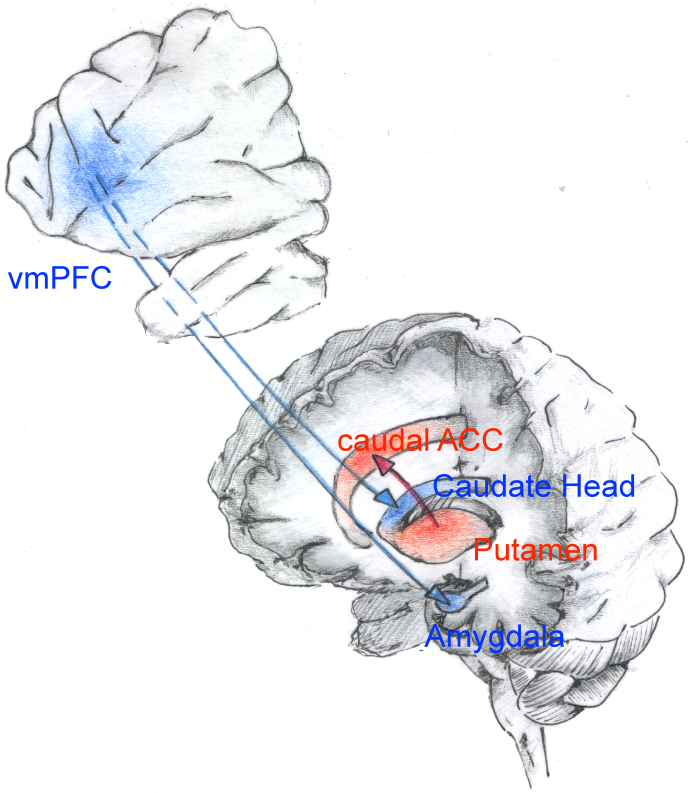
*Chapter 3* investigated specifically the neural correlates of symptoms generation and the neural mechanisms leading to compulsiveness in OCD. Recently, compulsivity in the context of OCD has been closely linked to an exaggerated habit-learning model, whereby compulsive behaviour may be explained by enhanced stimulus-response associations coupled with weakened influence of the ultimate goal (Fineberg et al., 2011). As highlighted in *Chapter 1*, this theory was originally put forward by Graybiel and Rauch (Graybiel & Rauch, 2000) after bringing together evidence implicating

cortico-striatal circuits in both the neurobiological basis of OCD and the neural basis of habit formation in healthy subjects. Although this hypothesis was raised more than a decade ago, only recently was empirically tested by Gillan and colleagues using an appetitive instrumental learning task (Gillan et al., 2011). Importantly, this study corroborated the above mentioned premise by showing a disruption in the balance between goal-directed behaviour and habit learning in OCD, but unfortunately did not went through to investigate the neural correlates of such imbalance. Following this, our study aimed to replicate these findings using a more ecological OCD paradigm, exploring them at a neural level.

Our novel paradigm brings realistically obsessive-compulsive experiences inside the fMRI scanner. By measuring on a trial-by-trial basis patient's avoidance responses under realistic exposure to obsessions, it interactively links obsessions and compulsions, allowing for the first time an integral assessment of the OCD symptomatology in the same experiment. This design provided the possibility to assess not only the neural correlates of intrusive thoughts and the urge to perform compulsive avoidance behaviour but also their relationship. Therefore, the general hypothesis that OCD is mediated by dysfunction in the balance between goal-directed behaviours and habit formation was investigated in a very specific OCD context. Based on the recent suggestion that compulsivity in OCD might arise from excessive avoidance habit formation (Gillan et al., 2013), alongside with the neural dichotomy between goal-directed and habitual systems extensively probed in rodents, we tested specifically if compulsivity in OCD would be associated with a decrease in caudate activity implicated in goal-directed behaviours and an increase in putaminal activity implicated in habitual behaviours.

We did identify a dichotomous pattern of activation/deactivation during exposure to symptoms characterized by a decreased activity in ventromedial (vmPFC) and dorsolateral prefrontal cortex (dlPFC) and caudate head, and an enhanced activity of bilateral putamen, caudal anterior cingulate cortex (cACC), pre- and supplementary

motor areas (SMA) and limbic regions. Effective connectivity analysis further allowed us to propose a simple causal model for compulsivity in OCD (Figure 1). In this model, two main structures causally influence the corticostriatal dissociation underlying symptom provocation: vmPFC and putamen. The former, a structure involved in cognitive control, gates deactivation of regions involved in goal-oriented behaviour such as the caudate nucleus and its connected regions in dlPFC. In contrast, putamen, a structure known to be involved in repetitive/non goal-oriented behaviour gates activation of structures mediating repeated-action patterns such as the cACC and the SMA. In other words, this proposal is consistent with the notion that vmPFC may underlie the integration of affective meaning and behaviour regulation and putamen may be critically involved in habit formation and repetitive response selection.



◄ **Figure 1:** Causal model inspired by integrating fMRI and causality results: prefrontal structures (ventromedial prefrontal cortex) gate the modulation of basal ganglia (caudate and putamen) and limbic areas (amygdala). In turn, the putamen, a structure involved in repetitive and habitual behaviour, gates the activation of structures mediating action monitoring and repeated action patterns such as the caudal dorsal cingulate cortex and the pre-supplementary motor area (not shown). vmPFC, ventromedial prefrontal cortex; ACC, anterior cingulate cortex.

By suggesting an imbalanced circuitry primary to habitual and goal-directed action control as a fundamental mechanism underlying compulsivity in OCD, our findings and our proposed model provide a direct explanation for the impaired cognitive control observed in patients with OCD as well as their ego-dystonic experience.

This corticostriatal dissociation, even though in line with our hypothesis, was a surprising finding considering previous studies in OCD that consistently report fronto-striato-limbic hyperactivation during symptom provocation. We argue that the different findings may be related with the methodological shift we have now provided by implementing a much more ecological paradigm. Symptom provocation may have been ineffective in previous studies because participants were in general asked merely to imagine, recognize or recall contexts related to past symptoms using exposure to words or images (Nakao et al., 2005; Simon et al., 2010). Furthermore, these studies were not designed to assess compulsivity, using subject driven feedback.

Our proposed neural model for compulsivity in OCD, which extends recent behavioural findings of disrupted goal-directed action and excessive reliance on habit in OCD (Gillan et al., 2013; Gillan et al., 2011) and in other disorders of compulsivity (Voon et al., 2014) and translates the compulsivity account from animal models (Dias-Ferreira et al., 2009) questions one of the most prominent theoretical accounts of OCD developed by Salkovskis (Salkovskis, 1985). In this account, cognitive biases such as exaggerated sense of responsibility, thought-action fusion and over-estimation of threat are considered the basis of obsessive thoughts, which produce

fear and anxiety to the individual. Compulsions are considered rational (goal-directed) avoidance behaviours that arise in response to fear and irrational beliefs. By contrast, the habit account of OCD recently proposed, which was corroborated by our study, puts forward the possibility that compulsivity in OCD may arise instead from an excess of stimulus-response habit formation as distinct from irrational cognition.

## INTEGRATION OF INDECISIVENESS AND COMPULSIVENESS FINDINGS

The studies presented in this thesis provided evidence for decision-making abnormalities in OCD, whereby both indecisiveness and compulsiveness co-exist. Both cognitive processes may interactively contribute to the complete phenotype of OCD, but the nature of their relationship could not be directly assessed by our studies because we investigated each process separately. Time constraints prevented us to assess the neural correlates of indecisiveness, which could have been measured by extending the experimental design described in *Chapter 2* to an fMRI study, or to propose a single experimental paradigm specifically designed to capture both processes. Therefore, the reader should be aware that this section solely embodies hypothetical theories that may explain the relationship between these 2 psychological processes.

Our theory grows in turn of these two processes: indecisiveness and compulsiveness. We propose that a persistent need to gather more evidence than what is usually required to form a decision is likely a trait that may constitute a vulnerability factor to develop OCD. In fact, it may underlie compulsive behaviours. Repetitive actions also known as compulsions (e.g. persistently reassurance seeking) that patients feel driven to perform over and over again, which result from irrational or automatic decisions, are perhaps bungling attempts to constantly gather evidence required to fulfil patient's intrinsic needs. Therefore, one may conceive compulsive behaviours as a

cycle of automatic and impulsive actions that are performed to respond to patients' internal demands for evidence. Subjective intolerance to uncertainty may be mediating these processes: high levels of uncertainty are likely to trigger anxiety and stress, which are known to promote habits and disturb decision-making (Dias-Ferreira et al., 2009; Schwabe, Dickinson, & Wolf, 2011). The immediate relief that follows each compulsion, promoted by a transient decrease in perceived uncertainty, may reinforce these behaviours. However, as the habit becomes progressively compulsive, the experience of relief may no longer be the driving force and these behaviours quickly become instead a maladaptive spiral out of control.

This link between compulsivity and indecisiveness was evident from the association between compulsive symptoms severity and evidence accumulation impairments observed in *Chapter 2*: patients with greater compulsive Y-BOCS scores had slower performance and higher cognitive investment in ambiguous trials. It is interesting to notice that this correlation was not found with the obsessive Y-BOCS scores, but only with the compulsive ones.

Decision-making is characterized by the parallel and balanced engagement of two distinct neural systems: goal-directed and habitual. *Chapter 3* showed that compulsivity in OCD might be explained by an imbalance circuitry favouring the habitual system. As previously outlined, we did not assess the neural underpinnings of the cognitive process of gathering evidence in OCD patients. However, based on existing knowledge from monkey physiology and healthy humans neuroimaging studies (previously reviewed in this chapter), one might hypothesize that evidence accumulation and compulsive abnormalities in OCD, though possibly associated to distinct neural mechanisms, may have potential neural overlaps. Prefrontal cortex is known to be involved in decision-making and in controlling multiple types of impulsivity. Dorsal lateral prefrontal cortex and anterior insula are implicated in detecting perceptual uncertainty. Anterior cingulate cortex has a key role in general monitoring of the decision outcomes. Finally, basal ganglia are extremely important

for motor performance and for adjusting behaviour. All these regions were found dysfunctional in our symptom provocation study, which may suggest relevant neural overlaps. Future studies are warranted to disentangle the neural basis of the different abnormal decisional processes in OCD.

## CLINICAL IMPLICATIONS AND FUTURE DIRECTIONS

The experiments employed in this thesis endeavoured to investigate decision-making abnormalities in OCD and further explored their link with the habit account recently proposed to explain the disease. This model is conceptually a new advance in OCD and still an emerging conceptual framework. Therefore, more research is warranted to establish this account.

In line with the hypothesized role of habits, behavioural interventions (particularly ERP, presented in *Chapter 1*) appear to be quite effective in treating OCD. Graded exposure to anxiety-provoking stimuli and prevention of the associated avoidance compulsions is thought to have therapeutic effects by breaking the pattern of compulsive behaviours, conferring patients with dominant control over the environment and thus reducing the need for further evidence accumulation. However, pharmacotherapy appears to be less effective and little is known about how it exerts therapeutic effects. An important topic for future research in this area is to investigate the effect of SSRIs and dopamine receptor antagonists on the habit formation bias in OCD. One might hypothesize that the anxiolytic properties of SSRIs might exert an influence on habits in OCD by reducing stress and anxiety that is known to promote habitual behaviour in rodents (Dias-Ferreira et al., 2009) and in humans (Schwabe & Wolf, 2009). Dopamine receptor antagonists, on the other hand, might also have a direct effect on the habit system, considering their efficacy in treating cases where patients have co-morbid tics (Bloch et al., 2006a), a feature thought to be also associated with the habit system (O'Connor et al., 2001).

Maladaptive perseveration of behaviour despite adverse consequences is found in several disorders that currently compose the OC-spectrum category in the DSM-V (e.g. trichotillomania and pathological skin picking). Compulsivity also characterizes the behaviours of substance dependent individuals (Everitt & Robbins, 2005), binge-eaters (Smith & Robbins, 2013) and alcoholics. Bearing in mind that compulsivity is a neurocognitive endophenotype, a construct not specific to OCD, it would be interesting to explore common bias towards habit formation and common structural and functional alterations associated with involvement of over-active habits across disorders.

Finally, our findings of an imbalanced neural circuitry in OCD may advocate future studies aiming to develop novel therapeutic strategies, including invasive approaches, which would be able to restore balance in these decision-making networks. It would be very interesting to investigate the effects of excitatory and inhibitory neuromodulation using, for example, transcranial magnetic stimulation. One could test to hinder the hyper activation of putamen related to repetitive behaviour networks or to enhance the activity of the inhibited frontocaudate circuits involved in goal-directed action control. Given our connectivity findings, the vmPFC appears to be an important target to explore, since it triggers changes in symptom related limbic and striatal structures, indicating loss of action control and engagement in repetitive behaviours in OCD. In sum, it might be worthwhile to pursuit future TMS or DBS research aiming to restore appropriate behavioural inhibition through learning, in addition to cognitive or pharmacological strategies helping to shift the bias away from maladaptive habit formation.

## CONCLUSIONS

This thesis investigated the neural basis of compulsive behaviours in OCD. We studied the mechanisms underlying impaired decision-making in OCD patients and further employed a realistic OCD-related experimental paradigm, which allowed to interactively link obsessions and compulsions, to investigate the neural substrates of symptom generation and overwhelming urges to engage in compulsive acts. We believe that our main findings provide strong implications for clinical neuroscience and may enable the development of future therapeutic approaches:

- *Patients with OCD demonstrate impairments in the cognitive process of gathering evidence, needing more perceptual evidence than healthy people.* This impairment may directly cause and perpetuate the abnormal cycle of compulsive behaviours.
- *OCD patients are sensitive to implicit salient incentives emphasizing speed, improving evidence accumulation and shifting away from pathological internal monitoring.* Training patients to shift their attention from their problematic perceptual focus using implicit incentives may be a good therapeutic approach to decrease subjective uncertainty and consequently avoid the need to compulsive actions.
- *Compulsivity in OCD is characterized by a corticostriatal dissociation that suggests an imbalanced habitual and goal-directed circuitry.* Novel therapeutic strategies aiming to alleviate such imbalance and focusing on suppressing habits may be helpful.

The work presented in this thesis corroborates the recent suggestion that dysfunction in the goal-directed response system and increased reliance on the habitual-response system are fundamental mechanisms that underlie the urge to perform compulsive acts in OCD. We went further by elucidating the neural basis of such mechanisms, therefore providing additional knowledge into the pathophysiology of this disease.

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# LIST OF PUBLICATIONS

**Banca P**, Voon V, Vestergaard MD, Philipiak G, Almeida I, Pocinho F, Relvas J and Castelo-Branco M. Corticostriatal dissociation during symptom provocation in Obsessive-Compulsive Disorder. *Manuscript submitted for publication.*

**Banca P**, Vestergaard MD, Rankov V, Mitchell S, Lapa T, Castelo-Branco M, Voon V. Evidence accumulation in Obsessive-Compulsive Disorder: the role of perceptual uncertainty and implicit incentives. *Manuscript submitted for publication.*

**Banca P**, Lange I, Worbe Y, Howell NA, Irvine M, Harrison NA, Moutoussis M, Voon V. Snap decisions in binge drinking: behavioural and volumetric correlates. *Manuscript submitted for publication.*

**Banca P**, Sousa T, Duarte IC, Castelo-Branco M, Visual motion imagery neurofeedback based on the hMT+/V5 complex: evidence for a neural circuit involving cortical and cerebellar regions in successful learners. *Manuscript submitted for publication.*

**Banca P**, Mole TB, Irvine M, Morris L, Porter L, Mitchell S, Lapis T, Harrison NA, Voon V. Dissociating novelty and conditioning to sexual rewards. *Manuscript in preparation.*

Vidal AC, **Banca P**, Pascoal AG, Cordeiro G, Sargento-Freitas J, Castelo-Branco M (2014). Inter-hemispheric interactions across basal ganglia and cerebellar circuits during motor control. *Manuscript submitted for publication.*

Rounis E, **Banca P**, Voon V. Deficits in limb praxis in patients with Obsessive Compulsive Disorder. *Manuscript in preparation.*

Saddington C, **Banca P**, Voon V, Harrison NA. Characterizing repetitive behaviours in Obsessive-Compulsive Disorder and Autism. *Manuscript in preparation.*

Morris L, **Banca P**, Irvine M, Mitchell S, Porter L, Lapa T, Potenza M, Voon V. Volume and connectivity differences in subjects with and without compulsive sexual behaviours. *Manuscript in preparation.*

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# AGRADECIMENTOS

*"Some people grumble that roses have thorns; I am grateful that thorns have roses"*
Alphonse Karr, *A Tour Round My Garden*

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*Paula Banca, 2014*

# CURRICULUM VITAE

Paula Banca was born on February 15, 1982 in Coimbra, Portugal. She completed her secondary school education at Escola Secundária Dr. Joaquim de Carvalho in Figueira da Foz. She obtained her degree in Psychology from the University of Coimbra in 2005 and worked as psychologist at Santa Casa da Misericórdia in Condeixa-a-Nova for 3 years. In 2007, she went back to the University of Coimbra to study Pharmaceutical Sciences. After the completion of the first 2 years of this course, she was accepted in the PhD Programme in Experimental Biology and Biomedicine, from the Center of Neuroscience, Coimbra. In 2010, she started working on her PhD project, under the supervision of Professor Miguel Castelo-Branco, at the Institute for Biomedical Imaging and Life Sciences, IBILI, at the Faculty of Medicine of the University of Coimbra. On May 2012, she moved to Cambridge to work with Dr. Valerie Voon at the Department of Psychiatry, University of Cambridge, to complete her PhD project.