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Abstract

Major Depressive Disorder is a cause of significant functional impairment, including interpersonal and social functioning. Theory of Mind is the ability to impute mental states to oneself and to others and is essential to the understanding of one's own and other people's behaviour, and so, essential to social functioning.

The main goal of this study was to examine whether depressed patients are impaired in their Theory of Mind and social cognition skills. To this goal, a specific assessment was applied to 17 women diagnosed with Major Depressive Disorder, from the female psychiatric ward of CHUC, which met the required inclusion and exclusion criteria. The assessment included relevant socio-demographic information, clinical and neuropsychological assessment with current depressive episode evaluation and cognitive assessment and Theory of Mind appreciation with Reading the Mind in the Eyes Test.

We obtained three main results. First, the data of our study suggested that depressed patients have impaired Theory of Mind skills. Second, we found a significant correlation between test used to assess psychopathology and cognitive functions. Finally, data supported a strong correlation between the results in cognitive tests and Reading the Mind with the Eyes Test, in which poor results in Theory of Mind tasks were associated with worse cognitive performance.

We concluded, in this study, the relevance of social cognition as an important part in the understanding of Major Depressive Disorder as well as, the difficulties in this setting

observed in depressed patients may, at least in part, be due to an impaired ability to interpret emotional stimuli and mental states.

Key Words

Major Depressive Disorder, Theory of Mind, Social Cognition, Empathy

Resumo

A Depressão Major é causa de disfuncionalidade grave, nomeadamente a nível do relacionamento interpessoal. A Teoria da Mente é a capacidade de atribuir estados mentais a si próprio e aos outros, sendo crucial para a compreensão do comportamento humano e do funcionamento social.

O principal objetivo deste estudo consistiu na avaliação da capacidade de Teoria da Mente e cognição social em doentes com Depressão Major. Para tal, foi elaborada uma avaliação específica que foi aplicada a 17 doentes do sexo feminino, com o diagnóstico de Depressão Major, internadas no Serviço de Psiquiatria do CHUC e, as quais, cumpriam os critérios de inclusão e exclusão inicialmente estabelecidos. Da avaliação fizeram parte informação sociodemográfica relevante; avaliação clínica e neuropsiquiátrica com apreciação do episódio depressivo atual e da função cognitiva e avaliação da capacidade de Teoria da Mente com o "Reading the Mind in the Eyes Test".

Os resultados obtidos agruparam-se em três principais linhas de força. Em primeiro lugar, a análise dos dados sugeriu um défice na capacidade de Teoria da Mente nos doentes com Depressão Major. Por outro lado, observámos uma correlação significativa entre os testes usados para avaliação da psicopatologia e testes de apreciação da função cognitiva. Finalmente, os dados suportaram uma correlação forte entre os resultados os testes de avaliação da função cognitiva e o "Reading the Mind in the Eyes Test", sendo que a obtenção de piores resultados nos testes de avaliação da Teoria da Mente se associou a piores desempenhos cognitivos.

Concluiu-se, neste estudo, a importância da cognição social na compreensão da Depressão Major e que, as dificuldades exibidas neste domínio podem dever-se, pelo menos em parte, a défices de interpretação e compreensão de emoções e estados mentais.

Palavras – Chave

Depressão Major, Cognição Social, Teoria da Mente, Empatia

Introduction

1. Major Depressive Disorder

1.1. Clinical concept

Major Depressive Disorder (MDD) is a highly prevalent lifetime psychiatric disturbance and a leading cause of disability worldwide causing chronic and significant functional impairment[1], including interpersonal and social functioning[2]. In the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 2013) the diagnosis of MDD is based on the presence of major depressive episodes that are defined by at least five of the following symptoms for at least two weeks duration: either anhedonia and/or depressed mood, appetite/weight disturbance, sleep disturbance, psychomotor change, loss of energy, worthlessness/guilt, concentration difficulties/indecisiveness and thoughts of death/suicide. In most patients, MDD is a chronic, recurrent disorder, with each subsequent episode increasing the probability of a further episode with longer duration and decreased recovery rate than the previous one.[3,4]

Cognitive dysfunction has been widely reported in persons suffering from MDD with impairments in psychomotor speed, attention, visual learning and memory, attentional switching, verbal fluency and cognitive flexibility.[5,6] There is a substantial heterogeneity in cognitive functioning of depressed patients and it remains unclear whether there are unique profiles of neuropsychological deficits that may distinguish patient subtypes.[7] Importantly, cognitive deficits are evident after remission of depression and predict worse response to treatment with serotonin-selective reuptake inhibitors[8-11] and poor functional outcome following a major depressive episode.[12-14] Persistent cognitive deficits following

depression are more severe in patients with recurrent episodes, in late-onset elderly cases (onset after 50–65 years of age) and among patients who have psychotic or melancholic features.[15] The most pronounced deficits in the late onset depression are observed in verbal memory, processing speed and some aspects of executive functions, including the Trail-Making Test part B.

1.2. Cognitive models of depression

The Beck's Cognitive Theory of Depression emerged in the sixties,[16] and was subjected to various subsequent reformulations. According to the Cognitive Theory of Depression a number of psychological factors contribute to the vulnerability, precipitation and maintenance of depression.[17] Depressive individuals hold implicit (non-conscious) representations of their self, called 'schemata', stable cognitive structures in which dominate themes of loss, failure, rejection, worthlessness, and hopelessness.[18] They alter information processing with negative self-referential thoughts about the self, the personal world and the future — also known as Beck's negative cognitive triad.[19]

1.3. Neurobiology

Accumulating evidence suggests that the elements of the cognitive model — biased attention, biased processing, biased thoughts and rumination, biased memory, and dysfunctional attitudes and schemas — have an underlying neurobiological basis.[20] Currently, the pathophysiology of MDD is thought to involve a complex interplay between biological, psychological and social factors acting throughout life. In Beck's Cognitive Model of Depression, schemata play a major role in the onset and maintenance of MDD, once they determine how an individual interprets their experiences in a given

context. Thus, adverse events that occur early in life might lead to the development of depressive schemata, which remain dormant till being activated by subsequent stressors in adulthood[21]. These psychological phenomena are associated with neurobiological alterations associated with depression, including genetic vulnerabilities, disturbed adult neurogenesis and altered synaptic connectivity.[22-24]

Several prefrontal and limbic structures and their interconnected circuits have been implicated in affective regulation, initiating and maintaining the cognitive bias.[22] There are pathways that begin with the hyperactivity of the limbic system, namely amygdala, hippocampus and nucleus accumbens, and proceed to frontal and prefrontal cortex. At the same time, the cognitive control (prefrontal areas) to subcortical areas that normally attenuates emotional activation, is diminished. Thus, there is a bottom-up activation, unchecked by top-down cognitive control, leading to persistent maladaptative schemas.[20] Particular important in this setting is the particular awareness for negative aspects of stimuli, dued to biases in emotional processing in higher cortical areas, which can maladaptively alter perceptions of the environment and social interactions.

2. Theory of Mind

Theory of Mind (ToM) is the ability to impute mental states to oneself and to others[25] and is essential to the understanding of one's own and other people's behaviour. *Intentions, desires and beliefs* are crucial mental states involved in this aptitude.

Recent theoretical models propose that ToM draws on both cognitive (e.g., understanding another's perspective) and affective (e.g., emotional response to feeling states of others) processing resources.[2]

Neuroimaging and behavioural studies of ToM implicate a core network of neural regions that serve diverse functions, and include cognitive, affective and memory systems, such as prefrontal cortex, anterior paracingulate, posterior cingulate, temporal poles.[26-28] Moreover, neuroimaging evidence also implicates the posterior superior temporal sulcus, involved in socially relevant directional cues such as the eye gaze of others, and the adjacent temporoparietal junction, which is involved in the attribution of beliefs to others, critical for ToM ability.[2]

The recognition of ToM's significance for social functioning has generated widespread investigation in clinical populations for whom challenges in social interaction are common, including individuals with autism spectrum disorders, schizophrenia and organic brain disorders.[29]

3. Theory of Mind and Major Depressive Disorder

The substantial interpersonal difficulties exhibited by individuals across the depressive spectrum highlight the importance of understanding the mechanisms that underlie social dysfunction in depression.[30] Surprisingly, only a few studies have investigated ToM abilities of depressed patients and a brief review of the literature reveals inconsistent data. Those in a current episode of MDD show impairment in their ToM

performance compared with healthy controls.[31,32] However, vulnerable individuals display enhanced ToM ability relatively to healthy controls.[33,34]

Similarly, studies of facial emotion processing in patients with MDD report a generalized emotion recognition deficit, with a processing bias involving heightened attention to and recognition of negative faces during active states of depression accompanied by a tendency to mislabel positive faces as sad and to overestimate the amount of negative emotion carried in faces.[35-39] Nevertheless, a recent study employing the Eyes task failed to find a significant difference between individuals with an MDD diagnosis and nondepressed individuals.[40] They concluded that it is possible that the low level of social functioning associated with depression can be ascribed partially to a ToM deficit.

4. Study aim

Even though MDD is associated with compromised social functioning, only a few studies have investigated ToM abilities of depressed patients. Therefore, the main goal of this study is to examine whether depressed patients are impaired in their ToM and social cognition skills.

Materials and Methods

1. Patient recruitment

Consecutive patients were recruited by clinical psychiatrists from the female psychiatric ward of CHUC from 1 September 2015 to 31 January 2016. Any patient admitted with a major depressive episode was invited to participate in the study. Female inpatients who were eligible and signed the written informed consent were included in the study.

2. Inclusion and Exclusion Criteria

Inclusion criteria were: a diagnosis of DSM-5 MDD, to be under treatment with antidepressant agents or to initiate this treatment, age between18 and 75 years and DSM-5 criteria.

Exclusion criteria were: history of medical conditions that could entail cognitive deterioration, history of head injury or neurological disorder, current psychotic symptoms, electroconvulsive therapy in the 6 months prior to the study, substance-related disorders; a Mini-Mental State Examination[41] score lower or equal to 20.

3. Baseline Assessment and Psychiatric History

A socio-demographic and clinical questionnaire was designed specifically for this study. Relevant socio-demographic information including gender, date of birth and age, marital status, education level and occupational status as well as clinical data regarding age of disorder onset, number of previous episodes and current pharmacological treatment (type of drug, mean dose and time of administration) was collected.

4. Clinical and Neuropsychological Assessment

4.1. Current depressive episode

The 21 item *Hamilton Rating Scale for Depression (HRSD)*[42] with 61 maximum points, was administered to determine the severity of depression symptoms. General psychopathology was documented with the 24 item *Brief Psychiatric Rating Scale (BPRS)*[43], which score varies between 24 and 168 points. *Clinical Global Impressions Scale (CGI-S)*[44], which rates illness severity (from 1 to 7 points), provided a brief assessment of the clinician's view of the patient's global functioning. The duration of the current depressive episode and the medication taken regularly in the previous month were assessed.

4.2. Cognitive Evaluation

Once recruited, the subjects were assessed with a neuropsychological battery containing the following instruments:

• *Trail Making Test Part A/B (TMT-A/B):* Both parts of the TMT (A and B) consist of 25 circles distributed over a sheet of paper. In Part A, the circles are numbered 1 – 25, and the patient should draw lines to connect the numbers in ascending order. In Part B, the circles include both numbers (1 – 13) and letters (A – L); as in Part A, the patient draws lines to connect the circles in an ascending pattern, but with the added task of alternating between the numbers and letters (i.e., 1-A-2-B-3-C, etc.). The TMT is a measure of attention, speed, and mental flexibility. It also tests spatial organization, visual pursuits, recall, and recognition. Part B tests cognitive demands including visual motor and visual spatial abilities and mental flexibility. Both sections are timed and the score represents the amount of time required to complete the task.

• *Stroop Color-Word Test (Stroop Test):* This test measures psychomotor speed and inhibition of automated responses. First, subjects should read colour names printed in black ink. The second task requires naming the colour of a series of "pink, grey, green, blue". In the third condition, colour names are printed in a non-matching colour and subjects should name the colour of the ink (Interference condition). The outcome measure was the number of colours named in 45 seconds in the interference condition.

• *Montreal Cognitive Assessment (MoCA, Portuguese version)*[66]: Was designed as a rapid screening of several cognitive domains. It includes an Alternating Trail Making, Visuoconstructional Skills (Cube and Clock), Naming animals, Memory test, Attention Test, Sentence repetition and Verbal fluency test, Abstraction trial,

Delayed Recall and Orientation test. The total possible score is 30 points; a score of 26 or above is considered normal.

• *Animal Naming Test (Verbal Fluency Test)*: Patients were instructed to tell names of animals starting by "M", "R" and "P" as quickly as possible, during 60 seconds.

5. Theory of Mind and Social Cognition Assessment

Patients were assessed with:

• *Reading the Mind in the Eyes Test (RMET)* (Baron-Cohen et al., 2001[45])*:* This test first appeared in the book "The Essential Difference" by Simon Baron-Cohen. It was developed as a test of adult theory-of-mind abilities and involves the identification of a wide range of complex mental states. Across 36 trials, participants are shown a picture of the eye region of the face surrounded by four mental state terms. Participants select from the four terms the one that best matches the mental state portrayed in the picture (Fig.1). The original general population sample in Baron-Cohen et al. 2001[45] scored 26,2 points.

Figure 1: Example of Reading the Mind in the Eyes Test.

• *Toronto Empathy Questionnaire (TEQ)*[46]*:* It was applied, recognizing the ability to empathize as a fundamental part of the social process.

6. Statistical analysis

Treatment and analysis of data were made using SPSS, version 21. Correlation between variables was determined by Spearman's rank correlation coefficient, a nonparametric measure of statistical dependence between two variables.

Results

1. Demographic and clinical data

The sample is formed by 17 female patients, aged between 33 and 69 years old.

Table 1: Demographic and Clinical Data

	Average
Age	*51,4 ± 11,2*
Hamilton Rating Scale for Depression (HRSD)	*19,8 ± 5,8*
Brief Psychiatric Rating Scale (BPRS)	*40,8 ± 4,9*
Clinical Global Impressions Scale (CGI-S)	*4 ± 0,9*
Duration of current episode (months)	*7,9 ± 6*
Number of previous episodes	*6,4 ± 7,6*
Age of the first episode	*35,6 ± 14,3*
Reading the Mind in the Eyes Test (RMET)	*17,1 ± 5,1*
Toronto Empathy Questionnaire (TEQ)	*64,1 ± 7,3*
	Distribution
Marital Status	*Single: 5,8%* *Married: 70,6%* *Divorced: 23,5%*
Education (years)	*1-4* *23,5%* *5-6* *5,9%* *7-9* *29,4%* *10-12* *17,6%* *>12* *23,5%*

The analysis of demographic and clinical data (Table 1) emphasizes an average age of 51,4 years old, an average age of the first depressive episode of 35,6 years and average number of depressive episodes of 6.4.

From all patients, 70.6% (n=12) were married, 23.5% divorced (n=4) and 5.8% single (n=1). In the evaluation of the current depressive episode patients achieved, on average, 19,8 points in *Hamilton Rating Scale for Depression (HRSD),* 40.8 points in *Brief Psychiatric Rating Scale (BPRS)* and 4 points in *Clinical Global Impressions Scale (CGI-S).*

2. Major Depressive Disorder and Cognitive Tests

It was found a relationship ($p < 0.05$) between cognitive function (*MoCA*, *TMT-A*, *TMT-B*, *Stroop 1-3* and *Verbal Fluency test*) and the psychopathological measures of the current depressive episode (*HDRS*, *BPRS* and *CGIS)* (Table 2 and Fig.2B). This relationship is established so that better results in cognitive assessment are associated with worse results in psychopathology evaluation.

Table 2: Correlation between psychopathology and cognitive function.

	MoCA	*TMT-A*	*TMT-B*	*Stroop1*	*Stroop2*	*Stroop3*	*Verbal Fluency ("P")*
HRSD	***0.612****	*-0,136*	***-0,533****	*0,251*	*0,291*	***0,487****	***0,696****
BPRS	***0,549****	*0,054*	*-0.223*	*0,106*	*-0,051*	*0,435*	***0,485****
CGI-S	*-0,154*	*0,302*	*0,072*	*-0,141*	*-0,403*	*-0,037*	*0,050*
Number of previous episodes	*-0.273*	*0,195*	*0,143*	*-0,165*	*-0,249*	*-0,122*	*-0,303*
Age of the first episode	*0,054*	*0,417*	*0,346*	*-0,407*	*-0,153*	*-0,195*	*-0,118*

Spearman correlation coefficient

p<0.05

****p < 0,01***

3. Major Depressive Disorder and Theory of Mind

The average score obtained in *Reading the Mind With the Eyes Test* was 17,1 points, while the original general sample in Baron in Baron-Cohen et al. 2001[45] scored 26,2 points.

We didn't observe a significant correlation between the severity of the depressive episode (*HDRS*, *BPRS* and *CGIS*) and ToM measures (*Reading the mind in the Eyes Test* and *Toronto Empathy Questionnaire*). However, the age of the first depressive episode was negatively associated with the results of the *Reading the Mind in the Eyes Test*, indicating that subjects with lower ages of depression onset had better performances (Table 3 and Fig.2C).

Table 3: Correlation between Theory of Mind and psychopathology.

	HRSD	*BPRS*	*CGI-S*	*Number of previous episodes*	*Age of the first episode*
Reading the Mind in the Eyes Test (RMET)	*0,469*	*0,409*	*0,061*	*-0,048*	***-0,523****

Spearman correlation coefficient
*******p<0.05*

4. Theory of Mind and Cognitive Tests

A strong correlation was found between the performance cognitive function (*MoCA*, *TMT-A*, *TMT-B*, *Stroop 1-3* and *Verbal Fluency test*) and the performance in *Reading the Mind in the Eyes Test*. (Table 4 and Fig.2A). Poor results in ToM tasks were associated with worse cognitive performance.

Table 4: Correlation between Theory of Mind and cognitive function.

	MoCA	*TMT-A*	*TMT-B*	*Stroop1*	*Stroop2*	*Stroop3*	*Verbal Fluency ("P")*
Reading the Mind in the Eyes Test (RMET)	***0,599****	***-0,571****	***-0,742****	***0,787****	***0,669****	***0,686****	***0.670****

Spearman correlation coefficient

***p < 0,05*

****p < 0,01*

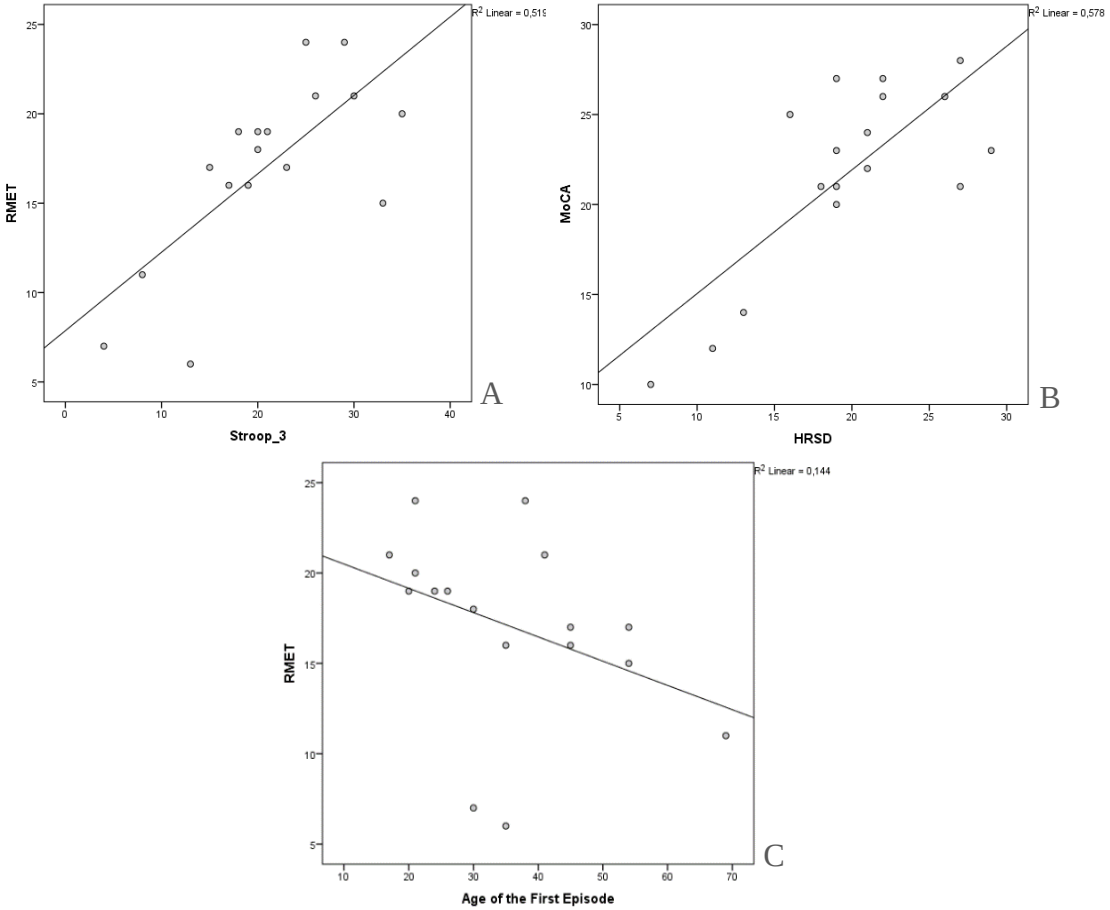

Figure 2: A - *Relationship between scores in RMET and performance in Stroop 3 test.* ***B -*** *Relationship between MoCA performance and HRSD.* ***C -*** *Relationship between scores in RMET and the age of first depressive episode.*

Discussion

1. Major Depressive Disorder and Cognitive Function

Correlation between tests used to assess cognitive function such as *Trail Making*, *MoCA* and *Stroop Tests* and psychopathology, evaluated by *HDRS*, *BPRS* and *CGI-S*, shows that, in our sample, lesser impairment in cognitive performance was associated with a greater severity of depressive episode.

It is widely accepted that cognitive impairment is a feature of MDD, particularly in the acute state.[47] Moreover, the available evidence suggests that executive function impairment is greater in patients with more severe depressive symptoms.[48,49] Executive function deficits observed in MDD[50] are likely to be a clinical correlate of structural and functional abnormalities in prefrontal cortex, including dorsolateral prefrontal cortex, ventrolateral prefrontal cortex and anterior cingulate cortex.[51-53] These regions of the brain have been implicated in the ability to regulate emotion and responses to negative information: lateral prefrontal cortex provides top-down control over responses to emotional material in the amygdala and associated limbic regions.[20,54] Patients with MDD have impairments in attention inhibition to negative emotional stimuli and may have difficulty preventing negative information from entering and remaining in working memory, leading to ruminating thoughts, biased attention and biased memory for negative stimuli.[20,55,56]

Our results do not follow this line. One explanation is that the assessment of depressive symptoms using scales depends on the cognitive function and the capacity to

communicate. Thus, patients with great cognitive impairment may have increased difficulties in reporting their depressive symptoms.

2. Major Depressive Disorder and Reading the Mind in the Eyes Test

The results of our study suggest that depressed patients have impaired ToM skills. Nevertheless, the severity of the depressive episode didn't relate with the test performance (no correlation between *HDRS* or *BPRS* and *Reading the Mind in the Eyes Test*).

Reading the Mind in the Eyes Test requires participants to interpret the affective mental state portrayed in various cropped images of eyes. Studies in face processing reveal an involvement of occipitotemporal areas implicated in the perceptual analysis, as well as an involvement of amygdala and other limbic structures, of orbitofrontal cortex and other regions of prefrontal cortex, of insular cortex and basal ganglia, all associated with facial emotional processing.[57]

The majority of studies found that depressed patients had impaired ToM abilities compared to controls.[31,32,34] However, Wolkenstein et al. 2011[40], found depressed patients to be, in fact, more accurate than matched controls in identifying a negative emotional state, without any difference for neutral and positive states. This may indicate a bias toward negative emotions expressed in face processing.

Our results also suggest that the lower the age of first depressive episode, lesser are the deficits in ToM. This may result from different etiopathogenic mechanisms involving depression with beginning at young age and depression of late onset, the latter with more evident executive dysfunction and therefore also with changes of greater intensity at the

level of ToM. Multiple sources of evidence suggest that the phenotypical heterogeneity of depression in the elderly translates different pathophysiologic pathways. The age of onset of depressive episodes is a strong indicator of these pathophysiological differences. Thus, the depressive disorders that manifest since adolescence/early adulthood are distinguished clinic and pathophysiologically of depressions that appeared for the first time after the 50-60 years.[58] While the first involves the deregulation of prefrontal-limbic networks[59], the latter one is associated with the occurrence of medical morbidities and to the contribution of vascular factors that induce structural disruption of fronto-subcortical circuits and placing the individual at risk of cognitive and functional deterioration.

3. Theory of Mind and Cognitive Function

The results support a strong correlation between the performance in cognitive tests and *Reading the Mind in the Eyes Test*. Indeed, neuroimaging and behavioural studies of ToM implicate a core network of neural regions including frontal and prefrontal areas.[60,61]

According to Martin Doherty 2008[62], there are three candidate theories for why executive function, closely linked to the frontal lobe, and ToM are related. Firstly, executive functions require understanding of one's own mental processes. Perner 1991[63] argues that metarepresentation is necessary for certain kinds of executive function. ToM may evolved as a self-monitoring mechanism, allowing much greater self-control and therefore more complex behaviour. Secondly, developing ToM skills may require a certain level of executive functioning. Russell et al. 1991[64] introduced the idea that executive inhibition may be critical to the development of ToM. However, Carlson et al. 2004[65] found that early executive function performance did not predict performance on

any of the standard ToM tasks. Finally, it is relevant to consider that ToM tasks have executive components.[64]

4. Limitations and Future directions

This study, with the limitations concerning the size of the sample, seeks an initial approach of issues concerning social cognition in depression. Thus, further investigations should be carried out, following the concerns presented here.

At the same time, other intriguing questions should be asked. Future investigation would benefit from exploring the influence of particular medication classes on social cognitive ability in MDD. Another important way for further studies is the development of more ecological tasks that assess empathy using realistic settings. The use of static images of facial expressions may reveal information different from that which would be obtained by the use dynamic social contexts, similar to those in real life. Future research should also seek to clarify neurobiological mechanisms which contribute to the selective processing towards negative stimuli as well as the neuronal alterations involved in depression that seem, in the literature available, related to the brain areas involved in ToM abilities and social cognition.

Conclusion

In healthy individuals, the brain areas involved in the ability of ToM and face processing are cortical areas with special emphasis to the prefrontal cortex and subcortical regions, namely the basal ganglia and limbic areas. These facts suggest an involvement of cognitive and emotional processing functions, specifically in the capacity of inferring that others think the same way we do (Theory of Mind by Bryna Siegel). The information on the neuronal alterations involved in depression suggests that the areas involved are coincident with the referred above.

These work puts in evidence social cognition as an important part in the understanding of MDD and worthy of more research. Indeed, difficulties with social interaction observed in this patients may, at least in part, be due to an impaired ability to interpret emotional stimuli and mental states. In fact, social cognitive performance in depression may impact on the development of the disorder through impairing social functioning.

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