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DISSERTAÇÃO DE MESTRADO

Funções executivas e atividade eletroencefalográfica em pacientes com depressão maior

Dissertação de mestrado apresentada no Programa de pós-graduação de psiquiatria e saúde mental, da Universidade Federal do Rio de Janeiro, como parte dos requisitos necessários à obtenção do título de Mestre em Saúde Mental.

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FUNÇÕES EXECUTIVAS E ATIVIDADE ELETROENCEFALOGRÁFICA EM PACIENTES COM DEPRESSÃO MAIOR

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Dissertação de Mestrado submetida ao Programa de Pós-graduação em Psiquiatria e Saúde Mental (PROPSAM) do Instituto de Psiquiatria da Universidade Federal do Rio de Janeiro - UFRJ, como parte dos requisitos necessários à obtenção do título de Mestre em Saúde Mental.

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SUMÁRIO

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LISTA DE ABREVIATURAS, SÍMBOLOS E SIGLAS

BAI Escala de Ansiedade de Beck

BDI Escala de Depressão de Beck

BETA III Teste não verbal de inteligência geral

DSM Diagnostic and Statistical Manual of Mental Disorders

NIH National Institute of Mental Health

TTC Teste de Trilhas Coloridas

UFRJ Universidade Federal do Rio de Janeiro

WCST Wisconsin Card Sorting Test

RESUMO

O transtorno de depressão maior costuma ser causa de incapacitação do individuo em função do seu curso crônico. As pesquisas têm sinalizado que os déficits encontrados têm repercussão social, comportamental e também biológica.

Essa pesquisa visa revisar a literatura a respeito das funções cognitivas e transtornos psiquiátricos e realizar um ensaio clinico comparando dados neuropsicológicos, de forma particular do funcionamento executivo, e eletrofisiológicos entre um grupo de pacientes com o transtorno de depressão maior e outro de sujeitos saudáveis (grupo controle), bem como correlacionar tais achados.

Foram realizadas três revisões da literatura e uma pesquisa clinica no período de 24 meses. Para a pesquisa clinica os instrumentos utilizados foram a Mini; BAI; BDI, Victoria Stroop Color-Word Test, TTC, WCST e Beta III e captação de EEG. Com esses dados foram publicadas 2 revisões, submetida mais uma revisão e um artigo com os dados da pesquisa clinica original.

Os resultados das revisões mostraram um número mais extenso de pesquisas envolvendo o transtorno de depressão maior do que o transtorno do pânico, e dados ainda bastante heterogêneos nos dois casos. Quanto a pesquisa clinica, foram encontradas diferenças significativas entre os grupos nas escalas BAI e BDI, nos testes TTC forma I e Beta III, bem como nos dados eletrofisiológicos. A partir dos dados encontrados, ratifica-se a possibilidade de marcadores biológicos no transtorno de depressão maior.

Palavras chave: funções executivas, transtorno de depressão maior, eletroencefalograma

ABSTRACT

The major depressive disorder is usually cause of disability because of their chronic course. Research has signaled that deficits have social, behavioral and biological repercussions.

This research aims to review the literature on cognitive and psychiatric disorders functions and conduct a clinical trial comparing neuropsychological data, particular of executive functioning, and electrophysiological among a group of patients with major depressive disorder and other healthy subjects (group control), as well as correlate these findings.

There were three literature reviews and one clinical research within 24 months. For clinical research instruments used were: Mini; BAI; BDI; Victoria Stroop Color-Word Test, Color Trail Test (CTT), Wisconsin Card Sorting Test (WCST) and Nonverbal of General Intelligence Test: Subtests Matrix Reasoning and Codes (Beta III) and capturing EEG signals. With these data were published two reviews, submitted further one review and another article with the data from the original clinical research.

The results of the review showed a more extensive research of major depressive disorder than panic disorder, and data still quite heterogeneous in both cases. As for clinical research, were found significant differences between groups in BAI and BDI scales, in TTC test form I and III Beta and in electrophysiologic data. From the data found, confirms the possibility of biological markers in major depression disorder.

Keywords: executive functions, major depressive disorder, electroencephalogram

Introdução

Segundo dados do National Institute of Mental Health (NIH), o transtorno de depressão maior é um dos mais comuns nos Estados Unidos. Por ano, aproximadamente 6,7% dos adultos americanos são diagnosticados, sendo as mulheres 70% mais propensas ao desenvolvimento do mesmo. A média de idade dos sujeitos é de 32 anos, porém 3,3% dos indivíduos entre 13 e 18 anos também são diagnosticados e têm graves limitações em seu cotidiano devido ao transtorno[1]. Outro ponto importante se refere ao elevado risco de suicídio nesses pacientes e na variedade de doenças físicas que podem ser associadas ao seu curso, como arritimia, asma, câncer, doenças cardiovasculares, diabetes, hipertensão, doenças crônicas respiratórias e doenças que se relacionam a dor crônica. Consequentemente, a presença de tais doenças traz para o paciente um aumento de custos, de limitações e de risco de mortalidade[2].

Em 2013, com a nova publicação do Manual Diagnóstico e Estatístico de Transtornos Mentais (Diagnostic and Statistical Manual of Mental Disorders – DSM) pela Associação Americana de Psiquiatria (American Psychiatric Association - APA) ocorreram algumas mudanças a respeito do critério diagnostico de alguns transtornos, dentre os quais os transtornos depressivos[3].

Tabela 1. Diferenças diagnósticas dos transtornos depressivos

DSM IV	DSM V
Transtorno bipolar em crianças	Transtorno de desregulação do humor
Apêndice B, Critérios que necessitam de maior estudo	Transtorno disfórico pré menstrual
Distimia	Transtorno depressivo persistente, o que

	inclui tanto o transtorno depressivo crônico quanto um transtorno distimico prévio.

Tabela 2. Novos critérios presentes no DSM V

Transtorno depressivo com características mistas: Existência de 3 sintomas maníacos dentro de episódio depressivo maior
O critério de exclusão de diagnóstico de transtorno depressivo maior nos casos de perda ou luto foi retirado.
A especificidade "with anxious distress" visa objetivar a severidade da ansiedade em indidivuos com transtorno bipolar ou depressivo.

A neuropsicologia tem sua origem no século XX, e em seu surgimento visava o estudo de alterações comportamentais decorrentes de lesões cerebrais. Sua fundamentação teórica era baseada nos achados tanto da neurologia quanto da psicologia. Atualmente, seu enfoque maior é a respeito do estudo do sistema nervoso central, das funções cognitivas e seus desdobramentos comportamentais. Sendo assim, sua fundamentação teórica também se voltou mais para a área das neurociências e ciências do comportamento[4]. A avaliação neuropsicológica é composta por uma esfera quantitativa e também qualitativa, que exige do profissional um treinamento tanto psicométrico e normativo dos testes, como uma análise global e processual do indivíduo, que leva em consideração variáveis que possam interferir em seu desempenho[5]. As pesquisas na área têm aumentado exponencialmente, de forma particular na possível correlação de déficits cognitivos nos transtornos psiquiátricos. Tais achados decorrentes de avaliação neuropsicológica podem trazer um aperfeiçoamento tanto teórico quanto prático, trazendo a possibilidade de tratamentos cada vez mais eficazes para os pacientes[5]. Diversas pesquisas têm demonstrado alterações cognitivas em pacientes com

depressão[6,7,8,9], mesmo após a remissão do transtorno[10,11], e dentre as funções afetadas se encontram as funções executivas.

Alexander Luria foi pioneiro em diversos estudos e apresentou o conceito do funcionamento cerebral a partir de três unidades. A terceira unidade seria a responsável pelo recebimento, armazenamento, execução e coordenação das ações. Através dela ações primariamente simples se tornam cada vez mais elaboradas e complexas. Surge então a primeira noção do que hoje é denominado como funções executivas[12]. Atualmente, o conceito de funcionamento executivo apresenta diferentes definições, como a de Lesak (1995) que o descreve como composto por quatro componentes: vontade, planejamento, intenção da ação e auto-monitoramento e regulação de performance. Já Carlson (2005) descreve tais processos a partir dos constructos de controle inibitório, planejamento, flexibilidade atencional, detecção e correção de erros e resistência a interferência. Apesar da heterogeneidade conceitual, a avaliação das funções executivas é de suma importância para o melhor entendimento do funcionamento psicopatológico dos transtornos[13]. Os instrumentos mais utilizados pela literatura são o Wisconsin Card Sorting Test (WCST)[8,9,10] e o Stroop Test[9,10,11], comumente conhecidos por abarcarem em suas avaliações quesitos como flexibilidade, perseveração e resolução de problemas.

Outra função cognitiva bastante estudada, e com algumas controvérsias concentuais é a atenção. Tomando por base suas execuções operacionais, a mesma é dividida em atenção sustentada, dividida e seletiva. A atenção sustentada é definida como a habilidade de se direcionar e focar a atividade cognitiva para um estimulo especifico, tornando-se primariamente importante no processamento das informações. Já a atenção dividida é entendida como a habilidade de se desenvolver mais de uma tarefa simultaneamente. E a atenção seletiva é o ato de se focar em um determinado objeto ou parte do ambiente por um

período de tempo enquanto se ignora outras informações que estejam ocorrendo simultaneamente[14].

Através do exame de eletroencefalograma (EEG), que se realiza pela colocação de eletrodos no escalpo torna-se possível a visualização gráfica das correntes elétricas originadas no córtex cerebral. A análise de EEG é caracterizada por variações de freqüência que vão de 0,5 a 70 Hz, com amplitudes entre 20 e 100 μV. Tais freqüências são divididas em quatro subcategorias, identificadas pelas letras gregas: alfa (8 a 12 hz), beta (12 – 35Hz), delta (1 a 4 Hz) e teta (4 – 8 Hz)[15]. Estudos demonstram que as atividades das bandas alfa e teta são eficazes na verificação de alterações de demandas cognitivas e atencionais, o que sugere a sensibilidade desse tipo de avaliação para se relacionar mudanças cerebrais em execução de tarefas cognitivas[16].

Pesquisas utilizando o EEG em pacientes com transtornos psiquiátricos também têm aumentado, em busca de evidencias de possíveis marcadores neurobiológicos. Uma das medidas de avaliação utilizadas em pacientes depressivos é a assimetria em alfa das regiões pré frontais. A assimetria é uma medida comparativa entre os hemisférios e inversamente proporcional a atividade cortical. Ou seja, quanto maior a assimetria de alfa em um hemisfério, menor está sendo a sua atividade. No caso dos pacientes depressivos, tem sido encontrado uma maior quantidade de alfa no hemisfério esquerdo em comparação com o direito, o que sinaliza uma menor ativação do hemisfério esquerdo quando comparado com o direito[17].

Um paradigma amplamente descrito e utilizado na literatura, com mais de 1000 publicações a respeito, é o paradigma “oddball”. Trata-se de uma tarefa que é realizada simultaneamente a captação eletrofisiológica em que o sujeito é instruído a apertar um botão apenas diante de determinados estímulos em detrimento de outros. Apesar da tarefa de

discrimar círculo e quadrado parecer simples, requer a ativação de diferentes componentes cognitivos, como a inibição de respostas automáticas, tornando o paradigma robusto e utilizado como marcador cognitivo[18].

Os tratamentos mais amplamente utilizados e recomendados para esses pacientes são o psicoterapêutico, na abordagem Cognitivo Comportamental e farmacológico, especialmente dos antidepressivos. Nesse sentido, algumas pesquisas têm comparado essas duas modalidades para testar a sua eficácia e os resultados mostram que embora as medicações melhorem os sintomas, como os relacionados ao sono por exemplo, a psicoterapia ajuda os pacientes a um melhor ajustamento social, interpessoal e profissional e também traz um efeito mais duradouro dos ganhos obtidos[19,20]. Outra opção possível é a intervenção de reabilitação cognitiva, tanto através de treinamento comportamental entre terapeuta e paciente, quanto através da utilização de recursos computadorizados[21,22]. Apesar desse tipo de intervenção ter evidencias satisfatórias, no que se refere aos transtornos psiquiátricos teve inicialmente enfoque apenas em déficits atencionais, lesões cerebrais e pacientes esquizofrênicos[23]. Nos últimos anos tem surgido evidencias a respeito de sua eficácia também em outros transtornos, como transtornos alimentares[24] e de transtornos de humor, através de melhora cognitiva e funcional para tais pacientes[21,22].

A presente dissertação é composta de uma compilação de artigos científicos, tanto empíricos quanto de revisão, realizados durante os 24 meses (fevereiro de 2013 a fevereiro de 2015) de curso de mestrado do PROPSAM – UFRJ – IPUB (Programa de Pós-Graduação em Saúde Mental da Universidade Federal do Rio de Janeiro). O projeto de pesquisa foi aprovado pelo CEP: "Correlação entre funções executivas e atividade eletroencefalográfica em pacientes com Depressão Maior".

Os 03 primeiros artigos científicos foram artigos de revisão, sendo o primeiro uma revisão sistemática sobre as alterações cognitivas em pacientes com transtorno do pânico, o

segundo uma revisão sistemática a respeito das alterações nas funções executivas em pacientes adultos jovens com depressão e o terceiro uma revisão sistemática a respeito das alterações nas funções executivas de pacientes idosos com depressão.

O último artigo científico foi feito a partir da realização de avaliação neuropsicológica e captação de dados eletrofisiológicos de EEG em 8 pacientes com transtorno de depressão maior e 8 sujeitos saudáveis. Foram aplicados os instrumentos MINI (*Mini International Neuropsychiatric Interview*), BAI (Escala Beck de Ansiedade), BDI (Escala Beck de Depressão), Victoria Stroop Color-Word Test, Testes de Trilhas Coloridas (TTC), Wisconsin Card Sorting Test (WCST) e Teste não verbal de inteligência geral: Subtestes Códigos e Raciocínio Matricial (Beta III).

Os quatro artigos se relacionam a partir da temática de avaliação cognitiva em transtornos psiquiátricos, sendo os três primeiros de revisão e o quarto um ensaio clinico original. O primeiro se diferencia dos demais tanto a respeito do transtorno estudado quanto das funções avaliadas, e foi possível notar diferenças no andamento das pesquisas. No caso do Transtorno do Pânico as pesquisas ainda são escassas, pouco especificas e com poucos instrumentos. Já no caso da depressão pode-se perceber um volume bem maior de pesquisas realizadas, embora os instrumentos utilizados também sejam heterogêneos.

A seguir, encontram-se listadas as referências dos artigos publicados resultante dos estudos durante o mestrado:

1) Alves, MRP, Pereira, V., Machado, S., Nardi, AE., Silva, AC. Cognitive functions in patients with panic disorder: a systematic review. Revista Brasileira de Psiquiatria. 2013 35(2):193-200.

2) Alves, MRP, Yamamoto, T., Carrion, OA, Rocha, NBF, Nardi, AE, Machado, S., Cardoso, A. Executive Function Impairments in Patients with Depression. 2014 13(6), pp. 1026-1040

Artigos submetidos em periódicos para publicação:

3) Alves-Peres, MRP, Machado, S., Yamamoto, T., Carrion, OA., Nardi, AE, Cardoso, A. Late-life depression and executive function impairment

(Submetido XXX)

4) Alves-Peres, MRP, Tanaka, GK, Cagy, M., Ribeiro, P., Velasques, B., Nardi, AE., Cardoso,A. Neuropsychological assessment of executive functions and EEG in patients with depression

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REVIEW ARTICLE

Cognitive functions in patients with panic disorder: a literature review

Mariana Rodrigues Poubel Alves,[1,2] Valeska Martinho Pereira,[1,2] Sérgio Machado,[2,3,4] Antonio Egidio Nardi,[1,2] Adriana Cardoso de Oliveira e Silva[2,5]

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Objective: To conduct a review of the literature on the possible neuropsychological deficits present in patients with panic disorder.
Methods: We performed a systematic review and search of the PubMed, ISI and PsycInfo scientific databases, with no time limits, using the following key words: cognitive, function, panic, and disorder. Of the 971 articles found, 25 were selected and 17 were included in this review. The inclusion criterion was at least one neuropsychological assessment task in patients with panic disorder.
Results: The number of publications has grown gradually, especially those assessing executive functions, corresponding to the neurobiological model most widely accepted. Of all the functions evaluated, these patients had lower performance in memory tasks and higher performance in affective processing tasks related to the disorder. However, these data require further investigation due to the high rate of comorbidities, the small sample sizes of the included studies and little standardization of instruments used.
Conclusion: The results showed a greater occurrence of deficits in memory and enhanced affective processing related to panic disorder.

Keywords: Panic disorder; cognitive function; memory; affective processing; executive functions

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Introduction

Panic disorder (PD) is characterized primarily by the presence of recurrent and unexpected panic attacks, followed by at least 1 month of persistent concern about other attacks, the possible consequences of attacks and a significant behavioral change related to the attacks. For a diagnosis of PD, the panic attacks cannot be better accounted for by another mental disorder, by physiological effects resulting from the use of substances or by other medical conditions, such as hypothyroidism.[1]

Regarding the prevalence of PD, a study found a lifetime rate of 1.6% and an annual rate of 1% in the city of São Paulo. However, this was not a representative sample of the Brazilian population.[2] Nevertheless, the annual rates are similar to those presented by the National Comorbidity Survey Replication, which estimated the prevalence of PD to be 5% in a lifetime and 1% annually in a representative sample of the U.S. population.[2]

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Neurobiology of panic disorder

The first studies that evaluated the neurobiology of anxiety used animal models because the behaviors of escape, fear and avoidance presented in these disorders are similar to certain responses presented throughout animal phylogeny, such as increase in heart rate and release of glucocorticoids when faced with adverse situations. However, some limitations, such as the inability to verbalize symptoms, resulted in a need for improved research models.[3] Thus emerged the current models of research, which have focused on the prevention of mental disorders due to their chronic and progressive aspects. Notable research lines include growing interest in neuropsychology and neuroimaging in an attempt to construct a cognitive profile of these populations.[2]

The neurocircuitry of fear includes two pathways for processing of sensory information. The shorter path consists of the rapid spread of autonomic and behavioral responses in potentially hazardous situations. In this case, the major regions involved are the anterior thalamus and the central and lateral regions of the amygdala. The latter is, in particular, the coordinator of this process because it triggers regions that themselves emit responses. In the longer path, the information

passes through several regions, including the cortex, which allows for a more refined analysis of inputs.[3]

In the case of PD, the hypothesis is that the neurocircuitry would result in dysregulated activation and coordination with increased subcortical activity and consequent neuroendocrine activation, both behavioral and autonomic.[3] Neuropsychological assessment can ratify or call into question the prevailing neurobiological model, because if cerebral regions are altered in PD, this would be expected to generate cognitive and behavioral responses accordingly.[4]

Neuropsychological assessment

Neuropsychological assessment has several objectives, such as identifying and describing possible changes in cognitive function. An evaluation may be recommended in a variety of cases, such as in patients who sustained an injury (e.g., traumatic brain injury or stroke) or in patients who are experiencing emotional or behavioral changes.

A detailed description of the different cognitive functions contributes to the establishment of more accurate diagnoses and prognoses, especially in cases where no functional changes are detected in neuroimaging studies. Furthermore, this description can assist in follow-up of individual cases when periodic reevaluation is recommended. Finally, this description contributes to a better understanding of the relationship between brain and behavior, demonstrating in practice what is theoretically established.[4]

The importance of establishing a relationship between neuropsychology and mental disorders arises from the need for more reliable and objective data about the abilities and deficits related to these disorders. As our behavioral and cognitive responses correlate with substrates and neural networks, when conducting a neuropsychological evaluation, we obtain a quantitative and qualitative picture of the workings of different cognitive functions and their related neural networks.[4] In the case of PD, few studies have been published; therefore, there is still uncertainty as to which cognitive functions could be affected by the disorder. The cognitive functions expected to be most affected are those related to regions involved in the fear network, i.e., the frontal cortex and limbic regions in particular. This would predominantly involve executive functions and emotional processing.

Understanding these relations in PD could lead to the development of better interventions.[5] These interventions may pertain to the field of neuropsychology, in the development of neuropsychological rehabilitation strategies, or even to the field of psychotherapy, enabling development of psychotherapeutic interventions that could be guided according to the cognitive profile of this group.

Thus, the objective of this study was to conduct a literature review of studies that included neuropsychological evaluations in patients diagnosed with PD, with or without agoraphobia, to investigate possible cognitive changes in this population.

Methods

A literature search of the PubMed, ISI Web of Knowledge and PsycInfo databases was conducted using the following terms: cognitive, function, panic, and disorder. The survey was conducted in August 2012; no time limits were set for any database.

A total of 971 references were found (315 in PubMed, 575 in ISI Web of Science, and 81 in PsycInfo). Of these, 45 articles were in a language other than English and 96 were duplicates, and were therefore excluded. This left 833 references for abstract analysis. Twenty-five articles were selected and recovered, of which only 17 were ultimately included. We excluded articles that only conducted neuroimaging or when the focus of neuropsychological assessment was a psychiatric disorder other than PD. Only articles describing neuropsychological assessment of PD patients, with or without agoraphobia, were included in this review. Studies were required to include at least one neuropsychological assessment task.

Data were stratified by functions evaluated: general intellectual functioning, memory, attention, executive function, psychomotor abilities and processing speed, verbal fluency, and affective processing measured in response to faces and words.

Results

The results of our literature review are summarized in Table 1.

General intellectual functioning

Overall cognitive functioning scores map a broad area and specify the patient's overall cognitive functioning. They are used to provide a rapid, initial assessment of the patient rather than a detailed analysis.[4] Only four articles examined general intellectual functioning; three of these used the Wechsler Adult Intelligence Scale (WAIS-R). The other study used Raven's Colored Progressive Matrices. The results were different in each article.

The first study[6] used four subtests of WAIS-R that assessed the verbal vs. performance IQ measures, as well as the full scale IQ, of patients (n=25) and compared them with a control group (n=25). The results showed lower performance on the picture completion subtest by patients with PD. In another article, patients with PD (n=69) scored approximately 10 points lower in verbal, performance and full scale IQ scores when compared to the control group (n=19).[7] Another study used four subtests of the WAIS-R and found lower scores in the block design subtest, which measures visuospatial constructional ability. This difference was common to patients with social phobia (n=18) and patients with PD (n=18) when compared to controls (n=16). However, the authors noted that there was no significant difference in the similarities subtest, which shows that this difference was not consistent.[8] The last study did not find any difference between the control group (n=15) and the other two groups, patients with PD with agoraphobia

Table 1 Summary of the studies included in the review

Study	n	M/F	Age	GIF	Mem	Att	EF	PAPS	VF	APFW	Neuropsychological Assessment Instruments	Results
Castillo et al. (2010)[5]	24 PD 24 C	13/11 13/11	30.9 30		X	X	X				- Digit span (DS) - Block Design - Stroop - Rey-Osterrieth Complex Figure Test (RCFT) - Facial Recognition Test - Word list, free and cued recall	Patients with PD showed deficits in executive functions, attention regarding the selection of relevant stimuli and working memory. Global scores for memory, attention and executive functions were lower than in the control group.
Lucas et al. (1991)[6]	25 PD 25 C	04/21 04/21	34.7 35	X	X						- Wechsler Memory Scale (WMS) - Selective Reminding(SR) - Benton Visual Retention Test (BVRT) - Four subtests of WAIS-R: Picture Completion, Vocabulary, Block Design, Similarities	Patients showed deficits in both functions evaluated. With respect to general intellectual functioning, their scores were lower in performance tests. PD patients also showed deficits in visual memory.
Gladsjo et al. (1998)[7]	69 PD 19 C	37/32 /	40.6 42.8	X	X	X		X	X		- Some subtests of the WAIS-R battery: DS, Vocabulary, Information, Arithmetic, Similarities, Picture Completion, Block Design, Digit Symbol - Verbal Fluency - California Verbal Learning Test (CVLT) - Continuous Visual Memory Test (CVMT) - Visual Selective Reminding Test (VSRT) - Warrington Recognition Memory Test (RMT) - Digit Vigilance - Trail-making test (TMT) - Finger Tapping Test	Of all the functions evaluated, the authors found deficits only in general intellectual functioning among patients with PD, who scored nearly 10 points lower than the control group in the verbal aspect, in performance and in total score. Memory, attention, psychomotor skills, processing speed and verbal fluency were preserved.
Asmundson et al. (1995)[8]	18 PD 18 SP 16 C	10/8 13/5 9/7	35.4 38.4 34.9	X	X	X	X	X			- Four subtests of the WAIS-R battery: Vocabulary, Similarities, Block Design, Picture Completion - CVLT - BVRT - TMT - Digit Cancellation Test (DCT)	Patients with PD exhibited deficits in processing speed and short-term memory free recall. The authors found a possible deficit in visuospatial ability, but this proved inconsistent. Attention, executive functions and visual memory were preserved.
Boldrini et al. (2005)[9]	25 OCD 15 PD 15 C	15/10 6/9 7/8	32.7 35.9 29.1	X	X		X				- Wisconsin Card Sorting Test (WCST) - Controlled Oral Word Association (COWA) - RCFT - Facial Recognition Test (BFRT) - Corsi Block Tapping Task (CBT) - DS - Buschke-Fuld Selective Reminding Test (SRT) - Raven Coloured Progressive Matrices (RCPM)	The authors only found deficits in spatial memory in patients with PD. General intellectual functioning and executive functions were preserved.
Kaplan et al. (2006)[10]	22 PD 22 C	7/15 7/15	36.2 36.9		X	X	X	X		X	- Two-subtest version of the Wechsler Abbreviated Scale of Intelligence - Seven subtests from the Cambridge NeuropsychologicalTest Automated Battery (CANTAB) - Spatial Working Memory (SWM) - Pattern Recognition Memory (PRM) - Spatial Recognition Memory (SRM) - Delayed Match to Sample (DMTS) - Rapid Visual Information Processing (RVIP) - Cambridge Gamble Task - Affective Go/No-go Task	Patients with PD showed no deficits in any of the functions evaluated. Memory, attention, executive functions, psychomotor skills, processing speed and processing affective were preserved.
Purcell et al. (1998)[11]	30 OCD 30 PD 20 DEP 30 C	20/20 6/24 8/12 12/18	40.6 38.9 37.5 40.8		X	X	X				- CANTAB - Spatial Span - SWM - Tower of London Planning Task - DMTS - Pattern Recognition - Spatial Recognition - Intradimensional-Extradimensional (ID-ED) Set Shift	The authors found that memory, attention and executive functions were unchanged in PD patients.

Continued on next page

Table 1 Continued

Study	n	M/F	Age	GIF	Mem	Att	EF	PAPS	VF	APFW	Neuropsychological Assessment Instruments	Results
Dratcul et al. (1998)[12]	14 PD 7 C	4/10 2/5	32.4 35.1		X	X		X			- Digit Cancellation - Symbol Copying Test (SCT) - Digit Symbol Substitution Test (DSST) - DS - Free Recall	The authors found alterations only in relation to memory (both immediate and delayed recall) in PD patients. Attention and executive functions were preserved.
Airaksinen et al. (2004)[13]	33 PD 32 SP 7 GAD 16 OCD 24 SPEC 175 C	7/26 10/22 2/5 4/12 8/16 89/86	43.6 38 41.7 35.7 43.2 43.9		X		X	X	X		- Episodic information to be remembered consisted by 32 neutral words -according to norms established by Nilsson (1973) - Word Association Test - TMT	The authors found deficits in episodic memory and executive functions in patients with PD. However, aspects of psychomotor skills, processing speed and verbal fluency were preserved.
Gordeev (2008)[14]	93 PD 36 C	30/63 12/24	31.2 30.1		X	X					- Münsterberg Test - Schulte tables - Short-term memory was tested for words	The authors found memory deficits with regard to words and numbers memory and also in attention, as regards selectivity and stability of attention.
Lautenbacher et al. (2002)[15]	21 PD 21 DEP 20 C	66%F 57%F 60%F	30.5 39 34.6			X					- Gesichtsfeld-/Neglectprüfung test of the Testbatterie zur Aufmerksamkeitsprüfung (TAP) - Signal Detection subtest of the Wiener Test system	The authors evaluated the attention function and found deficits in divided attention and preservation of selective attention.
Gorini et al. (2010)[16]	31 PD 31 C	7/24 12/19	35.52 30.23					X			- C-G Arena, a desktop-based computer-generated virtual space created to investigate place-learning abilities in humans	With regard to psychomotor skills and processing speed, the authors found changes in time and distance traveled to find the target, which was the goal of the task. However, these changes were characteristic of a subset of patients (older and longer duration of PD).
Lundh et al. (1998)[17]	30 PD 30 C	11/19 11/19	34.1 33.1							X	- Study 1:Black and white photographs of 80 persons (40 men, 40 women) were taken from a larger material originally used by BaËckman (1991). - Study 2: The photographs t used were the same as in Study 1 and in the earlier studies by Lundh and Oèst (1996a, 1996b)	The function of affective processing demonstrated that patients with PD showed bias for safe faces, but not to critical faces.
Reinecke et al. (2011)[18]	23 PD 22 C	70%F 13%F	28.6 26.2							X	- Facial Expression Recognition task - Faces Dot Probe task - Emotional Stroop task - Self Beliefs task	On assessment of affective processing, the authors found that patients with PD have greater vigilance to fearful faces, thus showing a bias for faces.
Neidhardt et al. (1998)[19]	60 PD 60 C	31/29 27/33	34 34.3							X	- Sixty words with either positive nor negative valence from two semantic categories (panic-related vs. no-panic-related) formed four word classes.	The authors evaluated affective processing of PD patients and found better performance for face recognition.
Pauli et al. (1997)[20]	15 PD 15 C	4/11 4/11	35.5 35.3							X	- Two types of word sets were relevant for this study: 40 body-related and 40 nonsomatic words. Stimulus words were written in black lowercase letters on a white background and were presented by a Kodak Carousel S-AV 2000	On assessment of affective processing, the authors found that patients with PD exhibit better processing for words that are related to bodily sensations.
Van den Heuvel et al. (2005)[21]	18 OCD 15PD 14 HYP 19 C	6/12 8/7 12/2 10/9	33.4 33.7 40.6 30.3							X	- Stroop	The authors evaluated affective processing with respect to words and found that patients with PD showed greater attention to information related to the disorder.

APFW = affective processing to faces and words; Att = attention; C = healthy control subjects; DEP = depression; EF = executive function; F = female; GAD = generalized anxiety disorder; GIF = general intellectual functioning; HPC = hypochondriasis; M = male; Mem = memory; OCD = obsessive-compulsive disorder; PAPS = psychomotor abilities and processing speed; PD = panic disorder; SP = social phobia; SPEC = specific phobia; VF = verbal fluency.

(n=15) and patients with obsessive-compulsive disorder (n=25).[9]

These differences may be related to the inhomogeneity of the paradigms used for assessment; although three of the studies used the same measurement instrument, there was a difference in the number and type of selected subtests.

Memory

Memory is fundamental to perception because, without it, we do not recognize people or representative objects of our history.[22] Most of the articles evaluated different aspects of this function, such as working memory, long-term memory and visual memory.

Of the 10 studies, only three did not find deficits in memory.[7,10,11] Another two identified impairment in one aspect and preservation of another.[6,8] In one study, patients with PD (n=18) or social phobia (n=18) had a significantly lower performance in total free recall when compared to the control group (n=16). However, the author notes that this finding may be related to loss of interest, fatigue, some other mediating factor or a state of depression or anxiety, which could have generated a bias in the results.[8] In another study, patients with PD (n=25) performed worse than controls (n=25) in visual memory tasks but not in verbal memory or concentration.[6]

The five remaining articles described differences in other areas of memory. In one study, there was impairment of both working memory and explicit memory in patients with PD (n=14) as compared with a control group (n=7). However, the authors emphasize that such deficits may be related to a high level of excitement and anxiety in patients at the time of task execution. Excitement and anxiety could lead to a loss of selective attention, which mediates the process of encoding information and support received.[12] Another study found spatial memory impairment in patients with PD with agoraphobia (n=15) and patients with obsessive-compulsive disorder (OCD) (n=25) as compared with a control group (n=15).[9]

Another study found that patients with different anxiety disorders (PD with and without agoraphobia (n=33), social phobia (n=32), obsessive compulsive disorder (n=16), specific phobia (n=24) and generalized anxiety disorder (n=7) tended to remember fewer words in free recall and cued recall as compared with healthy controls (n=175).[13] These findings were validated by a study that showed poorer short-term memory for numbers and words in patients with PD (n=93) as compared with healthy subjects (n=36).[14]

Finally, one article compared patients with PD (n=24) and a control group (n=24). The authors found significant deficits in working memory and in the curved means of the results, both in encoding and recall, in different categories. However, PD patients had higher face recognition scores.[5]

Attention

Studies conducted in the 1980s divided attentional processes into two classes: parallel processes that work with unlimited capacity and processes that are more focal and selective and, therefore, work with limited capacity. This distinction also implies that the second type would only be required for more complex tasks.[23] Another important characterization of attention is the distinction between automatic and controlled processes. Automatic processes of attention do not require that the subject be focused or willing to perform an action. They are a type of involuntary reaction in the face of innate or previously learned stimuli. Additionally, these processes usually operate from associative connections. The controlled process requires focused attention and, therefore, has a limited capacity. This limitation is a benefit, because it allows better handling of the matter that is under focus.[24]

Controlled processes were the second most evaluated function, reported in eight articles. Five of these articles found no differences between patients with PD and a control group.[7,8,10-12] Of the three articles in which differences were found, two reported differences in selective attention.[5,14] In one article, patients with PD (n=24) showed more difficulty in completing a task that required visual attention as compared with a control group (n=24). According to the authors, this result demonstrates the difficulty in selecting relevant stimuli and is related to symptoms of the disorder, in which patients find it difficult to perceive their surroundings because their attention is focused on bodily sensations and concerns.[5] In another study, patients with PD (n=93) were compared with healthy controls (n=36) and showed decreases in selectivity, switching of attention and lower work capacity and stability of attention.[14]

The third article's results were contradictory to those of the previous two, because the patients evaluated showed no differences in selective attention tasks, although differences were found in divided attention tasks. The authors compared patients with PD with (n=16) and without agoraphobia (n=5), patients with PD and major depressive disorder (MDD) (n=21), and a control group (n=20). In selective attention tasks, the three groups performed similarly, but in divided attention, patients with PD were slightly faster than the patients with MDD and slower than the control group. However, the authors emphasize that these results may be related to use of the dual-task paradigm, which requires a higher attentional load that is not found in selective attention tasks.[15]

Executive function

The articles note that Luria was the first author to discuss executive functions. Although he did not use that term, he conceptualized a series of disorders associated with frontal lesions that generated problems of initiative, motivation, development of goals and action plans, and difficulties in self-monitoring. The term 'executive function' was first described by Lesak, who defined it as the skills required for effective behavior that is creative and socially acceptable.[4,25]

Importantly, this function has different components, which hinders the uniformity of findings. This definition

includes decision-making, inhibition of automatic responses, flexibility, and categorization.

Despite the difficulty of homogenizing the definitions of executive functions, one of the authors defines it as the process that links ideas, actions and simple movements to guide the resolution of more complex behaviors.[25]

In total, six studies performed tests that assessed this cognitive function. Of these articles, four found no differences in patients with PD when compared to the control group.[8-11] One of these articles found no differences when patients had only the diagnosis of PD (n=22); however, when patients had PD and MDD (n=11), they demonstrated greater latency in decision-making when compared to a control group (n=22).[10]

Of the two articles that found differences in executive functions, one noted that high levels of anxiety in patients with PD could affect cognitive functioning in more complex, generating strategies, such as category formation, which is typically required in executive function. These studies added that such difficulties are related to prefrontal areas and the medial amygdala, part of the neuroanatomical circuit of conditioned fear.[5] The other study used patients with PD with and without agoraphobia (n=33), social phobia (n=32), obsessive-compulsive disorder (n=16), specific phobia (n=24), generalized anxiety disorder (n=7) and a control group (n=175). To measure executive function, the authors used the Trail Making Test, forms A and B. In form A, there was no significant difference between the overall group of anxiety disorder patients, or any of its subgroups, and the control group. However, in the case of form B, the overall anxiety group needed more time to complete the form, as compared with the control group. This included the subgroup of PD patients.[13]

Psychomotor abilities and processing speed

Visuospatial and psychomotor skills play an important role in daily life, but as they are more automatic than other processes, their importance is perceived clearly only when there is a deficit. For example, when challenged by identification, discrimination, and analysis of a complex stimulus in visual processing, we resort to visuospatial and psychomotor skills.[26]

Six of the included studies evaluated psychomotor abilities or processing speed. Of these, four found no difference between PD patients and the control group.[7,10,12,13] One article compared groups of different anxiety disorders, such patients with PD with and without agoraphobia (n=33), social phobia (n=32), obsessive-compulsive disorder (n=16), specific phobia (n=24) and generalized anxiety disorder (n=7) to a control group (n=175); there was no difference between the groups.[13] Two articles[7,12] compared only patients with PD (n=69; n=14) to a control group (n=19; n=7) and found no differences. Another study[10] used three subgroups: patients with PD (n=22), patients with MDD (n=11) and a control group (n=22).

Among the articles that found differences, one detected lower visuospatial skills in PD patients. However, it is important to note that these data are only a reflection of differences in processing speed.[8] The other article found differences in time and distance traveled by patients with PD (n=31) to reach the target of a game played virtually when compared to controls (n=31). However, the authors noted that not all patients had this difficulty, and were able to subdivide the group of PD patients. While one group had such difficulties, the other group's result matched the results of the control group. To understand this difference, the authors noted that the group with difficulties was older and had a longer history of PD. Thus, they proposed that age and the course of the disorder could lead to a greater propensity for changes in cognition and a worsening of behavioral strategies.[16]

Verbal fluency

Only two articles[7,13] assessed this cognitive function, finding no significant differences. While one study compared patients with PD (n=69) to a control group (n=19),[7] the other compared different groups of anxiety disorders (patients with PD with and without agoraphobia [n=33], social phobia [n=32], obsessive-compulsive disorder [n=16], specific phobia [n=24] and generalized anxiety disorder [n=7]) to a control group (n=175).[13]

Affective processing of faces and words

Six articles were found that evaluated affective processing. Of these, three evaluated face recognition.[10,17,18] In one study, patients with PD (n=30) showed no bias for critical faces, but they did show bias for safe faces, a finding that is consistent with the trend of avoiding dangerous situations and seeking the presence of safe people, when compared to a control group (n=30).[17] This finding is confirmed by other studies. Patients with PD with or without agoraphobia (n=23) show greater vigilance toward fearful faces when compared to a control group (n=22).[18] Another study used happy or sad faces with three comparative groups: patients with PD (n=16), PD patients with MDD (n=21) and a control group (n=20). The results showed that the control group made more errors in blocks of sad faces, while the clinical patients made more errors in blocks of happy faces. This suggests that while the controls paid more attention to blocks of happy faces, the patients paid more attention to blocks of sad faces. However, the group with PD showed no differences between sad or happy face blocks. This finding indicates that negative attentional bias could be related to the presence of depressive symptoms.[10]

Another article showed a difference in the time taken to recognize panic-related words in patients with PD with or without agoraphobia (n=60) when compared to a control group (n=60).[19]

The other two articles used neutral words and words related to the disorder; in both studies, PD patients showed an attentional bias for information related to the disorder.[20,21] One of the studies compared patients with PD (n=15) to a control group (n=15),[20] and the other study compared patients with OCD (n=18), patients with

PD (n=15), patients with hypochondriasis (n=14) and a control group (n=19).[21]

Discussion

Although many studies have evaluated cognitive functions in psychiatric patients,[4] research into such functions in patients with PD is limited, as observed in this review. Other mental disorders seem to receive more attention in this area.[27,28] Still, a few studies have included neuropsychological testing. Many studies use only a few tests rather than a complete neuropsychological battery, which is necessary for a more comprehensive evaluation.

Studies about the neurobiology of anxiety disorders, particularly in the case of PD, are the foundation for establishing a neuropsychological profile of these patients. Advanced neuroimaging studies and their possible relationship to the effects of psychotherapeutic treatment[2,3] is also important, as neuroimaging studies provide a detailed picture of possible neuroanatomical substrates involved in PD and sites of specific activity, and can thus help increase treatment effectiveness.[3] Neuropsychological assessment, in turn, seeks to contribute to a more accurate diagnosis and prognosis and to improve our understanding of possible changes to cognitive functioning resulting from the disorder.[4] Thus, both modalities seek to develop of a clinical profile of these patients.

Neuropsychological assessment aims to map possible cognitive dysfunction from the results of tests, social and individual history and neuroimaging studies. Therefore, a neuropsychological diagnosis is generated from quantitative and qualitative aspects. The quantitative aspects refer to the values obtained in tests and compared to a normative population. The qualitative aspects relate to clinical history, which takes into account not only educational attainment and sociocultural level, but also the timing and history of the presenting complaint, possible impacts of symptoms in activities of daily living, interactions with friends, and professional life, history of family risk factors, medication use and even perceptions about how alert and cooperative the patient is during the evaluation.[4]

The theoretical foundations of neuropsychological assessment come from the interface of different sciences, such as medicine, physiology and psychology. In mental disorders, neuropsychological assessment can contribute to a clarification of the possible cognitive limitations related to a disorder and suggest better medical and psychotherapeutic interventions.[4]

An interest in the potential for cognitive impairment in obsessive-compulsive disorder, especially in memory and executive function,[27,28] is observed in the literature. Initially, the hypothesis was that such patients could have a deficit in remembering their actions, which might account for their compulsions. However, investigations suggest that this memory deficit is secondary; some even question its existence. A new hypothesis suggests that patients exhibit organizational difficulty in processing information or in performing executive functions.[27,28]

As do studies of patients with PD, studies of obsessive-compulsive disorder suggest that larger sample sizes and attempts at better control for comorbidities are necessary in future research. It is unclear whether the findings of these studies represent the specific profile of a disorder or whether they reflect patient anxiety and mood in general. It is important to analyze patient intellectual ability prior to testing to avoid such issues.[27,28]

Findings regarding PD are still inconsistent and divergent; this might be explained by methodological issues. Such issues might include the difficulty of locating a large number of patients without comorbidities in most studies, the challenges of determining the severity of the disorder at the time of evaluation and a lack of methodological standardization. Comorbidities that may be present in patients with PD generate doubt as to whether any deficits found occur only in this specific disorder.[5-7,10] Furthermore, the anxiety of the patient while performing tasks can bias results.

A survey of these results raised some questions. Would memory deficits be found only if they were a reflection of the patients' anxiety? Have these patients turned their attention to anxiety to the extent that it prevents them from concentrating on a given task? These questions make even more sense when an increased attentional bias is present, i.e., if the task involves emotional processing, such as in exposure to faces or words that are reminiscent of the disorder.[5,12,17-21]

Another question concerns the possible relationship between a decrease in processing speed and a change in executive functions. This question stems from one study, which hypothesized that differences in this area in one group of patients could be a result of the group itself being more prone to difficulty in behavioral strategies. These strategies relate directly to problem solving, planning, decision making, and impulse control, among other characteristics of executive functions.[8] Although most of the articles did not find changes in executive functions, it is necessary to expand upon these studies because change would be expected and would confirm all existing biological models of PD.[3]

Notably, four of the six studies that evaluated executive functions were written after 2004; this fact seems to demonstrate a recent and growing concern with the influence of executive functions in PD. This is because executive functions are known to be strongly related to the frontal region, and the neurobiological model of panic takes into account a subcortical hyperactivation and consequent cortical hypoactivation, especially in the frontal regions. Thus, changes in these two areas seem to be related.

In this review, only memory and affective processing showed more consistent differences in patients with PD, compared with control groups or groups of patients with other mental disorders. In the case of memory, scores were lower in these patients, but in the case of affective processing, their performance was higher when information related to the disorder was presented. These findings, especially with regard to affective processing, are consistent with the clinical features of PD, as patients with the disorder are biased to show special attention to all information, images or contexts that relate to PD or to the imminence of a new attack. This reinforces the

importance of psychoeducation and exposure, so as to desensitize patients and progressively enable the management of these feelings and distorted thoughts.

Nevertheless, further studies, with larger sample sizes and greater methodological standardization, are required. Furthermore, future studies should be aware of the different degrees of severity of the disorder in patients recruited and their symptomatology. It is noteworthy that studies on PD, the theoretical foundations of neuropsychology and standardized tests are recent. Therefore, the relationship between these factors is still poorly characterized. The interface between the fields of neuropsychology/neuroscience and psychiatric disorders aims to better understand these relationships and provide better primary interventions for patients.

Disclosure

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Executive Function Impairments in Patients with Depression

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Abstract: Depression, the most prevalent psychiatric disorder, has a lifelong risk of 20% and is related to high rates of death among the patients. Thus, this study aims to conduct a systematic review of changes in executive functions of adult patients diagnosed with depression. We found 1381 articles; however, only 28 were selected and recovered. The inclusion criteria was the assessment of executive functions with at least one neuropsychological test, and articles that evaluated primarily adult individuals with depression, without comparison to other psychiatric disorders. Although most of the studies (25 out of 28 analyzed) have shown deficits in some executive subcomponents, these findings are not conclusive because they used different parameters of assessment. Moreover, many variables were not controlled, such as the different subtypes of the disorder, the high level of severity, comorbidity and the use of drugs. Most studies showed different deficits in executive functions in depressed patients, but further longitudinal studies are needed in order to confirm these findings.

Keywords: Cognitive impairment, depression, drugs, executive functions, neuropsychological assessment, psychiatric disorders.

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Executive Function Impairments in Patients with Depression

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Abstract: Depression, the most prevalent psychiatric disorder, has a lifelong risk of 20% and is related to high rates of death among the patients. Thus, this study aims to conduct a systematic review of changes in executive functions of adult patients diagnosed with depression. We found 1381 articles; however, only 28 were selected and recovered. The inclusion criteria was the assessment of executive functions with at least one neuropsychological test, and articles that evaluated primarily adult individuals with depression, without comparison to other psychiatric disorders. Although most of the studies (25 out of 28 analyzed) have shown deficits in some executive subcomponents, these findings are not conclusive because they used different parameters of assessment. Moreover, many variables were not controlled, such as the different subtypes of the disorder, the high level of severity, comorbidity and the use of drugs. Most studies showed different deficits in executive functions in depressed patients, but further longitudinal studies are needed in order to confirm these findings.

Keywords: Cognitive impairment, depression, drugs, executive functions, neuropsychological assessment, psychiatric disorders.

INTRODUCTION

Depression, the most prevalent psychiatric disorder, has a lifelong risk of 20% and is related to high rates of death among the patients [1]. Data from the World Health Organization (WHO) showed that depression is among the ten medical disorders that cause greater disability, due to not only the psychological frame, but to the risk of developing other diseases, such as diabetes and coronary diseases [1, 2]. This is neither the only nor the main reason that leads depression to impact the patients' lives: their manifestation can also worsen the prognostic of medical treatment which, due to physical, cognitive and quality of life impacts as a result of depression, can lead to avoidance/ deprivation of medical services [2].

Other important point is that most patients experience more than one episode of depression throughout life, and the chance of recurrence increases if the first episode occurred early in their lives and if there is a family history of disorder. Additionally, new episodes, stress and the duration of untreated illness influence the prognosis [1].

Depression also features a large heterogeneity regarding its clinical aspects depending on the timing of their manifestation (childhood, young adulthood, midlife, and elderhood), and this difference reflects a differential pathway to illness. In the case of younger patients changes in anxiety, sleep, appetite and energy are perceived [3].

NEUROBIOLOGY OF DEPRESSION

Concerning the psychobiological model of depression, animal and human studies have shown that this is an integrative model, with changes in various fields that interact with each other. For example, decrease in monoamine neurotransmission, low BDNF concentration, raised cytokines, dysregulation of the HPA axis, changes in cortical and subcortical brain areas and variations in genetic aspects [1].

Regarding the neurobiological aspects, research has advanced greatly because of different neuroimaging techniques, such as magnetic resonance imaging (MRI), positron emission tomography (PET) and functional MRI (fMRI). The brain areas involved include the limbic system (especially the amygdala and the hippocampus) and the

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prefrontal cortex (PFC). Changes in the activity of these areas are considered central to the pathophysiology of depression [1]. Thus, three regions seem to play a crucial role in the depression: the orbitofrontal cortex (OFC), the dorsolateral prefrontal cortex (DLPFC) and the anterior cingulated cortex (ACC) [3].

The PFC has an integrative function, since it gathers sensorimotor, motivational and affective information. This region can be subdivided into lateral (posterior dorsolateral, mid-dorsolateral, ventrolateral), orbitofrontal, ventromedial, basal, orbital, frontopolar, anterior and rostral [4]. Dorsolateral and ventromedial are connected with the cingulate gyrus and the hippocampus. Each one has different assignments and, possible dysfunctions have different roles in the maintenance of the psychopathology of depression [1]. The Amygdala is related to the selection and coordination of cortical and neuroendocrine responses, and emotional learning and memory. Therefore, abnormal activations of these regions have been related to the severity of depression [1]. Hippocampus is a brain structure that has been most studied in relation to depression, both in animals and humans, for several reasons, such as its association with learning, memory, emotional dependence and high capacity for neuroplasticity [1].

Specific studies of a neurobiological model of depression helped to develop a theoretical structure that can offer preventive interventions and better understanding of the possible cognitive functioning of these patients [3].

Neuropsychology of Depression

Neuropsychological assessment has been an important tool for assessing psychiatric disorders, since its findings allow an association between the behavioural and functional data of the patient and the neuroanatomical and neurophysiological findings [5]. Studies have shown that mood changes not only the areas, but also the process by which the thought occurs. Thus, in addition to clinical symptoms, depression may be accompanied by cognitive deficits, such as alterations in perception, attention, memory, processing speed, processing emotionally and, particularly, executive functions [6].

Executive Functions

Executive function is a term that comprises a set of cognitive processes [7]. Its first report was made by Luria, and although he has not used this term, he described a series of disorders related to executive dysfunctions, for instance, conduct problems, due to frontal lesions [8, 9]. Such understanding was improved, until we get to one of the most popular definitions of executive functions from Lesak, who defined the executive functions as the ability to formulate goals, plan and perform effectively [10, 11]. Therefore, it is an essential capability to make individuals independent, creative and socially integrated [12].

Executive functions are commonly associated with deficits from lesions in frontal regions and some psychiatric disorders, such as depression, which present marked frontal dysfunctions. These dysfunctions are so important to the patient's independence, that it becomes necessary to evaluate and better understand their possible effects in this psychopathology [7]. The studies that have begun to correlate depression and deficits in executive functions involved psychometrics and neuroimaging, and showed deficits in several aspects, such as abstraction ability, problem solving, loss of cognitive flexibility and tendency to perseverate [13].

Thus, this study aimed to conduct a systematic review of changes in executive functions of adult patients diagnosed with depression.

METHODS

A systematic search was conducted using the PubMed, ISI Web of Knowledge and PsycInfo databases using the following terms: "neuropsychological assessment", "depression" and "executive functions". The survey was conducted in February 2013; there was no time restriction given for any database.

A total of 1381 references were found (882 in Pubmed; 276 in ISI Web of Science; and 223 in PsycInfo). 65 of these articles were in a language other than English and 229 were duplicates; these were, therefore, excluded. Remained for abstract analysis 1087 references, and 28 articles were selected and recovered (see Fig. **1**). Only articles using at least one neuropsychological test for executive functions, evaluating only adult subjects and focusing on individuals with depression (without comparison to another psychiatric disorder) were selected. These exclusion criteria were necessary because of the extensive material in the literature, and also to focus the study only in patients with depression.

RESULTS

In neuropsychological assessment researches with adult patients with depression, many instruments are used and different functions are assessed. However, this study will rise only the findings related to executive functions in each of the studies (Table **1**).

Executive Functions in Adults with Depression

One study recruited 40 subjects with Major Depressive Disorder (MDD) and divided them into 2 subgroups: one with 20 subjects that have a history of 1 or 2 depressive episodes (mild group) with a mean age of 44.40 years and another subgroup of 20 subjects with a history of three or more depressive episodes (severe group) with a mean age of 48.15. There was also a group of 20 control subjects matched by age and education to the total group of 40 subjects with depression (before subdivision), with a mean age of 41.15 years. The Behavioural Assessment of the Dysexecutive Syndrome Q (BADS) was used to analyze task management, planning and monitoring, in order to assess executive functions. Two subtests of German word fluency task (RWT) were used to obtain cognitive flexibility related information; and visual and spatial backward memory span were also assessed by the Wechsler Memory Scale Revised (WMS-R) in order to measure sequenced coding. The results demonstrated that the control group showed better results than both patients' groups on all tests $F(3,55)=11.74$; $p<0.001$. And there is a relation between the severity of the disorder and worse performance. The findings showed that

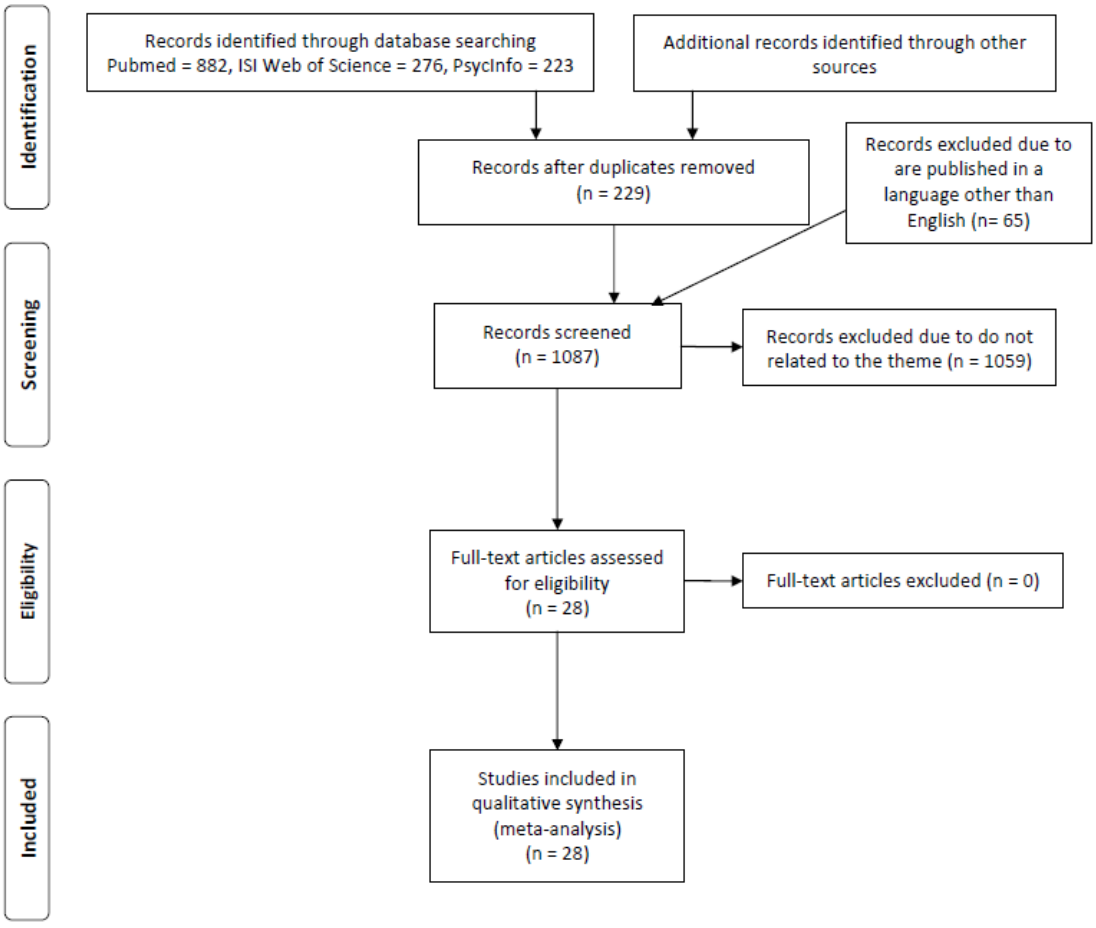

Fig. (1). Results of search strategy related to depression in elderly.

especially in the BADS test and backward memory span these differences were clearer F(3,55)=3.22; p=0.03 [14].

Another study conducted by neuropsychological evaluation in 123 patients with mild to moderate nonbipolar MDD without psychotic features and average age of 39.0 years in comparison to a control group of 36 subjects matched by age, gender and average age of 40.2 years old. The assessment of executive functions used four measures: 1) the Halstead-Reitan Categories Test of concept formation; 2) the Controlled Oral Word Association Test (COWAT); 3) the Wisconsin Card Sort Test (WCST), 4) the Trail Making Test Part B (TMT B). In addition, the Cambridge Neuropsychological Test Automated Battery (CANTAB) was used, combining a series of computerized tests that assess different functions, among which the executive functions, presented on a high-resolution touch-screen monitor. The results reveal that patients exhibit impairment on the WCST performance on various parameters, such as number of categories completed t=2.24; p=.03, perseverative responses t=2.39; p=.02, perseverative errors t=2.23; p=.03, and failures to maintain set t=2.01; p=.05. However, such deficits were not observed in the other three tests applied (Categories, Verbal Fluency and Trail B), as well as the CANTAB in their executive measures. The deficits found from the WCST suggest impairment in the ability to generate and maintain problem-solving strategies and setshifting ability. The authors suggest that the difference from this to other studies who often find deficits in other tests may be related to the severity of the disorder in these other patients [15].

One study compared 20 patients diagnosed with MDD and average age of 41.35 years with 20 subjects of a control group with average age of 38.4 years matched by gender and number of years of education. The authors want to assess the mechanisms of cognitive inhibitory facing emotional and neutral stimulus. For the evaluation of frontal executive functions the following tests were used: Modified six elements test, Brixton Spatial Anticipation Test, Dual-task

Table 1. Summary of the studies related to depression in elderly.

Authors	Subjects	M/F	Mean Age	Instruments for Executive Functions	Main Results	Ref.
Paelecke-Habermann, Y., Pohl, J., Leplow, B.	20 MG MDD 20 SG MDD 20 C	-	44.4 48.15 41.15	• Behavioural Assessment of the Dysexecutive Syndrome Q • Two subtests of German word fluency task • Visual and spatial backward memory span of the Wechsler Memory Scale Revised	The control group had better results on all tests in comparison with the patients' groups. In addition, the severity of the disorder was also a factor that worsened the performance tests.	[9]
Grant, M.M., Thase, M.E., Sweeney, J.A.	123 MDD 36 C	-	39.0 40.2	• Halstead–Reitan Categories Test of concept formation • Controlled Oral Word Fluency test of verbal fluency (form FAS) • Wisconsin Card Sorting Test • Trail Making Test (Part B). • Cambridge Neuropsychological Test Automated Battery with a series of computerized tests	The results showed that patients had worse performance on several parameters of the Wisconsin Card Sorting Test. However, this pattern was not sustained in any other test that assessed executive functions, suggesting a specific deficit in the ability to generate and maintain specific problem-solving strategies and to set shifting ability.	[10]
Gohier, B., Ferracci, L., Surguladze, S.A., Lawrence, E., Hage, W.E., Kefi, M.Z., Allain, P., Garre, J.B., Le Gall, D.	20 MDD 20 C	-	41.35 38.4	• Modified six elements test • Brixton Spatial Anticipation Test • Dual-task Performance • FAS verbal fluency test • Prose distraction task • Trail Making Test • Modified Card Sorting Test • Rule shift cards • Stroop Color Word Test • Hayling Sentence Completion test	Patients had worse performance on all tests, with the exception of the Modified Card Sorting Test.	[11]
Hammar, A., Sorenser, L., Ardal, G., Oedegaard, K.J., Kroken, R., Roness, A., Lund, A.	19 MDD C (-)	9 M 10 F -	42.5 42.0	• Stroop Color Word Test	The study was conducted at baseline and after six months. The scores didn´t differentiate, showing a group effect, where the depressed patients showed worse performance, but not an effect of severity of the disorder.	[12]
Lampe, I.K., Sitskoorn, M.M., Heeren, T.J.	23 MDD 60 C	23 F 60 F	64.0 64.8	• Wisconsin Card Sorting Test • Stroop Color Word Test	The authors found poorer performance of patients in both tests assessing executive functions. However, these deficits did not show a significant association with the duration of the disorder.	[13]
Cella, M., Dymond, S., Cooper, A.	19 MDD 20 C	-	35.8 35.1	• Iowa Gambling Task	The results demonstrated that, in stage 1, patients presented a worse performance in the latter blocks. And in phase 2 they showed a worse performance throughout the three shifts. Furthermore, when BDI was correlated with performance scores, negative correlations were found only in the block 9, 10 and 11.	[14]

(Table 1) contd…..

Authors	Subjects	M/F	Mean Age	Instruments for Executive Functions	Main Results	Ref.
Gualtieri, C.T., Johnson, L.G., Benedict, K.B.	38 MDD 31 MDD AM 69 C	18 M 20 F 9 M 22 F 25 M 44 F	38.11 43.55 41.30	• Stroop Color Word Test • Shifting attention test	The results showed the control group performed best in most of the variables assessed, followed by the group of depressed patients treated with antidepressants and, finally, by the depressed patients without any medication.	[15]
Porter, R.J., Gallagher, P., Thompson, J.M., Young, A.H.	44 MDD 44 C	15 M 29 F 15 M 29 F	32.9 32.3	• Controlled oral word association test • 'Exclude letter' fluency test • Vigil continuous performance test • Spatial working memory (CANTAB) • Tower of London (CANTAB).	The results showed poorer performance in patients with depression in comparison with the control group.	[16]
Crews Jr., W.D., Harrison, D.W., Rhodes, R.D.	30 MDD 30 C	30 F 30 F	20.33 20.20	• Design Fluency Test • Hand Dynamometer Tests of Grip Strength, Perseveration and Fatigue • FAS Test • Stroop Color Word Test • Trail Making Test (Parts A and B)	The results did not show significant differences between groups in any of the tests that assessed executive functions.	[17]
Langenecker, S.A., Bieliauskas, L.A., Rapport, L.J., Zubieta, J.K., Wilde, E.A., Berent, S.	21 MDD 20 C	21 F 20 F	32.2 29.5	• Modified Go / No-go test	Significant differences were found between groups in the test, as well as a significant interaction between the group and the performance in the task.	[18]
Mondal, S., Sharma, V.K., Das, S., Goswami, U., Gandhi, A.	30 MDD 30 C	19 M 11 F 20 M 10 F	31.77 31.47	• Trail Making Test (Part B) • Digit Span Backward	Results showed significant differences between groups in both tests, showing executive deficits in depressed patients.	[19]
Degl'Innocenti, A., Agren, H., Bäckman, L.	17 MDD 17 C	8 M 9 F 8 M 9 F	48.2 49.0	• Controlled oral word association test • Wisconsin Card Sorting Test • Stroop Color Word Test	The results found significant differences between depressed patients and the control group in all tests.	[20]
Stordal, K.I., Lundervold, A.J., Egeland, J., Mykletun, A., Asbjornsen, A., Landro, N.I., Roness, A., Rund, B.R., Sundet, K., Oedegaard, K.J., Lund, A.	45 MDD 50 C	18 M 27 F 25 M 25 F	35.56 32.92	• Controlled oral word association test • Tower of London • Paced Auditory Serial Addition Test • Digits Backward • Stroop Color Word Test • Wisconsin Card Sorting Test	The results showed significant differences between groups in all tests, where patients with depression performed worse. However, the level of commitment in each of the tasks was variable.	[21]
Stordal, K.I, Lundervold, A.J., Biringer, E., Egeland, J., Hammar, A., Landro, N.I., Roness, A., Rund, B.R., Sundet, K., Lund, A.	43 MDD 50 C	- -	35.2 32.9	• Paced Auditory Serial Addition Test • Digit Backward subtest • Controlled oral word association test • Wisconsin Card Sorting Test • Stroop Color Word Test	The results found significant differences in all measurements: set-maintenance, inhibition, working memory and verbal fluency. Depressed patients exhibited the worst performance.	[22]

(Table 1) contd.....

Authors	Subjects	M/F	Mean Age	Instruments for Executive Functions	Main Results	Ref.
Hammar, A., Strand, M., Ardal, G., Schmid, M., Lund, A., Elliott, R.	24 MDD 24 C	6 M 18 F 6 M 18 F	38.08 37.12	• D-KEFS Trail Making Test • D-KEFS Color - Word Interference Test • D-KEFS Verbal Fluency Test • D-KEFS Tower Test	A difference between groups in D-KEFS Verbal Fluency Test was observed, as well as a significant difference between groups in the condition 3 and 4 in the D-KEFS Color - Word Interference Test. Thus, the executive functions impaired in depressed patients are Inhibition, Inhibition / Switching and Category Fluency.	[23]
Withall, A., Harris, L.M., Cumming, S.R.	17 DMF 17 DWMF	64.7 % F 76.5 % F	46.12 41.59	• Digit span backwards • Stroop Color Word Test • Shortened Wisconsin Card Sorting Test • Modified Six Elements Test	The results showed differences between groups in all tests, while the melancholic group (DMF) had the worst outcomes.	[24]
Michopoulos, I., Zervas, I.M., Papakosta, V.M., Tsaltas, E., Papageorgiou, C., Manessi, T., Papakostas, Y.G., Lykouras, L., Soldatos, C.R.	11 DMF 11 DWMF 11 C	11 F 11 F 11 C	50.9 47.8 52.8	• Stockings of Cambridge task • Intradimensional/extradimensional (ID/ED) attentional set shifting task	The results did not show significant differences between the control group and the group of depressed patients. However, when this group was divided into melancholic and non-melancholic patients, there was a difference found in relation to Intradimensional/extradimensional (ID/ED) attentional set shifting task.	[25]
Markela-Lerenc, J., Kaiser, S., Fiedler, P., Weisbrod, M., Mundt, C.	11 DMF 12 DWMF 27 C	5 M 6 F 7 M 5 F 14 M 13 F	36.6 43.2 39.9	• Stroop Color Word Test	The results showed the patients presented impaired results in the reaction time when compared to a control group. When the patients' group was divided into melancholic and non-melancholic, the melancholic subtype exhibited impaired results in the first series of evaluation, showing greater susceptibility to distractors.	[26]
Quinn, C., Harris, A., Kemp, A.	65 DMF 59 DWMF	23 M 42 F 26 M 33 F	41.54 37.77	• Executive Maze task	The executive functions were measured from a cluster analysis and demonstrated a significant relationship between patients with melancholic subtype and cluster 1, representing lower performance. The melancholic subtype holds an association with cluster 2, representative of high levels of performance.	[27]

(Table 1) contd.....

Authors	Subjects	M/F	Mean Age	Instruments for Executive Functions	Main Results	Ref.
Bhardwaj, A., Wilkinson, P., Srivastava, C., Sharma, M.	20 R MDD 20 C	18 M 2 F 17 M 3 F	34.3 33.0	• Wisconsin Card Sorting Test	Given the parameters evaluated, patients showed a worse performance in three aspects: greater number of nonperseverative errors, fewer categories completed and greater number of trials required to complete the test.	[28]
Yamamoto, T., Shimada, H.	12 MDD 11 P MDD 19 C	5 M 7 F 2 M 9 F 7 M 12 F	21.08 19.27 19.79	• Behavioural Assessment of the Dysexecutive Syndrome • Verbal Fluency Test.	There were nOt found significant differences between the two patient groups and the control group.	[29]
Preiss, M., Kucerova, H., Lukavsky, J., Stepankova, H., Sos, P., Kawaciukova, R.	97 R MDD 97 C	46 M 51 F 46 M 51 F	46.3 46.1	• Trail Making Test (part B)	The results showed that the cognitive flexibility evaluated by the Trail Making Test (Part B) was in shortfall in patients. This demonstrates that such impairments remain even after remission of the disorder.	[30]
Hasselbalch, B.J., Knorr, U., Hasselbalch, S.G., Gade, A., Kessing, L.V.	88 UDRS 50 C	28 M 60 F 15 M 35 F	59.8 59.7	• Stroop Color Word Test • Wisconsin Card Sorting Test • Letter-Number Sequencing	The patients performed worse in all tests when compared to the control group.	[31]
Reppermund, S., Ising, M., Lucae, S., Zihl, J.	53 UD 13 C	25 M 28 F 6 M 7 F	43.5 46.4	• Simple and alternate verbal fluency tasks • Raven Standard Progressive Matrices • Three subtests of Cambridge Neuropsychological Test Automated Battery	This study found worse performance in the patients' group compared to the control group, but showed no significant difference between the patients' results before and after remission of the disorder.	[32]
Biringer, E., Lundervold, A., Stordal, K., Mykletun, A., Egeland, J., Bottlender, R., Lund, A.	30 MDD	12 M 18 M	35.8	• Wisconsin Card Sorting Test • Stroop Color Word Test	The results showed that recovery from depression would be responsible for the improvement of executive functions scores in 11% of cases. And the recovery group showed no significant difference compared to the control group.	[33]
Withall, A., Harris, M., Cumming, S.R.	48 MDD	66.7 % F	37.96	• Digit Span Backwards • Stroop Color Word Test • Shortened Wisconsin Card Sorting Test • Modified Six Elements Test.	The results showed that the scores of perseverative errors in Shortened Wisconsin Card Sorting Test were significant predictors of the Hamilton Depression Rating Scale in the follow-up group. However, this difference was not sustained after the Benjamini-Hochberg correction.	[34]

(Table 1) contd.....

Authors	Subjects	M/F	Mean Age	Instruments for Executive Functions	Main Results	Refs.
Boeker, H., Schulze, J., Richter, A., Nikisch, G., Schuepbach, D., Grimm, S.	28 MDD 28 C	15 M 13 F 15 M 13F	35.03 39.70	• Intradimensional/ extradimensional (ID/ED) attentional set shifting task	Impaired functioning was detected in several variables of the test applied. However, there was no significant difference between subjects in the acute phase of the disorder and subjects in the remission phase.	[35]
Westheide, J., Wagner, M., Quednow, B.B., Hoppe, C., Cooper-Mahkorn, D., Strater, B., Maier, W., Kuhn, K.U.	15 MDD 15 C	15 M 15 M	45.1 42.1	• Iowa Gambling Test • Go/No-Go Task • Delayed Alternation Task	There were not found any significant differences between groups.	[36]

C = Healthy Control Subjects; DMF = Depression with melancholic features; DWMF: = Depression without melancholic features; MDD = Major Depressive Disorder; MG = Mild Group; MDDAM = Major Depressive Disorder with antidepressant monotherapy; PMDD = partially met the DSM-IV-TR criteria for MDD; RMDD = Recovered Major Depressive Disorder; SG = Severe Group; UDRS = Unipolar Disorder Remitted State; UD = Unipolar Depression.

Performance and FAS verbal fluency test - a French version of FAS task. As for the evaluation of inhibition, three subdivisions were made. Regarding the Access function, the instrument used was Prose distraction task. The evaluation of deletion function was made with TMT, The Modified Card Sorting Test and Rule shift cards. And the Restraint function was mensured with Stroop test and The Hayling Sentence Completion test. There were differences found between groups assessing the Modified six elements test, where patients had worse performance when compared to the control group $F(1.38)=16.5$; $p<.001$. They also showed poorer performance in the simple task of the dual-task performance $F(1.38)=26.2$; $p<.001$ and in the semantic aspect of the verbal fluency $F(1.38)=32.6$; $p<.001$. The results showed that, regarding the access of information, depressed patients read slower than the control group in all subtests of the Prose distraction task. And they also read significantly more semantic distractors (T2) than the control group $F(1,38)=18.5$; $p<.001$. Concerning the aspect of deletion function patients were slower to complete both parts of the TMT A, $F(1,38)=37.9$; $p<.001$; Part B, $F(1,38)=23.9$; $p<.001$. In relation to the rule shift cards they took more time to execute the task for the first rule, $F(1,38)=35.8$; $p<.001$ and the second rule, $F(1,38)=79.3$; $p<.001$. However, no significant differences were found between patients and the control group in the Modified Card Sorting Test. In the assessing of the restraint function the time to execute the Stroop Test was significantly longer in the depressed group $F(1,38)=148.8$; $p<.001$, and was impaired in performance in the second part of the Hayling Sentence Completion Test, with longer time, $F(1,38)=53.4$; $p<.001$ and more errors, $F(1,38)=13.2$; $p<.001$. Thus, this study found deficits in all three aspects of inhibitory processing (access, deletion and restraint) in patients with depression [16]. These results confirm the hypothesis of a deficit in the anterior cingulate cortex in patients with depression, which leads to consequences in different cognitive functions such as error detection, anticipation of tasks, attention, motivation, and modulation of emotional responses [17].

A study using the Stroop paradigm evaluated 19 patients with recurrent unipolar MDD and average ages of 42.5 years, and compared them to a control group with a mean age of 42 years, matched by age, gender and level of education. Patients were evaluated at baseline along with the Hamilton Depression Rating Scale (HDRS; scored > 18) and after 6 months, when most patients already had a reduction of the symptoms. Results showed a performance impairment in the patients in the two periods of evaluation, showing an effect in the group $F(1,36)=7.51$; $p<0.05$; $g2=0.18$ but no association to the severity/course of the disorder [18]. A comparative study was conducted including 23 female patients, aged between 46 and 82 years and diagnosed with recurrent MDD, and 60 healthy age-matched females aged between 45 and 85 years. The executive functions were assessed using the WCST and Stroop test. The results showed that patients had worse outcomes in the assessment of executive functions, when compared to the control group $F(5.52)$; $d.f.=1.78$; $p=0.021$. However, these deficits do not have a correlation with the duration of the disorder $r=-0.18$. Thus, the results suggest that the recurrence of depressive episodes is not one more aspect that affects executive functions in these patients [19].

Another study assessed the flexibility of decision-making in 19 patients with MDD and average age of 35.8 years and 20 healthy control subjects with a mean age of 35.1 years. For this evaluation the Iowa Gambling Task (IGT) was used, by a contingency-shift phase where decks progressively changed reward and punishment schedule. The results were obtained by subtracting the disadvantageous choices from the number of advantageous for each block of 20 trials. The results showed that in the first phase the control subjects were better at learning, especially in the latter blocks, with a significant main effect of group $F(1, 37)=12.48$; $p=0.001$; and in phase 2, controls showed better levels of learning throughout the three shifts $F(1,37)=11.37$; $p=0.002$. The tests conducted on phase two showed that control subjects perform better in blocks 7, 9, 10 and 11 (all $p<0.05$). The results of this study can be correlated to the hypothesis that the orbitofrontal cortex has integrative function to signaling signals of reward/punishment for our actions and are able to detect and analyze details pertaining the overall situation [20]. To analyze the association between the severity of major depressive disorder and performance in the test, the authors examined the Beck Depression Inventory (BDI) scores in each of the blocks in this group. The results showed significant negative correlations in block 9 $r=-0.55$; $p<0.05$, block 10 $r=-0.48$; $p<0.05$ and block 11 $r=-0.62$; $p<0.001$. Therefore, these results suggest that the worst performance

in the three blocks of the test for patients with MDD would be due to alterations in sensitivity to reward and punishment by these patients [21].

One study recruited 38 subjects with unipolar nonpsychotic MDD without psychotropic drugs, 31 subjects with MDD treated with antidepressant monotherapy for at least four weeks and 69 subjects in the control group matched by age, race and gender. The neurocognitive evaluation was measured from the CNS Vital Signs, which is a computed battery composed of seven different tests that assess differents cognitive domains. With regard to the aspect of executive function evaluation, the corresponding tests were Stroop test and Shifting attention test. The results showed that there was a significant difference between the group with MDD without medication and the control group concerning the cognitive flexibility t=2.60; p=0.01. In fact, for most of the variables assessed the control group had the best scores, followed by patients with MDD treated with antidepressants and, finally, patients with MDD without medication [22].

Another study met 44 patients with a diagnosis of MDD all psychotropic medication-free for at least six weeks, with an average age of 32.9 years and a control group of 44 healthy subjects matched by age, gender, premorbid IQ, years of formal education and season of testing, with a mean age of 32.3 years. Furthermore, the women were matched by phase of menstrual cycle. For the evaluation of sustained attention and executive functions the following tests were used: COWAT, 'Exclude letter' fluency test, Vigil continuous performance test, Spatial working memory (CANTAB) and Tower of London (ToL - CANTAB). The results showed that patients with MDD issued fewer words in the Benton´s FAS test F(4.48); d.f.=1.86; p=0.037 and in the Exclude letter fluency F(8.75); d.f=1.84; p=0.004; had more errors of omission U=694.5; p=0.04 and commission U=684.5; p=0.04 in the Vigil continuous performance test, although there has been no difference between the groups regarding the time of latency F(1.04); d.f.=1,84; p=0.31; in the Spatial working memory (CANTAB) they had more errors than the control group at six t=2.91; d.f.= 85; p=0.005 and eight shape of problems t=2.92; d.f.=85; p=0.004 and had a less efficient search strategy F(8.22); d.f.=1,85; p=0.005; in ToL the only interaction obtained was initial thinking time F(3.88); d.f.=3,225; p=0.013 [23].

A study conducted only with women, compared 30 women with depression and a mean age of 20.33 years to a control group of 30 women and a mean age of 20.20 years without depression, with approximate ages and intellectual levels to assess the executive functions of the two groups. Neuropsychological assessment was conducted based on the following tests: Design Fluency Test, Hand Dynamometer Tests of Grip Strength, Perseveration and Fatigue, FAS Test, Stroop Test, and the TMT A and B. Regarding the results, no significant differences were found between groups (depressed and non-depressed) in any of the tests, but the authors noted that these findings may have some relation with some points, such as depressed patients in the study are not hospitalized (which could worse their performance) [24].

Another study carried out only with women compared 21 women with MDD and a mean age of 32.2 years to 20 women in a healthy control group with a mean age of 29.5 years. The modified Go/No-go test of inhibitory control was performed in order to assess executive functions. The results showed that there was a significant difference between the groups in the test conducted F(1.36)=4.42; p=.04; eta'=.111, as well as a significant interaction between the group and the level in the task F(1.36)=4.11; p=.05; eta"=.10. These results allowed measuring problem solving and sustained effort in depressed women [25].

A study was conducted with 30 patients diagnosed with MDD and a mean age of 31.77 years and 30 subjects in a control group with a mean age of 31.47 years, matched by age, sex, and socio-economic status. Of the tests used, those who had measures of executive functions were the TMT B and the Digits Backward (DB). In the analysis of the results the authors divided the findings into four possibilities: if $p>0.05$, the difference was not significant, if $p<0.05$ the difference was significant, if $p<0.01$ the difference was highly significant and if $p<0.001$ the difference was very highly significant. Regarding the comparison of performance between groups in the TMT B test the results were $p<0.001$, in other words, they were very highly significant. The comparison between groups in the DB test showed that $p<0.05$, or simply, a significant difference. These results showed that patients with depression demonstrate deficits in the executive functions [26].

A study carried out with 17 patients with MDD and a mean age of 48.2 years and 17 subjects in a control group with a mean age of 49.0 years evaluated possible executive deficits resorting to COWAT, WCST and Stroop Test. The results found more favorable scores for the control group in all variables of the COWAT, F(16.7); MSE=150.2; $p<0,0001$; $\omega^2=0.3$, as well as the number of trials F(5,0); MSE=399.9; $p<0,005$; $\omega^2=0.1$, the number of errors, F(4.8); MSE=395.2; $p<0,005$; $\omega^2=0.1$, the number of non-perseverative errors F(4.6); MSE=85.6; $p<0,005$; $\omega^2=0.1$, and the percentage of conceptual level responses F(5.4); MSE= 332.8; $p<0,005$; $\omega^2=0.1$, of the WCST. The Stroop Test also revealed a difference between groups, F(1,31)=9.7; MSE=2037.7; $p<0.01$; $\omega^2=0.2$ and condition F(3,93)=73.2; MSE=173,3; $p<0.0001$; $\omega^2=0.7$, demonstrating that depressive patients also proved to be slower than the control group and to have a slower performance on incongruent trials under a baseline. Thus, this study showed that patients with major depression exhibit deficits in different domains of executive functions [27].

A study was conducted with 45 patients with MDD, recurrent and non-psychotic, and a mean age of 35.56 years. These patients were in a moderate to severe phase of the disorder and their depressive episodes varied between two and five. A control group was also included containing 50 subjects with a mean age of 32.92 years. The six tests that assessed executive functions were: COWAT, ToL, Paced Auditory Serial Addition Test (PASAT), DB from WAIS-R, Stroop Test and WCST. The results showed that patients performed worse on all tasks in comparison to the control group. Significant differences were found in phonemic and categorical verbal fluency, the PASAT, DB, Stroop Test, the failure to maintain set and perseverative errors from WCST. The level of commitment in each of the tasks was variable, being between -0.15 and -0.89 and the reliability analysis across all executive functions tests yielded an alpha value of

0.827. The authors also calculated the total mean of executive function z-score difference, which was estimated to -2.15 s, 10= -0.22 s [28].

A study was conducted with 43 patients with a mean age of 35.2 years, diagnosed with recurrent moderate to severe MDD without psychotic features, with an average of 2 to 5 episodes of depression, and a control group consisting of 50 healthy subjects matched by age, gender, level of education and intellectual abilities, with a mean age of 32.9 years. The tests used for the evaluation of executive functions were: PASAT, DB from WAIS-R, COWAT, the Failure to Maintain Set variable from WCST and the Stoop Test. The measures of evaluation of the results were set-maintenance, inhibition, verbal fluency and working memory. The results found a significant difference between the groups in all measures used. However, the authors point out that despite such a significant difference exists there are patients without such deficits, as there are control groups/subjects with that feature, which shows that this variance can be explained by others factors than just the presence of the disorder. The authors found interactions between age and diagnosis as a way of predicting deficits executives, where patients with depression and older, have more chances of having such impairments b value of 0.286; p</0.093 in the linear regression model [29].

Another study compared 24 patients diagnosed with MDD and a mean age of 38.08 years and a control group of 24 healthy subjects matched by age, gender and years of education with a mean age of 37.12 years. For the neuropsychological tests the D-KEFS test battery was used. Concerning the executive functions, the D-KEFS Trail Making Test assesses the mental flexibility (setshifting) measured by condition 4, apart from other cognitive areas; The D-KEFS Color - Word Interference Test is a version of the Stroop paradigm and investigates the inhibitory capacity; The D-KEFS Verbal Fluency Test also assesses mental flexibility (set shifting) and The D-KEFS Tower Test is a version of ToL and assesses spatial planning, rule learning, and the ability to establish and maintain cognitive set. In the D-KEFS Color - Word Interference Test, there was a statistical difference between groups F(4,43)=3.81; p=0.010; Wilks' Lambda=0.74, partial eta-squared=0.26. In condition 3, which assessed inhibition, the patients took longer to complete the task F(1,46)=5,30; p=0.026, but there was no difference between groups in the number of errors. In condition 4, which evaluated Inhibition/Switching, patients also took significantly more time to complete the task F(1,46)=5,49; p=0.024, but this didn't affect the number of errors found. As for D-KEFS Verbal Fluency, there were also found significant differences between groups F(3,44)=3.202; p= 0.032; Wilks' Lambda=0.82, partial eta-squared=0.18. As for the D-KEFS Tower Test and D-KEFS Trail Making Test, no significant differences were found between groups. Thus, the executive aspects in which there were found impairments were Inhibition, Inhibition/Switch-ing and Category Fluency [30].

Executive Functions in Adults Presenting Melancholic and Non-Melancholic Subtypes of Major Depressive Disorder

One study recruited 34 patients diagnosed with MDD, 17 suffering from the melancholic subtype and 17 the non-melancholic subtype. The authors sought to know if the differences of these subtypes explain the contradictory findings regarding the evaluation of cognitive functions in patients with depression. The group suffering from the melancholic subtype had a mean age of 46.12 years and the non-melancholic subtype group had a mean age of 41.59 years. For the evaluation of executive functions there were used the DB test, the Stroop Test, the Shortened WCST and the Modified Six Elements Test. There were differences between groups in all these tests, and the melancholic subtype group showed worse outcomes. The results were, DB, F(1,29)=5.05; eta2=0.15; p≤0.05, SCWT interference score F(1,29)=7.00; eta2=0.19; p≤0.01, WCST categories completed F(1,29)=13.63; eta2=0.32; p≤0.001, WCST perseverative errors F(1,29)=8.81, eta2=0.23, p≤0.01 and SET score F(1,29)=8.94; eta2=024; p≤0.01. Thus, the initial results and follow-up of 3 months proved consistent with other studies that showed executive deficits related to patients suffering from the melancholic subtype of depression [31].

Another study was conducted only with women. In total, 33 women participated, 11 diagnosed with depression with melancholic features and a mean age of 50.9 years, 11 with depression without melancholic features and a mean age of 47.8 years and 11 control subjects matched by sex, age and education with a mean age of 52.8 years. Patients with depression were admitted through the Women's Mental Health Program in Athens University Department of Psychiatry. Neuropsychological assessment was performed through a computerized battery. The assessment of executive functions was composed by the following tasks: the Stockings of Cambridge task (SOC) that accesses the ability of strategic planning of the subject; and the Intradimensional/extradimensional (ID/ED) attentional set shifting task, that accesses the maintainability of attention despite of the stimuli. The results showed that, although the control group obtained higher scores than the group of depressed patients, this difference was not significant. However, when patients were divided into melancholic and non-melancholic, there was a significant difference in the ID/ED task between the control group and the melancholic patients. In other tasks that assess frontal striatal functions no differences were found, which may be related to the small sample. Thus, these results show that set shifting deficits may be specific to the melancholic subtype of depression [32].

Another study selected 23 patients diagnosed with unipolar MDD and a mean age of 40 years, and a group of 27 healthy subjects matched by gender, age and year of school education and a mean age of 39.9 years. The patients group was divided into melancholic depression (11 subjects) with a mean age of 36.6 years and non melancholic (12 subjects) with a mean age of 43.2 years. The executive functions, particularly the inhibition of a learned routine, were assessed from a trial mixed manual version of the Stroop Test, presented in the Stim software (Neuroscan Inc.). The evaluation of the results was made from the software itself, with reaction time and errors data. When comparing the entire group of patients with depression to the control group, the only significant difference was the time of reaction, which revealed that patients have slower reaction time than the control group F(1,48)=3.4; p<0.07. When the group of depressed patients were subdivided into melancholic and non melancholic, significant differences

were found in the non melancholic group when compared to the control group t=-2.1; p<0.05, but only on the first series of evaluation. However, no significant differences were found between the control group and the melancholic subgroup in any of the four series performed. These findings suggest that non melancholic depressed patients would be more susceptible to distractors than melancholic depressed patients or healthy control subjects. However, the authors emphasize the importance of further studies, especially with a larger number of subjects [33].

A group of 124 patients with a primary diagnosis of MDD, 65 suffering from the melancholic subtype and a mean age of 41.54 years and 59 suffering from the non melancholic subtype and a mean age of 37.77 years were evaluated in order to verify the possible difference in neuropsychological profile among groups. Neuropsychological assessment was computerized and, in the executive functions case, the measure used was the Executive Maze task, which is a computerized adaptation of the Austin Maze. The analysis of the results was made by means of cluster because this measure has the ability to "identify groupings, patterns of attributes or categories that can be interpreted as a meaningful set by identifying how each category differs from the others". According to this analysis, cluster 1 would be indicated by lower performance on neuropsychological assessment and higher levels of severity and symptoms of the disorder, whereas cluster 2 is the opposite of 1, indicating high levels of performance and low levels of severity and symptomatology. In the case of executive functions, higher scores indicate worse performance. A significant correlation was found between patients suffering from the melancholic and non melancholic subtypes and the measure of cluster $w^2(1)=7.495$; $p<.01$, where 58% of the melancholic subtype patients were associated to cluster 1 and 66% of non melancholic subtype patients were associated to cluster 2 [34].

Executive Functions in Patients Recovering from Depression

A study was conducted with a total of 20 patients recovering from depression with a mean age of 34.3 years and 20 control subjects matched by age group, sex and education, with a mean age of 33.0 years. The criteria of remission DSM IV was used, wherein remission occurred at least 2 months before. The WCST was used for the evaluation of executive functions, which found that the number of previous depressive episodes was significantly correlated with three parameters evaluated in this test, a greater number of non perseverative errors (p=0.02); fewer categories completed (p=0.03) and a greater number of trials required to complete the test (p=0.03). The problems with non perseverative errors may be related to the difficulty of strategy in problem-solving, and even to the control of the depressive symptoms (based on HDRS). This effect is not ceased, indicating it may be one more feature of the residual symptoms. Thus, there are two possibilities of explanation for this situation: greater vulnerability to depression in patients with impairment in executive functions; or consecutive episodes of depression would generate permanent damage in certain brain areas. However, there was no significant difference found regarding the perseverative errors, which can be related to the small sample size [35].

A study was conducted using three groups: the first consisted of 12 patients who had fully met the criteria for MDD (complete group) and have a mean age of 21.08 years; the second included 11 patients who had partially met the criteria (partial group) and have a mean age of 19.27 years; and the third consisted of 19 subjects in a control group with a mean age of 19.79 years. For the evaluation of executive functions the BADS, a battery composed of six subtests, and the Verbal Fluency Test were used. The results showed that the two groups composed of patients did not demonstrate a significant difference in both performance tests that assessed executive functions. These findings are different from those found in the literature, which stated that remitted MDD patients have executive dysfunctions. The authors explain these findings from different ages and duration of depressive episodes among the studies surveyed [36].

Another study also wanted to investigate the possible persistence of cognitive deficits despite the remission of depression. The study consisted of 97 patients in remission of MDD for at least 2 months with a mean age of 46.3 years, and 97 control subjects matched by age, education and gender, and mean age of 46.1 years. A valid Czech version of TMT B was used to assess executive functions, which is a test commonly used to evaluate cognitive flexibility. The results suggest impairment in cognitive flexibility in the group of patients Wilcoxon Matched Pairs Test, n=94; Z=2.132; p=0.033, showing that cognitive deficits persist even in the remission of the disorder [37].

One study enrolled 88 patients with diagnosed with unipolar MDD in a remitted state with a mean age of 59.8 years, and 50 individuals in a control group matched by age and gender with a mean age of 59.7 years. The executive functions were assessed by three tests: the Stroop test, the WCST and the Letter-Number Sequencing, which is included in the Wechsler Adult Intelligence Scale, third edition (WAIS III). The TMT A and B was used as a marker of attentional and processing speed, but part B also requires cognitive flexibility and may also be classified as a test for executive functions. In the first test, the data taken into account was interference, the ability to inhibit automatic responses to controlled responses, then being associated with cognitive control and performance monitoring. And in the WCST case, the evaluation was based on the total number of errors. The results showed that patients performed worse on all tests in comparison with the control group [38].

Another study compared young and middle-aged patients with depression in its acute stage, six months after the remission of symptoms and six months after such remission. His goal was to clarify the specifics of cognitive dysfunction during the course of the disorder. The study consisted of 53 patients with a mean age of 43.5 years, 16 with a depressive episode and 37 with recurrent depression. Furthermore, there was a control group, with 13 subjects and a mean age of 46.4 years, with no history of Axis I psychiatric disorders, matched by age, gender and education. For the evaluation of executive functions there were used: Simple and alternate verbal fluency tasks, for the evaluation of cognitive flexibility; Raven Standard Progressive Matrices (SPM) to test visual problem solving; and three subtests of CANTAB,

Delayed Matching to Sample Namely (DMS), (ID/ED) and Spatial Working Memory (SWM) for the evaluation of cognitive flexibility and working memory. The authors compared the cognitive deficits with variable remission of depression and found no significant data (all $p>0.05$). In other words, cognitive functions could not be regarded as a predictor of the course and remission of depression. Furthermore, patients with depression had inferior performance when compared with the control group [39].

A study tested 30 patients with a mean age of 35.8 years and diagnosis of recurrent unipolar MDD and retested the same about 2 years later when they were already partially or totally recovered from the disorder. The WCST and Stroop Test were used as measures for executive functions. The authors performed a correlation to find the association between the Hamilton Depression Rating Scale (HAM-D) and changes in executive functions. They found a positive Pearson's correlation coefficient $r=0.33$; $p=0.04$, one-tailed, and the depression recovery (measured through the HAM-D) explained 11% of the variance of EF improvement from T1 to T2 $r2=0.11$. Furthermore, the authors compared the results of the recovery group to a healthy group and there was not a significant group difference $p=0.190$, two-tailed. These results showed that improvement in depressive symptoms is also accompanied by an improvement in measures of executive functions, so even long-term does not produce determinant cognitive impairment [40].

Another study evaluated 48 patients diagnosed with MDD and reassessed them 4 months later to check for possible changes in cognitive scores in case of remission of symptoms. The criteria of remission was based on an improvement of at least 50% of the scores of HAM-D and don´t have more syndromic diagnosis of the disorder. The cognitive assessment of executive function consisted of the following tests: the DB test to evaluate the mental flexibility; the Stroop Test, which, among other parameters, assesses distractibility and response inhibition; the Shortened WCST, which is a measure of concept formation, abstraction, working memory, shifting set and the ability to utilize feedback; the Modified Six Elements Test, which accesses different components of executive functions. The results showed that at study entry patients have a moderate to severe score on HAM-D and prominent scores of executive dysfunction and apathy on Frontal Systems Behavior Scale (FrSBe), which evaluates apathy, disinhibition/emotional dysregulation and executive dysfunction. Furthermore, regarding the evaluation of cognitive executive functions the perseverative errors' scores in WCST-S were significant predictors of the HAM-D score in the follow-up group. However, this difference became nonsignificant after Benjamini-Hochberg correction ($p=0.07$). The perseverative errors' score from the Shortened WCST test also proved to be significant in predicting the score of the DSM-IV Social and Occupational Functioning Assessment Scale (SOFAS) at follow-up [41].

Another study was conducted with 28 patients diagnosed with MDD without comorbidities and a mean age of 35.03 years in two stages, in the acute state of MDD and after clinical recovery. In the first moment, these patients scored at least 24 in the HAM-D and the BDI tests. There was also a control group of 28 healthy subjects with no personal or first-degree family history of psychiatric disorders and mean age of 39.70 years. All subjects were assessed with the CANTAB test, and the executive function was assessed by ID/ED. The results showed impaired functioning in the number of stages $t=-2.24$; $p<0.05$), errors $t=2.18$; $p<0.05$), and trials $t=2.21$; $p<0.05$ in the ID/ED task in patients in the acute stage of MDD compared to healthy subjects. Changes in the HDRS scores $t=7.64$; $p<0.001$ and in the BDI $t=5.09$; $p<0.001$, indicate clinical recovery and, thus, a new analysis was performed with these patients. However, there were not significant differences between acute and remitted states regarding executive functions, which can mean a trait character of the disorder [42].

A study conducted only with men, focused to investigate the performance of patients with fully or partly remitted unipolar MDD without psychotic symptoms, compared to a control group. The group of patients consisted of 15 men with a mean age of 45.1 years, and a control group which also had 15 men, matched by age and IQ and a mean age of 42.1 years. The neuropsychological assessment of the executive functions was conducted through IGT, Go/No-Go Task and Delayed Alternation Task (DAT; 26). The results showed no significant differences in the IGT score between patients and the healthy control group. The ANOVA analysis between measures found a significant main effect of the factor block indicating a shift in drawing cards across blocks $F(3,84)=16.33$; $p=0.000$ but not an interaction between the factor block and the group $F(3,84)=0.27$; $p=0.844$. The authors also did not find significant differences between patients and controls in the Go/No-Go task and delayed alternation task, confirming the finding that these patients were unimpaired in the executive tasks associated with orbitofrontal function. However, the authors emphasize the limitations of the study, because of the small number of participants and exclusively male sample [43].

DISCUSSION

Depression, for its high rates of prevalence worldwide, has been widely studied in various aspects [44]. Studies of neuropsychological assessment have been conducted for a long time, but there are still many questions to be answered, among them the functioning of the executive functions in this disorder [45].

The neuropsychology approach aims to understand the correlation between behavioural and cognitive functioning and, how a deficit in this operation causes a particular symptom in neurological and non neurological disorders. In the case of psychiatric patients, in addition to clarifying the correlation symptom-cognitive functioning, it is also possible to measure the type and degree of impairment in specific disorders [45].

The executive functions have more than only one accepted definition, but it is known to be composed of several subcomponents, such as abilities of set-shifting, planning, inhibition, working memory and fluency, which are involved in controlling, integrating, organizing, inhibiting or even maintaining the functioning of other cognitive functions. Therefore, it becomes a centralizing function of cognitive functioning and deficits would impair personal, social, occupational and educational in the patient's

life, affecting their activities of daily living [45]. Although many studies assess executive functions in patients with depression, the findings are not yet conclusive. Therefore, making a revision that uses the survey instruments, the specific findings and the specific population studied, allows a more detailed outline of what needs to be deepened in the area, despite the growth of publications on the subject.

The survey showed that out of the 28 articles selected, 25 found changes in some construct of executive functioning. But this impairment involved functioning findings based on different analyzes, such as severity of the disorder [14], partial executive alterations [30], melancholic subtype [31, 32, 34], acute states of the disorder [39], among others. Thus, although the deficits appear in most articles, it does not mean uniformity of the findings.

One of the questions discussed by several studies was to whether cognitive changes in depression are belonging to acute conditions, and therefore have improved from the remission of symptoms, or if it would be a trait marker of the disorder and would remain so even after its remission. The authors suggest that an improved consistency of their findings would be possible with longitudinal studies, in contrast to the cross-sectional studies in order to avoid the possibility of the effect of any residual symptoms. So, the study should be long enough to ensure that there had been complete remission [14, 18, 27-30, 35, 36, 39, 40, 43].

Another important point is about the clinical heterogeneity of the disorder itself, which causes a difficulty in methodological studies. This is because besides the different possible subtypes (such as melancholic, non melancholic, psychotic for example), there is a high incidence of comorbidity and severity levels. Thus, the authors find it difficult to control all of these variables, which end up limiting the possibility of generalization of the findings. Furthermore, these patients are also medicated in most cases, which leads to doubt if there is a deficit found resulting from such therapy [14, 24, 31, 33, 34, 43]. Some authors call attention to the fact that the studies have focused on melancholic and non melancholic subtypes, and it would be necessary to expand this to other subtypes [31, 33, 34]. It´s not clear if this is a feature of depression, certain subtype specifics or of some other variable, such as level of severity and medication use.

It also has to be taken into consideration the difficulty in distinguishing patients with MDD and bipolar disorder. It can cause biased results, because literature has been evidenced the presence of executive deficits in bipolar patients [46, 47]. The recent changing of the criteria from DSM-IV diagnoses to DSM-V re-opens the discussion of divisors between MDD and bipolar disorder. In this new criteria, the dysphoric symptoms (previously attributed to bipolar disorder), are now regarded as typical of the DDM as of Bipolar Disorder. We do not know if there are specific dysfunctions related to dysphoric components, because these until now were considered "tout-court" bipolar.

Studies to further investigate the findings in cognitive functions, in particular executive functions, have a clinical impact, since many of these patients do not respond to psychotherapies and pharmacotherapies. Could this difficulty in answering to treatments have its root in cognitive problems? Does this patient develop clinically or have difficulty planning, problem solving and flexibility? Is that a functional and executive problem before a symptom clinic?

CONCLUSION

In this review, the majority of studies found alterations in some aspects of executive functioning in patients with depression. The importance of these studies is better understood by the cognitive profile of these patients and predicts possible outcomes of drug therapy and psychotherapy. Furthermore, it is important to clarify the relationship between performance on cognitive tests and the difficulties presented by these patients in their daily lives. One study emphasized the relationship between symptoms and cognitive performance, realizing that patients with depression took longer to complete the test, which meets the slow and attentional deficits characteristic of the disorder.

Another important point is the need to increase the sample of subjects and to try to control comorbidity, severity levels, and medications used. Furthermore, it is necessary to study different subtypes of the disorder, beyond the melancholic and non melancholic subtypes, which are more emphasized. Furthermore, longitudinal studies are recommended to understand if the deficits found are characteristic features of the disorder and therefore remain even after remission of the symptoms or if they manifest only in acute states.

LIST OF ABBREVIATIONS

BDI	=	Beck Depression Inventory
BADS	=	Behavioral Assessment of the Dysexecutive Syndrome Q
CANTAB	=	Cambridge Neuropsychological Test Automated Battery
COWAT	=	Controlled Oral Word Association Test
DAT	=	Delayed Alternation Task
DMS	=	Delayed Matching to Sample Namely
DB	=	Digits Backward
FrSBe	=	Frontal Systems Behaviour Scale
HAM-D	=	Hamilton Depression Rating Scale
ID/ED	=	Intradimensional/extradimensional
IGT	=	Iowa Gambling Task
MDD	=	Major Depressive Disorder
PASAT	=	Paced Auditory Serial Addition Test
SPM	=	Raven Standard Progressive Matrices
SOFAS	=	Social and Occupational Functioning Assessment Scale
SWM	=	Spatial Working Memory
SOC	=	Stockings of Cambridge task
TOL	=	Tower of London
TMT B	=	Trail Making Test Part B

WMS-R = Wechsler Memory Scale Revised

WSCT = Wisconsin Card Sort Test

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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Artigo 3

Pacientes idosos com depressão e prejuízo das funções executivas

Late-life depression and executive function impairment

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Resumo

Objetivo: O presente estudo tem por objetivo realizar uma revisão sistemática da literatura a respeito de possiveis deficits nas funções executivas. Metodologia: Foi realizada uma revisão sistemática da literatura no PubMed, ISI Web of knowledge e PsycInfo, sem restrição de ano de publicação. Dos 1381 artigos encontrados, 20 foram selecionados. O critério de inclusão foi a realização de ao menos um teste neuropsicologico das funções executivas em pacientes idosos com depressão e a avaliação primária da depressão em comparação com outros transtornos psiquiátricos. Resultados: Os estudos selecionados avaliaram se havia correlação entre a depressão e o funcionamento executivo, a influência da severidade do transtorno e dos altos índices de apatia nesses pacientes. Conclusão: Muitos estudos encontraram correlação entre depressão em idosos e deficits em funções executivas.

Palavras chave: idosos, depressão em idosos, funções executivas, deficit cognitive, apatia

Abstract

Objetive: The current study aimed to systematic review about possible impairment of executive function in late-life depression. Methods: We performed a systematic review in PubMed, ISI Web of knowledge and PsycInfo with no time restriction. Of the 1381 articles found, 20 were selected. The inclusion criterion was assessment of executive functions with at least one neuropsychological test in older subjects and evaluated primarily depression without comparison with other psychiatric disorders. Results: The selected studies evaluate if there is correlation between depression and executive functioning, the influence of the disorder severity and high rates of apathy influence. Conclusion: Most studies have correlated late life depression with deficits in executive functioning.

Key words: eldery, late-life depression, executive function, cognitive impairment, apathy

Introduction

Depression in the elderly has become an increasing public health problem, since it is associated with high rates of morbidity and mortality[1]. With regard to its prevalence, studies still find data with high variability (from 1 to 20% of the elderly population) due to methodological differences[2].

The course of disorder is commonly associated with chronic diseases and cognitive deficiencies, and tends to generate family problems, functional disability and worsening of medical illness. Furthermore, depression may originate from medical conditions such as viral, hypothyroidism, hyperthyroidism, cerebrovascular diseases, metabolic disorders, among others. Or have been induced through the use of specific substances that can lead to decreased interest and pleasure or develop sad mood, such as benzodiazepines, steroids, oestrogens, anti-parkinsonian drugs, and others[3].

To better understand the context of depression in late life, it is necessary to take into account causal aspects (such as age-related brain changes, disease-related changes and allostatic response to adversity), physiological brain that may be in the origin and maintenance the disorder (Hypometabolism of dorsal neocortical stuctures; Hypermatabolism of ventral limbic structures), aspects of psychosocial adversity (as low economic power, poor quality of physical health, disability, social isolation, and relocation) and vulnerability factors (in the biochemical, hereditary or psychological)[3].

Its characteristic heterogeneous leads to a difficulty in recognizing and treat the disorder in the best way[1]. Regarding the cognitive part, it is important to note that even in a normal aging is expected some degree of decline, particularly as regards the speed of information processing[4].

An important aspect of clinical features are confounding between depression and cognitive problems. There is both high rates of cognitive problems in elderly patients with depression, and high (9-68%) rates of depression in dementia patients[5].

Many studies have been showing that the presence of depression is associated with worse performance on cognitive tests in a particular way in processing speed and executive processing in working memory. In the case of processing speed for example, this becomes a confounding effect because it can appear both in cases of impaired normal aging, as in some degree of cognitive impairment, and in cases of depression[4]. Studies have shown that even in cases of non-demented elderly, after remission of depression the cognitive difficulties have some degree of improvement, but still remain[3].

It is expected that with increasing age there is a greater mental inflexibility, and a susceptibility to distractors and perseveration. However, as these capabilities also show compromised in depression (particularly in the most severe cases), then comes the difficulty of distinguishing if the poor performance refers to age, disorder or both[6]. Some studies showed that the impairment in EF seems to be related to late age at onset of first lifetime depressive episode[1]. Another point that does not have a conclusive answer is whether the cognitive deficits present in elderly also would cause difficulties in their daily life activities, in their everyday functioning[7]. Thus, the objective of this study is to investigate if executive dysfunction is associated with late life depression. In addition, we aim to examine if there is a relationship among executive functions and severity of depression and among executive functions, apathy and depression in elderly individuals.

Methods

Elegibility criteria

The structure of the methods in this study will follow the proposals of PRISMA (Preferred Reporting Items is Systematic reviews and Meta-Analyses. Thus, we will adopt the PEAKS (population, intervention group being compared, results and research design) recommendation to determine the elegibility.

1 - Study design - randomized controlled trials and nonrandomized studies that evaluated the executive dysfunction in late life depression in elderly;

2 - Types of participants - elderly men and/or women diagnosed with depression, aged from 60 years;

3 - Types of intervention - undergoing to neuropsychological assessment, which can consist of a control group, comparing the executive dysfunction using neuropsychological tests as measures.

4 - Types of measures investigated - executive functions will be analyzed through neuropsychological tests.

Sources

The studies were retrieved from a MEDLINE/PubMed, ISI Web of Knowledge and PsychInfo. Experts on the subject of the present study were also contacted to send articles. To find additional articles, all tables were examined for evidence of previous systematic reviews and found references to randomized controlled trials and controlled as necessary. In addition, we analyzed the references of all selected articles. Searches were closed on the 10th of May of 2014.

Search

Search was conducted in all databases using the following terms: OR executive functions OR neuropsychological assessment AND depression AND with elderly OR late life.

Selection of studies

The selection of studies was performed by two independent researchers that in case of disagreement sought a consensus on the selection. The evaluation consisted of a selection of studies by analysis of the title, followed by analysis of the summary and then the analysis of the full text. With the disagreement between the two researchers, a third one was requested to finish the process. Relevant articles were obtained and assessed for inclusion and exclusion criteria described below.

Data collection

The following data were extracted from the articles: sample size, participant characteristics, neuropsychological instruments used, and main significant results. In addition, other information about the methods and outcomes were collected. These procedures were performed by two independent investigators, who reached a consensus in case of disagreement. Only articles that used at least one neuropsychological test of executive function, evaluated late life depression and that focus in individuals with depression compared to depressed or healthy individuals (without comparison with another psychiatric disorder) were selected.

Exclusion Criteria

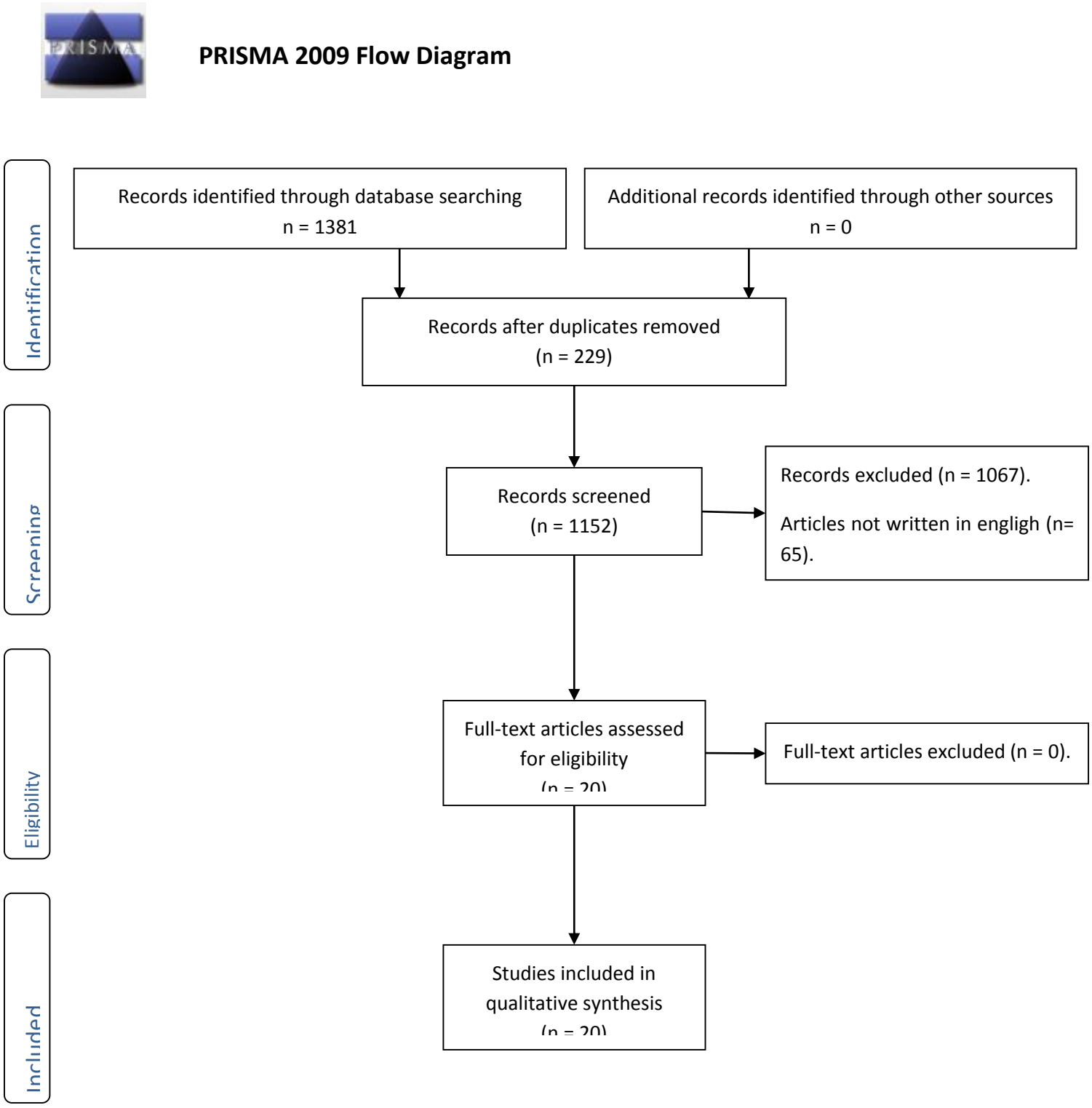
We excluded articles that had articles investigating other type of cognitive functions associated with depression that could create a risk of bias in the study, samples composed of adults, children and adolescents, individuals with other mental illness or neurological disorders, those who do not have detailed statistical procedure applied, or not presented the results of executive functions.

Risk of bias in studies

For assessing the risk of bias of each article included were analyzed the following factors: the presence of eligibility criteria for participants in the sample, the results of all moments from the analysis of more than 85% of the sample, presence of the control group, presentation of results and intergroup variability of results.

Results

Based on the defined criteria, a total of 1381 articles were found in the search conducted in the literature (882 in Pubmed, 276 in ISI Web of Science, and 223 in PsychInfo). These, 229 articles were duplicates and 65 articles were not in English language and were therefore excluded, totalizing 1087 articles. After the screening, 1067 articles were excluded, which were not related to the proposed theme. Twenty articles remained, and after new screening all of them were selected which were properly met the criteria for this review (see figure 1).



The table 1 built allowed visualization of the most commonly used tests and results, in order to further clarify the results of studies already conducted.

Out of 20 articles evaluated, 11 evaluated patients with depression compared to a control group to verify if that there were difference of performance between them. Nine out of

11 found that patients had worse performance in EF when compared to the control group ([8,9,10,11,12,13,14,15,16]).

The results of the remaining nine studies that did not use a control group are controversial with regard to some specific topics of executive functioning. One study found impaired in initiation and perseveration[17] and another did not found chance in this regard[18]. Beyond these specific differences, all nine studies showed greater impairment in executive functioning in patients with depression ([17,18,19,20,21,22,23,24,25]).

Authors	Subjects	M/F	Mean Age	Instruments of Executive Functions	Main Results
Alexopoulos, G.S., Kiosses, D.N., Heo, M., Murphy, C.F., Shanmugham, B. & Gunning-Dixon, F.	112 MDD	58 F 54 M	73.17	• Dementia Rating Scale • Stroop Test	The results showed that the index scores compromised in initiation and perseveration tasks were predictors of limited changes in depressive symptoms in those patients treated with citalopram.
Baba, K., Baba, H., Noguchi, I., Arai, R., Suzuki, T., Mimura, M. et al.	10 MDD	6 F 4 M	69.2	• Behavioral assessment of the dysexecutive syndrome (BADS)	The results showed a significant effect of age. . As for the evaluation of the disorder and the interaction between them were not found significant results.
	10 C	4 F 6 M	67.8		
Baudic, S., Tzortzis, C., Barba, G.D. & Traykov, L.	21 MDD	-	71.8	• COWAT • Cognitive Estimates Test (CET) • Hayling Test • Stroop Test • TMT A • TMT B • Graphic Sequences of Luria • Modified Card Sorting Test (MCST)	The results showed that patients had worse executive performance in all tests (with the exception of the Hayling Test), when compared with the control group. Regarding the severity of the disorder, the results showed that patients considered more severe from the MADRS had correlation with several tests: overall score of COWAT, the Hayling test, the TMT B and the number of criteria and perseverations of the MCST.
	19 C		73.6		
Beblo, T., Baumann, B., Bogerts, B., Wallesch, C. W. & Hermann, M.	41 MDD	28(68%)F	56	• Design fluency • Controlled Oral Word Association Test (COWAT)	In baseline evaluation the patients with MDD had worse executive performance (in a particular construct of flexibility and semantic fluency).In the follow-up, the patients improved performance in both tests and the subjects that better responders to medication also had greater improvement in cognitive tasks.

Boone, K.B., Lesser, I.M., Miller, B.L., Wohl, M., Berman, N., Lee, A., et al.	73 MDD	38 F 35 M	61.4	• Stroop Test (part C) • Auditory Consonant Trigrams (ACT) • WSCT • COWAT	The results shows significant differences between the groups with MDD and control groups, where the group with moderate depression had worse scores on executive skills than the other two.
	110 C	58 F 52 M	63.1		
Cui, X., Lyness, J.M., Tu, X., King, D.A. & Caine, E.D.	709 MDD	448(63.2)F	49.7% between 65-74 years	• Initiation-perseveration subscale of the Mattis Dementia Rating Scale • Trail Making Tests A (TMT A) • B (TMT B)	The results showed that antecedent depression was a predictor independent only of executive dominance of set shifting, assessed using the TMT B, and the time spent in the test. The evaluation of processing speed (assessed using the TMT A) and category fluency/perseveration (evaluated from the Mattis initiation-perseveration subscale score) did not found this relation.
Delaloye, C., Moy, G., de Bilbao, F., Baudois, S., Weber, K., Hofer, F. et al.	30 EOD	80% F	65.00	• Stroop Test	The authors did not found differences in performance in the three groups studied.
	11 LOD	63.64% F	75.82		
	30 C	73.33% F	70.83		
Dombrovski, A.Y., Butters, M.A., Reynolds III, C.F., Houck, P.R., Clark, L., Mazumdar, S. et al.	32 SD	53% F 47% M	70.2	• Executive Interview (EXIT)	The suicidal patients had worse performance in EXIT than the non-suicidal depressed participants.
	32 NSD	62% F 38% M	71.5		
Elderkin-Thompson, V., Mintz, J., Haroon, E., Lavretsky, H. & Kumar, A.	63 MDD	47(75%)F	69.2	• California Verbal Learning Test(CVLT) • WCST • Letter-Number Sequences • Stroop Test	The results showed that the depression had correlation with semantic clustering, serial clustering, Letter-Number Sequences and WCST.
	32 MD	16(50%)F	71.6		
	71 C	42(59%)F	71.5		

Feil, D., Razani, J., Boone, K. & Lesser, I.	89 MDD	52% F	62	• Stroop Test • WSCT • COWAT	The authors found a significant relationship between measures of apathy and Stroop test and nonverbal executive scores of WSCT.
Ganguli, M., Snitz, B., Bilt, J.V. & Chang, C.H.	1687 individuals selected from the electoral rolls of the U.S. community	61.1% F	77.6	• TMT B • Clock Drawing • Verbal fluency for initial letters P & S	The results showed that in a population-based cohort consisting of regular or midly impaired cognition, most had no depressive symptoms. But among those who had was an association between higher levels of depressive symptoms and lower scores in all cognitive functions, especially in the case of executive functions.
Jungwirth, S., Zehetmayer, S., Hinterberger, M., Kudrnovsky-Moser, S., Weissgram, S., Tragl, K.H. et al.	45 MDD	36(80%) F	75.78	• TMT B • Verbal Fluency	The results showed that subjects who had depression had worse score in Verbal Fluency and were slower in TMT B, when compared to control group.
	242 C	146(60.3%) F	75.76		
Marin, R.S., Butters, M.A., Mulsant, B.H., Pollock, B.G. & Reynolds III, C.F.	52 MDD	40 F 12 M	74.4	• EXIT	The authors did not found correlation between patients with depression, apathy and executive functions.
Nakano, Y., Baba, H., Maeshima, H., Kitajima, A., Sakai, Y., Baba, K. et al.	24 MDD	18 F 6 M	68.9	• Wisconsin Card Sorting Test (WSCT) • Stroop Test • Verbal Fluency Test (VFT)	The results shows that both in Stroop Test and VFT, was a effect of age and diagnosis where older patients with MDD had a worse performance than all other groups.
	25 C	22 F 3 M	66.6		
Pisijar, M., Pirtosek, Z., Repovs, G. & Grgie, M.	16 LOD R	-	72.8	• Computer version of Stroop Test	The results showed a difference in reaction time, where the patients showed slower than the control group.
	16 C		72.8		
Potter, G.G., McQuoid, D.R., Payne, M.E., Taylor, W.D. & Steffens, D.C.	46 MDD without difficulties in instrumental activities of daily living	52.17% F	69.22	• Intra-Extra Dimensional Set Shift test (FDI) from the Cambridge Neuropsychological Testing Automated Battery (CANTAB)	The results showed that the group of patients who had difficulties in instrumental activities of daily living showed worse performance on 5 itens, namely: extra-dimensional shift erros, reversal learning erros, number of stages completed, percent completing the task and proportion completing the extra-dimensional shift stage.
	43 MDD one or more problems in this regard	81.40% F	71.93		

Rapp, M.A., Dahlman, K., Sano, M., Grossman, H.T., Haroutunian, V. & Gorman, J.M.	39 NC MDD NL MDD	21(53.85%)F	84.05	• TMT B	The results showed a main effect for the presence of current MDD, presence or absence of a lifetime diagnosis of MDD and in interaction between current and lifetime MDD.
	37 NC MDD LMDD	24(64.86%)F	82.83		
	21 CMDD LMDD	14(66.67%)F	83.09		
	19 CMDD NL MDD	11(57.89%)F	83.57		
Sair, H.I., Welsh-Bohmer, K.A., Wagner, H.R. & Steffens, D.C.	129 MDD	59% F	73.4	• Ascending Digits Task (ADT)	The control group had better results on this test in comparison with the patients group.
	129 C	73% F	76.2		
Sexton, C.E., McDermott, L., Kalu, U.G., Herrmann, L.L., Bradley, K.M., Allan, C.L. et al.	36 MDD	24(67%) F	71.8	• Digit Span • Letter Fluency • TMT B	The results showed a poorer performance of patients compared to the control group. Moreover, when compared to other cognitive functions that the authors evaluated, the executive functions were the most affected, with index below 10% in 44% of participants. With respect to the severity of the disorder, no correlation was found.
	25 C	16(64%) F	71.8		
Story, T.J., Potter, G.G., Attix, D.K., Welsh-Bohmer, K.A. & Steffens, D.C.	177 MDD	110(62%)F	69.1	• TMT A • TMT B • Symbol Digit Modalities Test	The patients who better response to antidepressant medication also showed better performance in Symbol Digit Modalities Test. In TMT test that was no significant difference between the groups with and without pharmacological response.

Note: MDD = Major Depressive Disorder; C = Healthy Control Subjects; EOD = Early-onset depression; LOD = Late-onset depression; NC MDD = Not current MDD; NL MDD = not lifetime MDD; L MDD = Lifetime MDD; C MDD = Current MDD; MD = minor depression; LOD R = Late-onset depression in remission; SD = suicidal depressed; NSD = nonsuicidal depressed;

Assessment of risk of bias revealed that seven out of eleven articles selected met 3 to 5 criteria. Only four articles did not meet the four criteria (table 2)

Table 2. Risk of bias in articles that investigated executive function impairments in patients with late-life depression

Estudos	CE	GC	DA	RA	RI	RVR
Alexopoulos, G.S. et al 2005	Sim	Não	Não	Sim	Sim	Sim
Baba, K. et al 2010	Sim	Sim	Não		Sim	Sim
Baudic, S. et al 2004	Sim	Sim	Não		Sim	
Beblo, T et al 1999	Sim	Não	Não		Sim	
Boone, K.B et al 1995	Sim	Sim	Não		Sim	
Cui, X. et al 2007	Sim	Não	Não		Não	
Delaloye, C. et al 2010	Sim	Sim	Não		Sim	
Dombrovski, A.Y. et al 2008	Sim	Não	Não		Sim	
Elderkin-Thompson, V. et al 2007	Sim	Sim	Não		Sim	
Feil, D. et al 2003	Sim	Não	Não		Não	
Ganguli, M. et al 2009	Sim	Não	Não		Não	
Jungwirth, S. et al 2011	Sim	Sim	Não		Sim	
Marin, R.S. et al 2003	Sim	Não	Não	Sim	Não	Não
Nakano, Y. et al 2008	Sim	Sim	Não		Sim	
Pisijar, M. et al 2008	Sim	Sim	Não		Sim	
Potter, G.G. et al 2012	Sim	Não	Não		Sim	
Rapp, M.A. et al 2005	Sim	Não	Não		Sim	
Sair, H.I. et al 2006	Sim	Sim	Não		Sim	

Sexton, C.E. et al 2012	Sim	Sim	Não	Sim
Story, T.J. et al 2008	SIm	Não	Não	Sim

CE, Critérios de elegibilidade; GC, Grupo controle; DA, Distribuição aleatória; RA, Resultados a partir do mínimo de 85% da amostra; RI, Resultados intergrupos; RVR, Resultado do desvio da medida;

Discussion

Here, we aimed to verify if executive dysfunction is associated with late life depression and to investigate if there is a relationship among executive functions and severity of depression and among executive functions, apathy and depression in elderly people.

Controlled studies

A study was conducted with 258 subjects, divided into two groups: 129 subjects with a diagnosis of MDD and 129 nondepressed subjects. The patient group consisted of 59% female, mean age of 73.4 years and the control group was composed of 73% women and average age of 76.2 years. For the evaluation of EF was used the Ascending Digits Task (ADT), in which subjects need to reorder the numbers in ascending order, from smallest to largest. The results showed that the controls had 1.75 units higher than patients (9.52 versus 7.75; t=245, df=5.74, p<0.0001). The authors describe that these results may represent a deficit in central EF of the patients, since the task involves the manipulation of information held in working memory[8].

A study was conducted in patients with MDD divided through age into 2 groups, and 2 control groups also divided through age. The group with the disorder and more than 60 years comprised 24 participants, with a mean age of 68.9 years, 18 females and 6 males. The control group had 25 participants, mean age of 66.6 years, 22 women and 3 men. For the

evaluation of EF were used three tests: Wisconsin Card Sorting Test (WSCT), Stroop Test and Verbal Fluency Test (VFT). Measures of categories achieved and perseverative errors were selected to evaluate the performance of the participants from WSCT. The results showed that there was an effect of age, but not in diagnosis performance. For both CA and PE on the WCST, a significant main effect was found for age (i.e., $p < 0.001$ and $p = 0.003$ respectively), but not for diagnosis. As for the Stroop Test, a significant main effect was observed in age as well as in diagnosis ($p < 0.001$), showing poorer performance of patients with MDD, regardless of age. And in VFT, there was a significant main effect for age ($p < 0.001$) and disorder ($p = 0.042$), where older patients with MDD had a worse performance than all other groups[9].

Another study evaluated 287 subjects divided into two groups: 242 subjects without depression and 45 subjects with depression. In both groups, there were no subjects with any type of dementia symptoms. Participants without depression had mean age of 75.76 years and 146 (60.3%) were women. Patients with depression had mean age of 75.78 years and 36 (80%) were women. Were performed a 5-year follow-up of these participants, to determine if the cognitive functions have related with depression or other causes over time. For the assessment of EF were used: TMT B and Verbal Fluency (according to CERAD). The results showed that subjects who had depression had worse score in Verbal Fluency (p=.008) and were slower in TMT B ($p<.0001$), when compared to the other group[10].

A crosssectional study was conducted with 63 patients with MDD, 32 patients with minor depression and 71 healthy comparison subjects. Patients with MDD had a mean age of 69.2 years and 47 (75%) were women and the group with minor depression had a mean age of 71.6 years and 16 (50%) were women. The control group had a mean age of 71.5 years and 42 (59%) were women. The neuropsychological battery comprised the following tests: California Verbal Learning Test (CVLT), WCST, Letter-Number Sequences and Stroop Test. The

results showed that the depression had correlation with semantic clustering (*B*=−.47, *S.E*=.17, *p*=.004), serial clustering (*B*=−.75, *S.E*=.24, *p*=.002), Letter-Number Sequences (*B*=−.77, *S.E*=.39, *p*=.05), and WCST (*B*=−.82, *S.E*=.27, *p*=.003)[12].

Another study was conducted in 16 elderly patients with late-onset depression in remission and 16 participants in a control group matched for age and education. Both groups had a mean age of 72.8 years, and were evaluated on their executive functions through computer version of Stroop Test. The results showed a difference in reaction time, where the patients showed slower than the control group, which could be a measure of global cognitive functioning over slowed[13].

A study was conducted with 73 patients, 38 women and 35 men, mean age of 61.4 years and 110 individuals in the control group, composed of 58 women and 52 men, mean age of 63.1 years. For the evaluation of EF were used: Stroop Test (part C), Auditory Consonant Trigrams (ACT), WSCT and COWAT. The results showed that the patients performed worse than the control group (M-W=5.72, *p*=.017). And when the scores obtained in the Hamilton Depression Rating Scale (Ham-D) were compared with neuropsychological assessment was found one significant correlation. For further investigation of this possible correlation between the severity of the disorder and neuropsychological scores, the 73 patients were divided into 2 groups: 36 with moderate depression and 37 with mild depression. The comparisons performed revealed significant differences between the groups with MDD and control groups, where the group with moderate depression had worse scores on executive skills than the other two. In relation to the tests, the difference remained in four of the five scores found: COWAT (K-W=14.91, *p*=.001), Stroop C (K-W=5.03, *p*=.08), ACT (K-W=5.00, *p*=.08) and WSCT categories (K-W= 6.30, *p*=.04)[14].

A study was conducted with a group of 21 patients with MDD and an average age of 71.8 years and a control group consisting of 19 participants with a mean age of 73.6 years. The assessment of severity of depression was assessed using three scales: Montgomery and Asberg Depression Rating Scale (MADRS), Geriatric Depression Scale (GDS) and a rating scale of psychomotor retardation (ERD). For the evaluation of EF were used 7 tests, in order to include the evaluation of different executive domains: COWAT, Cognitive Estimates Test (CET), Hayling Test, Stroop Test, TMT A and TMT B, Graphic Sequences of Luria and Modified Card Sorting Test (MCST). The results showed that patients had worse executive performance in all tests (Wilks lambda = 0.519, $F(11, 28) = 2{,}363$, $p < .05$), with the exception of the Hayling Test, when compared with the control group. Regarding the severity of the disorder, the results showed that patients considered more severe from the GDS does not show any correlation with executive performance in any of the tasks performed. However, when the severity of depression was measured by the MADRS, correlation with several tests: overall score of COWAT, the Hayling test, the TMT B and the number of criteria and perseverations of the MCST[15].

A study was conducted with 36 patients with MDD and 25 participants in a control group, and studied different cognitive domains, among which the EF. Patients had a mean age of 71.8 years and 24 (67%) were female. The control group also had mean age of 71.8 years, but its composition was 16 women (64%). The assessment of EF was performed using the following tests: Digit Span, Letter Fluency and TMT B. The results showed a poorer performance of patients compared to the control group ($p<0.001$). Moreover, when compared to other cognitive functions that the authors evaluated, the executive functions were the most affected, with index below 10% in 44% of participants. With respect to the severity of the disorder, no correlation was found between this index and the performance of cognitive functions, assessed from scales Ham-D and GDS[16].

Another study, want to know the possible association between EF in elderly patients with MDD and suicidal ideation and attempts. For this, a study of case-control consisted of 32 suicidal depressed participants, with a mean age of 70.2 years and 47% of men. These 5 were diagnosed with MDD with psychotic features, 21 without psychotic features, 1 with adjustment disorder with depressed mood, 2 with depression secondary to medical condition and 3 with MDD not otherwise specified. The other group was composed of 32 nonsuicidal depressed participants, with a mean age of 71.5 years and 38% of men. The assessment of EF was made by Executive Interview (EXIT) rating scale composed of 25 items representing the spectrum of executive cognitive capacities and symptoms. The suicidal patients had worse performance in EXIT than the non-suicidal depressed participants (F=14.96, df=1,61, p=0.0003). To confirm this difference between the groups the authors excluded the eleven participants with substance use disorders, five with psychotic depression and seven with dementia and other cognitive disorders and significant differences still remained in all cases[19].

A study was conducted in order to analyze the possible cognitive differences between patients with late-onset MDD and recurrent geriatric MDD. For this, the authors used 4 groups: 39 participants with neither a current nor a lifetime diagnosis of major depressive disorder, 37 participants with a lifetime but not a current diagnosis of major depressive disorder, 21 participants with a lifetime and a current diagnosis of major depressive disorder and 19 participants without a lifetime but with a current diagnosis of major depressive disorder. The first group had a mean age of 84.05 years and consisted of 21 women (53.85%), the second group had mean age of 82.83 years and had 24 women (64.86%); the third group had mean age of 83.09 years and 14 females (66.67%) and the fourth group had a mean age of 83.57 years and 11 females (57.89%). The TMT B test was used as a measure of EF. In analyzing the results, the authors noted that there was a main effect for the presence of current MDD (F=4.25, df=1, 112, p<0.05), a main effect for the presence or absence of a lifetime

diagnosis of MDD (F=5.37, df=1,112, p<0.05), and in interaction between current and lifetime MDD (F=6.24, df=1,112, p<0.01). Moreover, the results also indicated that depressive patients with a history of MDD had worse executive and attentional performance (t=2.78, df=38, p<0.01)[24].

Another study was also conducted with four groups of participants, 2 control groups and 2 of patients with MDD separated by age. The group of older patients consisted of 10 participants (6 women and 4 men) with a mean age of 69.2 years. The control group that combined with this group consisted of 10 participants (4 women and 6 men) with a mean age of 67.8 years. For the evaluation of EF, were used the Behavioral assessment of the dysexecutive syndrome (BADS), composed of six subtests. The authors evaluated the effects of age, the diagnosis and the interaction between them on the neuropsychological assessment of EF. The results showed a significant effect of age (F=13.66, df=1,45, p<0.001), where older patients (both with MDD as the control group) had worse performance than the adult subjects. As for the evaluation of the disorder and the interaction between them were not found significant results[26].

A study was conducted using three groups: a group of 30 patients with early-onset depression (depression onset before 60 years), a group of 11 patients with late-onset depression (depression onset after 60 years) and a control group of 30 participants . For the assessment of EF was used Stroop Test, in order to seek information about the construct of flexibility. The results showed that the executive function had remained preserved in the three groups studied, with no significant differences in the patients compared to the control group (p=0.091)[27].

Open studies

One study evaluated 41 patients with MDD, and 28 (68%) were female. They had no severe illness, history of neurological disorders or developing Alzheimer's disease. Of these, 27 have carried out a follow-up assessment after 4 and half weeks from baseline consisting of 17 (63%) of women. For the evaluation of EF were used: Design fluency and Controlled Oral Word Association Test (COWAT). The results showed that the baseline evaluation in patients with MDD had worse executive performance (in a particular construct of flexibility and semantic fluency) compared to a control group of 20 subjects matched for age, sex and education. Already in the follow-up evaluation, the patients improved performance in both the COWAT (phonological fluency, p=.0151; semantic fluency, p=.0017) and in the design fluency (p=.0037). Not all patients showed improved in mood from pharmacological treatment with antidepressants. Thus, the authors divided these patients into responders and non responders to medication and realized that patients respondents had greater improvement in cognitive tasks, the particular form of executive functions[11].

A study of 112 elderly patients with MDD (58 women and 54 men) evaluated the effect of the drug citalopram over 8 weeks with 40 mg, and its relationship with the executive functions assessed by the Dementia Rating Scale and Stroop Test. Upon baseline all subjects were classified as having moderate depression from the Ham-D. For analysis of the results, patients were divided into 2 groups: respondents (who had improvement of at least 50% in the indices of the Ham-D in comparison to the baseline time) and not respondents. Patients respondents medication had mean age of 71.56 years and the non-respondents 75.66 years. The results showed that the index scores compromised in initiation and perseveration tasks were predictors of limited changes in depressive symptoms in those patients treated with citalopram. So, patients with rates of initiation and perseveration below the median had higher HAM-D scores than participants with higher IP scores at 4 weeks (t(127)=2.47, p<015), 6 weeks (t(97.6)=2.90, p<.0047), and 8 weeks (t(78.7)=2.68, p<.009) after the baseline

assessment and at themean of the follow-up period (t(91.8)= 2.20, p<.03). In relation to the Stroop Test, also there was association with depressive symptoms. Patients who obtained scores at the lowest quartile had higher HAM-D scores in 2 weeks (t(99.1)=2.57, p<.017), 4 weeks (t(117)=3.17, p<.002), and 6 weeks (t(94.5)=2.72, p<.0079) after the baseline assessment and at the mean of the follow-up period (t(91.6)=2.10, p<.038)[17].

One study followed by two years depressed patients with a minimum age of 65 years. Upon baseline the authors recruited 709 subjects, one year later obtained information from 431 subjects and two years after 284 participants. Regarding the age and gender of the sample, in 3 times for collecting the highest percentage comprised subjects who were aged 65-74 years and females. The evaluation of EF was performed by applying the initiation-perseveration subscale of the Mattis Dementia Rating Scale and Trail Making Tests A (TMT A) and B (TMT B). Of the 709 participants recruited initially, 38 died during the period of follow-up, 79 withdrew from the study and others had to be excluded due to incomplete information during the monitoring period. The results showed that antecedent depression was a predictor independent of executive dominance of set shifting, assessed using the TMT B, and the time spent in the test. However, this does not happen with relation to processing speed (assessed using the TMT A) and category fluency/perseveration (evaluated from the Mattis initiation-perseveration subscale score)[18].

One study recruited 89 subjects aged between 50 and 85 years, of both sexes (52% female) with MDD, to determine their rates of apathy and cognitive performance and check if there was any relationship between these items. For the evaluation of EF were used: Stroop Test, WSCT and COWAT. For the assessment of apathy was used a four-item measure of apathy of 21-item Ham-D. The authors found a significant relationship between measures of apathy and Stroop test (R^2=0.100, p=0.001), COWAT (R^2=0.070, p=0.010), and nonverbal

executive scores of WSCT (R^2=0.13, p=0.001). Thus, apathy could be a predictor of the results of executive functioning in elderly patients[20].

A study was conducted with 1687 individuals aged from 65 years, mean age of 77.6 years and average 61.1% of women. Participants were selected from the electoral rolls of the U.S. community, and individuals with moderate and severe degrees of cognitive impairment were excluded. For the assessment of EF were used: TMT B, Clock Drawing and Verbal fluency for initial letters P & S. The results showed that in a population-based cohort consisting of regular or midly impaired cognition, most had no depressive symptoms. But among those who had, found an association between higher levels of depressive symptoms (assessed from Epidemiologic Studies Depression Scale) and lower scores in all cognitive functions (<0.001), especially in the case of executive functions. These associations remained significant even after adjustment for demographics data[21].

Another study conducted with 52 subjects (12 men and 40 women), mean age of 74.4 years and diagnosis of MDD without psychotic features also evaluated the relationship between apathy and executive cognitive dysfunction. The assessment of apathy was also performed from the four-item measure of the Ham-D as a proxy measure of apathy and Apathy Evaluation Scale (AES). The evaluation of EF was made from the EXIT. The results showed that the patients studied had moderate to severe depression and levels of apathy in mild to moderate. However, the indices of executive cognitive dysfunction in this sample had little range and severity, which the authors explain the fact that no correlations were found between these indices and apathy. Thus, the study suggests that in some elderly patients with depression, apathy and executive functions may be independent[22].

Another study with 89 subjects who met minimum age of 60 years with MDD want to examine the association between self-reported functional disability in these subjects and two

types of EF processes: attentional set shifting and reversal learning. This group was divided between patients who not had difficulties in instrumental activities of daily living (n = 46), mean age of 69.22 years and 52.17% females and those who had one or more problems in this regard (n = 43) with mean age of 71.93 years and 81.40% female. The evaluation of these cognitive processes of EF were made from the Intra-Extra Dimensional Set Shift test (FDI) from the Cambridge Neuropsychological Testing Automated Battery (CANTAB). The results showed that the group who had difficulties in instrumental activities of daily living showed worse performance on 5 questions of evaluation, namely: extra-dimensional shift erros (t=3.70, df= 87, d=0.78, p=0.0004), reversal learning erros (t=2.84, df=83, d=0.62, p=0.0057), number of stages completed (t=-3.08, df=68.6, d=-0.66, p=0.0030), percent completing the task (χ^2=6.98, df=1, OR= 3.16, p=0.0082) and proportion completing the extra-dimensional shift stage (χ^2= 10.81, df=1, OR=4.42, p=0.0010). The authors describe that these results show the association between certain aspects of executive functioning and deficits in activities of daily living in elderly patients with MDD[23].

A study investigated the cognitive functions in patients with late life depression treated with antidepressant medication, to investigate the possible difference between those who responded and did not respond to medication. Were recruited 177 subjects, mean age of 69.1 years and 110 women (62%). Of the 177 participants recruited initially, 103 were evaluated by a follow up performed 1 year later. Patients who made the evaluation of follow up were divided from the difference of responses upon pharmacological treatment. The evaluation of EF was held from TMT A, TMT B and Symbol Digit Modalities Test. Among the patients who had follow-up evaluation, those who had a better response to drug treatment also showed better performance in some of the baseline neuropsychological measures, as the testing of Symbol Digit Modalities Test F=1,93, df=5.951, p=.017, η2=.060). In the TMT test, no

significant difference between the groups with and without pharmacological response pharmacological response (F(1 95)=3.026, p=.085, $\eta 2$=.031)[25].

Relationship among executive functions, apathy, and severity of depression in elderly

It is important to note that these differences were of different constructs of EF, assessed by different neuropsychological tests. For example, while one study found deficits in manipulation of information of working memory[8], other found changes in flexibility and semantic fluency[11], and another about the slowness of these patients[13]. Another parameter of comparison used in some studies verify if there was difference of executive performance among patients with depression according to the severity of their disorder. Of the 5 articles that took into account this aspect, 3 found a correlation between disorder severity and worse performance ([14,19,21]) did not find this correlation[16] and the other found a correlation depending on which measure he utilized to analyze the results[15].

Among the possibilities for such divergences, we raise the hypothesis that the concept of executive functions is broad and consists of different sub-items. A patient may be compromised on one aspect of executive functioning and not in another.

Another important point to be emphasized is that 2 articles found age effect, where older patients performed worse than younger patients[9,26]. Furthermore, the studies were dealing with elderly patients, and it is important to make sure if there was any deficit resulting of mild cognitive impairment or early stage dementia, which discard the direct link between executive functioning and depression.

Another 2 articles verify if there is a correlation between apathy and performance of EF, and while one found this correlation (indicating apathy as a possible predictor of decline in EF),[20] another did not find[22].

Of the remaining two studies, one evaluated patients with and without difficulty in activities of daily living and demonstrated that patients who had more difficulties in these activities also had more difficulty in EF in neuropsychological assessment[23]. The other study followed depressed patients and evaluated at 1 year and 2 years after the baseline time. The authors found that depression could be considered a predictor of decline in some aspects executives, as set shifting[18].

Were found a correlation between depression in elderly and deficit in EF. However, in addition to the points already raised, it is important to remember that neuropsychological tests are not composed of a pure construct, a test of executive functioning can require attentional functioning, working memory or language[10].

To try to reduce this bias, one possibility would be make evaluation with standardized test of EF and also attentional, working memory and language focusing on the comparison of performance. This could verify if the deficit is effectively of EF or another cognitive function that supports a good executive functioning.

Conclusion

In this review, most of studies showed changes in some aspect of executive functioning in late-life depression. The relevance of the studies is provide understanding about the cognitive profile of these patients and predict possible outcomes to guide new treatments, e.g., drug therapy and psychotherapy. In addition, it is important to clarify the relationship between cognitive performance on tests and the difficulties presented by these patients in their daily lives. Executive functions are essential to help patients remain independent and safely.

Another relevant point is the need to increase the sample of patients and to control comorbidity, severity levels, and medications used. Furthermore, it is necessary to study

different subtypes of the disorder, beyond subtypes melancholic and non melancholic that is more emphasized. Furthermore, longitudinal studies are recommended to understanding if the deficits found are characteristic features of the disorder and therefore remain even after remission of symptoms or if manifest only in acute states.

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Note

Table 1. Summary of the studies about executive function impairments in patients with late-life depression.

Artigo 4

Neuropsychological assessment of executive functions and EEG in patients with depression

Avaliação neuropsicológica das funções executivas e EEG em pacientes com depressão

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Neuropsychological assessment of executive functions and EEG in patients with depression

Avaliação neuropsicológica das funções executivas e EEG em pacientes com depressão

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ABSTRACT

The present study aimed to evaluate patients with depression and compare to a control group through neuropsychological assessment and execution of the oddball paradigm during electroencephalogram. The final analysis took comparison between the two groups in neuropsychological tests Color Trail Test (CTT), Nonverbal of General Intelligence Test: Subtests Matrix Reasoning (RM) and Codes (Cod.) (Beta III) and Wisconsin Card Sorting Test (WSCT) and frequency of absolute alpha power on the frontal hemisphere. The tests results showed significant differences between groups only in CTT form I and Beta III. In the absolute power of alpha, patients had a higher alpha frequency in the left hemisphere, while the controls showed a higher alpha frequency in the right hemisphere. The results showed consistent electrophysiological data about the difference between the groups, confirming the possibility of neurobiological markers in psychiatric disorders.

Key words: depression, executive function, cognitive impairment, electroencephalogram, absolute alpha power

1.Introduction

Studies with major depressive disorder (MDD) has shown about his interference in the cognitive aspects of the individual [1] and in their ability to manage finances, social and occupational relations. This chronic and continuous aspect tends to affect life, limiting it and changing their behavior in many different ways[2].

As regards off cognitive changes, studies have shown deficits in different domains, among which attention [3] and executive function[4,5]. Executive functions are described as a set of skills that are interrelated with other cognitive functions, helping them in their regulation and execution, and your metabolism is primarily assigned to frontal brain regions. The executive functioning and his integration makes it possible that simple actions can be organized and become more complex. Among these mechanisms: flexibility, impulse control and problem solving[6].

The electroencephalogram (EEG) is a tool which the main feature is to to detect the electrical activity in different brain regions during the execution of a task. Among the different possibilities of variables to be analyzed, asymmetry detects the energy balance between the two hemispheres and cortical áreas[7]. Through the analysis of asymmetry in the alpha band (8 ± 13 Hz), the data research that seek to trace its parallel with MDD still have conflicting results. The measure itself is reliable, however, its potential as a biomarker for depression is still not entirely clear and consistent[8].

This study aimed to assess cognitive and electrophysiological functioning of patients with MDD and compare them with a control group, through neuropsychological assessment and an electroencephalogram (EEG). We hypothesized:

1. Patients had a worse performance in neuropsychological assessment when compared to the control group;
2. Patients would present greater activity of absolute alpha power in the left hemisphere when compared to the control group;

2.Methods

Eight healthy controls with average age of 44.25 (HC) and eight patients with MDD, with average age of 43.62 (6 women and 2 men in both groups) were enrolled in this study. The groups were matched for gender and age. The patients and the controls were interviewed using Mini International Neuropsychiatric Interview (MINI)[9]. All participants had normal or

corrected-to normal vision and no sensory and motor deficits. Volunteers who proved to have no present or past psychiatric condition and to be medically healthy. All participants provided written informed consent approved by the Ethics Committee before entering the study and the experimental conditions were described in detail.

The research consisted of two steps. The first stage lasted about 1 hour and a half and consisted of sociodemographic interview, application of Beck anxiety inventory (BAI), Beck depression inventory (BDI) and a battery of neuropsychological tests consists of the following tests: Color Trail Test (CTT), Wisconsin Card Sorting Test (WCST) and Nonverbal of General Intelligence Test: Subtests Matrix Reasoning (RM) and Codes (Cod.) (Beta III). The neuropsychological battery of tests evaluate the executive and attentional functioning. The second stage lasted about 40 minutes and was composed by the capture of electrophysiological data, through the electroencephalogram equipment at rest and during the oddball paradigm.

Regarding the neuropsychological assessment: The Victoria Stroop Color-Word Test is a brief version of the original Stroop task. The application time is around 3-5 minutes and aims to evaluate selective attention and executive functioning components such as inhibitory control[10]. The CTT has two steps, and the application arrives of 10 minutes. The form 1 evaluated perception, sustained attention and motor skills. In the form 2 the same functions are evaluated, as well as divided attention[11].The WCST has been increasingly used in the literature as an evaluation measure of executive function, especially in frontal lobes dysfunctions. It requires individual planning, problem solving, impulse control, and environmental feedback to shift cognitive sets. The application does not have limited time, and the will vary according to the subject[12]. Beta III evaluates intellectual capacity through visual, spatial and non-verbal processing, speed processing and fluid intelligence. The two subtests have limited time. The subtest Codes with duration of 2 minutes (120 seconds) and Matrix Reasoning subtest with maximum of 5 minutes[13].

The electrophysiological data were performed in a soundproof room, with lights off during the task to minimize interference from other visual stimuli beyond the video monitor. The capture of electroencephalographic begin with 4 minutes in rest and open eyes. Then, the subjects performed the task based on the oddball paradigm. In this paradigm, two stimuli are presented randomly, with one occurring relatively infrequently. Subjects were asked to discriminate target (infrequent) from non-target or standard stimuli (frequent). In the present

experiment, target stimuli were represented by a square and non-target stimuli by a circle. Subjects were instructed to respond as quickly as possible to the target stimulus by pressing a button in a joystick (Model Quick Shot- Crystal CS4281). Each stimulus duration was 2.5 seconds, the same time interval with the off screen between stimuli. The visual stimulus was presented on the monitor by the event-related potential (ERP) acquisition software, developed in Delphi 5.0 (Inprise Co.). Each subject was subjected to 6 blocks of 10 tracks. In other words, the square was presented 10 times in each block. In each block, there was a 75% chance from 1 to 4 non-target stimuli preceding a target stimulus. Upon completion of the task a new capture of EEG was performed at rest for 4 minutes with open eyes.4

The International 10/20 EEG electrode system (Jasper 1958) was used with a 20-channel EEG system (Braintech-3000, EMSAMedical Instruments, Brazil). The 20 electrodes were arranged on a nylon cap (ElectroCap Inc., Fairfax, VA, USA) yielding monopolar derivations using the earlobes reference. Impedance of EEG and EOG electrodes was kept between 5-10 kΩ. The data recorded had a total amplitude of less than 70μV. The EEG signal was amplified with a gain of 22,000, analogically filtered between .01Hz (high-pass) and 80Hz (low-pass), and sampled at 200 Hz. The software Data Acquisition (Delphi 5.0) from the Brain Mapping and Sensory Motor Integration Lab was employed with the digital filter: notch (60 Hz).

The International 10/20 system for electrodes16 was used with a 20-channel Braintech-3000 EEG system (EMSA-Medical Instruments, Brazil). We used 20 electrodes arranged on a nylon cap (ElectroCap Inc., Fairfax, VA, USA), yielding mono-pole derivations to linked earlobes, set as reference points. In addition, we attached two 9mm-diameter electrodes above and on the external corner of the right eye, in a bipolar electrode montage, to monitor artifacts on eye-movements (EOG). We kept the impedance of EEG and EOG electrodes between 5 and 10 KΩ. The data acquired had total amplitude of less than 100 μV. We amplified the EEG signal, with a gain of 22,000, analogically filtered between 0.01 Hz (high-pass) and 100 Hz (low-pass), and sampled at 240 Hz. For the reference data analysis, we applied a visual exam and an independent component analysis (ICA) to eliminate the possible sources of artifacts produced by the task. We excluded data of individual electrodes which lost contact with the scalp or which showed high impedance (> 10 kΩ), as well as data from blocks with movement artifact excess (± 100 μV). Then, we applied ICA to identify and remove any remaining artifacts after the initial visual inspection. ICA is a group of blind source separation methods, which aim at estimating the maximum independent components

from a statistic point of view. The ICA-filtered data were then re-inspected for residual artifacts, using the same rejection criteria described above. We applied a classic estimator for the power spectral density (PSD), or directly from the square modulus of the FT (Fourier Transform), which was performed by MATLAB (Matworks, Inc.).

We utilized the average EEG records (n=6 measures per subject). Data was log transformed (ln+1) to reduce data variation and tested using Levene test for Homoscedasticity. After transformation we used a factorial ANOVA to test the effects of group (depressed vs control) and moment (rest vs task) on the EEG records.

The questionnaire results between depressed and non-depressed groups were compared using the non-parametric Mann-Whitney test. We also performed the Spearman correlation test between EEG records and the results of the questionaries' applied to the subjects. The correlations were separated by group and by moment.

Results:

Hypothesis concerning the performance in neuropsychological assessment of the patients compared to control group

To analyze the comparison between Patient Group and Control Group we applied the Mann-Whitney Test.

We found significant difference between the groups in BDI (z=3.38566, p=0.000710), BAI (z=3.31304, p=0.000923), CTT form 1 (z=-2.68543, p=0.007244), Beta III RM (z=-2.32417, p=0.020117) and Beta III Cod. (z=-3.09141, p=0.001992). In CTT form 2, CTT measure of interference and all the variables of WCST were not found significant diferences.

Hypothesis concerning direction of frontal alpha power asymmetry

The hypothesis predicted that the patients with MDD will show right hemisphere overactivation in frontal cortical áreas and lower asymmetry alpha in comparison with the left hemisphere. The hypothesis was tested by examining Fp1/Fp2 and F3/F4 alpha absolute power frontal asymmetry. The analysis was made between groups and between moments.

Log transformed EEG data present variance homogeneity according to Levene test. Depressed group presented significant higher values of fp1/fp2 compared to control groups according to ANOVA (figure 1). The effect of moment (rest vs task) on fp1/fp2 was not significant between groups. The interaction between group and moment was not significant (table 1).

Figure 1

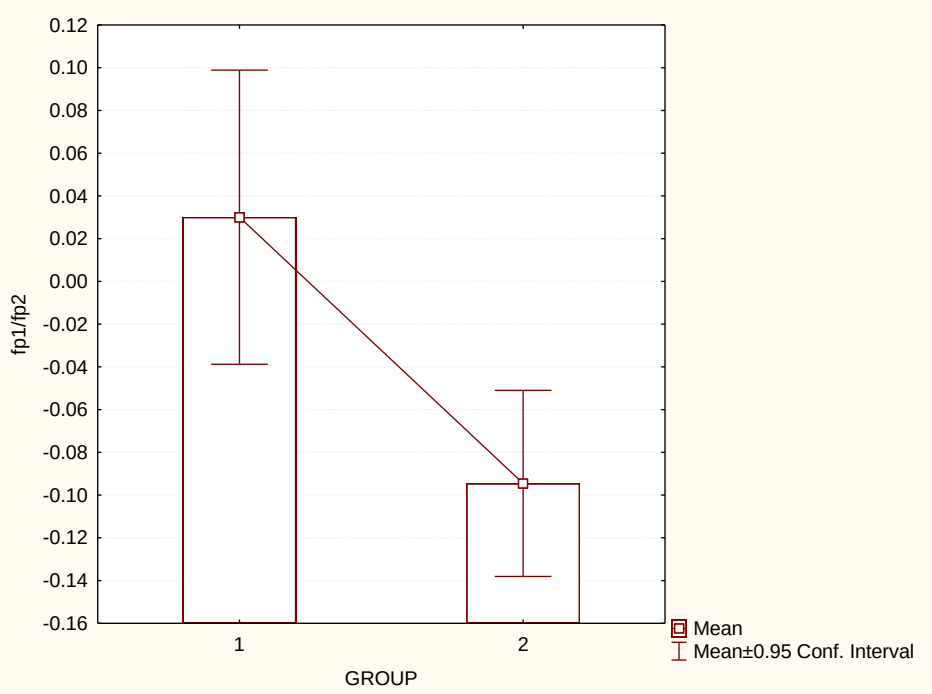

Table 1

	SS	Degr. Of	MS	F	p
Intercept	0.033197	1	0.033197	2.661725	0.113988
GROUP	0.124209	1	0.124209	9.958911	0.003807
MOMENT	0.000591	1	0.000591	0.047422	0.829190
GROUP*MOMENT	0.000680	1	0.000680	0.054544	0.817036
Error	0.349220	28	0.012472		

Discussion:

The comparisons between patients and control group assessed cognitive functioning through tests of attention, global cognitive functioning and executive functions and also by electrophysiological analysis. The results showed differences between subjects with depression and the control group in the tests and in EEG, corroborating the hypotheses of biological markers for the disorder.

The results of neuropsychological tests demonstrate that patients and control group had differences on the results of CTT form I and Beta III (in both tests). The test CTT form I assess attention and the literature has shown that depressed patients show deficits in this cognitive function[14,15]. One research hypothesis was that performance in divided attention could be an important predictor of the course of the depressive disorder and the effectiveness of the treatment performed[15].

However, no differences were found in any of the WCST variables. This finding was in disagreement with most of the literature which considers this test as one of the most frequent measures of performance between groups. In a review of 28 articles that evaluated executive function in depressed patients, 10 used the WCST as a measure and in 8 were found deficits[16]. One of the hypotheses would be the number of the subjects in this research, which appears sensible to analyze the EEG data, but possibly not as sensitive in detecting WCST findings. The research that was described in the review used a most significant number of patients, with the minimum of 17[17], and the maximum of 123 patients[18].

In the analysis of the EEG data, we found a positive asymmetry alpha to the group of patients and negative asymmetry to the control group in the electrodes pair Fp1 / Fp2. We found that in the group of patients is more alpha in the left prefrontal cortex compared to the right prefrontal cortex, and opposite result is observed in the control group. The pair of Fp1 / Fp2 electrodes are located in the prefrontal cortex, refer to area 10 of Broadman and related to executive functions. The pair F3 / F4 are related to area 8 of Brodmann and are associated with the motor functions.[19].

Therefore, the results related to the direction of alpha asymmetry in depressed patients show an increased of alpha in Fp1 when compared to Fp2, meaning a lower activity in the area Fp1 to Fp2. These findings in depressed patients has been widely discussed and ratified in the literature[19,20,21,22].

The inter-hemispheric differences are described about cognitive functions and emotional functioning. The cognitive functions of the left hemisphere is described as related to language, verbal skills, logic, verbal memory and arithmetic, while the right hemisphere is more relate with visual spatial skills, complex geometry, prosody, musical skills and nonverbal memory[23]. The cortical activity can be understood from a proportional relationship between activity and performance, where a high activity mean good performance and low activity a bad performance. But the concept of neural efficiency brings another possibility, by the explanation of greater activity may represent greater effort in performing certain task and demanding a greater recruitment of this area[24]. Therefore, the poor performance of depressed patients in the Beta III test which requires visuospatial skills, could represent this difficulty, where despite increased cortical activation, there was not necessarily a better performance.

The studies about the inter-hemispheric emotional functioning proposed that the increased activity in left hemisphere would be more associated with positive emotional responses, while the ativity in right hemisphere to negative emotions. Thus, patients with depression would present a higher right cortical activity, and therefore more responding to negative affection[23,25].

Conclusion:

The data found confirm theoretical concepts about the inter-hemispheric cortical functioning, with respect to cognitive tasks and emotional aspects. The objective is approach the intersection of neuropsychology and neuroscience, bringing the possibility of electrophysiological analysis during a task, since most of the literature uses individuals at rest.

This study have limitations like the size of the population, which difficults more consistent about the results, the presence of anxiety comorbidities in some patients, which could interfere especially in the execution of the tests and the use of psychotropic medications for all patients which could bring some changes in the EEG analysis.

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Discussão:

O artigo *Cognitive functions in patients with panic disorder: a systematic review*, que foi publicado na revista brasileira de psiquiatria, é uma revisão sistemática que visava descobrir as possíveis alterações neuropsicológicas presentes em pacientes com transtorno do pânico. Foram selecionados 17 artigos que avaliavam diferentes funções cognitivas nesses pacientes. A análise dos artigos foi separada a partir das funções cognitivas avaliadas: funcionamento cognitivo global, memória, atenção, funções executivas, habilidades psicomotoras e velocidade de processamento, fluência verbal e processamento afetivo de faces e palavras.

Embora os estudos mostrem que as pesquisas com avaliação neuropsicológica sejam amplamente utilizadas[25], ainda o são em pouco numero quando se referem ao transtorno do pânico. Muitos destes utilizam apenas alguns testes, ao invés de uma bateria neuropsicológica completa, o que dificulta uma discussão mais ampla dos resultados. Outro ponto de destaque é a observação que 4 das 6 pesquisas que avaliam o funcionamento executivo foram feitas a partir de 2004, sinalizando um enfoque mais recente a respeito dessa função, especialmente nos pacientes com pânico. Porém, são necessários mais estudos, com populações mais numerosas e uma metodologia mais delimitada, o que tornará possível a aproximação mais clara dos dados neuropsicológicos em pacientes com transtornos psiquiátricos.

O artigo *Executive Function Impairments in Patients with Depression*, aceito para publicação na CNS & Neurological Disorders-Drug Targets, traz uma revisão bibliográfica sistemática sobre os déficits no funcionamento executivo em pacientes adultos com depressão, e foi composto por 28 artigos.

Diferentemente do que foi observado no artigo anterior com pacientes com transtorno do pânico, as pesquisas com pacientes depressivos têm número expressamente maior, e houve a opção do enfoque apenas nos déficits executivos em detrimento das outras funções. Tal

opção se relaciona com todo o relato da literatura a respeito do mecanismo neurofisiológico da depressão que tem relação central com a atividade da área do córtex pré frontal[26], também marcadamente conhecida como relacionada ao funcionamento executivo[27]. Apesar dos achados mostrarem-se em ampla maioria com evidencias de déficits executivos nesses pacientes (25 dos 28 artigos), os constructos teóricos e os instrumentos de avaliação ainda são muito diversos, não trazendo uniformidade aos dados.

O artigo intitulado *Late-life depression and executive function impairment*, submetido a Revista de Psiquiatria Clínica trata-se de uma revisão sistemática composta por 20 artigos que avaliam os déficits encontrados nas funções executivas em pacientes depressivos idosos.

A separação de pacientes depressivos com perfil adulto jovem (do artigo anterior) e idosos (desse artigo), se deve pelas diferenças características de cada um dos grupos. Pacientes idosos tendem a se tornar mais inflexíveis e sucetíveis a distrações e perserverações com o avançar da idade, e como tais características cognitivas estão também comprometidas na depressão, torna-se difícil a distinção se o déficit está relacionado a idade, ao transtorno ou ambos[28]. Nesse sentido, a proposta de mais estudos longitudinais possibilitaria o acompanhamento dos déficits cognitivos ao longo do tempo e um maior esclarecimento sobre sua manutenção ou descontinuação.

E o artigo *Neuropsychological assessment of executive functions and EEG in patients with depression*, foi submetido para Journal of Psychiatric Research e trata-se de um estudo com 8 pacientes depressivos e 8 sujeitos de um grupo controle, pareados através de idade e sexo, através de avaliação com uma escala sociodemográfica, uma avaliação neuropsicológica e um exame de EEG. A avaliação neuropsicológica era composta pela Escala Beck de Ansiedade (BAI), Escala Beck de Depressão (BDI), Victoria Stroop Color-Word Test, Teste de Trilhas Coloridas (TTC), Wisconsin Card Sorting Test (WCST) e Teste não verbal de

inteligência geral, subtestes Raciocinio Matricial e Códigos (Beta III). Já a captação dos sinais eletrofisiológicos através do EEG envolvia um momento pré de repouso com os olhos abertos, 6 blocos de uma tarefa e um momento pós de repouso com os olhos abertos.

A análise dos dados se concentrou em três hipóteses: pacientes teriam um pior desempenho na avaliação neuropsicológica em detrimento do grupo controle, pacientes apresentaria maior atividade de alfa no hemisfério esquerdo quando comparados ao grupo controle e haveria uma correlação positiva entre os achados neuropsicológicos e neurofisiológicos. Os resultados confirmaram apenas parte da primeira hipótese, mostrando um pior desempenho dos pacientes apenas na forma 1 do TTC e nos dois subtestes do Beta III. Já a segunda hipótese foi comprovada, embasando ainda mais os estudos já existentes na literatura, e a terceira hipótese foi corroborada apenas parcialmente, mostrando uma correlação apenas em quatro de todas as variáveis envolvidas nos testes.

Os quatro trabalhos que compõem essa dissertação se integram a partir do conceito que pacientes com transtornos psiquiátricos apresentariam determinados déficits cognitivos, trazendo a possibilidade de marcadores biológicos relacionados aos transtornos. Embora as pesquisas na área venham avançando, alguns transtornos ainda carecem de investigações mais profundas e cuidadosas, que permitam um real embasamento dos dados encontrados, como o transtorno do pânico. As pesquisas envolvendo pacientes com depressão maior se configuram com um número mais expressivo, mas ainda encontram divergências entre si devido a variáveis como comorbidades e gravidade do transtorno.

Uma das limitações das pesquisas realizadas no Brasil tem relação com a pouca oferta de testes neuropsicológicos padronizados e validados, especialmente no que se refere a sujeitos idosos. Outra dificuldade encontrada na avaliação dessas populações se refere ao uso

medicamentoso contínuo, já que sua ação sobre a neurobiologia do indivíduo pode interferir sobre os resultados apresentados tantos em testes quanto em exames.

Conclusão:

O objetivo dos estudos realizados, tanto das revisões quanto do estudo original, visa o maior aprofundamento a respeito de dados neuropsicológicos e neurofisiológicos em pacientes psiquiátricos. Trata-se de uma análise contínua e global de diferentes fatores: biológicos, sociais e histórico/comportamentais. Dependendo do objetivo e enfoque da pesquisa a ser realizada, essa se utilizará mais de instrumentos objetivos ou subjetivos e analisará mais os aspectos coletivos e comuns de um transtorno ou aspectos mais individuais. Portanto, mais do que os considerar como áreas separadas, os pesquisadores devem estar atentos a sobreposição de variáveis e comorbidades.

Nesse sentido, uma avaliação neuropsicológica e com EEG, que primariamente se refere ao caráter biológico, busca levar conhecimentos não apenas a essa área, mas também ao funcionamento e possível déficit apresentado por esse individuo em sua vida social, familiar e laboral. Essa análise integrativa permite o avanço da ciência não apenas restrito aos pesquisadores, mas que busca ir ao encontro do indivíduo e suas limitações. Isso pode permitir a melhora nos tratamentos propostos, sejam eles psicoterapêuticos, medicamentosos ou de reabilitação neuropsicológica, e consequentemente uma melhora na qualidade de vida dos pacientes e prevenção de possíveis recaídas.

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