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Executive Dysfunction in Depression: A Systematic Review

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Abstract

Among the alterations observed in depression, volumetric reduction of the prefrontal cortex is commonly reported, which affects executive functions (EF), though this relationship has not been systematically evaluated. To address this gap, we conducted a systematic review using the PRISMA protocol to assess the presence of executive dysfunction (ED) in individuals with depression. We searched PubMed, Embase, and SciELO using a search strategy that combined the terms "Depression" and "Executive Dysfunction", with no publication date or language restrictions. Eligible studies included longitudinal or cross-sectional analytical articles that evaluated EF using standardized or validated scales and tests, involving patients without comorbidities matched to controls. Literature reviews, studies involving patients with psychiatric comorbidities, and non-human models were excluded. The search yielded 672 articles from PubMed, 51 from Embase, and 4 from SciELO (total n = 727), of which 22 were selected for full-text review. Six studies included patients with comorbidities, leading to the inclusion of 16 studies. Most studies found impaired EF in depression, with EF performance appearing to be inversely proportional to symptom-induced stress levels. Evidence suggests that ED may reduce the likelihood of remission, though psychotherapeutic interventions can help mitigate these executive impairments. Additionally, ED appears to persist even after symptom remission, with more pronounced effects in older adults. Overall, these findings highlight the need for further investigation into ED in depression, as ED may serve as a potential biological marker for the disorder.

Keywords: depressive disorder, executive function, cognitive dysfunction, review, metacognition

DISFUNÇÃO EXECUTIVA NA DEPRESSÃO: UMA REVISÃO SISTEMÁTICA

Resumo

Dentre as alterações observadas na depressão, a redução volumétrica do córtex pré-frontal é frequentemente relatada e afeta as funções executivas (FE), embora isso ainda não tenha sido avaliado sistematicamente. Para preencher essa lacuna, realizamos uma revisão sistemática utilizando o protocolo PRISMA, com o objetivo de avaliar a presença de disfunção executiva (DE) em indivíduos com depressão. As buscas foram realizadas nas bases de dados PubMed, Embase e Scielo, por meio de uma estratégia de busca que combinou os termos "*Depression*" e "*Executive Dysfunction*", sem restrições quanto à data de publicação ou idioma. Foram elegíveis estudos longitudinais ou transversais analíticos que avaliaram as FE utilizando escalas e testes padronizados ou consolidados, envolvendo pacientes sem comorbidades equiparados a controles. Revisões de literatura, estudos com pacientes com comorbidades psiquiátricas e modelos não-humanos foram excluídos. Nossa busca identificou 672 artigos na PubMed, 51 na Embase e 4 na Scielo (total n=727), dos quais 22 foram selecionados para leitura completa. Seis desses estudos incluíam pacientes com comorbidades, resultando na inclusão de dezesseis estudos. A maioria dos estudos mostrou comprometimento das FE na depressão e o desempenho das FE parece proporcionalmente inverso ao nível de estresse induzido pelos sintomas. Evidências sugerem que a DE pode dificultar a chance de remissão, embora intervenções psicoterapêuticas atenuem os prejuízos executivos. Além disso, a DE parece persistir mesmo após a remissão, com efeitos mais pronunciados em adultos mais velhos. Esses achados destacam a necessidade de investigação adicional sobre a DE na depressão, que pode servir como um potencial marcador biológico do transtorno.

Palavras-chave: transtorno depressivo, função executiva, disfunção cognitiva, revisão, metacognição

DISFUNCIÓN EJECUTIVA EN LA DEPRESIÓN: UNA REVISIÓN SISTEMÁTICA

Resumen

Entre las alteraciones observadas en la depresión, la reducción volumétrica del córtex prefrontal es frecuente y afecta las funciones ejecutivas (FE), aunque esto aún no se ha evaluado sistemáticamente. Para abordar esta brecha, realizamos una revisión sistemática siguiendo el protocolo PRISMA, con el objetivo de evaluar la presencia de disfunción ejecutiva (DE) en individuos con depresión. Se realizaron búsquedas en las bases de datos PubMed, Embase y Scielo, utilizando una estrategia que combinó los términos "Depresión" y "Disfunción Ejecutiva", sin restricciones de fecha o idioma. Los estudios elegibles fueron analíticos longitudinales o transversales que evaluaron las FE con escalas y pruebas estandarizadas o validadas,

incluyendo pacientes sin comorbilidades comparados con controles. Se excluyeron revisiones de literatura, estudios con pacientes con comorbilidades psiquiátricas y modelos no humanos. La búsqueda identificó 672 artículos en PubMed, 51 en Embase y 4 en Scielo (n=727), de los cuales 22 fueron seleccionados para lectura completa. Seis de estos estudios incluían pacientes con comorbilidades, resultando en la inclusión de dieciséis estudios. La mayoría encontró deterioro de las FE en la depresión, y el rendimiento de las FE parece ser inversamente proporcional al nivel de estrés inducido por los síntomas. Las evidencias sugieren que la DE puede dificultar la remisión, aunque la psicoterapia puede mitigar los daños ejecutivos. Además, la DE parece persistir incluso tras la remisión de los síntomas, con efectos más marcados en adultos mayores. Estos hallazgos subrayan la necesidad de investigar más sobre la DE en la depresión, que podría servir como marcador biológico del trastorno.

Palabras-clave: trastorno depressivo, función ejecutiva, disfunción cognitive, revision, metacognición

Executive functions (EF) play an indispensable role in our daily lives (Friedman & Miyake, 2017). While working memory, inhibition, and cognitive flexibility are frequently identified as central components of EF (Roca et al., 2019), they can also be conceptualized as meta-cognitive systems that regulate behavior across various cognitive domains (Salehinejad et al., 2021). Impairments in goal-directed behavior are commonly associated with lesions in the prefrontal cortex (PFC), highlighting its important role in the manifestation of EF (Friedman & Miyake, 2017). In this context, Kolb (2007) suggests that the prefrontal cortex is instrumental in the temporal organization of behavior. This includes maintaining an ongoing record of sensory experiences and current movements, selecting relevant information while inhibiting irrelevant inputs, facilitating behavioral flexibility, and continuously monitoring the outcomes of actions. In addition, neuropsychological studies have evaluated EF in both healthy individuals (Friedman & Miyake, 2017) and those with psychiatric disorders (Snyder et al., 2015). Overall, impairments in EF are known as executive dysfunction (ED) or executive syndrome. This observation aims to account for the direct interferences in patients' daily lives and the prognosis of the condition, even when they demonstrate proficiency in interviews and standardized assessment tests (Elkana, 2024).

Feelings of joy or sadness constitute the affective background of normal psychological life. Tobore (2023) argues that contemporary society is characterized by an obsession with happiness, defining sadness as a condition to be avoided. However, it is essential to recognize that experiences of sadness, along with feelings of distress, loneliness, anguish, and grief, can be beneficial to human lives. These emotional states may enhance social judgments, facilitate memory consolidation, and support motivation, enabling individuals to cope with life's challenges. Conversely, when coping mechanisms are ineffective, the persistence of profound sadness and anhedonia may indicate a depressive condition (American Psychological Association [APA], 2022), a disorder that severely impairs psychosocial functioning and overall quality of life (Malhi et al., 2018). Charlson et al. (2019) conducted a meta-analysis to provide standardized age-specific estimates of the global prevalence of depression. The authors reported a prevalence of 10.8% for depression in all its forms (severe, moderate, mild, and without functional impairment), and 5.3% without comorbid anxiety. For the severe form, which is expected to result in the most significant functional impairments and a risk of suicide, the prevalences were 1.1% with and 0.6% without comorbid anxiety. These prevalences may have increased following the COVID-19 pandemic (COVID-19 Mental Disorders Collaborators, 2021).

While mood disturbances and anhedonia are well-established central symptoms of depression, cognitive changes are also important indicators of the condition. Specifically, the symptom of "diminished ability to think or concentrate, or indecisiveness, nearly every day" is a recognized marker of depression (APA, 2022, p. 183). Porto et al. (2002) highlight that cognitive impairments, such as deficits in working memory and attention, are frequently observed in depressed individuals. Neuropsychological assessments of these impairments reveal that compromised cognitive domains include delayed recall, attention, memory

acquisition, concentration, cognitive flexibility, and abstraction. Additionally, Zhang et al. (2018) documented alterations in frontal lobe function in depressed patients, which Martins et al. (2015) identified as also being important for regulating emotional behavior. When EF is compromised, individuals may struggle more with interrupting rumination, engaging in adaptive coping strategies, and shifting to positive thoughts, which are vital for mitigating suicidal ideation (Snyder et al., 2015). Consequently, impairments in EF may be particularly relevant to the worsening of self-harming behaviors in depression, including suicide attempts.

In addition, the persistence of ED after euthymia in patients with bipolar disorder has already been characterized, with consequences for occupational functioning (Koene et al., 2022). Rozenthal et al. (2005) argue that relevant EF alterations in patients with mood disorders are related to motivation for initiating tasks and decision-making, which involves a longer deliberation phase and the use of less confident strategies. Similarly, Ávila and Bottino (2006) found that older adults with late-life depression (LLD) exhibited impairments in both verbal and non-verbal memory, psychomotor skills, learning, reading, verbal fluency, and EF. They noted that greater difficulty arises in complex tasks involving the prefrontal cortex, for instance, when intention and decision-making are required, while more automatic processes remain less compromised.

Despite substantial evidence, the relationship between EF and depression remains an area of ongoing investigation. In this context, Feijs et al. (2024) failed to establish a connection between broad dimensions of psychopathology, specifically internalizing, externalizing, and thought disorders, and EF in a heterogeneous sample of psychiatric patients, which included individuals with major depressive disorder. It should be emphasized that the authors used EF tests that do not adequately represent the most prevalent model of EF. Although ED has not yet clearly been defined as a secondary outcome of depression, it may serve as a marker for depression in the absence of evident neurological damage to the PFC. Given the impairments in processes such as decision-making, properly identifying ED can be useful for improving patient care and appropriately adjusting therapeutic goals. Accordingly, this systematic review aimed to investigate the presence of ED in depression by examining studies that quantified EF in depressive patients.

Method

This systematic literature review followed the recommendations of the Systematic Reviews and Meta-Analyses (PRISMA) statement (Page et al., 2021). It aimed to identify international evidence of ED in individuals with depression in the literature. Systematic literature reviews are employed to provide unbiased syntheses of the available knowledge on a specific topic, whether using meta-analyses or not (Aromataris & Muun, 2020; Page et al., 2021; Moher et al., 2009). This review was not previously registered.

The searches were conducted in the PubMed, Embase, and SciELO electronic databases. All the information presented was extracted solely from the articles included in the article selection process, without seeking further information from the authors.

Eligibility criteria

The search strategy was conducted using the combination of terms (depression OR "depression" OR "depressive disorder") AND ("executive dysfunction") in the PubMed and SciELO databases. In the Embase database, the PICO strategy was employed for the search, including only patients with depression as the population (depression) and executive dysfunction as the outcome ("executive dysfunction"). The searches were carried out between December 2022 and August 2023. The eligibility criteria were organized following the PICO strategy (Santos et al., 2007):

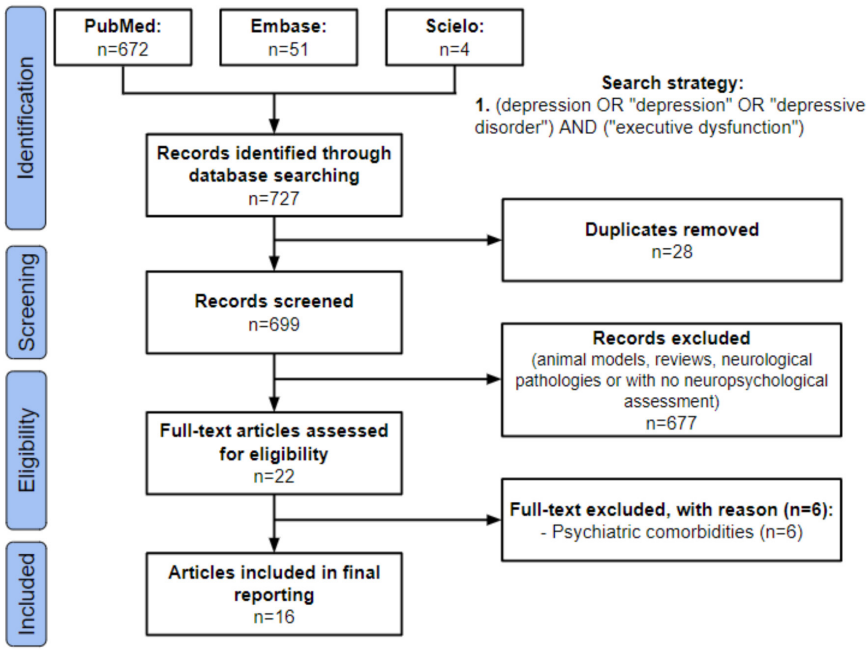
1. Individuals of all ages and both sexes, with depression diagnosed through clinical evaluation or standardized scales were included.
2. All studies that directly assessed EF performance using standardized scales or tests well-established in the literature of cognitive sciences were considered.
3. Comparisons were made between groups of depressive patients and controls or between sessions in patients with depression (longitudinally).
4. The outcome investigated was Executive Dysfunction.

There were no restrictions regarding the date and language of publications when applying the inclusion criteria based on the abstract. Only articles in Portuguese, Spanish, or English, the languages within the reviewers' proficiency, were considered for the final selection. The selection of studies encompassed all analytical, experimental, or observational articles that investigated the presence of ED in depressive patients compared to control individuals, either cross-sectionally or longitudinally, with a baseline measurement. Studies with non-human models or samples with comorbidities impacting executive performance, such as neurodevelopmental disorders or psychotic disorders, were excluded. Studies that involved manipulations potentially affecting EF, such as training subjects on the tasks used, were also excluded.

The information was extracted from the included studies by two evaluators using a standardized form: author, publication date, study type, participants (number, mean age, gender ratio), exposure or intervention, outcome, follow-up time, and losses. Executive dysfunction was considered based on the identification of executive impairment compared to controls and/or the decline in patients' EF over time. After removing duplicates and applying the inclusion and exclusion criteria (Figure 1), a total of 16 articles that effectively assessed EF in patients with depression were selected.

Figure 1

A flowchart based on the PRISMA protocol depicting the article selection process regarding executive dysfunction in depressive patients.



Risk of bias

A risk of bias analysis was performed using the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2; Sterne et al., 2019) or the Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I, Sterne et al., 2016), following the GRADE recommendation (Guyatt et al., 2008).

Results

The use of the expression "executive dysfunction" in the selected studies encompassed a range of impairments, ranging from difficulties with routine tasks to impairments in decision-making and cognitive flexibility. Table 1 summarizes the key information about each of the included studies, with a particular focus on the outcome related to ED.

Table 1

Summary of the studies found in the systematic literature review, focusing on the outcomes identified. Further details are in the main text.

Authors	Study type	Sample (n)	Concluding remarks
Cristancho et al. (2023)	Longitudinal	17 older adults	Bilateral intermittent theta burst stimulation (iTBS) in the dorsolateral prefrontal cortex did not improve depressive symptoms or EF.
Ngan et al. (2023)	Transversal	63 patients 58 controls All older adults	ED and anhedonia were associated with impaired reward learning in depression.
Warren et al. (2021)	Transversal	1,123 undergraduate students	Depressed mood and increased anxiety impaired all domains of executive functions, and excessive worry impaired cognitive flexibility.
Liao et al. (2021)	Transversal	41 patients 50 controls	Elevated serum copper levels in depression correlated with ED
Liu et al. (2021)	Longitudinal	95 patients 111 controls	Shifting and verbal fluency remained impaired in depression after remission.
Mac-Giollabhui et al. (2019).	Longitudinal	288 adolescents	Body mass index had a positive correlation with interleukin-6 (IL-6) and more severe depressive symptoms. Elevated IL-6 was negatively associated with EF.
Koo et al. (2019)	Transversal	20 patients 20 controls	Patients with depression exhibited ED and asymmetry in the EEG in the prefrontal cortex and lower levels of alertness.
Rajtar-Zembaty et al. (2017)	Transversal	87 patients 100 controls	ED may play a role in the persistence of depressive symptoms. There was a relationship between executive control and the level of depression.
Light et al. (2017)	Transversal	39 patients	Mu-opioid receptor availability in the ventrolateral prefrontal cortex mediated increased EF in depression.
Khan et al. (2015)	Transversal	50 patients 50 controls	Lower volume of the left hippocampus and cognitive flexibility impairment in patients.
Nunes et al. (2014)	Transversal	50 patients 35 controls	ED was related to the severity of depression.
Fiorentino et al. (2013)	Transversal	49 bv-DFT 30 patients 26 controls	ED was present in behavioral variant Frontotemporal Dementia (bv-DFT) and in depression. The level of ED, measured by INECO Frontal Screening, can be used to differentiate bv-DFT and depression.
Alexopoulos et al. (2011)	Longitudinal	221 older adults	Both problem-solving therapy (PST) and supportive therapy were effective in reducing ED at the beginning of treatment. PST was more effective at the end of treatment.
Drakeford et al. (2010)	Transversal	16 patients 16 controls	Depression leads to a decline in recognition memory, even in the absence of ED in patients.
Osorio et al. (2009)	Transversal	20 older adults 10 controls	ED was possibly considered a biological marker for late-life depression.
Nakano et al. (2008)	Transversal	79 patients 85 controls	ED persisted even after the remission of depression symptoms. The impairments varied with age.

Table 2 lists the tests and scales used in each of the selected articles and the functions assessed by each of them. Table 3 presents the bias risk analysis of the articles, showing that the majority of them had a low risk, with no articles having a high risk of bias.

Table 2

List of tests and scales used by the articles included in the review and the functions assessed by them.

Authors	Cognition	Attention / Inhibition	Cognitive flexibility	Mood
Cristancho et al. (2023)	FrSBe	Flanker	DCCS	MADRS
Ngan et al. (2023)	HK-MoCA	DS, TMT, VFT	TMT	HAM-D
Warren et al. (2021)	BRIEF-SR	BRIEF-SR	BRIEF-SR	PSWQ, MASQ
Liao et al. (2021)	DSST	DSST, TMT, VFT	TMT, WCST	HAM-D, YMRS
Liu et al. (2021)		DS, TMT, Stroop, VFT	TMT	SCID-IV, HAM-D
Mac-Giollabhui et al. (2019)	FOS	TEAch, TEA	FOS	CDI
Koo et al. (2019)		TMT, Stroop, VFT	TMT	BDI, HAM-D
Rajtar-Zembaty et al. (2017)	MMSE	TMT, GNG, VFT	TMT	GDS-SF
Light et al. (2017)	NEO		WCST	HAM-D
Khan et al. (2015)			WCST	
Nunes et al. (2014)	MMSE, IFS, BADS	IFS, BADS	IFS, BADS	BDI
Fiorentino et al. (2013)	MMSE, IFS, ACE-R	IFS	IFS	
Alexopoulos et al. (2011)	FrSBe	TMT, Stroop	DRS-IP, TMT, WCST	SCID-R, HAM-D
Drakeford et al. (2010)		WMS	WCST	BPRS
Osório et al. (2009)	MMSE, EXIT-S	EXIT-S	EXIT-S	GDS
Nakano et al. (2008)	JART	Stroop, VFT	WCST	HAM-D

Note: BADS – Behavioural Assessment of the Dysexecutive Syndrome; BDI – Beck Depression Inventory; BPRS – 19-item Brief Psychiatric Rating Scale; BRIEF-SR – Behavior Rating Inventory of Executive Function – Self-Report; CDI – Children's Depression Inventory; DCCS – Dimensional Change Card Sort Test; DRS-IP – Mattis Dementia Rating Scale initiation/perseveration domain; DS – forward and backward Digit Span; DSST – Digit Symbol Substitution Test; Flanker – Flanker Inhibitory Control and Attention Test; FOS – Future Orientation Scale; FrSBe – Frontal Systems Behavior Scale; EXIT-S – Executive Interview; GDS – Geriatric Depression Scale; GNG – Go/no-go task; HAM-D – Hamilton Depression Rating Scale; HK-MoCA – Hong Kong Chinese version of the Montreal Cognitive Assessment; IFS – INECO frontal screening; JART – Japanese Adult Reading Test; MADRS – Montgomery-Asberg Depression Rating Scale; MMSE – Mini Mental State Examination; MASQ – Anxiety Symptom Questionnaire; NEO – NEO Personality Inventory-3 (positive emoticons facet); PSWQ – Penn State Worry Questionnaire Mood; SHAPS – Snaith-Hamilton Pleasure Scale; Stroop –Stroop Test; TEA – Test of Everyday Attention; TEACh – Test of Everyday Attention for Children; TMT – Trail Making Test; VFT – Verbal Fluency Test; WCST – Wisconsin Card Sorting Test; WMS - Wechsler Memory Scales, Letter-Number Sequence subtest only; YMRS – Young Manic Rating Scale.

Table 3

Risk of bias analysis for the articles included in the review.

Authors	*Risk*			
RoB 2 tool	**Low**	**Some concerns**		**High**
Cristancho et al. (2023)	X			
Alexopoulos et al. (2011)	X			
ROBINS-I tool	**Low**	**Moderate**	**Serious**	**Critical**
Ngan et al. (2023)	X			
Warren et al. (2021)	X			
Liao et al. (2021)	X			
Liu et al. (2021)	X			
Mac-Giollabhui et al. (2019)	X			
Koo et al. (2019)	X			
Rajtar-Zembaty et al. (2017)	X			
Light et al. (2017)	X			
Khan et al. (2015)		X		
Nunes et al. (2014)	X			
Fiorentino et al. (2013)	X			
Drakeford et al. (2010)	X			
Osório et al. (2009)	X			
Nakano et al. (2008)	X			

Cristancho et al. (2023) investigated the efficacy of bilateral intermittent theta burst stimulation (iTBS), a specific type of transcranial magnetic stimulation, in improving symptoms of LLD and EF when applied to the dorsolateral prefrontal cortex to improve symptoms of LLD and EF. They randomized 17 patients with depression and ED to iTBS in the dorsolateral prefrontal cortex or sham for six weeks. The intervention was applied by an operator blinded to the conditions. No differences were found between the iTBS and the sham conditions. Interestingly, all patients' depression symptoms improved according to the Montgomery-Asberg Depression Rating Scale (MADRS), suggesting that the improvement in attention given alone could be effective in mitigating symptoms. This evidence is supported by no differences found for the EF throughout the six weeks span.

Anhedonia is one of the central symptoms of depression and is commonly experienced by patients with LLD. Ngan et al. (2023) defend that it is an important prognostic factor for these patients. They investigated the reward responsiveness of 63 patients and 58 healthy controls aged 60 or more through the probabilistic reward learning task. Results revealed trends of reduced response bias and reward learning in LLD. In addition, anhedonia severity was correlated to impaired reward learning and global cognition, working memory, and attention measures,

which explains the response bias of both groups. The authors argue that ED and anhedonia may have decreased the ability to detect differences in reward, which impairs learning.

The association between ED and depression could be restricted to some, but not all of its core components. Warren et al. (2021) evaluated this association in a sample of undergraduate students with depression or anxiety. The evaluation of anxiety symptoms was conducted using the Penn State Worry Questionnaire (PSWQ), as well as the Anxious Arousal subscale of the Mood and Anxiety Symptom Questionnaire (MASQ). Symptoms of depression were assessed using the Anhedonic Depression subscale of the MASQ. Executive functions were assessed through a self-report scale, the Behavior Rating Inventory of Executive Function – Self-Report (BRIEF-SR), specifically focusing on items related to working memory, inhibitory control, and cognitive flexibility. The findings indicate that anxious arousal, or somatic anxiety (Burdwood et al., 2016), and depressive symptoms are associated with impairments across all components of EF, characterizing ED. Additionally, anxious apprehension showed a significant association with cognitive flexibility. Taken together, these findings suggest that the heightened vigilance state induced by anxiety and depressive symptoms may give rise to features of ED, and that persistent anxiety-related worry promotes inflexibility. The authors also concluded that executive impairments may be contributing factors in the maintenance of mood disorders, highlighting the potential relevance of therapeutic strategies specifically targeting ED for symptom remission.

Some authors investigated organic factors linked to depression that could be the reason for EF impairment. Liao et al. (2021) evaluated whether the interaction between serum copper levels and neurometabolic alterations could be involved in ED in unmedicated patients with depression. A total of 41 patients and 50 control subjects had their serum copper levels measured, along with the EF using the Trail Making Test-B (TMT-B), Digit Symbol Substitution Test (DSST), Wisconsin Card Sorting Test (WCST), and semantic verbal fluency test (SVFT). The findings showed worse performance in patients compared to controls and that higher serum copper levels were negatively associated with cognitive flexibility and general cognition, which led the authors to conclude that high serum copper levels could be related to ED in depression.

Liu et al. (2021) used the same EF tests (TMT-B and SVFT) to investigate 95 depressive patients before and after paroxetine treatment, compared to 111 healthy controls. After six months of treatment, 56 patients achieved clinical remission. Patients in remission, however, still had worse verbal fluency and cognitive flexibility, suggesting that impairments from depression could be related to functional connectivity changes and, therefore, be state-independent. Furthermore, the authors found differences among frontoparietal networks that were related to ED in remitted patients in comparison to those that still had depressive symptoms.

Biomarkers were also investigated by Mac-Giollabhui et al. (2019). The authors hypothesized that ED could be associated with metabolic impairments in patients with depression. They investigated whether higher levels of interleukin-6 (IL-6), a significant inflammatory marker, and/or the body mass index (BMI) would predict ED in adolescents with depression. A total of 288 participants, both boys and girls (51.4% of the sample), with a mean age of 16.33,

were assessed over a three-year period. They provided measurements of weight and height, blood samples for IL-6 levels, completed the Children's Depression Inventory (CDI), and tests of EF: subscales of the Test of Everyday Attention for Children (TEAch), Test of Everyday Attention (TEA), as well as the Future Orientation Scale (FOS). The results indicated that BMI was positively associated with higher levels of IL-6 and depressive symptoms. Interleukin-6 levels also showed an inverse correlation with EF tests, meaning that higher IL-6 levels were associated with poorer performance. Additionally, chi-square tests demonstrated that more severe depressive symptoms were predictors of higher IL-6 levels, and both the severity of symptoms and higher BMI were predictors of poorer future executive performance through increased IL-6 levels. The authors concluded that more severe depressive symptoms and higher BMI may lead to ED through elevated IL-6 levels.

Koo et al. (2019) explored the usefulness of combining the interaction between EF tasks, motor activity, and neurophysiological patterns from EEG for depression diagnosis. A neuropsychological battery that included the TMT-A and TMT-B, Stroop Task, and VFT was applied, in addition to the Motor Agitation and Retardation Scale (MARS), an actigraphy to record the daily motor activity and the EEG with the 10/20 international system, with a sample of 20 patients with depression and 20 age-matched healthy controls. Results showed ED and psychomotor abnormalities (longer reaction times, decrease in total activity, and higher MARS scores) in depressive patients. Data from the EEG revealed more cerebral dysregulation, meaning asymmetry in alpha power which translates to a reduction in alertness. The asymmetry index of the EEG alone could discriminate between patients and controls with 78% accuracy. The combination of EEG recordings, motor activity, and EF tasks raised the discrimination to 81%, leading to the conclusion that combining these data is a more reliable tool to identify patients with depression than EF tasks alone.

Light et al. (2017) used EEG recordings to highlight that the Mu-opioid receptor availability in the ventrolateral prefrontal cortex (VLPFC) mediates increased EF in depression. The authors recruited 26 participants with depression and assessed cognitive flexibility by means of the WCST and the opioid neurotransmission in the VLPFC traced by [11C]carfentanil, a Mu-opioid receptor selective radiotracer, in a positron emission tomography (PET) scan. Positive emotions were accessed through the NEO Personality Inventory-3 (NEO), as the authors proposed that positive emotionality could correlate to EF through opioid levels. Results suggest that increased mu-opioid activity in the VLPFC mediates the relationship between increased trait positive emotionality and more efficient executive functioning. No ED assessments were made on the patients, with the WCST being the only test used, although the article hypothesizes that lower opioid levels could correlate with ED.

Rajtar-Zembaty et al. (2017) also investigated LLD. They assessed the cognitive functions of 87 older adult patients with LLD compared to 100 control individuals matched for gender, age, and education level. The depressive condition was clinically evaluated and confirmed by scoring over 6 points on the Geriatric Depression Scale (GDS). Cognitive functions were measured using

the TMT, VFT, and a go/no-go task (GNG). All participants were screened for cognitive deficits using the Mini-Mental State Examination (MMSE), with no deficits detected. The results indicated poorer performance on all cognitive function measures in older adults with depression. Specifically, decreased psychomotor speed, cognitive flexibility, semantic fluency, and inhibitory control were observed. These findings suggest that depression can lead to cognitive impairment even when it occurs later in life, supporting the findings of Ngan et al. (2023). Furthermore, they imply that cognitive impairment may serve as a potential marker of the depressive process.

Executive function impairments are supported by studies using magnetic resonance imaging (MRI). Khan et al. (2015) used MRI to investigate whether EF performance is associated with hippocampal changes. The authors measured hippocampal volume and used the Wisconsin Card Sorting Test (WCST) to assess cognitive flexibility in 50 depressed patients and 50 controls. The results showed a smaller volume of the left hippocampus, even in patients experiencing their first depressive episode. Additionally, patients' performance on the WCST was worse, with a positive correlation between the volume of the right hippocampus and the number of categories completed in the test, suggesting better performance due to preserved hippocampal volume. The authors also found that the number of perseverative errors, a key indicator of cognitive flexibility, was higher in patients with more severe levels of depression. Although the authors concluded that it is not possible to establish a correlation between hippocampal volume and ED, the use of only one test to assess ED limits the strength of this conclusion.

A more comprehensive assessment was provided by Nunes et al. (2014), who investigated the EF of 50 patients diagnosed and treated for depression for at least one year, compared to control individuals of the same age and education level, with no psychiatric history. The authors used the INECO Frontal Screening (IFS) neuropsychological battery, which assesses all components of EF. They found executive impairment in patients, as well as a strong negative association between the level of depression and executive performance, assessed through Pearson's correlation. A similar pattern of results was shown with the Behavioral Assessment of the Dysexecutive Syndrome (BADS). Comparable findings were reported by Fiorentino et al. (2013), who also used the IFS to evaluate patients with depression and patients with the behavioral variant of Frontotemporal Dementia (bv-FTD), compared to controls. The results showed lower IFS scores in both patient groups compared to controls, with worse performance in the bv-FTD group. This led the authors to suggest that performance on the IFS may serve as a good criterion for differential diagnosis between depression and bv-FTD. Overall, both Nunes et al. (2014) and Fiorentino et al. (2013) support the presence of ED in depression.

In an attempt to mitigate ED, Alexopoulos et al. (2011) specifically investigated patients with depression and ED to determine whether problem-solving therapy (PST), a methodology similar to cognitive-behavioral strategies, would be more effective than supportive therapy (ST), a person-centered therapeutic approach, in reducing executive impairments and improving depressive symptoms. The authors followed 221 older adult patients (≥ 60 years) over 36 weeks, during which they underwent 12 sessions of either PST or ST. The results showed that both

interventions reduced ED within the first six weeks of treatment. However, PST proved to be more effective by the end of the intervention period, between weeks 9 and 12. The findings support that PST is more effective in reducing ED in older adults, with sustained benefits even at the end of treatment. These results also suggest that it is possible to mitigate executive impairments in depression, even in patients who are refractory to medication.

In a small sample of 16 adult patients, Drakeford et al. (2010) were unable to detect ED. It is important to note that all patients had remitted symptoms, with two being medication-free and 14 taking antidepressant drugs. Executive functions were assessed using the Letter-Number Sequence subtest of the Wechsler Memory Scales and the WCST. Results showed no significant differences from a control group (n = 16) matched for gender, age, premorbid IQ, and ethnicity in both tests, although some borderline differences were observed. For example, not all patients completed all categories of the WCST, which was also true for controls. Although ED was not detected, adults with depression had worse outcomes in the remember/know paradigm, which can distinguish recollection from familiarity. Results indicated impairment in recollection performance, with no differences for familiarity, suggesting that depression can disturb recollection even in the absence of ED.

Osório et al. (2009) also assessed older adults with depression (n = 20) compared to controls with no history of mood disorders (n = 10). In this study, patients were selected from the outpatient care of a mental health clinic, and controls were selected from primary care in the same region. Mood assessment was conducted using the GDS scale, and EF were evaluated using the Executive Interview (EXIT-S). The EXIT-S scale includes different tests that assess cognitive flexibility, inhibitory control, impulsivity, motivation, and imitation, and incorporates verbal fluency tests, go/no-go tasks, and the Stroop interference task. The final score ranges from 0 to 50 with higher scores indicating greater cognitive impairment. Scores above 15 are significantly correlated with cognitive impairments and behavioral changes (Osório et al., 2009). The authors' results showed no differences in age, education, GDS scale, and MMSE. However, the EXIT-S scale revealed significant differences between the groups, with depressive patients showing worse performance, a result that persisted even when the GDS scale was included as a covariate in the statistical test (ANCOVA). Accordingly, the authors suggest that ED may be a potential biological marker of LLD.

Aiming to assess ED associated with the treatment of depression, Nakano et al. (2008) compared the performance of patients with depression in remission (n = 79), to controls with no history of mood disorders (n = 85) on the WCST, the Stroop test, and the Verbal Fluency Test (VFT). Since both younger and older participants were included, both groups were further divided into young and older adult groups (≥ 60 years). The results show an age effect on cognitive flexibility performance, assessed through the WCST, as expected, with no differences due to the diagnosis of depression, suggesting that this skill may recover in a remission state. However, attention, and inhibitory control, assessed by the Stroop test, were affected by both age and the presence of depression, with older adults with depression showing the worst performance of all

subgroups. For verbal fluency, the worst performance was associated only with the diagnosis of depression, not age, despite symptom remission. Collectively, the authors suggest that depression causes ED that persists despite symptom remission, with specific deficits potentially varying with age, however.

Taken together, these results underscore that ED is a significant outcome of depression that should be considered during clinical evaluation. Identifying and addressing executive deficits is important for reducing the risk of relapse, given that ED can persist even after remission, as well as for mitigating the risk of suicide (Snyder et al., 2015).

Discussion

This study aimed to conduct a systematic review on the occurrence of ED in patients with depression. Although widely cited, few studies in the literature have systematically investigated ED by rigorously evaluating the EF of patients in comparison to control groups or through longitudinal monitoring. In general, the identified studies confirm the presence of ED in patients with depression, even after symptom remission, highlighting the need to routinely assess EF and, whenever possible, continue monitoring patients.

The risk of bias analysis ensures that results are consistent across most selected studies in the review, supporting the idea that, although assessments are not always conducted in a blinded manner and some samples are small, ED is an important consequence of depression. However, the findings presented here are limited by the low number of longitudinal studies and the absence of randomized clinical trials, therefore these results need to be expanded, evaluated through randomized clinical trials, and investigated in other patients with mood disorders, a recommendation already noted in the literature (Hyman, 2008). Additionally, specific diagnosis or severity of depressive symptoms was not considered an eligibility criterion, although most studies characterized the diagnosis as major depressive disorder (APA, 2022).

The findings presented here are consistent with several previous reviews in the field and show similar results to those observed in patients with Bipolar Affective Disorder (Koene et al., 2022). McLennan and Mathias (2005) conducted a meta-analysis to assess the Depression-Executive Dysfunction model, which suggests that depressive patients do not respond to antidepressant medication due to ED, a hypothesis raised by Alexopoulos (2001). However, the results of the meta-analysis are inconsistent with this model because the performance on EF tests with relevant results in depressive patients, such as the Stroop test and the Trail Making Test, is not a good predictor of drug response. This indicates that some patients respond adequately to medication while others do not, regardless of their performance on these tests. More recently, Tunvirachaisakul et al. (2018) considered ED as a predictor of the prognosis of depressive episodes. However, only three studies that analyzed EF were included, with findings based solely on the Trail Making Test. Overall, the presence of ED is associated with a lower chance of depression remission, according to the authors, as also suggested by Rajtar-Zembaty et al. (2017). Finally, Lima et al. (2022) conducted an analysis to evaluate the relevance of the

P300 component of event-related potentials (ERPs) in ED caused by sleep deprivation. The authors concluded that the P300 is a valuable marker for evaluating ED following sleep deprivation. Considering the sleep disturbances often associated with depression, further investigations need to be conducted to investigate the role of sleep deprivation in the development of ED.

Our systematic review contributes to the existing literature by emphasizing the relevance of always investigating EF in patients with depression. As previously noted, ED is potentially associated with lower remission rates in depressive patients (Tunvirachaisakul et al., 2018). However, our findings reveal that ED may act as a biological marker for depression (Osorio et al., 2009), possibly even persisting in the remissive state (Nakano et al. 2008, Liu et al. 2021), and could contribute to the persistence of symptoms (Rajtar-Zembaty et al., 2017). Furthermore, patients with depression may experience problems related to reward learning (Ngan et al., 2023) and exhibit difficulty in recalling memories (Drakeford et al., 2010). Together, these findings emphasize the need to promptly identify symptoms and make a diagnosis, aiming for immediate intervention and reduction of the symptom severity. Our results also suggest that ED could be a useful indicator of depression severity, as the extent of dysfunction correlates directly with the severity of depressive symptoms.

Recently, Singh et al. (2023) conducted an umbrella review and found that physical exercise can be as effective as medication in reducing symptoms of depression, anxiety, and stress. Interestingly, the effectiveness of this intervention tends to decrease with longer treatments, which could be related to ED hindering decision-making and worsening the depressive condition. Given the well-established benefits of physical exercise in reducing chronic stress and restoring the proper functioning of the prefrontal cortex (Davidson & McEwen, 2012), including exercise as an essential part of depression treatment should not be overlooked. Additionally, executive impairments in depression may be associated with metabolic factors, making physical activity an important therapeutic ally (Mac-Giollabhui et al. 2019, Liao et al. 2021). Finally, the results of Alexopoulos et al. (2011) support cognitive-behavioral therapeutic strategies for better symptom remission and reduced executive impairments, in contrast to iTBS (Cristancho et al., 2023), a type of transcranial magnetic stimulation.

Future studies should aim to correlate the intensity and duration of depressive symptoms with the level of executive impairment. This relationship could further highlight the importance of early intervention to reduce ED. The role of large-scale neural networks, including their organization, functioning, and how they change over time, is already well-established for several psychiatric conditions, including depression (Menon, 2011). Furthermore, as research continues to emphasize the impact of depression on EF, it is essential to distinguish between cognitive changes and the behavioral outcomes of these impairments. This differentiation could provide a more nuanced understanding of the ED observed in depression.

The small number of studies that effectively measured the state of EF suggests that this important set of skills has been overlooked in the management of these patients. Given the

importance of EF in planning and decision-making, disregarding the development of ED means missing an important therapeutic opportunity that could provide patients with a deeper understanding of their own condition. Additionally, this oversight fails to provide patients with strategies for personal reorganization, which can be decisive in instilling hope and relief for those living with depression.

Final Considerations

In summary, the included articles allow us to assert that ED accompanies the depressive condition, and EF performance appears inversely correlated with stress levels induced by depressive symptoms. This finding reinforces the evidence that ED can both reduce the chances of remission and worsen the prognosis of depression. However, psychotherapeutic monitoring seems capable of minimizing executive impairments. Lastly, there is evidence that ED persists even after symptom remission, with more noticeable impairments in older individuals.

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