Chapter 12
Executive Dysfunction in Depressive Disorders

Mónica Rosselli, Merike Lang and Fernanda Arruda

12.1 Introduction

Depression is defined as a mood disorder associated with a persistent emotional state of sadness and loss of interest that affects thoughts and behavior, leading to physical and cognitive problems. Therefore, depression includes cognitive (i.e., memory deficits), behavioral (i.e., less daily activity), emotional (i.e., feeling misery), motivational (i.e., lack of initiative and despondency), and physical (i.e., disturbances in sleep and eating) symptoms (Comer, 2016). Some of the cognitive symptoms described in depression may include deficits in executive functions (EFs). Research has demonstrated that patients diagnosed with major depression had widespread cognitive impairment (Ravnkilde et al., 2002). However, not all depressed individuals have cognitive defects; the manifestation of depressive symptoms may be due to an interaction between motivation, emotional, and cognitive symptoms (Austin, Mitchell, & Goodwin, 2001).

EFs, a set of cognitive abilities that guide behavior toward the completion of a goal, are involved in the conscious control of thought and action (Kerr & Zelazo, 2004). EFs permit quick set-shifting and inhibition of inappropriate behaviors (Jurado & Rosselli, 2007). Lezak (1983) viewed EFs as the dimension of human behavior that deals with 'how' behavior is expressed. It is an umbrella term that includes a wide variety of components such as planning, set-shifting, updating, cognitive flexibility, working memory, inhibitory control, multitasking, and abstraction (Jurado

M. Rosselli (✉) · M. Lang · F. Arruda
Department of Psychology, Florida Atlantic University, Davie, FL, USA
e-mail: mrossell@fau.edu

M. Lang
e-mail: mlang2015@fau.edu

F. Arruda
e-mail: farruda2016@fau.edu

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& Rosselli, 2007; Miyake et al., 2000; Snyder, 2013). Moral and ethical behaviors also represent EFs (Ardila & Surloff, 2004).

An important distinction in the classification of EFs accounts for whether they are affective or cognitive processes. EFs that have an affective/emotional component are considered 'hot' EFs, while those that are relatively abstract and non-affective, relating to cognition (e.g., working memory and multitasking), are known as 'cool' or 'cold' EFs, although some authors argue that both should be viewed as multidimensional and in a dynamic continuum rather than in dichotomy (Kluwe-Schiavon, Viola, Sanvicente-Vieira, Malloy-Diniz, & Grassi-Oliveira, 2017). 'Cool' EFs include self-management skills with no involvement of emotion such as updating, inhibition, and set-shifting (Ho, Hsu, Lu, Gossop, & Chen, 2018). The 'hot' EFs include affective decision making for events with emotionally significant consequences (i.e., meaningful rewards and/or losses) (Kerr & Zelazo, 2004). Ardila (2013) suggested that cool EFs constitute a metacognitive group of cognitive abilities, whereas the hot EFs comprise emotional/motivational processes. The latter EFs include abilities required to fulfill basic impulses following socially accepted strategies in which inhibitory control plays a major role.

EFs rely heavily on the prefrontal cortex (PFC). Three main subdivisions of the PFC relevant to EFs are the dorsolateral prefrontal cortex (DLPFC), the orbitofrontal cortex (OFC), and the medial prefrontal cortex (MPFC) (Ochsner & Gross, 2007; Goldman-Rakic, 1995). Studies have demonstrated that the DLPFC plays a major role in metacognitive EFs, whereas the OFC and MPFC are relevant to the mediation of EFs in which emotions are involved (Ardila, 2013). More recently, an emphasis has been placed on the ventromedial frontal lobe (Farrar, Mian, Budson, Moss, & Killiany, 2018; Peters, Fellows, & Sheldon, 2017) and the ventrolateral prefrontal cortex (VLPFC) as relevant structures in the decision-making and regulatory processes of behavior (Light et al., 2011), respectively.

Some depressed individuals present deficits in EFs such as shifting, inhibition, working memory, and planning as part of their neuropsychological profiles (Zakzanis, Leach, & Kaplan, 1998; Lockwood, Alexopoulos, & van Gorp, 2002; Snyder, 2013). Since the PFC demonstrates changes in depressive symptoms, there is an overlap of the areas involved in depression and the neural mechanisms of EFs (Pizzagalli, 2011; Rogers et al., 2004). Therefore, the dysexecutive syndrome has been suggested for depressed individuals. This depression-dysexecutive syndrome has been considered a distinct type of depression characterized by psychomotor retardation and a reduced interest in activities, as well as reduced verbal fluency (Alexopoulos, 2001).

The main purpose of this chapter is to review the current knowledge surrounding the association between depression and cognitive processes, particularly those abilities involved in EFs. The first section will define the different depressive disorders and will be followed by a description of the proposed neural substrates of the executive system in depressed individuals across the lifespan.

12.1.1 Defining Depressive Disorders

Clinical depression can manifest with major depressive episodes (MDE) and major depressive disorder (MDD). An MDE is a period of two or more weeks marked by at least five symptoms of depression, which include sad mood and/or loss of pleasure. An MDE is considered recurrent when there is an interval of at least two consecutive months between separate episodes (DSM-5; American Psychiatric Association, 2013). People who experience recurrent MDEs without having any history of mania receive a diagnosis of MDD (APA, 2013). MDD is diagnosed when, for at least two weeks, a patient has experienced depressed mood or loss of interest or pleasure associated with other symptoms such as a change in appetite and body weight, sleep alteration, psychomotor agitation or retardation, fatigue, negative feelings about the self, decreased concentration, and suicidal ideation (APA, 2013). The International Statistical Classification of Diseases and Related Health Problems (ICD-10; World Health Organization, 2004) criteria distinguish three degrees of severity in depressive episodes: mild (few distressing symptoms and minor social/occupational impairment), moderate (greater intensity and number of symptoms with functional impairment), and severe (intense symptoms which are distressing/unmanageable and interfere with social/occupational functioning).

Persistent depressive disorder (dysthymia) is the consolidation of two diagnoses from the DSM-IV: chronic MDD and dysthymic disorder. This diagnosis refers to those who present depressed mood for most of the day for at least two years; children and adolescents can receive this diagnosis when symptoms are present for at least one year, and they may additionally experience irritable mood (APA, 2013). A third type of depressive disorder (DD) is premenstrual dysphoric disorder, a diagnosis given to women who repeatedly have clinically significant depressive and related symptoms, such as marked affective lability, irritability or anger, depressed mood, and anxiety, during the week before menstruation in the majority of menstrual cycles. These symptoms must cause significant distress and interfere with the patient's social and/or work life.

The DSM-5 divides mood disorders into two groups: bipolar and related disorders, and depressive disorders (APA, 2013; Tandon, 2015). The bipolar and related disorders section includes major depression in combination with episodes of mania and is placed between the section of the schizophrenia spectrum/other psychotic disorders and the section pertaining to depressive disorders. This change from the DSM-IV was made with the consideration that bipolar disorder shares both clinical features with unipolar depression and with schizophrenia (Tandon, 2015).

Table 12.1 includes a list of all depressive disorders according to the DSM-5. The common feature of all of these disorders is the presence of sadness, emptiness, or irritability in mood, accompanied by somatic and cognitive changes that significantly affect the individual's capacity to function. Duration, timing, or presumed etiology distinguishes them.

Disruptive mood dysregulation disorder, a childhood depressive disorder, is characterized by children and adolescents who have severe and recurrent temper outbursts

Table 12.1 Depressive disorders (DD) based on the DSM-5 (APA, 2013)

Disruptive mood dysregulation disorder
Major depressive disorder (including major depressive episode)
Persistent depressive disorder (dysthymia)
Premenstrual dysphoric disorder
Substance/medication-induced depressive disorder
Depressive disorder due to another medical condition
Other specified depressive disorder
Unspecified depressive disorder

that are out of proportion to the given situation and express a persistent irritable or angry mood (APA, 2013).

12.2 Executive Function and Depression

12.2.1 Child/Adolescent MDD and Executive Dysfunction

There is no consistency in the findings regarding the association between depression and EFs for children and adolescents. Some studies have shown that they score similarly to healthy controls on neuropsychological tasks measuring EFs. Favre et al. (2009) found that 39 children and adolescents (between the ages of 8–17 years) with a diagnosis of MDD had similar EF scores compared to healthy controls ($n = 24$) on the Wisconsin Card Sorting Test (WCST), Trail Making Test (TMT), Control Oral Word Association Test (COWAT) and the Stroop test. Only mental processing speed was significantly lower in those with MDD, as demonstrated by the processing speed index from the Wechsler Intelligence Scales (third edition; WISC-III and WAIS-III). The authors suggested that lower processing speed may be due to lower motivation and psychomotor retardation (a symptom of MDD), and not likely due to deficits in attention and concentration. In addition, this study included ten participants with comorbid ADHD, and this subgroup of ADHD and MDD performed worse on the WCST and TMT-B compared to depressed children without ADHD. The authors speculated that with a larger sample, these differences would have been detected.

Metanalytic reports have found significant impairments in some EFs for children and adolescents suffering from depression. Wagner, Müller, Helmreich, Huss, and Tadić (2015) analyzed 17 studies relating to intelligence, EFs, verbal memory, and attention in 447 patients (age range of 9–15.3 years) with an MDD diagnosis. These individuals were compared to 1347 healthy participants (ranging in age from 9–15.8 years). The EF measures included inhibition (Stroop Color-Word interference test), set-shifting (TMT-B, Cambridge Neuropsychological Test Automated Batteries [CANTAB], supervisory attention system [SAS] and shifting attention test [SAT]), working memory (digit span [Wechsler Intelligence Scale for Children—WISC],

n-back, symbol digit encoding [Amsterdam Neuropsychological Tasks—ANT] and spatial working memory), planning (Tower of Hanoi and Stockings of Cambridge [CANTAB]), and verbal fluency (phonemic and semantic fluencies). Their results demonstrated significantly lower EF test performance in MDD, especially for inhibition capacity, semantic verbal fluency, sustained attention, verbal memory, and shifting/planning. In addition, healthy children and adolescents had higher full-scale IQ scores (on verbal and performance measures) compared to MDD patients. Günther and collaborators (2011) also reported difficulties in EF tasks of inhibitory control such as go/no-go and set-shifting tasks of 61 children with depressive disorders including MDD and dysthymic disorder (age range of 10–15) compared to healthy controls.

In a systematic review of the literature (from 1994 to 2014), Vilgis, Silk, and Vance (2015) identified 33 studies of children and adolescents (age range 6–19 years) with depressive disorders (MDD or dysthymia, according to DSM-IV criteria) in which EFs were tested. All articles met the inclusion criteria of having a nonclinical control group and a sample size of 10 or more participants in the clinical group. The specific EF domains of interest were attention, response inhibition, set-shifting, working memory, planning, and verbal fluency. Results showed that of the nine studies assessing the ability to sustain attention (e.g., Continuous Performance Test) in children and adolescents with depressive disorders, only five reported difficulties in the group of patients with depression. None of the five studies that included measures of selective attention (i.e., target detection in a visual array of similar-looking items) found differences between patients and healthy controls. Only three of the 16 investigations that examined response inhibition (e.g., Stroop test, go/no-go) showed lower scores in the depressed sample compared to controls. It is important to note that only one of the five studies that used the Stroop test as a measure of inhibitory control found worse performance in the clinical group. On the go/no-go task, there was no significant difference between healthy children and patients with MDD and dysthymia, matched for age. Differences in set-shifting (i.e., TMT-B and WCST) between the two groups were observed in three out of ten studies. Two of these studies used the TMT-B, and one used a combined score of the perseverative errors from the WCST and the TMT-B. The TMT-B is a good measure for assessing set-shifting because the patient is required to alternate between numbers and letters (two mental sets) while connecting circles in sequential and alphabetical order. One study that used the WCST alone as a measure of cognitive flexibility did not find differences between the groups. Using the CANTAB set-shifting task, there were no differences in error rate for two of the studies, although differences were detected in reaction time. Five reports were found comparing healthy controls and those diagnosed with depressive disorders in visuospatial working memory tasks (Vilgis et al., 2015). In three of these studies, no differences were observed between groups for adolescents, although one study found more errors for depressed adolescent girls compared to healthy controls. Using the spatial working memory task of the CANTAB, one study reported worse performance from depressed patients.

Moreover, Vilgis et al. (2015) also examined whether depression was associated with reduced verbal working memory. The digit span from the Wechsler Intelligence

Scale for Children (WISC) was used in two of the studies discussed. One of them found a reduced digit span in both adolescents with MDD and those with dysthymia or a depressive disorder not otherwise specified, and the other found no deficits in children with anxiety and depression on digit span compared to the healthy control group. Two of the three studies also reviewed by Vilgis et al. (2015) found difficulties in planning (e.g., Tower of London/Hanoi tasks) in clinical participants with depression. Verbal fluency deficits (e.g., generation of words within phonemic categories) were additionally noted in the depressed groups for two of the four studies.

In terms of attentional bias and affective manipulations of 'cold' EFs, depressed individuals demonstrate attentional biases toward negative stimuli. Neshat-Doost, Moradi, Taghavi, Yule, and Dalgleish (2000) compared the performance of MDD, dysthymia, and controls on the dot-probe task. This is a task of selective attention in which neutral and threatening stimuli are presented simultaneously, and the latency to indicate the location of a dot that is presented after the stimuli is recorded. Performance differences have been observed between clinical and healthy controls, although this was not seen in depressed children utilizing stimuli of emotional words. Depressed groups were biased toward the sad face stimuli, while anxious groups had biases toward both angry and sad faces, with an apparent gender bias for boys but not girls in avoiding happy faces. Four studies found that affective manipulation of stimuli did not show a task performance effect for depressed participants. However, other studies utilizing similar tasks showed shorter reaction times for negative as opposed to positive stimuli only for the acute MDD group, compared to the remitted MDD patients and controls, although this did not correlate with symptom severity.

Vilgis et al. (2015) additionally reviewed studies of 'hot' EFs. They discussed performance on the Iowa gambling task (IGT; a task simulating real-life decision making by sampling four virtual decks of cards that represent reward or punishment) of 31 children diagnosed with MDD compared to 30 controls. There were two studies that showed that boys with dysthymia or MDD selected more disadvantageous cards compared to healthy controls and chose a large reward less often, even when the probability of winning was high. However, one study failed to show differences in IGT comparing self-harming adolescents with MDD and healthy controls. Another study showed no group differences in decision making with betting options across similar groups, although two other studies showed diminished reward seeking and task performance associated with the severity of depressive symptoms. Additionally, Vilgis et al. (2015) cited the study in which incentives were less effective in modulating the performance of adolescents with MDD on a rewarded antisaccade task. Healthy controls showed reductions in the mean 'velocity' or unwanted reflexive saccades/eye movements in reference to punishment or reward compared to patients with MDD, as well as shorter latencies in eye movements for both positive and negative incentive conditions relative to no incentive conditions. No differences were observed in latency by condition for MDD patients.

Wagner, Alloy, and Abramson (2015) observed 486 adolescents in a balanced sample of Caucasians and African Americans with the goal of determining the deficits in EFs associated with rumination and depression among early adolescents (ages 12–13), which is considered a critical developmental period. Rumination is con-

ceptualized under the response styles theory as a way of responding to distress and involves focusing repetitively and passively on present thoughts and events as well as the possible causes and consequences of them. The authors found that the current level of depression was associated with attention, and rumination predicted better-sustained attention in those with low levels of depressive symptoms. Worse-sustained attention was observed in those with high levels of depressive symptoms. The authors found that controlling for depressive symptoms, higher levels of trait rumination (an abstract information processing mode of constantly anticipating present events on future experiences/consequences that remains a stable characteristic throughout changes in depressive symptoms; Kocsel et al., 2017) did not predict poorer attentional set-shifting or better-sustained attention in adolescents. Additionally, rumination was associated with better attentional abilities, only when there was little or no depression present, which contradicted the predicted results. The authors recommended interpreting their findings with caution given the small effect sizes and the small number of significant associations obtained. However, they also offered a possible interpretation of their results, suggesting that trait ruminators, only when not actively depressed/engaging in rumination during task completion, may have a particular cognitive profile that renders them with better performance on certain tasks of EFs possibly due to a narrowed attentional scope, facilitating performance for ignoring distractors and irrelevant information.

Förster et al. (2018) investigated the relationship between EF and social cognitive performance in late adolescence and young adulthood ($M_{age} = 20.60$ years; $SD_{age} = 3.82$ years) with current and remitted depression ($n = 118$) compared to controls ($n = 61$). Social cognitive performance was assessed through three social perception subtests: affect naming, prosody face matching, and prosody pair matching. Four EFs were assessed: set-shifting (or cognitive flexibility; Card Sort Task based on the WCST), planning ability (Tower of London), working memory (updating; n-back task with three different conditions of one-back, two-back, three-back recall), and inhibitory control (Stroop task using the Victoria Stroop Test, a version of the Stroop for French speakers, Bayard, Erkes, & Moroni, 2011; Tremblay et al., 2016). Social cognition and EFs did not significantly differ between healthy and depressed patients. There was no association between EFs and social cognitive function in healthy controls. Depressed adolescents and young adults exhibited lower cognitive flexibility, associated with lower facial-affect recognition and theory of mind. The authors concluded that deficits in cognitive flexibility may lead to a more 'rigid' perception of ambiguous social stimuli.

In summary, many of the studies presented in this section do not demonstrate robust differences in EFs among depressed children and adolescents compared to healthy controls (Vilgis et al., 2015; Wagner, Alloy et al., 2015). Evidence of poorer performance among depressed youths relative to controls has been reported on tests of sustained attention, shifting, planning, verbal memory, and inhibitory control (Wagner, Müller et al., 2015), although other studies have obtained no indication of EF impairments on similar tasks of selective attention as well as mixed findings for visual and verbal working memory measures (e.g., Vilgis et al., 2015). Inconsistencies may be explained partly by methodological limitations, including the use of small and

heterogeneous samples, and the fact that many of the samples had differing inclusion criteria for depressed groups, medication use, and other possible comorbid disorders (Vilgis et al., 2015). Further research is needed to establish the role of EFs in depression for children and adolescents to determine whether this influence is dissimilar to the effects of mood states in adults' EFs.

12.2.2 Adult MDD and Executive Dysfunction

Most of the evidence demonstrating that depressive disorders are associated with impairments in EFs has come from studies with adult populations. It is common for adults diagnosed with this mood disorder to present problems in tasks of cognitive inhibition, problem solving, and planning (Fossati, Ergis, & Allilaire, 2002). However, not all EFs are impaired in adults with MDD. Zakzanis et al. (1998) conducted a meta-analysis (726 patients with depression and 795 healthy normal controls) and reported impairments in specific EFs such as verbal fluency (both semantic and phonemic) and inhibition (e.g., Stroop test), but no deficits in shifting (e.g., TMT-B, WCST) or verbal working memory (e.g., backward digit span).

Snyder (2013) conducted another meta-analysis comparing participants with MDD ($M_{age} = 46$) to healthy controls ($M_{age} = 45$) on measures of EFs such as inhibition, shifting, updating, verbal working memory, visuospatial working memory, planning, and verbal fluency. For moderator analyses, they used current depression severity, age, use of psychotropic medication, and the presence of other mental disorders as a comorbidity. They included 113 studies with 7707 participants (3936 patients and 3771 healthy controls, similar in age and gender). MDD was associated with significant impairments on all measures of EFs. Additionally, the use of medication and symptom severity affected EF performance. The use of psychotropic medications predicted greater impairment on the composite score for inhibition, TMT-B, verbal working memory, visuospatial working memory composite scores, and verbal fluency measures, while controlling for symptom severity and age. The severity of depressive symptoms predicted impairment on inhibition composite scores, shifting composite scores, the WCST, verbal working memory manipulation composite scores, backward digit span, and verbal fluency while controlling for age and the use of medication.

Another meta-analysis was conducted by McDermott and Ebmeier (2009), who correlated the severity of depression with cognitive function across 14 studies. Composite scores for timed and untimed tests for each functional domain (episodic memory, EFs, processing speed, semantic memory, and visuospatial memory) were calculated. There were significant correlations between depression severity and episodic memory, EFs, and processing speed, for both timed and untimed measures, in which increased depression severity was associated with reduced cognitive performance. The analyses in this study included patients with major or minor depression according to the DSM-III-R/DSM-IV criteria, leaving uncertainty as to whether these results may apply to MDD, specifically.

Dotson, Resnick, and Zonderman (2008) used a longitudinal design to investigate the relationship between current depressive symptoms and cognitive performance for a sample of older adults. They looked at whether depressive symptoms at baseline predicted cognitive decline and whether chronic or persistent depressive symptoms were associated with cognitive decline in assessments completed at 1- to 2-year intervals for up to 26 years. Their total sample consisted of 1586 participants, but the sample size varied for each cognitive test, ranging from 799 to 1484 participants, and the follow-up interval ranged from 0 to 26 years. Higher average depressive symptoms were related to greater executive dysfunction (measured by letter fluency and TMT-B) and a longitudinal decline in memory (assessed with the California Verbal Learning Test; CVLT), attention (using digits forward), and general cognitive status (using the MMSE). Their results suggested that prolonged/persistent depressive symptoms may have more deleterious effects on cognition than transient ones, with greater association to cognitive decline. Some limitations of this study include lack of information on comorbidities and age of onset of depressive symptoms. Additionally, there was limited diversity in the demographic characteristics of the sample, which mainly consisted of white and highly educated males.

Most studies involving EFs assess the 'cool' or cognitive EFs, but fail to address 'hot' or affective EFs. Studies on executive dysfunction and depression generally have demonstrated deficits specifically in 'cool' EFs. Moreover, deficits in 'cool' EFs have been reported for depressed patients with suicide attempts, in addition to impaired decision making as well as biased attention to negative valence stimuli (Ho et al., 2018). These authors conducted a study comparing MDD with a history of suicide attempts, MDD with no history of suicide attempts, and healthy controls, all of them between 20 to 60 years of age. They computed four indices: general inhibition, general set-shifting, emotion-specific inhibition, and emotion-specific set-shifting. Their results demonstrated that the two MDD groups performed similarly to healthy controls on 'hot' EF tasks and had disrupted 'cool' EFs, which has been consistently shown in previous studies with adolescents in affective decision-making involving reward-seeking behavior (Vilgis et al., 2015). However, there is limited research investigating depressive disorders and 'hot' EFs in adults. Malloy-Diniz, Miranda, and Grassi-Oliveira (2017) reviewed 13 articles describing the relationship between EFs and psychiatric disorders. These authors identified cognitive deficits in bipolar depressed patients, but did not investigate 'hot' EFs.

Despite the numerous studies aimed at understanding the underlying role of EFs in depression, it is still unclear whether executive dysfunction observed in MDD is the result of preexisting trait markers (impairment that remains regardless of severity of symptoms) or if it is state-related deficits that change with depressive symptoms. Additionally, they could be 'scar' impairments that remain during periods of remission and worsen with illness progression (Allott, Fisher, Amminger, Goodall, & Hetrick, 2016). Some studies provide evidence that symptom severity increases EF impairments (Snyder, 2013; McDermott & Ebmeier, 2009), and other studies have observed stable EF impairments even after symptom remission (Paelecke-Habermann, Pohl, & Leplow, 2005). Moreover, there is empirical support for persistent EF impairments in inhibition, switching, and semantic fluency, despite

a reduction in depressive symptoms over the course of a 12-month period (Schmid & Hammar, 2013). Finally, other research has observed deficits in sustained attention and EFs (planning, monitoring, cognitive flexibility, and coding) in individuals with MDD even after remission of symptoms, which supports the idea that they are associated with trait markers of depression (Paelecke-Habermann et al., 2005). Therefore, whether aspects of EFs are dependent on symptom severity or whether they are stable traits independent of current depression severity remains unclear (Snyder, 2013).

In summary, there is robust evidence of EF impairment in adults with MDD, particularly at an advanced age. The most frequent deficits are observed in verbal fluency tasks and in tasks that require inhibitory control and shifting. However, it is important to note that there are many methodological limitations in the published studies described above such as a lack of cultural diversity in samples, small sample sizes, absence of uniformity in defining depression and the lack of consideration of comorbid diagnoses, which all need to be accounted for in future studies to confirm these findings.

12.2.2.1 Late-Onset Versus Early-Onset Depression

The age of onset of the depressive disorder seems to be relevant in the characterization of the disorder for older adults and geriatric populations. There are distinctions between early-onset depression (EOD; develops before age 60 with low medical comorbidity, prolonged release of cortisol leading to early hippocampal damage and reduction in neurotrophic factors important for neurogenesis, higher suicidal ideation, and less cognitive impairment) and late-onset depression (LOD; develops after age 60 with high medical comorbidity, increased white matter lesions, faster hippocampal atrophy, fronto-subcortical disruption, lower symptoms of suicidal ideation, and more cognitive impairment). Additionally, it seems that EOD has a better prognosis for treatment (Espinoza & Kaufman, 2014). This is important to distinguish because evidence suggests that the dysexecutive syndrome observed in depressed individuals is more likely to occur among individuals who develop LOD (Herrmann, Goodwin, & Ebmeier 2007).

Moreover, Herrmann et al. (2007) conducted a review comparing individuals with EOD, LOD, and healthy controls. Results suggested that LOD patients suffered mainly from impairments in EFs and processing speed when compared to EOD and controls. Episodic and working memory impairments were similar between LOD and EOD; both groups performed worse on these tasks compared to healthy controls.

Albert, Potter, McQuoid, and Taylor (2017) examined cognitive performance in antidepressant-free depressed adults with early-onset recurrent depression and healthy controls. They analyzed whether the duration of depression was associated with cognitive performance across several cognitive domains (episodic memory, EFs, processing speed, and working memory). Their sample included 91 participants between 20 and 50 years of age that were diagnosed with recurrent MDD according to the DSM-IV and experienced the onset of the first depressive episode before the age of 35. These participants were not currently being treated with psychotherapy and

were not using antidepressants within the last month. In addition, their control group was composed of 105 individuals with no history of depression. For measures of EFs, they used the COWAT (verbal fluency), the TMT-B (set-shifting), semantic fluency, and the Stroop Color-Word interference condition (inhibition). No group differences were observed in EF tasks, episodic memory, and working memory, which contrasts with previous findings from studies that mainly analyzed isolated neuropsychological tests and may be explained by deficits in specific cognitive task components. Effects of depression severity on performance were also not significant. There was a significant interaction between depression duration and age with processing speed and EF variables, and no significant interaction between working and episodic memory, which is in line with the cumulative effect of depression on cognition that may interact with age. Older depressed participants with a longer duration of depression exhibited slower processing speed and worse EF performance. Results from this study may be specific to younger adults with EOD. One limitation of this study is that the EF tasks also utilized a timed component, making it difficult to distinguish variance explained by depression on EF tasks separately from processing speed.

12.2.3 Late in Life Depression and Executive Dysfunction

Late-life depression (LLD) is defined as depression occurring after 60 years old with varying age of onset (Espinoza & Kaufman, 2014). The DSM-IV had criteria for LLD, although the DSM-5 no longer makes this distinction by age. Therefore, the clinical criteria for depression remain the same, independent of the individual's age. Some authors have identified the 'depression-executive dysfunction syndrome' (DED) as occurring in late life, characterized by depressive symptoms such as a loss of interest in activities and psychomotor retardation, as well as executive dysfunction (Alexopoulos, Kiosses, Klimstra, Kalayam, & Bruce, 2002). Reduced processing speed appears to be the core of the cognitive difficulties for individuals with LLD (Butters et al., 2004; Koenig, Bhalia, & Butters, 2014). Deficits in tasks such as the TMT-B are found in individuals diagnosed with LLD (Butters et al., 2004) and even in those older than 75 with depression, but without dementia (Jungwirth et al., 2011).

Lockwood et al. (2002) compared 40 adults with MDD and 40 healthy control subjects (half of them were 20–60 years old, and the other half were 61 years or older) in four cognitive domains: selective attention (Connor's Computerized Continuous Performance Test, Visual and Auditory Cancellation Tests, Stroop Color and Word Test, and the CVLT), sustained attention (WAIS-III digit symbol subtest, category fluency test, sustained finger tapping, color-word condition from the Stroop Color and Word Test), inhibitory control (commission errors on the Connor's Computerized Continuous Performance Test, perseverative errors on the WCST, CVLT and category fluency test, and completion time for TMT-B) and focused effort or intensity of directed attention involving working memory, speed of processing, and complex mental operations (e.g., number of items completed for the WAIS-III digit symbol subtest; items completed for the WAIS-III digits backward). It was found that

depressed individuals, regardless of age, performed more poorly than non-depressed subjects on selective attention and sustained attention domains. A significant age–depression interaction was found for inhibitory control and focused effort domains. The older depressed adults evidenced significantly greater impairment on tasks requiring set-shifting, problem solving, and initiation of novel responses. The authors concluded that depression-related executive dysfunction is more pronounced during advanced age. Morimoto et al. (2011) observed that deficits in semantic fluency were significantly associated with poorer remission of depressed individuals older than 60 years of age.

Cognitive decline in LLD is associated with structural brain changes. Köhler et al. (2010) conducted a study to observe the level of cortical atrophy and white matter hyperintensities correlating with cognitive deficits for older depressed adults. The differences observed in memory and EFs were associated with white matter hyperintensities (such as lesions in deep white matter and paraventricular regions). Participants with depression who had a higher amount of white matter hyperintensities also had EF and memory scores that were 2–3 standard deviations below the mean compared to healthy controls.

In sum, the studies on LLD emphasize the mediation of age on the negative association between depression and cognitive abilities, particularly with EF skills dependent on the speed of processing. In addition, emotional and cognitive behaviors correlate with structural brain abnormalities.

12.3 Anatomy of Executive Dysfunction in Depression

The behavioral association between depression severity and poor performance on EF tasks suggests a relationship or overlap between the brain circuitries that control both mood disorders and EFs. Rogers et al. (2004) conducted a review of empirical findings related to prefrontal areas and EFs in unipolar depression. Results showed that the regions mainly involved in the various 'cool' EF tasks with depression recruit the prefrontal cortex, particularly, the dorsolateral prefrontal cortex (DLPFC). Hypoactivation of the DLPFC has been reported in cases of depression. Depression also seems to be related to hyperactivation of the anterior cingulate cortex (ACC), an area related to conflict resolution. Ottowitz, Tondo, Dougherty, and Savage (2002) reviewed deficits in attention and EFs in MDD, emphasizing the role of the orbitofrontal cortex (OFC), ACC, and DLPFC in the neurobehavioral domains that are involved in EFs. The meta-analysis of neuroimaging studies by Pizzagalli (2011) described reduced rostral anterior cingulate cortex (rACC) and DLPFC volume for depressed patients compared to healthy controls after 3 years of follow-up; demyelination of these structures, particularly in those with treatment-resistant depression, was also reported. The authors also indicated that reduced gray matter volume in the left DLPFC predicted longer illness duration and increased depression severity. Additionally, reduced right DLPFC volume was associated with worse EFs due to attentional biases toward negative cues. Other studies in this meta-analysis showed

blunted activation in neuroimaging of the dorsal anterior cingulate (dACC), rACC, and the left DLPFC, for MDD patients with higher activation in these areas seen during normal performance on EF tasks.

Pizzagalli (2011) aimed to identify regions implicated in frontocingulate dysfunction observed in depression. Heightened activity of the rACC is a promising predictor of treatment outcome for depression. He utilized a three-pronged approach to investigate the reliability of increasing rACC activity for treatment response in depression and the mechanisms that support this relationship. The first prong contained a meta-analysis of the association between resting rACC activity and treatment, arguing that this region plays an important role in treatment due to being the 'hub' of the default mode network or an active network including the posterior cingulate cortex, precuneus, MPFC, and angular gyrus while thinking about the self, others and recalling past events (deactivated during certain tasks). The second prong was the proposal that elevated resting rACC activity led to better treatment outcomes. The third prong provided neuropsychological, electrophysiological, and neuroimaging data for frontocingulate dysfunction in depression in order to confirm the relationship between the rACC and treatment for depression.

Additionally, Pizzagalli (2011) discussed studies with Diffusion Tensor Imaging (DTI) that have also supported the importance of the PFC and ACC in MDD (for adolescents, young adults, and the elderly). DTI measures the flow of water (fractional anisotropy, or FA) in one direction along the myelinated axons allowing for the mapping of connectivity, fiber density, and axonal diameter. Reduced FA within the PFC and ACC white matter tracts for adolescents, young adults, and the elderly has been found. This circuit has also been implicated in EF. Reduced FA in tracts connecting the supragenual ACC and the right amygdala has been additionally demonstrated, which may suggest a possible diminished regulatory input to the amygdala (Cullen et al., 2010). Pizzagalli (2011) described another study in which FA in the left frontal and dACC white matter correlated with total days depressed, indicating an increased disconnection in the frontocingulate pathways due to the duration of depression. Non-remission after a 12-week trial of serotonin reuptake inhibitor (SSRI) medication was associated with reduced FA in the rACC, dACC, and DLPFC, which also supports the importance of these areas and their subcortical connectivity in the presence and maintenance of depressive symptoms. Finally, preserved integrity of myelinated white matter tracts positively correlated with better Stroop performance, suggesting the importance of these tracts for EFs.

In general (for adults and older adults), the most important structures of the prefrontal cortex such as the ACC, DLPFC, OFC and their connection to the amygdala are involved in the mechanisms of depression (Pizzagalli, 2011), overlapping with areas recruited by EFs (the DLPFC, the OFC, and the ACC) related to tasks of working memory, behavioral regulation/monitoring, planning and goal formation (Jurado & Rosselli, 2007). In addition, in late life, depression and deficits on EF tasks are associated with damage to the white matter or the connectivity of the neurons in the prefrontal circuitry, leading to a higher probability of impairment on tasks of EF.

12.4 Executive Functions and Depression in Abnormal Aging

Thomas et al. (2009) discussed executive dysfunction syndrome and risks for the elderly. They indicated that major cognitive deficits in patients with LLD were related to fronto-subcortical circuit dysfunction in disorders of vascular dementia, Alzheimer's disease, Lewy body dementia, fronto-temporal dementia, and mild cognitive impairment (MCI). These disorders may cause damage to the lateral frontal cortices leading to impairment in motor structures such as perseveration/inertia (is defined as disturbance in motor output and compulsive repetition) or the functions related to the 'cool' EFs. Additionally, the orbital/medial areas are linked with limbic/reticular systems leading to disinhibition and changes in affect or function related to the 'hot' EFs. In this study, they examined the dysexecutive dysfunction syndrome (see Sect. 12.2.3 for description), analyzing patients with neurological disorders compared to controls. DED syndrome was associated with a loss of autonomy, risk of fall, and malnutrition. Motivation was additionally altered in depression, and in patients with dementia, depression significantly increased behavioral disorders as well as precipitated the risk of fall and malnutrition.

Thomas and O'Brien (2008) reviewed neurocognitive impairment and depression in MCI. They indicated that neurocognitive impairment persists in older depressed individuals even after recovery from depression, specifically manifesting as slowed information processing speed and executive dysfunction. Additionally, they found that decreased white matter contributes to LLD, and depression also worsens vascular outcomes in this group of patients.

Depression and risk of developing dementia were observed by Byers and Yaffe (2011). In this review, they analyzed evidence linking earlier and late-life depression and dementia, as well as treatment approaches (pharmacological and behavioral interventions). Such interventions for depression may improve cognitive performance (including memory) as well as reduce any pathophysiological alterations that may be associated with dementia and Alzheimer's Disease (AD). Although early-onset depression and/or depressive symptoms have been associated with more than a twofold increase in the risk of dementia, studies remain inconsistent regarding the nature of this association. It is still unclear whether depression is a prodrome (Mosoiu, 2016), a consequence, or a risk factor for dementia (Bennett & Thomas, 2014). The link between depression and dementia may be explained by various underlying biological markers which include vascular diseases, alterations in glucocorticosteroid levels, hippocampal atrophy, increased deposition of beta-amyloid, neurofibrillary tau tangles, inflammatory changes, and deficiency in nerve growth factors. The presence of these biological markers compromises the structural integrity of the prefrontal cortex and its connections with various cortical/subcortical areas, leading to deficits in EFs and depressive symptoms.

Steenland et al. (2012) analyzed 5607 normal subjects ($M_{age} = 72$) and 2500 with MCI ($M_{age} = 74$) at 30 Alzheimer Disease Research Center (ADRC) locations in the USA between 2005 and 2011 to observe whether depression played a role in

the transition from normal to MCI or MCI to AD. They provided data on depression within the last two years as determined by judgment according to DSM-IV guidelines. Depression diagnoses included MDD, situational depression, bipolar disorder, and other mood disorders. They additionally defined depression based on the pattern across visits as (1) always depressed across all visits, (2) initially depressed and later considered as nondepressed, (3) intermittently depressed across visits, and (4) never depressed across all visits. At baseline, patients with normal cognition that were in one of the depressed categories performed worse on cognitive tests and had an increased risk of progression from normal to MCI, whereas normal subjects with initial depression but later considered nondepressed still had a heightened, yet lower risk of progression. This suggests that improvement in depression may diminish the risk of progression to MCI or AD. The participants who were always depressed also had a modest increased risk of progression from MCI to AD. This indicates that LLD is a strong risk factor for progression to MCI among cognitively normal patients.

Gonzales et al. (2017) investigated the association of cognitive decline and cortical atrophy in individuals with MCI and subsyndromal depression (defined as one depressive symptom such as depression/dysphoria, apathy/indifference, or loss of appetite endorsed by the Neuropsychiatric Inventory—NPI). The subsyndromal depressive (SSD) group had decreased scores in global cognition, memory, information processing, and semantic fluency. Also, the SSD group had accelerated frontal lobe and anterior cingulate atrophy. Paterniti, Verdier-Taillefer, Dufouil, and Alpérovitch (2002) examined depressive symptoms predicting cognitive decline in elderly people with normal cognition utilizing the Mini-Mental State Examination (MMSE). Higher levels of depressive symptoms predicted a higher risk of cognitive decline at the 2- and 4-year follow-up. Therefore, the presence of depressive symptoms has been strongly associated with higher cognitive decline.

12.5 Conclusions

The reviewed literature on executive dysfunction in depressive disorders (MDD) across age, as assessed by EF neuropsychological performance, revealed weak differences between children and adolescents with MDD and controls, failing to support the existence of executive dysfunction in MDD. On the other hand, adults with MDD have lower neuropsychological performance across several EF domains (inhibition, set-shifting, problem solving, planning, verbal fluency, processing speed, sustained attention, and verbal memory). Deficits were negatively correlated with the severity of depression and the duration of the depressive disorder. Age seems to be an additional risk factor for the development of DED in depressed individuals, with elderly patients suffering from more impairments in EFs and processing speed compared to younger depressed individuals. There is an overlap of the brain structures that mediate EFs and those producing functional abnormalities in MDD, including the PFC, the DLPFC, and the ACC. Finally, a heightened level of depression is a risk factor for increased cognitive decline in abnormal aging.

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