REVIEW ARTICLE

International Journal of Geriatric Psychiatry

Executive dysfunction and treatment response in late-life depression

Monique A. Pimontel[2], Michelle E. Culang-Reinlieb[2], Sarah S. Morimoto[3] and Joel R. Sneed[1,2,4]

[1]Queens College, City University of New York, NY, USA
[2]The Graduate Center, City University of New York, NY, USA
[3]Weill Cornell Medical College, NY, USA
[4]Columbia University and the New York State Psychiatric Institute, NY, USA
Correspondence to: J. R. Sneed, PhD, E-mail: js2627@columbia.edu

Objectives: Executive dysfunction in geriatric depression has been shown to predict poor response to antidepressant medication. The purpose of this review is to clarify which aspects of executive functioning predict poor antidepressant treatment response.

Methods: Literature review.

Results: From our review, the aspects of executive functioning that appear to be associated with antidepressant response rates are verbal fluency and response inhibition. There is some indication that the semantic strategy component may account for the effects of verbal fluency, although evidence comes from one study and needs replication. Processing speed has been proposed as a substrate that may underlie the effects of executive dysfunction on treatment response. Although processing speed does not appear to account for the relationship between response inhibition and treatment outcome, this issue has yet to be assessed with respect to verbal fluency.

Conclusions: Verbal fluency and response inhibition are specific aspects of executive dysfunction that appear to impact antidepressant response rates. Disruption of the frontostriatal limbic circuit (particularly the anterior cingulate and dorsolateral prefrontal cortex) may explain the relation between these two mechanisms.

Key words: executive dysfunction; response inhibition; treatment outcome; geriatric depression; late-life depression; antidepressant medication
History: Received 11 May 2011; Accepted 30 August 2011; Published online in Wiley Online Library (wileyonlinelibrary.com).
DOI: 10.1002/gps.2808

Depression is a common problem among older adults (Belsher and Costello, 1988; Judd, 1997). At least 8–25% of the older adults in the general population may experience depression Kessler *et al.*, 1994. Depression in late life is associated with negative outcomes including but not limited to increased disability and higher rates of mortality (Charney *et al.*, 2003). Older patients with depressive symptoms report nearly twice the functional impairment of older adults without depressive symptoms (Callahan *et al.*, 1998). Although antidepressant medication is the first choice of treatment for geriatric depression, only roughly one-third of patients respond (Thase, 2001).

Antidepressant nonresponse in geriatric depression is understandably a topic of great concern and has received considerable attention in the field (Mohlman, 2005; McLennan and Mathias, 2010). Research has specifically focused on the impact that cognitive impairment such as executive dysfunction has on treatment outcome. Cognitive impairment is common in late-life depression (Butters *et al.*, 2004b) with executive dysfunction being particularly prevalent (Lockwood *et al.*, 2002; Elderkin-Thompson *et al.*, 2003; Nebes *et al.*, 2003). Relative to their younger counterparts, depressed older subjects score significantly worse on neuropsychological tests that require intact executive functioning, such as tasks of response initiation and inhibition, active switching, processing speed, and complex mental manipulation (Lockwood *et al.*, 2002).

A number of studies have shown that executive dysfunction in late-life depression predicts poor response to antidepressant medication (Lockwood *et al.*, 2002; Alexopoulos *et al.*, 2005; Sneed *et al.*, 2007). However, executive functioning is a broad construct that some have described as "vague and ill defined" (Gunning-Dixon and Raz, 2003). Often, studies demonstrating an association between executive dysfunction and poor treatment response have used a single concept to refer to a wide variety of functions. Furthermore, not all studies have used the same tests or measured the same components. Therefore, it is difficult to know which aspects of the executive functions predict poor response.

This raises a number of important questions. First, what is meant by the use of the term executive dysfunction in geriatric psychiatry? Second, which aspect(s) of executive dysfunction predicts poor response to antidepressant medication? A third question is whether a substrate can account for the findings. Finally, what underlies the relationship between executive dysfunction and poor antidepressant treatment response?

What is executive functioning?

Executive functioning refers to a broad class of cognitive processes mediated primarily by the frontal cortex that allow adaptive and goal-directed behavior (Burgess *et al.*, 1998; Stuss *et al.*, 1998; Miyake *et al.*, 2000). Despite wide acceptance of the term, a formal definition of the executive functioning construct has yet to be established (Alvarez and Emory, 2006; Jurado and Rosselli, 2007). One particular area of controversy is whether executive functioning represents a single construct or a cluster of related but distinct components.

Early models of executive functioning often describe a single executive component that serves as a top–down control system (Baddeley and Hitch, 1974; Norman and Shallice, 1985). For example, Luria (1962, 1973) proposed that the prefrontal cortex, one of three functional units in the brain, is a superstructure that modulates mental activity and behavior. In Baddeley's theory of working memory (Baddeley and Hitch, 1974), a central executive oversees the phonological loop and visuospatial sketchpad, which are responsible for short-term retention of verbal and visual information, respectively. Comparable to the central executive is the supervisory attentional system (Norman and Shallice, 1985; Shallice, 1988), which is activated in novel situations that require goal-directed, planned, non-habitual behavior.

In contrast, other models propose a cluster of separate cognitive processes that may act autonomously. In one study, factor analysis revealed three distinct factors including inhibition, intentionality, and executive memory (Burgess *et al.*, 1998). Lezak et al. (2004) alternatively proposed that executive functioning consists of four components: volition, planning, purposive action, and effective performance. Interestingly, Miyake *et al.* (2000) examined the relationship among three often-postulated executive functions (i.e., shifting, updating, and inhibition) and concluded that although clearly distinguishable, these factors were moderately correlated, indicating an underlying commonality. In fact, neuroimaging data have indicated that these three executive functions activate both common and distinct brain regions (Collette *et al.*, 2005).

Given the lack of consensus on the definition of executive functioning, the use and the interpretation of executive function measures in geriatric psychiatry are challenging (Jurado and Rosselli, 2007). For instance, different measures of executive functioning may assess different components of the construct. Therefore, performance on one executive function measure may not be predictive of performance on another (Burgess *et al.*, 1998). Furthermore, tests of executive functioning may require the integration of several cognitive processes, making it difficult to determine a source of impairment when it exists.

Which aspects of executive functioning predict poor antidepressant response?

Studies that have examined the impact of executive dysfunction on antidepressant response have relied on a number of different tests with each test potentially tapping a different aspect of the construct (Lezak *et al.*, 2004). As a result, it is unclear whether a single underlying component interferes with treatment response or whether several different components predict poor response.

A recent meta-analysis examining the relationship between pretreatment cognitive impairment and response to antidepressant medication demonstrated that among seven tests of executive dysfunction, only the Initiation/Perseveration (I/P) subtest of the Dementia Rating Scale (DRS) predicted poor antidepressant treatment response (McLennan and Mathias, 2010). Indeed, the DRS I/P has been found to be associated with poor or delayed antidepressant response in several studies (Kalayam and Alexopoulos, 1999; Alexopoulos *et al.*, 2005). For example, impaired performance on the DRS I/P was associated with poor treatment response in a study of 112 older patients with major depression (Alexopoulos *et al.*, 2005). Similarly, in a study of 49 depressed older patients, abnormal scores on the DRS I/P were found to be related

with poor or delayed response to antidepressant treatment (Kalayam and Alexopoulos, 1999).

The DRS I/P has shown poor internal consistency, attributable to the heterogeneous items that comprise the subscale (Lezak *et al.*, 2004). The DRS I/P subtest consists of 11 tasks that assess semantic verbal fluency, auditory articulation of vowel and consonant patterns, double alternating motor movements, and simple graphomotor skills (Mattis, 1988). Because performance on these subscales may not be consistent, the composite score may not provide a reliable representation of executive functioning. This raises an important question: which aspects of the DRS I/P subtest predict antidepressant nonresponse?

To address this issue, Morimoto *et al.* (2010) examined the relationship of DRS I/P subtests to treatment response in late-life depression. Only the verbal fluency item of the DRS I/P subtest predicted remission, which is consistent with findings of previous studies that have shown other measures of verbal fluency to be predictive of remission (i.e., Controlled Oral Word Association Test) (Baldwin *et al.*, 2004; Taylor *et al.*, 2006).

To further elucidate the relationship between verbal fluency and antidepressant response, Morimoto *et al.* (2010) examined the mediating role of semantic strategy (i.e., the mental reorganization of verbal material into semantic clusters) on the DRS I/P verbal fluency task and found that the use of semantic strategy explained the difference in performance between responders and nonresponders. This suggests a top–down processing effect in which impairment in semantic strategy interferes with the generation of words in verbal fluency tasks.

Although the importance of semantic strategy should be confirmed in other studies of verbal fluency, similar results have been found in a study of verbal list learning. Effective semantic strategy use on the Hopkins Verbal Learning Test—Revised was associated with higher rates of remission with antidepressant treatment in older depressed patients (Morimoto *et al.*, 2011). In addition to providing further evidence for the mediating role of semantic strategy in verbal tasks, these findings indicate that an executive factor may also underlie deficits in non-executive measures that have been associated with poor treatment response, such as episodic memory or verbal memory (McLennan and Mathias, 2010).

Performance on the Stroop Color and Word Test has also been found to predict nonresponse to antidepressant medication (Alexopoulos *et al.*, 2005; Alexopoulos *et al.*, 2008; Sneed *et al.*, 2010). Although only the word and color naming trials (generally considered measures of processing speed) and not the color–word inhibition trial (an executive functioning measure of response inhibition) were found to be predictive of treatment response in the recent meta-analysis by McLennan and Mathias (2010), several studies were not included in this analysis (Baldwin *et al.*, 2004; Bogner *et al.*, 2007; Sneed *et al.*, 2007). One study examining the predictive utility of response inhibition on antidepressant treatment response in depressed patients age 75 and older found that performance in the most impaired quartile on the color–word inhibition trial of the Stroop predicted lower remission rates to citalopram (Sneed *et al.*, 2007). In another study, depressed older adults who remained symptomatic showed greater deficits on the color–word inhibition trial at baseline as compared with patients who achieved remission (Baldwin *et al.*, 2004). In a primary care study of depressed older adults receiving monotherapy, those impaired on the color–word inhibition trial had lower remission and response rates than those showing no deficits (Bogner *et al.*, 2007). Consistent with these results, other tests with a response inhibition component, such as the Attention Network Test (Murphy and Alexopoulos, 2006), the Wisconsin Card Sorting Test (Dunkin *et al.*, 2000; Withall *et al.*, 2008), and the Go/No-Go Task (Alexopoulos *et al.*, 2007), have been predictive of treatment response.

There does not yet appear to be a single aspect of executive functioning that reliably predicts response in older depressed patients. Many predictive measures appear to contain a component of either verbal fluency or response inhibition. It is not clear what these two factors have in common. Moreover, although several studies have shown that verbal fluency and response inhibition in late-life depression predict poor response to antidepressant medication (Alexopoulos *et al.*, 2005; Sneed *et al.*, 2007; Morimoto *et al.*, 2010), not all studies agree (Butters *et al.*, 2004a; Marcos *et al.*, 2005; Saghafi *et al.*, 2007). Because some executive measures tap into multiple cognitive processes, it is possible that a substrate underlies the relationship between verbal fluency, response inhibition, and poor treatment response. This position is further supported by the inability to pinpoint a single executive component that predicts poor antidepressant treatment response (Kalayam and Alexopoulos, 1999; Butters *et al.*, 2004a; Taylor *et al.*, 2006; Gallagher *et al.*, 2007; Story *et al.*, 2008).

Is there a substrate that can account for the findings?

Executive processes are by definition complex, higher-order mental operations that may depend on the integration of component processes (Lezak *et al.*, 2004). One possibility, therefore, is that a substrate like processing

speed accounts for the effect of executive dysfunction on treatment response (Story *et al.*, 2008). For example, a decrease in processing speed may disrupt executive processes when relevant operations cannot successfully be completed within the necessary time frame or when the products of early processing are not available for later processing (Salthouse, 1996). Indeed, several studies have shown that processing speed mediates performance on executive functioning tasks in depressed older adults (Degl'Innocenti *et al.*, 1998; Nebes *et al.*, 2000; Butters *et al.*, 2004b). One study in particular showed that neuropsychological deficits in executive functioning as well as in visuospatial, language, and memory abilities were mediated by slowed processing speed in a sample of depressed older adults (Butters *et al.*, 2004b).

Processing speed has also been shown to independently predict antidepressant nonresponse (Taylor *et al.*, 2006). A recent meta-analysis (McLennan and Mathias, 2010) found that the word naming and color naming trials of the Stroop Color and Word Test (considered measures of processing speed) significantly predicted treatment resistance in adult and late-life depression. One study found that improvement in depressive symptoms was significantly associated with better baseline performance on measures of processing speed (Trail Making Test—Part A and Digit Symbol Test) (Story *et al.*, 2008). In another study, a composite score that consisted of three measures of processing speed (Digit Symbol Test, Stroop color naming trial, and Trail Making Test—Part A) significantly distinguished responders to antidepressant medication from nonresponders (Sheline *et al.*, 2010). In two similar studies (Devanand *et al.*, 2003; Gallagher *et al.*, 2007), depressed older adults who failed to achieve remission demonstrated poorer performance on a task of processing speed (Digit Symbol Test) when compared with patients who achieved remission. Finally, longer latency of the P300 wave, a physiological means of examining psychomotor speed, has predicted delayed response to antidepressant medication (Kalayam and Alexopoulos, 1999).

Several studies that have included both tests of executive functioning and processing speed, however, have shown that only tests of executive functioning predict poor response (Dunkin *et al.*, 2000; Sneed *et al.*, 2008; Morimoto *et al.*, 2010). In one study, nonresponders made significantly more errors on the color–word inhibition trial of the Stroop compared with responders, but no differences were found in the number of items completed in 45 s (Dunkin *et al.*, 2000). In another study, responders and nonresponders differed significantly in their DRS I/P verbal fluency score but not on a measure of processing speed (Trail Making Test—Part A) (Morimoto *et al.*, 2010). In another study, including reaction time (as measured by reaction time to correct responses on the choice reaction time and judgment of line orientation test) as a covariate in the analyses did not eliminate the effect of impaired performance on the color–word inhibition trial on treatment outcome (Sneed *et al.*, 2007). Although processing speed is a fundamental cognitive process that may independently predict response, it does not appear to fully account for the relationship between response inhibition and treatment outcome. This issue has yet to be assessed with respect to verbal fluency.

What underlies the relationship between verbal fluency, response inhibition, and treatment response?

We have identified two distinct executive processes that each independently predicts poor treatment response in geriatric depression: verbal fluency and response inhibition. Cognitive control (i.e., the ability to adjust and maintain goal-directed cognitive processes) is impaired in geriatric depression and may explain the relationship between verbal fluency, response inhibition, and poor antidepressant treatment response (Katz *et al.*, 2010).

The cognitive control theory delineates distinct roles for the anterior cingulate cortex (ACC) and dorsolateral prefrontal cortex (DLPFC) (Langenecker *et al.*, 2007). The ACC monitors for the presence of response conflict processes and activates the DLPFC to resolve the conflict using adjustment processes (i.e., the inhibition of responses to task-irrelevant stimuli) (Milham *et al.*, 2003; Erickson *et al.*, 2004). In other words, although the DLPFC and ACC have distinct roles, they are interdependent components in the cognitive control process (MacDonald *et al.*, 2000).

Deficits in cognitive control processes have been found in depressed adults. In one neuroimaging study, a sustained attention task with emotional distracters was used to assess cognitive control in depressed adults and age-matched controls (Fales *et al.*, 2008). During the event-related functional magnetic resonance imaging, participants were either instructed to attend to or ignore fear-related stimuli. The control group showed increased activity in the DLPFC after making an error on the task or when ignoring fear-related stimuli, whereas the depressed group showed no change in DLPFC activity. These findings suggest that abnormalities in the DLPFC compromise cognitive control processes (Beevers *et al.*, 2010) and may result in impaired emotional processing.

In healthy adults, the DLPFC appears to regulate the amygdala by inhibiting its response to emotional, particularly fear relevant, stimuli (Fales *et al.*, 2008). Therefore, underactivation of the DLPFC in depression has been associated with overactivation in limbic structures such as the amygdala (Siegle *et al.*, 2007). In fact, compared with controls, depressed patients with reduced activity in the DLPFC had an enhanced amygdala response when ignoring fear-related stimuli (Fales *et al.*, 2008). This suggests that abnormalities in the DLPFC may result in sustained overactivation of the amygdala and, subsequently, emotion dysregulation (Mayberg *et al.*, 1999; Davidson *et al.*, 2002; Ochsner *et al.*, 2002, 2004).

Antidepressant treatment appears to alleviate impairment in this inhibitory control circuit. Functional MRI findings have shown that successful antidepressant treatment normalizes DLPFC and amygdala activation (Fales *et al.*, 2009). For instance, patients who achieved remission after eight weeks of antidepressant treatment no longer differed from controls in either DLPFC or amygdala activity in response to negative emotional stimuli (Fales *et al.*, 2009). Not surprisingly, disruption of this inhibitory control circuit may be associated with poor remission rates. For example, depressed younger adults who failed to achieve remission had reduced gray matter volume in the DLPFC as compared with patients who did achieve remission (Li *et al.*, 2010).

The DLPFC is indirectly linked to the amygdala through the ACC (Siegle *et al.*, 2007). Therefore, damage to the ACC may also result in sustained overactivation of the amygdala and resistance to antidepressant treatment (Ghashghaei and Barbas, 2002; Siegle *et al.*, 2002). Indeed, depressed younger adults who failed to achieve remission had hypometabolism of glucose in the ACC compared with patients who did achieve remission (Mayberg *et al.*, 1997). Furthermore, depressed older adults who failed to remit had diminished functional connectivity between the DLPFC and the ACC (Aizenstein *et al.*, 2002), suggesting the importance of white matter tract integrity for remission.

Similar neuroanatomical abnormalities may also underlie impairment in verbal fluency and response inhibition. Consistent with the cognitive control theory, there is evidence that the ACC and the DLPFC have distinct but related roles in both verbal fluency and response inhibition. In normal adults, the use of semantic clustering in free recall tasks (e.g., Hopkins Verbal Learning Test—Revised) has been associated with activation of the DLPFC (Owen, 2000; Savage *et al.*, 2001; Long *et al.*, 2010), suggesting that the DLPFC may be also be involved in the use of semantic strategy in verbal fluency tasks. Activation of the ACC in verbal fluency tasks has alternatively been related to performance monitoring (Fu *et al.*, 2002). This suggests that damage to the DLPFC may cause impaired semantic strategy, whereas damage to the ACC may be associated with an increase in errors.

On measures of response inhibition, the left DLPFC has shown activity when subjects are read the instructions, with activity increasing as the complexity of the instructions increases. Both the ACC and the right DLPFC have been found to be active during the actual response phase of the task and to increase in activity with the need for response inhibition (MacDonald *et al.*, 2000; Vanderhasselt *et al.*, 2009). These findings suggest that the ACC and the right DLPFC are involved in the implementation of response inhibition.

In conclusion, disruption of the ACC may result in response inhibition deficits, whereas disruption of the DLPFC is more likely to result in decreased performance on verbal fluency tasks. However, disruption of the DLPFC, the ACC, or white matter tracts connecting the DLPFC and the ACC to the amygdala may result in depression and resistance to antidepressant treatment.

Conclusion

Although there is considerable evidence that executive dysfunction is associated with poor response to antidepressant medication in geriatric depression, a number of critical issues remain. We identified four areas that are vital to further elucidate the relationship between executive dysfunction and antidepressant treatment response: (i) clarifying the executive function construct; (ii) determining which aspects of the executive functions are involved; (iii) ruling out the possibility that another substrate accounts for the existing findings; and (iv) determining what underlies the relationship between the different components of executive dysfunction and poor antidepressant treatment response. We have argued that response inhibition and verbal fluency appear to be the aspects of executive dysfunction that impact antidepressant treatment response. Their effect seems to be independent of processing speed and contingent upon the integrity of structures within the frontostriatal limbic circuit including the ACC and the DLPFC. A better understanding of these issues is necessary to improve the treatment of patients with late-life depression and executive deficits through alternative treatment strategies. For example, activation of specific brain systems through targeted cognitive remediation (Bae *et al.*, 2006) or improvement of skills relying on these systems using problem solving therapy (Arean

et al., 2010; Alexopoulos *et al.*, 2011) may alleviate both executive deficits and depression in late life.

Conflict of interest

None declared.

Key points

- Verbal fluency and response inhibition appear to be specific aspects of executive dysfunction that impact antidepressant response in late life.
- Evidence that semantic strategy may account for the effects of verbal fluency needs replication.
- Processing speed does not appear to account for the relationship between response inhibition and treatment outcome. This issue has yet to be assessed with respect to verbal fluency.
- Disruption of the frontostriatal limbic circuit may explain the relation between verbal fluency, response inhibition and antidepressant response.

Acknowledgements

This research was supported by the National Institute of Mental Health grants K23 MH075006 and R21 MH087774 to Joel R. Sneed.

References

Aizenstein HJ, Nebes RD, Meltzer CC, et al. 2002. The relation of white matter hyperintensities to implicit learning in healthy older adults. *Int J Geriatr Psychiatry* 17: 664–669.

Alexopoulos G, Kiosses D, Moonseong H, et al. 2005. Executive dysfunction and the course of geriatric depression. *Biol Psychiatry* 58: 204–210.

Alexopoulos GS, Murphy CF, Gunning-Dixon FM, et al. 2007. Event-related potentials in an emotional go/no-go task and remission of geriatric depression. *Neuroreport* 18: 217–221.

Alexopoulos GS, Murphy CF, Gunning-Dixon FM, et al. 2008. Microstructural white matter abnormalities and remission of geriatric depression. *Am J Psychiatry* 165: 238–244.

Alexopoulos GS, Raue PJ, Kiosses DN, et al. 2011. Problem-solving therapy and supportive therapy in older adults with major depression and executive dysfunction: effect on disability. *Arch Gen Psychiatry* 68: 33–41.

Alvarez JA, Emory E. 2006. Executive function and the frontal lobes: a meta-analytic review. *Neuropsychol Rev* 16: 17–42.

Arean PA, Raue P, Mackin RS, et al. 2010. Problem-solving therapy and supportive therapy in older adults with major depression and executive dysfunction. *Am J Psychiatry* 167: 1391–1398.

Baddeley A, Hitch G. 1974. Working memory. *Psychol Learn Motiv* 8: 47–90.

Bae JN, Macfall JR, Krishnan KR, et al. 2006. Dorsolateral prefrontal cortex and anterior cingulated cortex white matter alterations in late-life depression. *Biol Psychiatry* 60: 1356–1363.

Baldwin R, Jeffries S, Jackson A, et al. 2004. Treatment response in late-onset depression: relationship to neuropsychological, neuroradiological and vascular risk factors. *Psychol Med* 34: 125–136.

Beevers CG, Clasen P, Stice E, Schnyer D. 2010. Depression symptoms and cognitive control of emotion cues: a functional magnetic resonance imaging study. *Neuroscience* 167: 97–103.

Belsher G, Costello C. 1988. Relapse after recovery from unipolar depression: a critical review. *Psychol Bull* 104: 84–96.

Bogner HR, Bruce ML, Reynolds CF 3rd, et al. 2007. The effects of memory, attention, and executive dysfunction on outcomes of depression in a primary care intervention trial: the PROSPECT study. *Int J Geriatr Psychiatry* 22: 922–929.

Burgess PW, Alderman N, Evans J, Emslie H, Wilson B. 1998. The ecological validity of tests of executive function. *J Int Neuropsychol Soc* 4: 547–558.

Butters MA, Bhalla RK, Mulsant BH, et al. 2004a. Executive functioning, illness course, and relapse/recurrence in continuation and maintenance treatment of late-life depression: is there a relationship? *Am J Geriatr Psychiatry* 12: 387–394.

Butters MA, Whyte EM, Nebes RD, et al. 2004b. The nature and determinants of neuropsychological functioning in late-life depression. *Arch Gen Psychiatry* 61: 587–595.

Callahan CM, Wolinsky FD, Stump TE, et al. 1998. Mortality, symptoms, and functional impairment in late-life depression. *J Gen Intern Med* 13: 746–752.

Charney DS, Reynolds CF 3rd, Lewis L, et al. 2003. Depression and Bipolar Support Alliance consensus statement on the unmet needs in diagnosis and treatment of mood disorders in late life. *Arch Gen Psychiatry* 60: 664–672.

Collette F, Van der Linden M, Laureys S, et al. 2005. Exploring the unity and diversity of the neural substrates of executive functioning. *Hum Brain Mapp* 25: 409–423.

Davidson RJ, Pizzagalli D, Nitschke JB, Putnam K. 2002. Depression: perspectives from affective neuroscience. *Annu Rev Psychol* 53: 545–574.

Degl'Innocenti A, Agren H, Backman L. 1998. Executive deficits in major depression. *Acta Psychiatr Scand* 97: 182–188.

Devanand DP, Pelton GH, Marston K, et al. 2003. Sertraline treatment of elderly patients with depression and cognitive impairment. *Int J Geriatr Psychiatry* 18: 123–130.

Dunkin JJ, Leuchter AF, Cook IA, et al. 2000. Executive dysfunction predicts nonresponse to fluoxetine in major depression. *J Affect Disord* 60: 13–23.

Elderkin-Thompson V, Kumar A, Bilker W, et al. 2003. Neuropsychological deficits among patients with late-onset minor and major depression. *Arch Clin Neuropsychol* 18: 529–549.

Erickson KI, Milham MP, Colcombe SJ, et al. 2004. Behavioral conflict, anterior cingulate cortex, and experiment duration: implications of diverging data. *Hum Brain Mapp* 21: 98–107.

Fales CL, Barch DM, Rundle MM, et al. 2008 Altered emotional interference processing in affective and cognitive-control brain circuitry in major depression. *Biol Psychiatry* 63: 377–384.

Fales CL, Barch DM, Rundle MM, et al. 2009. Antidepressant treatment normalizes hypoactivity in dorsolateral prefrontal cortex during emotional interference processing in major depression. *J Affect Disord* 112: 206–211.

Fu CH, Morgan K, Suckling J, et al. 2002. A functional magnetic resonance imaging study of overt letter verbal fluency using a clustered acquisition sequence: greater anterior cingulate activation with increased task demand. *Neuroimage* 17: 871–879.

Gallagher P, Robinson LJ, Gray JM, Porter RJ, Young AH. 2007. Neurocognitive function following remission in major depressive disorder: potential objective marker of response? *Aust N Z J Psychiatry* 41: 54–61.

Ghashghaei H, Barbas H. 2002. Pathways for emotion: interactions of prefrontal and anterior temporal pathways in the amygdala of the rhesus monkey. *Neuroscience* 115: 1261–1279.

Gunning-Dixon F, Raz N. 2003. Neuroanatomical correlates of selected executive functions in middle-aged and older adults: a prospective MRI study. *Neuropsychologia* 41: 1929–1941.

Judd L. 1997. The clinical course of unipolar major depressive disorders. *Arch Gen Psychiatry* 54: 989–991.

Jurado M, Rosselli M. 2007. The elusive nature of executive functions: a review of our current understanding. *Neuropsychol Rev* 17: 213–233.

Kalayam B, Alexopoulos G. 1999. Prefrontal dysfunction and treatment response in geriatric depression. *Arch Gen Psychiatry* 56: 713–718.

Katz R, De Sanctis P, Mahoney JR, et al. 2010. Cognitive control in late-life depression: response inhibition deficits and dysfunction of the anterior cingulate cortex. *Am J Geriatr Psychiatry* 18: 1017–1025.

Kessler R, McGonagle K, Nelson C, et al. 1994. Sex and depression in the National Comorbidity Survey. II: Cohort effects. *J Affect Disord* 30: 15–26.

Langenecker SA, Kennedy SE, Guidotti LM, et al. 2007. Frontal and limbic activation during inhibitory control predicts treatment response in major depressive disorder. *Biol Psychiatry* 62: 1272–1280.

Lezak M, Howieson D, Loring D, Hannay H, Fischer J. 2004. *Neuropsychological Assessment*, 4th ed. Oxford University Press: New York.

Li C, Lin C, Chou K, et al. 2010. Structural and cognitive deficits in remitting and non-remitting recurrent depression: a voxel-based morphometric study. *Neuroimage* 1: 347–356.

Lockwood KA, Alexopoulos GS, van Gorp WG. 2002. Executive dysfunction in geriatric depression. *Am J Psychiatry* 159: 1119–1126.

Long N, Oztekin I, Badre D. 2010. Separable prefrontal cortex contributions to free recall. *J Neurosci* 30: 10967–10976.

Luria AR. 1962. *Higher Cortical Functions in Man*. Library of Congress Number: 65–11340. Moscow University Press: Moscow, Russia.

Luria AR. 1973. *The Working Brain: An Introduction to Neuropsychology*. Basic Books: New York, USA.

MacDonald AW 3rd, Cohen JD, Stenger VA, Carter CS. 2000. Dissociating the role of the dorsolateral prefrontal and anterior cingulate cortex in cognitive control. *Science* 288: 1835–1838.
Marcos T, Portella MJ, Navarro V, et al. 2005. Neuropsychological prediction of recovery in late-onset major depression. *Int J Geriatr Psychiatry* 20: 790–795.
Mattis S. 1988. *Dementia Rating Scale*. Psychological Assessment Resources: Odessa, FL.
Mayberg HS, Brannan SK, Mahurin RK, et al. 1997. Cingulate function in depression: a potential predictor of treatment response. *Neuroreport* 8: 1057–1061.
Mayberg HS, Liotti M, Brannan SK, et al. 1999. Reciprocal limbic-cortical function and negative mood: converging PET findings in depression and normal sadness. *Am J Psychiatry* 156: 675–682.
McLennan SN, Mathias JL. 2010. The depression-executive dysfunction (DED) syndrome and response to antidepressants: a meta-analytic review. *Int J Geriatr Psychiatry* 25: 933–944.
Milham MP, Banich MT, Claus ED, Cohen NJ. 2003. Practice-related effects demonstrate complementary roles of anterior cingulate and prefrontal cortices in attentional control. *Neuroimage* 18: 483–493.
Miyake A, Friedman NP, Emerson MJ, et al. 2000. The unity and diversity of executive functions and their contributions to complex "frontal lobe" tasks: a latent variable analysis. *Cogn Psychol* 41: 49–100.
Mohlman J. 2005. Does executive dysfunction affect treatment outcome in late-life mood and anxiety disorders? *J Geriatr Psychiatry Neurol* 18: 97–108.
Morimoto SS, Gunning FM, Kanellopoulos D, et al. 2011. Semantic organizational strategy predicts verbal memory and remission rate of geriatric depression. *Int J Geriatr Psychiatry*. DOI: 10.1002/gps.2743
Morimoto SS, Gunning FM, Murphy CF, et al. 2010. Executive function and short-term remission of geriatric depression: the role of semantic strategy. *Am J Geriatr Psychiatry* 19: 115–122.
Murphy CF, Alexopoulos GS. 2006. Attention network dysfunction and treatment response of geriatric depression. *J Clin Exp Neuropsychol* 28: 96–100.
Nebes RD, Butters MA, Mulsant BH, et al. 2000. Decreased working memory and processing speed mediate cognitive impairment in geriatric depression. *Psychol Med* 30: 679–691.
Nebes RD, Pollock BG, Houck PR, et al. 2003. Persistence of cognitive impairment in geriatric patients following antidepressant treatment: a randomized, double-blind clinical trial with nortriptyline and paroxetine. *J Psychiatr Res* 37: 99–108.
Norman D, Shallice T. 1985. Attention to action: Willed and automatic control of behavior. In Davidson RJ, Shwartz GE, Shapiro D (eds.), *Consciousness and self-regulation: Vol. 4. Advances in research and theory*. Platinum Press: New York, 2–18.
Ochsner KN, Bunge SA, Gross JJ, Gabrieli JD. 2002. Rethinking feelings: an fMRI study of the cognitive regulation of emotion. *J Cogn Neurosci* 14: 1215–1229.
Ochsner KN, Ray RD, Cooper JC, et al. 2004. For better or for worse: neural systems supporting the cognitive down- and up-regulation of negative emotion. *Neuroimage* 23: 483–499.
Owen AM. 2000. The role of the lateral frontal cortex in mnemonic processing: the contribution of functional neuroimaging. *Exp Brain Res* 133: 33–43.
Saghafi R, Brown CB, Butters MA, et al. 2007. Predicting 6-week treatment to response to escitalopram pharmacotherapy in late-life major depressive disorder. *Int J Geriatr Psychiatry* 22: 1141–1146.
Salthouse TA. 1996. The processing-speed theory of adult age differences in cognition. *Psychol Rev* 103: 403–428.
Savage CR, Deckersbach T, Heckers S, et al. 2001. Prefrontal regions supporting spontaneous and directed application of verbal learning strategies. *Brain* 124: 219–231.
Shallice T. 1988. *From Neuropsychology to Mental Structure*. Cambridge University Press: New York, USA.
Sheline YI, Pieper CF, Barch DM, et al. 2010. Support for the vascular depression hypothesis in late-life depression: results of a 2-site, prospective, antidepressant treatment trial. *Arch Gen Psychiatry* 67: 277–285.
Siegle GJ, Steinhauer SR, Thase ME, Stenger VA, Carter CS. 2002. Can't shake that feeling: event-related fMRI assessment of sustained amygdala activity in response to emotional information in depressed individuals. *Biol Psychiatry* 51: 693–707.
Siegle GJ, Thompson W, Carter CS, Steinhauer SR, Thase ME. 2007. Increased amygdala and decreased dorsolateral prefrontal BOLD responses in unipolar depression: related and independent features. *Biol Psychiatry* 61: 198–209.
Sneed J, Roose S, Keilp J, et al. 2007 Response inhibition predicts poor antidepressant treatment response in very old depressed patients. *Am J Geriatr Psychiatry* 15: 553–563.
Sneed JR, Keilp JG, Brickman AM, Roose SP. 2008. The specificity of neuropsychological impairment in predicting antidepressant non-response in the very old depressed. *Int J Geriatr Psychiatry* 23: 319–323.
Sneed J, Culang M, Keilp J, et al. 2010. Antidepressant medication and executive dysfunction: a deleterious interaction in late-life depression. *Am J Geriatr Psychiatry* 18: 128–135.
Story TJ, Potter GG, Attix DK, Welsh-Bohmer KA, Steffens DC. 2008. Neurocognitive correlates of response to treatment in late-life depression. *Am J Geriatr Psychiatry* 16: 752–759.
Stuss DT, Alexander MP, Hamer L, et al. 1998. The effects of focal anterior and posterior brain lesions on verbal fluency. *J Int Neuropsychol Soc* 4: 265–278.
Taylor BP, Bruder GE, Stewart JW, et al. 2006. Psychomotor slowing as a predictor of fluoxetine nonresponse in depressed outpatients. *Am J Psychiatry* 163: 73–78.
Thase ME. 2001. Overview of antidepressant therapy. *Manag Care* 10: 6–9; discussion 18–22.
Vanderhasselt MA, De Raedt R, Baeken C. 2009. Dorsolateral prefrontal cortex and Stroop performance: tackling the lateralization. *Psychon Bull Rev* 16: 609–612.
Withall A, Harris LM, Cumming SR. 2008. The relationship between cognitive function and clinical and functional outcomes in major depressive disorder. *Psychol Med* 39: 393–402.