REVIEW ARTICLE

International Journal of Geriatric Psychiatry

Executive dysfunction and treatment response in late-life depression

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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. Copyright © 2011 John Wiley & Sons, Ltd.

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 18 October 2011 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.

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