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The impact of executive function on response to cognitive behavioral therapy in late-life depression

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Abstract

Objective: Late-life depression (LLD) is a common and debilitating condition among older adults. Cognitive behavioral therapy (CBT) has strong empirical support for the treatment of depression in all ages, including in LLD. In teaching patients to identify, monitor, and challenge negative patterns in their thinking, CBT for LLD relies heavily on cognitive processes and, in particular, executive functioning, such as planning, sequencing, organizing, and selectively inhibiting information. It may be that the effectiveness of CBT lies in its ability to train these cognitive areas.

Methods: Participants with LLD completed a comprehensive neuropsychological battery before enrolling in CBT. The current study examined the relationship between neuropsychological function prior to treatment and response to CBT.

Results: When using three baseline measures of executive functioning that quantify set shifting, cognitive flexibility, and response inhibition to predict treatment response, only baseline Wisconsin Card Sort Task performance was associated with a significant drop in depression symptoms after CBT. Specifically, worse performance on the Wisconsin Card Sort Task was associated with better treatment response.

Conclusions: These results suggest that CBT, which teaches cognitive techniques for improving psychiatric symptoms, may be especially beneficial in LLD if relative weaknesses in specific areas of executive functioning are present.

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Conflict of interest

None declared.

Keywords

late-life depression; executive function; cognitive behavioral therapy; neuropsychological performance; treatment response

Introduction

Eight to sixteen percent of community-dwelling older adults report clinically significant symptoms of depression (Blazer, 2003). Late-life depression (LLD), or significant clinical depression in individuals over 60 years of age, appears to be more recurrent and chronic than depression in younger patients, with higher relapse rates after treatment (Andreescu and Reynolds, 2011). LLD is associated with reduced quality of life and increased illness, disability, utilization of medical services, and institutionalization (Blazer, 2003; Pinquart *et al.*, 2006).

A reciprocal relationship exists between LLD and late-life neurocognitive function. Increased rates of affective and other psychopathological symptoms are seen in older adults with cognitive impairment, and LLD confers a twofold to threefold increase risk of developing dementia (Barnes *et al.*, 2012). Moreover, 20–50% of patients with LLD have cognitive impairment, greater than that in age-matched and education-matched controls. Individuals with LLD often have documented impairments in executive functioning, memory, visuospatial ability, and psychomotor speed (Butters *et al.*, 2004; O'Hara *et al.*, 2006). Executive dysfunction, which includes impairments in planning, sequencing, organizing, and selectively inhibiting information, occurs in a large percentage of older adults with depression, and these cognitive deficits appear to influence the course of the depression (Alexopoulos *et al.*, 2002). Moreover, the level of executive dysfunction has been associated with the severity of depression (Boone *et al.*, 1995).

Given the reciprocal relationship between depression and neurocognitive function in older adults, it is important to consider the impact of cognitive capacity on treatment response in LLD. Executive functioning may be especially important in predicting treatment response. Among participants taking antidepressant medication to treat depression, executive dysfunction has been associated with poorer response and increased rates of relapse (Kalayam and Alexopoulos, 1999; Story *et al.*, 2008). However, others have failed to replicate this finding (Butters *et al.*, 2004; Bogner *et al.*, 2007). Memory, attention, and general cognitive function have not been found to relate to relapse of depression in older adults (Kalayam and Alexopoulos, 1999; Butters *et al.*, 2004).

Antidepressant medication and psychotherapy are the two most common treatments for depression in older adults; these treatments yield moderate-to-large effect sizes and are slightly larger for psychotherapy. Across studies, nearly half of participants with LLD receiving psychotherapy show clinically meaningful treatment response (Pinquart *et al.*, 2006). Cognitive behavioral therapy (CBT) is a widely used, evidence-based psychotherapy for depression with well-established efficacy for LLD (Pinquart *et al.*, 2006); the focus of this treatment is modifying maladaptive patterns of thoughts, feelings, and behaviors. Examined meta-analytically, treatment effect sizes are larger for CBT than for other

psychotherapies and for pharmacotherapy (Pinquart *et al.*, 2006). The large effect sizes for psychotherapy are encouraging; however, further research is warranted that investigates those factors in an individual that predict treatment response.

The effect of executive function capacity on treatment response may be especially important for individuals receiving psychotherapy and, in particular, CBT. Cognitive processes such as organization, focusing, planning, and strategizing are integral to effective utilization of CBT and if impaired may reduce the effectiveness of this therapeutic approach. Alternatively, CBT may be most effective for those individuals with difficulties in these areas because the treatment helps teach or hone these skills. Of note, psychotherapy has demonstrated effectiveness for treating depression in older adults with executive dysfunction (Alexopoulos *et al.*, 2003). In the Alexopoulos *et al.* (2003) study, the investigators used problem-solving therapy (PST), which has been found to operate through similar psychological processes as CBT (Warmerdam *et al.*, 2010). Expanding on this finding, the primary aim of our study was to investigate the influence of particular measures of executive function on treatment response to CBT among older patients with depression.

Methods

Participants

One hundred and fifty-six participants were recruited, of whom 60, aged 60 years and older and who met diagnostic criteria for a current episode of major or minor depressive disorder as a primary diagnosis, were enrolled in the study. Inclusion in the study was based on a score of greater than 15 on the Center for Epidemiologic Studies Depression (CES-D) scale (Radloff, 1977) and a primary diagnosis of major depression or dysthymia on the Mini-International Neuropsychiatric Interview (MINI) (Sheehan *et al.*, 1998). All participants completed a Beck Depression Inventory II (BDI-II) of self-reported depressive symptoms at intake; there was not a baseline threshold for inclusion as enrollment was determined with the CES-D and the MINI. For some participants who did not meet the CES-D criteria but had a sufficient level of depression on the MINI and self-reported depression on BDI-II, the clinical determination was made that the depression would be considered subsyndromal and warranted treatment. As such, participants in this study covered the spectrum from subsyndromal ($N=22$) through major depressive disorder ($N=33$), leading to greater variability across participants. Patients were excluded for active suicidality, psychosis, or abusing drugs or alcohol, or if they reported a manic episode within the last year. Presence of current dementia as indicated by a score less than 25 on the Mini-Mental Status Examination (Folstein, Folstein, & McHugh, 1975) and/or performance on a broad battery of neuropsychological tests standardly used for diagnosis of dementia was also exclusionary. Following neuropsychological testing, for those participants showing any deviations from normal performance, expert review was conducted for presence of dementia or mild cognitive impairment (MCI). Three subjects had evidence of dementia, were referred for further follow-up, and did not participate in the CBT. MCI was not exclusionary, and 22 (38%) met the criteria for MCI, with 13 of these 22 participants meeting MCI criteria based on executive impairments. In total, 57 participants had complete neuropsychological data and were included in the analyses reported here. However, two individuals were removed

from analyses involving the Wisconsin Card Sorting Test (WCST) because of their scores being more than three standard deviations from the mean; thus, a total of 55 subjects were included in our analyses.

Procedures

Participants were administered a clinical evaluation and a cognitive battery prior to participating in CBT; these measures were re-administered immediately following treatment. The type of CBT used in this study was a 12-session individual protocol emphasizing behavioral activation, cognitive restructuring, and social skills training. Additional information about inclusion/exclusion procedures, assessment, and treatment protocol can be found elsewhere (Thompson *et al.*, 2015).

Measures

Depression.—Level of depression was measured using BDI-II (Beck, 1996) obtained before and after treatment. BDI-II is a 21-item self-report scale that assesses somatic and psychological symptoms in the past 2 weeks. A measure of depression symptoms percentage change was calculated $([BDI-II \text{ pre} - BDI-II \text{ post}] / BDI-II \text{ pre})$, wherein higher values represented a greater decrease in symptoms over the course of treatment.

Executive function.—The current study focused on executive functioning using the following measures: verbal fluency, the Stroop task, and the WCST. A summary score for each task was included in analyses. We used the semantic verbal fluency (letter fluency) task, which requires participants to generate words beginning with a specified letter on each of three separate trials. The letter fluency task, as compared with the category fluency task, is thought to rely more heavily on frontal executive regions. Total fluency score was calculated as the total number of correct words produced across the three trials, with higher scores indicating better executive functioning (Ruff *et al.*, 1997). In the Stroop task (Delis *et al.*, 2001), participants view a list of names of colors; in two trials, color words are printed in congruent ink colors (i.e., the word “red” printed in red ink) and in the third trial, color words are in incongruent ink colors (i.e., the word “red” printed in green ink). In the first two trials, participants have to read off as quickly as possible the word in one trial and the ink color in the other. In the third trial, participants are instructed to name, as quickly as possible, the color of the ink for each item, inhibiting the natural tendency to read the word. To control for individual differences in general processing speed, an overall inhibition score was created by predicting incongruent color word reading time from congruent color word and color naming time and saving the residuals.¹ These residual scores were then used as a measure of inhibition with longer times and higher scores indicating poorer inhibition. On the WCST (Berg, 1948; Heaton *et al.*, 1993), participants are asked to sort a single card at a time, by trial and error, to one of three target cards based on an intuited rule (color, form, or number); participants receive immediate feedback about whether or not each answer is correct in order to guide the next choice. The sorting condition (based on color, form, or number) changes after 10 correct answers. We used the total number of conceptual level

¹There are numerous ways to calculate interference (Jensen and Rohwer, 1966). We chose residualized scores over other methods because this resulted in a distribution that best approximated normality.

responses (correct responses that occur in sequences of three or more) with higher scores indicating better performance.

Results

Of the 55 participants included in this study, 36% of them were men, and they were on average 69 years old. See Table 1 for additional sociodemographic information. The majority of participants were white (70%). In general, participants showed a positive response to CBT, with a 38% decrease in depression symptoms from pre-treatment to post-treatment. In a linear regression with age, gender, and years of education entered in the same step, there were no significant demographic predictors of BDI symptom change (all p 's > 0.05). We performed a linear regression, including age, gender, and years of education as covariates. The three executive function measures (verbal fluency, Stroop, and WCST) were entered in the same step. Still, none of the demographic variables significantly predicted CBT treatment response (all p 's > 0.05). Verbal fluency was not a significant predictor of treatment response ($\beta = 0.07$, $p > 0.05$), nor was the Stroop task ($\beta = -0.04$, $p > 0.05$).

However, WCST did significantly predict treatment response ($\beta = -0.40$, $p = 0.01$), with worse performance on the WCST predicting greater reductions in depression symptoms after CBT (Table 2).

Discussion

The results of this study are among the first to describe neuropsychological predictors of positive response to CBT in individuals with LLD. Specifically, we examined multiple measures of executive functioning and found that worse performance on the WCST predicted better response to CBT. Two other measures of executive functioning, verbal fluency and the Stroop task, did not significantly predict CBT treatment response. Optimizing recovery from depression is a topic of great concern in geriatric psychiatry; identifying predictors of treatment response may allow clinicians to modify treatment options earlier in the course of the disease. This study represents an important step in tailoring psychiatric treatments to individuals' particular arrays of symptoms and capacities.

Cognitive capacities and in particular executive functioning represent an important arena for examining the correlates of treatment response. Executive dysfunction is a common occurrence in LLD, and the degree of executive dysfunction correlates with depression severity (Boone *et al.*, 1995). Multiple studies have found that worse executive functioning at baseline predicts poor response to antidepressants and a greater risk of relapse and recurrence of depression (Kalayam and Alexopoulos 1999; Potter *et al.*, 2004; Alexopoulos *et al.*, 2005; Sneed *et al.*, 2007; Story *et al.*, 2008). However, it is important to note that on multiple occasions, these results have not been replicated (Butters *et al.*, 2004; Bogner *et al.*, 2007). Regardless, these data highlight the need to examine alternative forms of treatment of LLD and the importance of investigating underlying factors predicting treatment response. Moreover, the factors underlying response to psychotherapeutic interventions may differ from those underlying pharmacological interventions.

Psychotherapy shows high effectiveness for treating LLD. In one study, 70% of participants were depression-free at a 2-year follow-up (Thompson *et al.*, 1987). Moreover, many older adults report that they are more likely to accept psychotherapy over pharmacotherapy (Rokke and Scogin, 1995). Importantly, psychotherapy has demonstrated effectiveness with individuals with executive functioning impairments (Alexopoulos *et al.*, 2003) and even with people with dementia (Teri *et al.*, 1997). The current study builds on these data to show that psychotherapy is not only feasible but also potentially advisable in the context of specific cognitive weaknesses, especially when deciding between medications and psychotherapy.

Two commonly utilized psychotherapies for LLD (CBT and PST) are said to operate through similar mechanisms of change (Warmerdam *et al.*, 2010). These treatments teach individuals to utilize cognitive techniques and may provide compensatory tools for certain difficulties. Alexopoulos *et al.* (2003) found that the mechanisms by which PST alleviated depressive symptoms were improving participants' ability to generate alternatives and make decisions. Despite similarities between PST and CBT, it is important to note that in a previous study, scores on the WCST (as well as other cognitive domains) did not predict treatment outcome to PST or supportive therapy (Areán *et al.*, 2010). This raises the possibility that those with executive dysfunction may benefit more from specific forms of psychotherapy like CBT than others. CBT aims to change or modify maladaptive thought patterns, and in turn the dysfunctional attitudes thought to precipitate and maintain depressive beliefs. The very process of modifying thoughts is an exercise in executive functioning—a person is actively practicing cognitive flexibility. The effectiveness of CBT for individuals with worse executive functioning may be explained in part by its ability to target cognitive deficit areas that negatively impact mood. Moreover, meta-cognition (or stepping back and responding to negative thoughts as temporary) is both a central mechanism for treatment change in CBT and a form of trained executive processing. It may be that the fewer individuals in our study were able to independently engage in cognitive flexibility and problem-solving (in the service of managing depression-related thoughts), the more CBT was able to provide a compensatory mechanism for managing for these difficulties.

This interpretation is further supported by functional neuroimaging data collected on a subset of the participants included here and reported in a separate paper (Thompson *et al.*, 2015). A version of the WCST was projected into the scanner using a series of mirrors, and participants used an electronic response button box during functional neuroimaging. We previously found that CBT outcomes were associated with areas of greater and lesser activation in frontal brain regions, while participants completed a scanner version of the WCST. Specifically, greater activity in the left superior frontal gyrus and right middle frontal gyrus was associated with better CBT response, while lower activity in the left frontal inferior triangle and right superior frontal gyrus predicted better CBT response (Thompson *et al.*, 2015). Executive functions rely on multiple pathways involving different regions of the prefrontal cortex (Cummings, 1995). We suggest that CBT may help augment broad impairments in executive function abilities and neurocircuitry as indicated by WCST performance and left frontal inferior triangle and right superior frontal gyrus activity during an Executive function task. Future research may want to address whether pre-treatment training in strategies for increasing cognitive flexibility and attentional processes may

increase the benefit that older individuals are able to derive from an intellectually challenging form of psychotherapy like CBT. As well, future studies would benefit from examining changes in both brain function and neuropsychological performance from pre-therapy to posttherapy. Studies with younger adults have found that new patterns of brain circuitry can be created by the end of a course of CBT (Goldapple *et al.*, 2004; Ritchey *et al.*, 2011); these need to be explored fully and replicated with persons with LLD. It is important to note that in the current study, performance on only one of our three measures of executive functioning predicted CBT outcome. The verbal fluency and the Stroop task performance were not significantly associated with treatment outcome. In previous investigations, worse performance on these tasks was related to worse treatment outcome to antidepressant medications (Kalayam and Alexopoulos, 1999; Baldwin *et al.*, 2004; Sneed *et al.*, 2010; Morimoto *et al.*, 2011). There were suggestions in these studies that overall slowing, as a proxy for psychomotor retardation, represents that best predictor of antidepressant non-response. Additionally, Sneed *et al.* (2010) found that the association between worse executive functioning and poor response to medications was only true for those participants receiving active medications and not those receiving placebos, again suggesting that the cognitive predictors of response are highly dependent on the intervention selected.

This study should be interpreted in the context of several limitations. Specifically, a control group was not used in this study, and future investigations should examine the role of executive functioning as a predictor of response to CBT in the context of a randomized controlled trial. It should also be noted that, although our sample size was large enough to test the proposed research question, it was not large enough to perform meaningful subgroup analyses that would have allowed for a finer grained analysis of moderators of the association between executive function and treatment response. Larger studies may wish to examine moderators, such as age, concurrent psychiatric medication use, and/or comorbid psychiatric disorders.

In summary, this study presents a step toward understanding the circumstances in which psychosocial interventions are most effective for treating LLD. In this case, worse executive functioning as measured by the WCST was associated with greater decreases in depressive symptoms over the course of CBT. Psychotherapy, and particularly CBT, is already considered a well-validated treatment for LLD. These data suggest that in particular for people demonstrating mild executive functioning impairments, where antidepressants may be less likely to be effective, CBT should be considered a first-line treatment. Moreover, in clinical settings, brief neuropsychological testing may assist providers with making treatment recommendations and considering prognosis.

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Key points

- The relationship was examined between cognitive performance at baseline and response to cognitive behavioral therapy.
- Worse initial executive function in select areas was associated with better response to cognitive behavioral therapy.
- Performance on Wisconsin Card Sort Task specifically predicted treatment response.

Table 1

Demographic characteristics for participants who completed the CBT and neurocognitive testing

Age (years), mean (SD)	69.4 (7.1)
Sex (% female)	64
Education, mean (SD)	14.3 (2.0)
BDI-II baseline, mean (SD)	22.2 (10.5)
BDI-II post-treatment, mean (SD)	13.8 (10.8)
Major depression (%)	60
Subsyndromal depression (%)	40
MMSE, mean (SD)	28.3 (1.7)
MCI (%)	38

SD, standard deviation; BDI, Beck Depression Inventory; MMSE, Mini-Mental Status Examination; MCI, mild cognitive impairment. Sociodemographic characteristics and level of depressive symptoms for participants who completed cognitive behavioral therapy and had completed neuropsychological data ($N = 55$).

Table 2

Results of linear regression with EF measures predicting CBT treatment response

	β	t	p
Verbal fluency	0.07	0.48	0.63
Stroop	-0.04	-0.27	0.79
Wisconsin Card Sort Task	-0.40	-2.64	0.01 [*]

Verbal fluency, Stroop, and Wisconsin Card Sort Task scores were entered into the same linear regression analysis predicting percent change score of depression symptoms from baseline to post-treatment. Age, sex, and years of education were entered as covariates.

^{*} denotes $p < .05$.