Psychological Medicine (2015), **45**, 3111–3120. © Cambridge University Press 2015
doi:10.1017/S0033291715001075

ORIGINAL ARTICLE

Cognitive control, reward-related decision making and outcomes of late-life depression treated with an antidepressant

G. S. Alexopoulos[1]*, K. Manning[2], D. Kanellopoulos[1], A. McGovern[1], J. K. Seirup[1], S. Banerjee[3] and F. Gunning[1]

[1] *Department of Psychiatry, Weill Cornell Medical College, White Plains, NY, USA*
[2] *Department of Psychiatry, University of Connecticut Health Center, Farmington, CT, USA*
[3] *Department of Public Health, Weill Cornell Medical College, New York, NY, USA*

Background. Executive processes consist of at least two sets of functions: one concerned with cognitive control and the other with reward-related decision making. Abnormal performance in both sets occurs in late-life depression. This study tested the hypothesis that only abnormal performance in cognitive control tasks predicts poor outcomes of late-life depression treated with escitalopram.

Method. We studied older subjects with major depression ($N = 53$) and non-depressed subjects ($N = 30$). Executive functions were tested with the Iowa Gambling Test (IGT), Stroop Color-Word Test, Tower of London (ToL), and Dementia Rating Scale – Initiation/Perseveration domain (DRS-IP). After a 2-week placebo washout, depressed subjects received escitalopram (target daily dose: 20 mg) for 12 weeks.

Results. There were no significant differences between depressed and non-depressed subjects on executive function tests. Hierarchical cluster analysis of depressed subjects identified a Cognitive Control cluster (abnormal Stroop, ToL, DRS-IP), a Reward-Related cluster (IGT), and an Executively Unimpaired cluster. Decline in depression was greater in the Executively Unimpaired ($t = -2.09$, df = 331, $p = 0.0375$) and the Reward-Related ($t = -2.33$, df = 331, $p = 0.0202$) clusters than the Cognitive Control cluster. The Executively Unimpaired cluster ($t = 2.17$, df = 331, $p = 0.03$) and the Reward-Related cluster ($t = 2.03$, df = 331, $p = 0.0433$) had a higher probability of remission than the Cognitive Control cluster.

Conclusions. Dysfunction of cognitive control functions, but not reward-related decision making, may influence the decline of symptoms and the probability of remission of late-life depression treated with escitalopram. If replicated, simple to administer cognitive control tests may be used to select depressed older patients at risk for poor outcomes to selective serotonin reuptake inhibitors who may require structured psychotherapy.

Received 16 December 2014; Revised 7 May 2015; Accepted 7 May 2015; First published online 14 July 2015

Key words: Executive function, late-life depression, remission, cognitive control, reward processing

Introduction

Late-life depression is classified as a mood disorder, yet abnormalities in various executive functions often occur during depressive episodes (Elliott *et al.* 1998; Eshel & Roiser, 2010; Vrieze *et al.* 2013). A large body of literature suggests that executive processes consist of two distinct sets of cognitive functions: one concerned with cognitive control and the other with reward-related decision making (Glascher *et al.* 2012; Roiser & Sahakian, 2013). Cognitive control processes include response inhibition, planning, problem solving, and working memory. Reward-related decision-making processes include valuation, reward learning, and decision making. Cognitive control and reward-related decision making are instantiated in distinct neuroanatomical circuits, which interact to generate adaptive behavior. Abnormalities in both cognitive control and reward-related decision-making tasks (Elliott *et al.* 1998; Eshel & Roiser, 2010; Vrieze *et al.* 2013) have been reported in depression. Determining which of these functions is central to perpetuating the syndrome of late-life depression is an important heuristic and clinical question.

Impairment in some cognitive control functions has been associated with poor outcomes of late-life depression when treated with antidepressants. In particular, tests of initiation/perseveration, cognitive inhibition, and semantic clustering have been associated with poor or slow improvement of late-life depression to antidepressants (Alexopoulos *et al.* 2005; Sneed *et al.*

* Address for correspondence: G. S. Alexopoulos, M.D., Department of Psychiatry, Weill Cornell Medical College, 21 Bloomingdale Road, White Plains, NY 10605, USA.
(Email: gsalexop@med.cornell.edu)

2010; Morimoto *et al.* 2011, 2012, Pimontel *et al.* 2012). Performance in these tests requires integrity of the anterior cingulate cortex (ACC) and the dorsolateral prefrontal cortices (DLPFC) (Elliott *et al.* 1997; Dagher *et al.* 1999; MacDonald *et al.* 2000; Beauchamp *et al.* 2003; van den Heuvel *et al.* 2003; Goethals *et al.* 2004; Ruocco *et al.* 2014). These neuropsychological findings parallel structural and functional neuroanatomical changes associated both with cognitive control dysfunction and with poor outcomes of late-life depression treated with antidepressants. These include white-matter hyperintensities (Gunning-Dixon *et al.* 2010), microstructural white-matter changes (Alexopoulos *et al.* 2008), low volume of the anterior cingulate (Gunning *et al.* 2009), hypoactivation of the cognitive control network in response to a cognitive control challenge (Aizenstein *et al.* 2005), and reduced resting functional connectivity of the cognitive control network (Alexopoulos *et al.* 2012). Taken together, these findings lend support to the hypothesis that depression with cognitive control dysfunction is a distinct syndrome of late-life depression (Alexopoulos, 2001) with poor outcomes following treatment with antidepressants.

In addition to cognitive control dysfunction, abnormal performance in reward-related decision-making tasks has been reported in depression (Eshel & Roiser, 2010; Vrieze *et al.* 2013). Performance in such tasks requires integrity of the ventromedial prefrontal cortex (VMPFC) (Rogalsky *et al.* 2012). Neuroimaging, neuropathologic, and lesion analysis findings implicate the VMPFC in the pathophysiology of major depression (Drevets, 2007). Severity of depression is inversely correlated with physiological activity in parts of the posterior lateral and medial orbitofrontal cortex and cerebrovascular lesions in this region predispose to depression. Posterior lateral and medial orbitofrontal cortex function may also be impaired in mood disorders, as these patients have low gray-matter volume, histopathologic abnormalities, and altered hemodynamic responses to emotionally valenced stimuli, probabilistic reversal learning, and reward processing. Impairment in reward-related decision making is mediated by the VMPFC and in late-life depression is associated with critical clinical outcomes including functional impairment and suicidality (Jollant *et al.* 2005, 2010; Dombrovski *et al.* 2012). Despite these findings, it is unknown whether abnormal performance in tasks requiring integrity of the VMPFC is linked to change of late-life depression during treatment with antidepressants.

The goal of this study was to examine whether performance in cognitive control and reward-related decision-making tasks predicts change of symptoms and signs of late-life major depression during treatment with a selective serotonin reuptake inhibitor (SSRI). To this end, we used a set of cognitive control tasks [Stroop Color-Word, Tower of London (ToL), and Dementia Rating Scale – Initiation/Perseveration domain (DRS-IP)] and a reward-related decision-making task [Iowa Gambling Test (IGT)]. Based on earlier literature (Alexopoulos *et al.* 2005; Sneed *et al.* 2010; Morimoto *et al.* 2011, 2012; Pimontel *et al.* 2012), we hypothesized that depressed older patients with abnormal performance in cognitive control tasks constitute a group with poor outcomes (decline in depressive symptoms and probability of remission) to treatment with the SSRI escitalopram, while patients with abnormal performance in a reward-related decision-making task, but relatively unimpaired cognitive control performance, will have outcomes similar to those of patients with unimpaired executive functions (null hypothesis).

Method

Subjects

The subjects were consecutively recruited older adults with major depression and non-depressed comparison subjects who had completed the following four executive function tests during their baseline assessment: IGT (Bechara, 2007), Stroop Color-Word test (Golden, 1978), ToL (Culbertson & Zillmer, 2001), and DRS-IP (Mattis, 1989). Additional inclusion criteria for the depressed subjects were: (1) age $\geqslant$ 60 years; (2) unipolar, non-psychotic major depression by SCID (First *et al.* 1995; DSM-IV); (3) Mini-Mental State Examination (MMSE; Folstein *et al.* 1975) $\geqslant$ 24; (4) capacity to consent. Exclusion criteria were: (1) intent or plan to attempt suicide in the near future; (2) history or presence of psychiatric diagnoses other than unipolar, non-psychotic major depression or generalized anxiety disorder; and (3) use of psychotropic drugs or cholinesterase inhibitors other than mild doses of benzodiazepines. The inclusion criteria for the non-depressed comparison group were: (1) age $\geqslant$ 60 years; (2) absence of presence or history of psychiatric disorders; and (3) use of psychotropic agents. The study was approved by the Weill Cornell Medical College Institutional Review Board.

Treatment

Depressed subjects had a single-blind, 2-week drug-washout phase during which they received placebo identical to escitalopram tablets. This phase was followed by treatment with 10 mg/day escitalopram for 1 week followed by an increase to the target dose of 20 mg/day. Subjects who were unable to tolerate

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20 mg/day received 15 mg or 10 mg/day. Subjects unable to tolerate 10 mg exited the study. The primary treatment outcome was severity of depression assessed with the 24-item Hamilton Depression Rating Scale (HAMD; Hamilton, 1960).

Assessment of executive functions

Stroop Color-Word

Response inhibition was tested with the Stroop Color-Word test. Subjects are presented with a list of the words 'red', 'blue', and 'green' printed with an incongruent ink color, e.g. the word 'red' printed with blue ink. Subjects were instructed to name the ink color of each word and inhibit the prepotent competing response of reading the word. Scores represent the total number of responses in 45 s. We used the Stroop Interference score, which takes into consideration processing speed (Golden, 1978). To this end, we first calculated the Predicted Color-Word score (Color score × Word score/Color score + Word score). The Interference score consists of the Color-Word score minus the Predicted Color-Word score. Functional neuroimaging studies have shown ACC activation during Stroop performance (MacDonald *et al.* 2000). Abnormal Stroop-induced ACC activation has been reported in fMRI studies of depressed individuals (Liotti & Mayberg, 2001; Kikuchi *et al.* 2012).

ToL

Planning was tested with the ToL, 2nd edn (Culbertson & Zillmer, 2001). The test consists of two pegboards with three pegs of different lengths. Each pegboard has three beads of different colors (red, green, blue), and subjects are asked to move their beads one at a time to replicate the bead pattern on the examiner's board. After a demonstration and two practice trials, subjects conduct 10 trials replicating increasingly difficult bead configurations. The score for each trial consists of moves made above the minimum required to replicate that bead configuration. The total moves for each of the 10 trials are summed for the total reported score. Performance in the ToL task activates the DLPFC and caudate nucleus (Elliott *et al.* 1997; Dagher *et al.* 1999; Beauchamp *et al.* 2003; van den Heuvel *et al.* 2003; Goethals *et al.* 2004; Ruocco *et al.* 2014).

DRS-IP

The IP domain tests: (1) verbal initiation/perseveration, i.e. naming of all things one can buy in a supermarket over 1 min; (2) alternating hand movements; and (3) graphomotor design, e.g. reproduce XOXO. The IP has high criterion validity against standard neuropsychological measures of verbal initiation and perseveration (Marson *et al.* 1997). Functional neuroimaging studies suggest that functions tested by the IP subscale require integrity of circuitry including the ACC and the DLPFC (Jueptner *et al.* 1997; Sakai *et al.* 1998).

IGT

This test consists of 100 playing cards from four decks (A, B, C, D) (Bechara, 2007). Some cards are followed by reward (monetary gain), whereas others are followed by punishment (monetary loss). Subjects are instructed to choose cards from one of the four decks with the aim to win as much money as possible. Decks with higher immediate reward (A and B) have higher long-term punishment, yielding an overall net loss. Decks (C and D) with lower immediate gain have lower long-term punishment, yielding an overall net gain (advantageous decks). A performance score is calculated by subtracting the number of risky deck choices (A and B) from the number of conservative deck choices (C and D), i.e. $[(C + D) - (A + B)]$. Performance in the IGT predicts performance on other decision-making tasks such as temporal discounting (Halfmann *et al.* 2014) and consumer decision making (Denburg *et al.* 2007). Human lesion (Glascher *et al.* 2012) and neuroimaging studies (Rogalsky *et al.* 2012) have shown that performance in the IGT requires integrity of the VMPFC.

In addition to executive function tests, overall cognitive impairment was assessed with the Mini-Mental State Examination (MMSE; Folstein *et al.* 1975) and memory was assessed with the Hopkins Verbal Learning Test – Revised (HVLT; Benedict *et al.* 1998).

Assessment of psychopathology, medical burden, and disability

Diagnosis was assigned in research conferences by agreement of two clinician investigators after review of history and the SCID-R (First *et al.* 1995). Age at onset of first episode of major depression was derived from the SCID-R. All other research data were obtained by interviewers trained by the Weill Cornell Institute of Geriatric Psychiatry.

Anxiety was assessed with the Clinical Anxiety Scale (CAS; Snaith *et al.* 1982), hopelessness with the Beck Hopelessness Scale (BHS; Beck *et al.* 1974), neuroticism with the 12-item subscale of the NEO (Costa & McCrae, 1992), and life satisfaction with the 13-item Life Satisfaction Index (Wood *et al.* 1969). Disability was quantified by the interviewer-administered 12-item World Health Organization Disability

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Assessment Schedule II (WHODAS) (Epping-Jordan & Ustun, 2000). The WHODAS yields a composite score of disability after assessing the domains of: understanding and communicating, getting around, self-care, getting along with others, household and work activities, and participation in society. Medical burden was quantified with the Charlson Comorbidity index (CCI) (Charlson *et al.* 1987).

After baseline assessment, the HAMD was assessed weekly for 4 weeks then every other week until week 12. Payment for transportation or transportation arrangements were provided to all meetings. Compensation was offered for time spent in assessments.

Data analysis

We conducted agglomerative hierarchical cluster analysis using Ward's method (Ward, 1963) with squared Euclidean distance to identify clusters based on performance on four tests of executive function; all subjects had data on the variables used in the cluster analysis. This method classifies subjects into clusters and aims to increase within-cluster homogeneity and between-cluster heterogeneity, i.e. within each cluster subjects have similar test performance but clusters are distinct from each other. The choice of the number of clusters was based on maximizing the Calinski–Harabasz index (CH index; Calinski & Harabasz, 1974), a ratio of between-cluster to within-cluster variation, size of each cluster ($\geqslant$10) and clinical judgment. Group comparisons (depressed *v.* non-depressed and comparisons among the three clusters) of demographic and clinical characteristics was performed with analysis of variance (ANOVA). Age and education were used as covariates in all comparisons of cognitive performance tests.

We used mixed-effects linear regression analyses (Laird & Ware, 1982) to compare HAMD scores among the resultant clusters over a period of 12 weeks. The model included random effects for intercept and slope and fixed effects for cluster, time trend parameter(s) and time × cluster interaction. We examined a model which included a cluster-specific random intercept and nested random intercept for patients within clusters, but the estimate for cluster-specific random intercept was zero and this model was not selected.

To evaluate remission of depression (HAMD $\leqslant$ 10), we used a mixed-effects logistic regression model to analyze the longitudinal trajectory of the probability of remission. HAMD $\leqslant$ 10 is commonly used to define remission of late-life depression (Lecrubier, 2002). Age and gender were included as covariates in all analyses and retained in the model if significant or improved model fit.

Results

A total of 83 subjects met criteria for this analysis. Of these, 53 met criteria for major depression and 30 had no psychopathology. The depressed subjects had greater severity of depression and disability and worse performance in the memory task (HVLT) and in one of the executive function tasks (DRS-IP) than non-depressed subjects (Table 1). However, there were no differences between depressed and non-depressed subjects in demographics, medical burden, and overall cognitive impairment (MMSE).

Exploratory cluster analysis

We used exploratory hierarchical cluster analysis to classify the depressed subjects according to their performance on four executive function tests, i.e. the Stroop Color-Word, the ToL, the DRS-IP, and the IGT. Based on a CH index (30.9) and clinical/biological relevance, a three-cluster solution was chosen: a Cognitive Control cluster (abnormal Stroop, ToL, DRS-IP), a Reward-Related cluster (abnormal IGT), and an Executively Unimpaired cluster. A two-cluster solution (Cognitive Control *v.* Combined Reward-Related and the Executively Unimpaired clusters combined into one) had a slightly higher CH index (31.4) but the three-cluster solution was chosen because the Reward-Related cluster and Executively Unimpaired cluster represent heuristically distinct groups.

Clinical profile

Subjects in the three clusters had similar age and education (Table 2). Age at depression onset, severity of depression (HAMD), severity of anxiety (CAS), medical burden (CCI), overall cognitive impairment (MMSE), and disability (WHODAS) were similarly distributed across the three clusters. The Cognitive Control cluster had lower hopelessness (BHS) scores than the Reward-Related cluster and the Cognitively Unimpaired cluster ($F = 3.64$, df = 2, $p < 0.034$).

Treatment

Of the 53 depressed subjects who participated in this analysis, one exited the study prior to receiving any treatment. The remaining subjects were treated with escitalopram. Of the 52 treated subjects, 88% (46/52) received the target dose of 20 mg/day, 4% (2/52) received 15 mg/day and 8% (4/52), received 10 mg/day. Both dosages and duration of treatment were similarly distributed across the three clusters. Specifically, subjects within the Cognitive Control cluster received a mean daily dose of 19.00 mg (S.D. = 3.16), subjects within the Reward-Related cluster 18.97 mg (S.D. = 2.80), and subjects within the Executively Unimpaired

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Table 1. *Clinical and cognitive functioning characteristics of 53 participants with major depression and 30 non-depressed participants*

	Group		Statistics		
Variable	Depressed ($N = 53$)	Non-depressed ($N = 30$)	F	df	p
Demographics					
Age (years)	72.18 (7.56)	72.83 (5.95)	0.165	1	0.686
Education (years)	16.30 (2.96)	16.33 (2.12)	0.003	1	0.959
Psychopathology					
HAMD	23.40 (3.90)	0.60 (0.89)	990.764	1	<0.001
Medical burden					
Charlson comorbidity index	1.55 (1.29)	1.30 (1.60)	0.587	1	0.446
Cognition[a]					
Mini-Mental State Examination	28.34 (1.74)	28.57 (0.86)	0.672	1	0.415
DRS-IP[b]	−0.20 (1.16)	0.35 (0.47)	6.319	1	0.014
Stroop interference score[b]	0.04 (0.91)	−0.08 (1.16)	0.204	1	0.653
Tower of London[b]	0.14 (1.02)	−0.25 (0.92)	3.236	1	0.076
Iowa Gambling Task[b]	−0.04 (1.03)	0.07 (0.96)	0.254	1	0.616
HVLT learning total[b]	−0.16 (1.05)	0.28 (0.86)	4.988	1	0.028
HVLT recall total[b]	−0.021 (1.06)	0.37 (0.78)	8.469	1	0.005
Disability					
WHODAS	37.14 (13.02)	22.21 (3.62)	37.61	1	<0.001

HAMD, 24-item Hamilton Depression Rating Scale; DRS-IP, Dementia Rating Scale – Initiation/Perseveration domain; HVLT, Hopkins Verbal Learning Test; WHODAS, World Health Organization Disability Assessment Scale II.

[a] Controlled for age and education.

[b] Z scores.

cluster 19.23 mg (S.D. = 2.77). The corresponding means of duration of escitalopram treatment were 11.80 weeks (S.D. = 0.63), 10.38 weeks (S.D. = 3.62), and 12.00 weeks (S.D. = 0).

Treatment outcomes

We compared the trajectory of depression severity (HAMD) of the three clusters with a linear mixed model with fixed effects for linear week, quadratic week and week × cluster interaction and subject-specific random effects for intercept and slope. Week and quadratic week were significantly different from zero indicating that all clusters had a reduction in HAMD over time. The week × cluster interaction was significantly different ($F_{2,\ 331} = 3.03$, $p = 0.0497$) indicating different HAMD progression in the paths of each cluster (Fig. 1). The decline in severity of depression (HAMD) was greater in the Executively Unimpaired cluster ($t = -2.09$, df = 331, $p = 0.0375$) and the Reward-Related cluster ($t = -2.33$, df = 331, $p = 0.0202$) than in the Cognitive Control cluster.

Remission was achieved in one (out of 10) subjects in the Cognitive Control cluster, 18 (out of 30) in the Reward-Related cluster, and eight (out of 13) in the Executively Unimpaired cluster. A mixed-effects analysis of depression remission (HAM-D $\leqslant$ 10) trajectory as a binary outcome was performed with fixed effects for linear week, quadratic week, cluster, and cluster × week interaction and a subject-specific random intercept. There was a week × cluster interaction ($F_{2,\ 331} = 4.31$, $p = 0.0648$). The Cognitive Control cluster had a lower probability of remission than the Executively Unimpaired cluster ($t = 2.17$, df = 331, $p = 0.03$) and the Reward-Related cluster ($t = 2.03$, df = 331, $p = 0.0433$) (Fig. 2).

Discussion

The principal finding of this study is that older adults with major depression and abnormal performance in cognitive control tasks had less decline of depressive symptoms during treatment with escitalopram than depressed subjects with abnormal reward-related decision making or executively unimpaired patients. Moreover, subjects of the abnormal cognitive control cluster had lower probability of remission during the 12-week escitalopram treatment period.

To our knowledge, this is the first study to observe that abnormality in tasks of cognitive control, but not in reward-related decision making, influence the trajectory of symptoms and the attainment of remission of late-life depression during treatment with an

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Table 2. *Clinical characteristics in three clusters of executive functions of 53 older patients with major depression*

	Cognitive function clusters		
	Reward-related cluster ($N = 30$)	Cognitive control cluster ($N = 10$)	Executively unimpaired cluster ($N = 13$)
Demographics			
Age (years)	70.88 (7.44)	79.47 (6.96)	69.59 (4.68)
Education (years)	16.67 (3.22)	14.70 (3.53)	16.69 (0.95)
Psychopathology			
Age of depression onset (years)	48.59 (22.89)	57.10 (27.25)	52.23 (23.20)
HAMD	23.47 (4.59)	23.30 (1.64)	23.31 (3.59)
Clinical Anxiety Scale	4.31 (4.88)	3.60 (3.69)	2.69 (2.84)
Beck Hopelessness Scale	9.17 (5.86)	5.20 (3.91)	11.38 (5.59)
NEO neuroticism	27.00 (8.49)	20.44 (8.58)	25.38 (7.14)
Life satisfaction	3.97 (2.93)	4.56 (2.35)	4.15 (2.38)
Medical burden			
Charlson comorbidity index	1.53 (1.38)	2.10 (1.29)	1.15 (0.99)
Cognition			
Mini-Mental State Examination	28.30 (1.75)	27.80 (2.44)	28.85 (0.90)
DRS-IP[a]	−0.28 (1.37)	−0.55 (1.08)	0.25 (0.27)
Stroop interference score[a]	0.08 (0.83)	−0.44 (1.05)	0.34 (0.88)
Tower of London[a]	−0.07 (0.59)	1.66 (0.73)	−0.54 (0.87)
Iowa Gambling Test[a]	−0.62 (0.68)	0.03 (0.90)	1.24 (0.47)
HVLT learning[a]	−0.19 (1.05)	−0.74 (1.11)	0.37 (0.74)
HVLT recall[a]	−0.25 (1.05)	−0.78 (1.18)	0.33 (0.74)
Disability			
WHODAS	36.67 (13.95)	40.65 (10.23)	35.54 (13.14)

HAMD, 24-item Hamilton Depression Rating Scale; DRS-IP, Dementia Rating Scale – Initiation/Perseveration domain; HVLT, Hopkins Verbal Learning Test; WHODAS, World Health Organization Disability Assessment Scale II.

[a] Z scores.

antidepressant. This observation is consistent with neurobiological findings suggesting that these two sets of functions rely on distinct brain networks. Cognitive control functions, such as those tested by the Stroop Color-Word, the ToL and the DRS-IP, are mediated by a rostro-caudal hierarchy of structures organized for behavioral control and planning (Glascher *et al.* 2012). This hierarchy includes the DLPFC and its connections to posterior cortical areas in the parietal lobe. The rostral ACC has been found to be activated by cognitive control tasks of set shifting and error detection in fMRI studies (Braver *et al.* 2001; Lie *et al.* 2006) and lesions in the anterior sectors of ACC impair rule-switching in primates (Buckley *et al.* 2009). More posterior regions within the dorsal ACC and the DLPFC may be recruited during error detection (Braver *et al.* 2001) and conflict monitoring (MacDonald *et al.* 2000; Botvinick *et al.* 2001), while parietal regions are responsible for selective attention (Roberts & Hall, 2008). Reward-related decision making, such as that tested by the IGT, is mainly mediated by ventromedial structures of the prefrontal cortex and has strong connections to the limbic system. Lesion studies have shown that damage of the VMPFC impairs performance in the IGT but spares performance in cognitive control tasks (Stuss *et al.* 2000; Glascher *et al.* 2012). Both the cognitive control and the reward-related networks converge at the ACC, which serves as the point for their interaction (Glascher *et al.* 2012) and plays a role in symptom change during treatment with antidepressants (Seminowicz *et al.* 2004; Drevets *et al.* 2008; Liston *et al.* 2014; McGrath *et al.* 2014). It is tempting to speculate that facilitation of decline in symptoms of depression during treatment with antidepressants is mediated by input of cognitive control structures to the ACC, which in turn exerts control over limbic structures. Input of VMPFC structures to ACC, although important for reward-related decision making, may not be related to outcomes of antidepressant drug treatment.

Our findings are consistent with reports that impairment on some cognitive control tasks predicts little change in symptoms of late-life depression during

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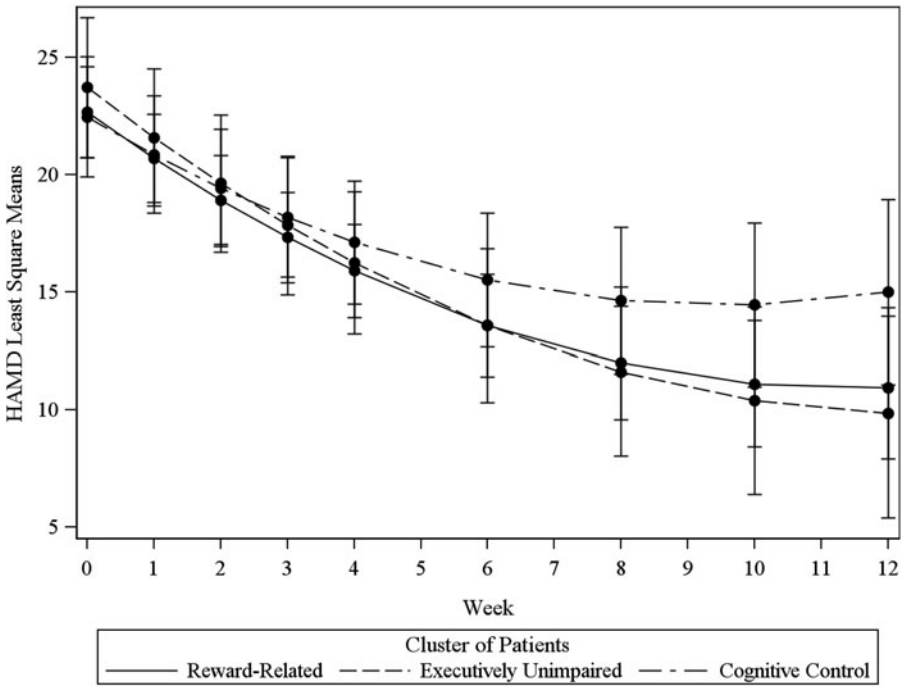

Fig. 1. Trajectory of 24-item Hamilton Depression Rating Scale (HAMD) scores in three clusters of older patients with major depression ($N = 53$) treated with escitalopram.

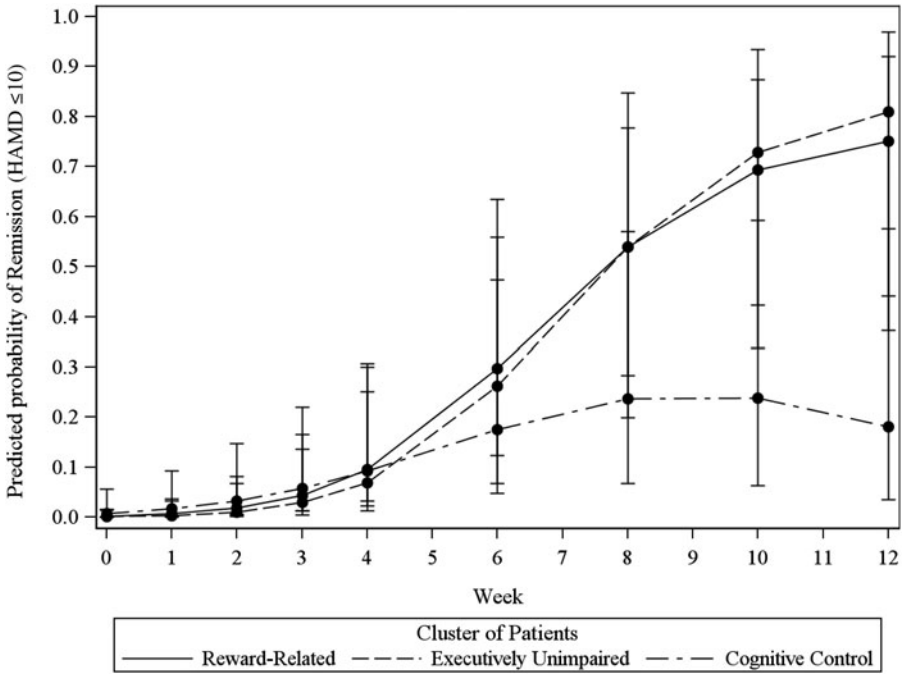

Fig. 2. Longitudinal trajectory of the probability of remission (HAMD $\leqslant 10$) in three clusters of older patients with major depression ($N = 53$) treated with escitalopram. HAMD, Hamilton Depression Rating Scale.

treatment with antidepressant drugs (Alexopoulos *et al.* 2004, 2005; Morimoto *et al.* 2011). It has been suggested that this relationship is rather specific to cognitive control tasks. A study of old-old patients with major depression treated with citalopram found that performance on the Stroop Color/Word task – but not overall cognitive impairment or poor performance in choice reaction time, spatial judgment, or selective

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reminding – influences antidepressant response (Sneed *et al.* 2008). Our findings further support the specificity of the relationship between cognitive control abnormalities on the one hand and change in depressive symptoms and remission rate during treatment with escitalopram.

The findings of this study should be viewed in the context of its limitations. These include the small sample, the uncertainty of hierarchical clustering in identifying clusters, the limited number of neuropsychological tests, and the effect of processing speed on these tests. Processing speed moderates performance on other neuropsychological instruments (Butters *et al.* 2004). Therefore, we cannot exclude that slow processing did not influence the relationship of cognitive control abnormalities to change in depressive symptoms during escitalopram treatment. Other limitations include the absence of a placebo-treated group, and the use of a single antidepressant. However, testing of depressed subjects occurred after a 2-week placebo/washout phase that might have reduced the influence of prior psychotropic treatment on test performance and the inclusion of placebo responders. Further, most of our subjects tolerated high dosages of escitalopram, and there were no significant dosage and length of drug treatment differences among the three clusters. Finally, there was high retention of subjects in all three groups. Therefore, differences in change in depressive symptoms and in time in remission may not be attributed to under-dosage, unequal intensity or length of treatment, or selective drop-out. Nonetheless, replication of this study is necessary.

The clinical significance of this study's findings is their potential use for treatment selection. While a convergence of findings suggests that poor performance in cognitive control tasks is a rather specific predictor of poor outcome to treatment with at least some antidepressants (Alexopoulos *et al.* 2004, 2005; Sneed *et al.* 2008; Morimoto *et al.* 2011), it is possible that such patients may do well with other antidepressant strategies, e.g. other psychotropic agents, transcranial magnetic stimulation, other psychotherapies. In fact, problem-solving therapy improved depression (Arean *et al.* 2010) and disability (Alexopoulos *et al.* 2011) in older adults with major depression and cognitive control dysfunction more than supportive therapy even though performance in a cognitive control tests improved equally in the two treatment groups (Mackin *et al.* 2013).

In sum, impairment in cognitive control functions, but not in reward-related decision making, appears to adversely influence outcomes of geriatric depression to escitalopram. The theoretical significance of this finding is that it provides a target for neuroimaging studies of outcomes of antidepressants focusing on the structural and functional connectivity of cognitive control structures to rostral ACC and to limbic structures. In addition to its theoretical significance, if our finding is replicated, simple to administer cognitive control tests may be used to select depressed older patients at risk for poor outcomes with some SSRI antidepressants who may require a structured, learning-based therapy.

Acknowledgements

Personnel cost for this work was supported by NIMH grants R01 MH065653, R01 MH079414, T32 MH019132 and the Sanchez Foundation. Escitalopram and placebo were provided free of cost by Forest Pharmaceuticals, Inc.

Declaration of Interest

None.

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