COGNITIVE CONTROL AND CONFLICT PROCESSES IN GERIATRIC DEPRESSION

by

THEODORA KANELLOPOULOS

A dissertation submitted to the Graduate Faculty in Neuropsychology in partial fulfillment of the requirements for the degree of Doctor of Philosophy, The City University of New York

2013

This manuscript has been read and accepted for the
Graduate Faculty in Neuropsychology in satisfaction of the
dissertation requirement for the degree of Doctor of Philosophy.

Lisa D. Ravdin, Ph.D., ABPP

Date | Chair of Examining Committee

Maureen O'Connor, Ph.D.

Date | Executive Officer

Lisa D. Ravdin, Ph.D., ABPP

Faith Gunning, Ph.D.

Joel Sneed, Ph.D.
Supervisory Committee

THE CITY UNIVERSITY OF NEW YORK

ABSTRACT

COGNITIVE CONTROL AND CONFLICT PROCESSES IN GERIATRIC DEPRESSION

by

Theodora Kanellopoulos

Advisor: Dr. Lisa D. Ravdin

Major depressive disorder is often accompanied by disturbances in aspects of cognitive control that impair goal-directed behavior. In particular, depressed individuals have been found to have deficits in conflict processing, which manifest as inadequate inhibition of maladaptive environmental stimuli and thought patterns. Insufficient cognitive inhibition of irrelevant negative information may contribute to, and perpetuate the depressive syndrome. Prior studies have hypothesized that the neural network that underlies conflict processing consists of the dorsal anterior cingulate and dorsolateral prefrontal cortex. This network has been shown to be compromised by depression in young adults, as well as by the aging process. However, the temporal properties of conflict processing, within this conflict-control network, have not been fully examined in geriatric depression.

In this study, the N2 event-related potential was recorded during a Stroop paradigm administered to 44 depressed and 24 healthy older adults. Depressed subjects exhibited smaller N2 amplitudes to incongruent relative to congruent stimuli. Among healthy non-depressed subjects, there was no difference in N2 amplitudes between conditions. Notably, there were no overall differences in task accuracy or reaction time between the depressed and non-depressed groups. Larger N2 amplitudes were associated with executive dysfunction (i.e., poorer performance on a set-shifting measure) in healthy

older adults; however, this relationship was not observed in the depressed group. These results suggest that neural processing abnormalities within the conflict-control network may exist in geriatric depression, above and beyond those attributable to normal age related changes. Furthermore, alternate neural networks may be recruited for successful conflict processing in depressed older adults. Additional characterization of abnormalities within specific conflict processing networks, as well as examination of how these abnormalities relate to the course and treatment of depression can help inform pharmacological and psychotherapeutic interventions.

ACKNOWLEDGEMENTS

This dissertation would not have been possible without the contributions of many wonderful people, to whom I owe my genuine gratitude. First and foremost, I would like to thank my advisor and dissertation chair, Dr. Lisa Ravdin for her unwavering support throughout my graduate school experience. Dr. Ravdin's direct but always warm guidance through the various stages this dissertation project, was the catalyst which led to the enthusiastic completion of this project. Through her assistance and support I have been able to develop my skills as a neuropsychologist in both clinical and research settings.

I would also like to thank my mentor Dr. George Alexopoulos, for nurturing my intellectual curiosity and for believing in me. Through his direct contributions, I have become a better scientist. His ongoing support and encouragement continues to motivate me to strive for excellence every day. Without him, this project would not have been possible. I am grateful for all of his previous assistance and look forward to a long-lasting relationship, and to our future collaborations.

I would like to thank my dissertation committee, Dr. Faith Gunning and Dr. Joel Sneed who both challenged and supported me throughout the dissertation writing process. Dr. Gunning, it was through your love of, and passion for neuropsychology that I came to find my direction in life. I am forever grateful to you for showing me this world and helping me navigate towards my dream. I would also like to thank my outside readers Dr. Dimitris Kiosses and Dr. Hilary Gomes who provided new perspective and insightful comments, and assisted in refining this dissertation.

These studies would not have been possible without the hard work and dedication of the members of the Weill Cornell Institute for Geriatric Psychiatry. I am grateful for the role they played in recruitment and data collection. However, I am most thankful for the camaraderie, friendship, and support that they have provided over the years.

With all my love and gratitude, this dissertation is dedicated to my family without whom I would not be where I am today. Thank you to my parents who have never set limits on my dreams, and who have encouraged me to do what I love. Thank you to my brothers for their friendship, warmth, and support throughout my life but also during many difficult times in graduate school. Thank you to my extended family of friends that have navigated this challenging process with me by listening and providing me with valuable advice and support. Thank you to my husband, Viktor, for his love, humor, kindness, and encouragement through years of late nights, hard work and productive (well sometimes unproductive) procrastination. Viktor, you inspire me to strive for my dreams – I am forever grateful for all that you do, and all that you are to me.

TABLE OF CONTENTS

Page

Abstract……iv

Acknowledgements……...……...vi

List of Tables……..……..ix

List of Figures……...…….....xi

Introduction……1

Specific Aims…….……...……...1

Conflict Processing: A closer look……...…….……...6

Inhibition Paradigms…….……...8

Neural Networks Underlying the Conflict-Control Loop .....……11

Conflict- Control Processes in Aging……13

Cognitive Control and Depression: Focus on Late-Life…….……..….15

Summary…….……...19

Methods

Participants……..21

Procedure……...….22

Data Reduction…….……..……26

Data Analysis……...…28

Results…….33

Discussion……...43

References……...54

LIST OF TABLES

Page

1. Descriptive characteristics of baseline clinical variables…….....28

2. Frequency of tasks administered by difficulty level….……...29

3. Hierarchical regression analyses of peak N2 waveform amplitudes predicting performance on neuropsychological variables……...……42

LIST OF FIGURES

Page

1. Schematic representation of the conflict control loop……..……7

2. Example of timing of computerized behavioral (Stroop) task……..…….24

3. Stroop task accuracy rate by group and congruency condition……..……34

4. Stroop task reaction time by group and congruency condition …….35

5. Average latency of N2 waveform minimum peak by group and congruency condition……36

6. Grand average minimum amplitude of N2 waveform minimum peak by group and congruency condition……..……37

7. Grand average waveform distribution by group and congruency condition.…….……38

8. Topographic voltage maps by group and congruency condition …..39

Introduction

Specific Aims

Geriatric depression is often accompanied by cognitive impairment that improves, but is rarely eliminated, during periods of remission (Murphy & Alexopoulos, 2004). The persistence of cognitive impairment suggests that geriatric depression occurs in the context of dysfunction of brain networks associated with cognitive function. The causes of impairment of these networks are heterogeneous and include pronounced age-related changes, vascular, inflammatory, and neurodegenerative processes. Impaired functioning of the cognitive control network in particular has been implicated in the pathophysiology of depression. Deficits in cognitive control are consistently found in samples with depression (Butters et al., 2004; Elderkin-Thompson et al., 2003; Lockwood, Alexopoulos, & van Gorp, 2002). Geriatric depression lends itself to the study of dysfunction in cognitive control processes, due to: the variability in cognitive functioning introduced by the aging process; the relative stability of cognitive control impairments in late life depression; and the influence of aging on brain structures critical for cognitive control. However, the processes underlying cognitive control in geriatric depression have not been fully examined.

Cognitive control is an aspect of executive functioning necessary for individuals to carry out goal-directed behavior. Specifically, cognitive control functions by making the appropriate adjustments in perceptual selection, response bias, and in the maintenance of contextual information, so that individuals can adapt to changing environmental demands (Botvinick, Braver, Barch, Carter, & Cohen, 2001). Successful cognitive control

requires focused attention to relevant stimuli and inhibition of irrelevant stimuli (Hertel, 2004).

Conflict arises when relevant and irrelevant information is simultaneously presented and is processed in parallel. The irrelevant information causes cognitive conflict, and interferes with goal- directed behavior. Conflict may also arise when an internal representation of the correct response to a stimulus does not match an actual response (Botvinick et al., 2001; Carter & van Veen, 2007). Conflict processes include both the detection and the resolution of conflict. Furthermore, conflict may be detected initially at the stimulus perception level, or subsequently at the response preparation level. Subsequent to detection, conflict at each of these levels must be resolved through either cognitive inhibition (at the stimulus perception level), or by motor response inhibition (at the response preparation level), in order for appropriate goal-directed behavior to be carried out (Mansouri, Tanaka, & Buckley, 2009).

Dysfunction of cognitive inhibition may be especially relevant to the behavioral manifestations of late life depression (Beats, Sahakian, & Levy, 1996; Elliott et al., 1996; Murphy, Michael, Robbins, & Sahakian, 2003). For example, aging related impairment of cognitive inhibition (R. West, 2004) is often exacerbated in patients with late-life depression (Lockwood et al., 2002). Failure of cognitive inhibition is closely related to salient aspects of depressive symptomatology (e.g., rumination) (Joormann & Gotlib, 2010), and is associated with poor outcomes in elderly depressed individuals (C. F. Murphy et al., 2007; Sneed et al., 2007).

Cognitive symptoms of depression are associated with abnormalities in brain networks critical for conflict detection and resolution. Within these networks, the anterior

cingulate cortex (ACC) and the dorsolateral prefrontal cortex (DLPFC) are particularly relevant structures. The dorsal ACC (dACC) has been implicated in the control of cognitive function, while the rostral ACC has been implicated in regulation emotional function (Bush, Luu, & Posner, 2000). Reduced activation and hypometabolism of the dACC has found in several studies of depression, suggesting that the dACC may have an overlapping role (Alexopoulos, Gunning-Dixon, Latoussakis, Kanellopoulos, & Murphy, 2008; Ochsner & Gross, 2005) in cognitive and affective function. The DLPFC has also been found to be hypoactive in functional and metabolic studies of depressed individuals (Baxter et al., 1989; Drevets, 2000b). However, the poor temporal resolution of structural and functional imaging methods is unsuitable for examining conflict detection and resolution processes which often occur within milliseconds.

Event Related Potential (ERP) waveforms elicited utilizing high conflict paradigms can elucidate the functional neuroanatomy of conflict processing both within aging and in mood disorders. ERPs provide information about neural changes and behavioral actions in response to discrete stimuli with high temporal accuracy (Luck, 2005), an attribute which allows for examination of rapidly occurring cognitive processes. Moreover, ERP waveforms are believed to be indicators of the functional integrity of the underlying brain structures that generate them. Consequently, research utilizing ERP methodology in geriatric depression can provide insight into the functional integrity of brain structures integral to conflict processes. Furthermore, use of ERP methodology can elucidate how disruption of conflict-control processes may produce some of the cognitive and mood symptoms often observed in late-life depression.

In summary, 1) changes in cognitive control and in the function of brain structures that underlie cognitive control have been found in aging and depression; 2) ERP methodology is ideal for the study of cognitive control processes, due to its high temporal resolution and to the empirical identification of waveforms (i.e., N2) sensitive to high conflict tasks and which engage cognitive control; 3) geriatric depression lends itself to the study of cognitive control processes because it is a disorder in which compounding vulnerabilities from the influence of both aging and depression may a) impact the structure and function of neural substrates of conflict processing; and b) lead to measureable behavioral manifestations of cognitive control (e.g., poor cognitive inhibition, rumination).

This study aims to examine conflict processing at the initial level of stimulus conflict detection. This specific aspect of conflict processing was selected due to literature suggesting a bias towards detection of negative environmental information in depressed individuals (Broomfield, Davies, MacMahon, Ali, & Cross, 2007; Gotlib, Krasnoperova, Yue, & Joormann, 2004; Joormann & Gotlib, 2006). Inadequate suppression of negative yet irrelevant information at the initial perceptual processing level may be related to the pathophysiology of depression and to antidepressant treatment outcomes in depression (Fales et al., 2009; Fales et al., 2008).

Attention to deficits of cognitive inhibition processes in geriatric depression is therefore important because poor cognitive inhibition may be related to poor treatment outcomes in older adults (Murphy et al., 2007; Sneed et al., 2007) particularly when they are treated with antidepressants (Sneed et al., 2010). Characterization of the neural substrates of cognitive inhibition deficits in older adults with depression may define a

subgroup with distinct depression etiologies (e.g., vascular depression subtype)(Alexopoulos, Meyers, Young, Campbell et al., 1997; Alexopoulos, Meyers, Young, Kakuma et al., 1997; Sneed et al., 2010; Sneed et al., 2007), which may respond to unique therapies.

Furthermore, evidence of impairment in a functional marker of conflict processing (N2) in depression may help in identify mechanisms of depression. Associations between this functional marker and specific tests of executive function may help to better characterize executive dysfunction in the context of late life depression.

Depressed and non-depressed participants underwent an electrophysiological recording while completing a computerized Stroop task. An ERP component generated by the ACC (Van Veen & Carter, 2002b) and associated with conflict detection at the perceptual level, the "anterior N2," was the focus of this investigation (Folstein & Van Petten, 2008; Luck, 2005). The N2 represents the earliest electrophysiological waveform related to conflict detection preceding cognitive inhibition (Van Veen & Carter, 2002b).

The current study evaluated the following hypotheses: H1. Depressed medication-free older adults will have altered N2 amplitudes when compared to non-depressed older subjects during high interference trials of a cognitive control task; H2. Aberrant N2 amplitude in patients with geriatric depression relative to non-depressed comparison subjects will be related to poorer performance on neuropsychological tests of executive function.

Beyond characterizing neural processes associated with poor cognitive control in geriatric depression, this study may be the basis for further research leading to treatment development. For example, if a subgroup of depressed elders with processing

abnormalities is identified by the study they may be targeted with treatments influencing neurotransmitters that participate in the regulation of frontolimbic pathways. Furthermore, psychosocial interventions aimed at reducing depression by addressing poor cognitive control, can aim to address both cognitive and affective symptoms of depression.

Conflict Processing: A closer look

According to the conflict monitoring hypothesis (Botvinick et al., 2001; Carter & van Veen, 2007) when the brain detects conflicting stimuli it recruits cognitive control to resolve the conflict and to facilitate adaptive behavior. Within this framework, conflict processes are defined as those processes that encompass both the detection of conflict and its resolution through upregulation of cognitive control. Subsequent to conflict detection, cognitive control systems are engaged to upregulate attention to task-relevant information, while inhibiting processing of task-irrelevant information (Botvinick et al., 2001; Botvinick, Cohen, & Carter, 2004; van Veen & Carter, 2002a, 2006). The relationship between conflict detection processes and cognitive control has been termed the "Conflict-Control Loop" (Carter & van Veen, 2007).

Conceptually, conflict processing is necessary for successful inhibition to occur. Conflict may arise at two levels of processing according to the conflict monitoring hypothesis: 1) the stimulus or sensory level when two sensory features (task-relevant vs. task-irrelevant) are processed or 2) at the response level when two behavioral responses (correct vs. incorrect representation of a response) compete to gain control over behavior. Therefore successful suppression of task-irrelevant stimulus features requires cognitive

inhibition, whereas the suppression of an improper motor response requires response inhibition.

If cognitive inhibition and response inhibition fail, an error occurs (Figure 1; adapted from (Mansouri et al., 2009). In the case of an error commission, conflict processing is engaged in subsequent trials to further up-regulate cognitive control towards future goal directed responses (Carter & van Veen, 2007).

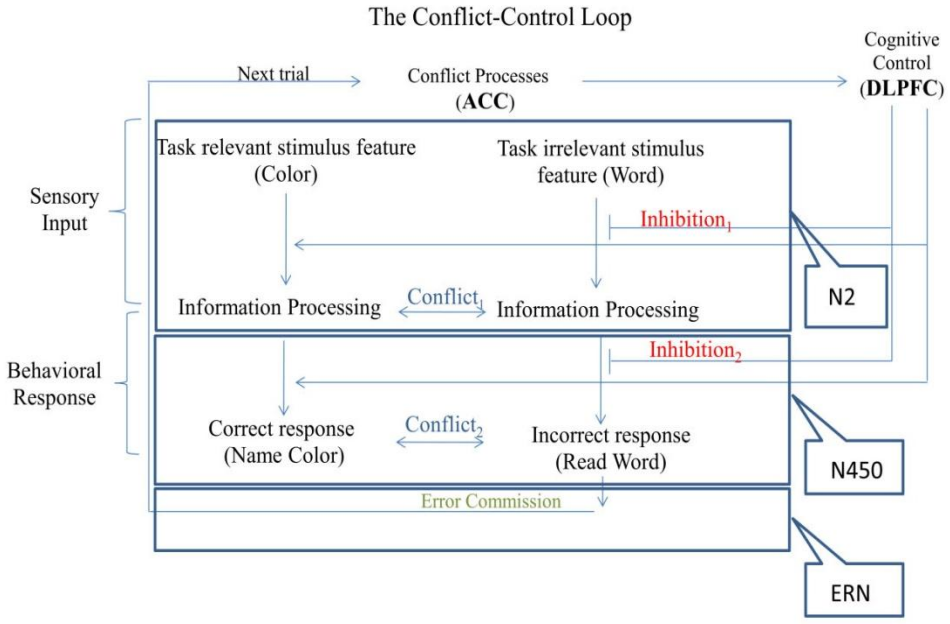


Figure 1: Conflict processes as proposed by conflict-monitoring theory (Botvinick et al, 2001, Carter et al, 2007) using the Stroop Color Word Interference Task (Stroop CW; Golden,1978) as an example. In the Stroop CW Interference condition, subjects are presented with color words (e.g., RED, GREEN, BLUE), printed in incongruent color ink (e.g., RED, GREEN, BLUE) and asked to name the color of the ink. Conflict arises when subjects have to ignore the task irrelevant response (reading the word) in order to produce the task relevant response (name the color). Conflict is detected when task relevant (ink color) and task irrelevant (word) information is received. Conflict related information (ink color vs. word) is conveyed to areas responsible for cognitive control which then adjust the level of cognitive control accordingly. Implementation of cognitive control may occur at two stages: when two sensory stimuli are perceived to be conflictual (ink color vs. word), or when two behavioral responses compete (correct response: name ink color vs. incorrect response: read word). In either situation, cognitive inhibition is necessary to achieve a correct response. If cognitive inhibition fails, and error commission occurs, conflict processing is upregulated in subsequent trials to increase cognitive control. The anterior cingulate cortex (ACC) is thought to be involved in conflict processing during cognitive inhibition and error commission. The ACC therefore is thought to be a conflict monitor that identifies interference between task irrelevant and task relevant information or between correct and incorrect response tendencies. The ACC is then thought to signal the DLPFC of the need for recruitment of cognitive control in order to improving subsequent performance by suppressing irrelevant task information or incorrect response tendencies (Botvinick et al,

2001, Carter et al, 2007). The N2 event related potential (ERP) waveform component is a negative deflection elicited by interference tasks and associated with conflict detection, at the sensory input stage. The N450 is a negative deflection that occurs following the presentation of an incongruent trial. This component is thought to index the detection of conflict at the behavioral response preparation stage. The ERN is a negative deflection that occurs after an error commission. This component is thought to index error monitoring.

Evidence for impairments of both cognitive inhibition and response inhibition exists in mixed-age depression (Compton et al., 2008; Feil, Razani, Boone, & Lesser, 2003; Gohier et al., 2009; Holmes & Pizzagalli, 2008; Nakano et al., 2008; Porter, Gallagher, Thompson, & Young, 2003) and in late life depression (Broomfield et al., 2007; Kindermann, Kalayam, Brown, Burdick, & Alexopoulos, 2000; C. Murphy et al., 2007; Pisljar, Pirtosek, Repovs, & Grgic, 2008; Sneed et al., 2007).

Failure of cognitive inhibition has been linked to emotional processing dysfunction in depression (Broomfield et al., 2007; Fales et al., 2008; Gotlib et al., 2004; Joormann & Gotlib, 2006). Inability to properly inhibit irrelevant negative environmental information results in a "negativity bias" among depressed individuals whereby negative cues become more salient and neutral environmental cues are interpreted as negative (Dai & Feng, 2011; Watters & Williams, 2011). Inadequate cognitive suppression of negative irrelevant information may be related to the pathophysiology and treatment of depression (Fales et al., 2009; Fales et al., 2008). The mechanism by which cognitive inhibition failure occurs in geriatric depression is of primary interest in the current investigation, as conflict processes within this illness have not been fully examined.

Inhibition Paradigms

Several cognitive paradigms have been developed and empirically tested to elicit, engage, and evaluate conflict processes in cognitive and response inhibition. Most frequently these paradigms require the participant to inhibit relatively automatic, but task-

inappropriate responses. Examples of such paradigms include the Stroop Color Word Interference Test, the Flanker task and the Go/No-Go task. Each of these paradigms is briefly described.

Stroop Color Word Interference Test

An adaptation of the classic Stroop Color Word Interference Test (Golden, 1978) consists of 3 words (green, red, blue) printed in 1 of 3 different colors of ink (green, red, blue). Trials of this task are either congruent (e.g., the word GREEN, printed in green ink), or incongruent (e.g., the word GREEN, printed in red ink). Participants are asked to respond as quickly and accurately as possible to the ink color. The incongruent condition is presented less frequently than the congruent condition. Incongruent trials elicit conflict between reading the word (task-irrelevant response) and naming the color ink (task-relevant response). The task-irrelevant response (reading the word) is imbedded in the stimulus, and must be cognitively overridden to achieve the task-relevant response (naming the ink color). Although a motor response is required for this task, it is not specifically designed to elicit motor response inhibition.

Flanker Task

In a typical Flanker paradigm (Eriksen & Eriksen, 1974), subjects are presented with rows of letters and instructed to respond to the middle letter (target). Flanker letters (non-targets) are presented on either side of the target letter; subjects are instructed to ignore these letters. Target letters are assigned to one of two response keys. In congruent trials, flanker letters are the same as the target letter (e.g., HHHHH) in incongruent trials flanker letters are not the same as the target letter (e.g., SSHSS). Incongruent trials elicit conflict between responding to the flanker letter (task-irrelevant response) and

responding to the target letter (task-relevant response). The task-irrelevant response (responding to the non-target letters) is not embedded in the stimulus but still must be overridden to achieve the task-relevant response (responding to the central target letter).

Go/no-go Task

In the Go/No-go paradigm (Aron, 2007; Dillon & Pizzagalli, 2007), subjects are asked to respond to a target letter (e.g., X), and withhold responses to a non-target letter (e.g., Y). The non-target letters appear less frequently. Due to the frequency of Go trials, participants tend to prepare the target response to each stimulus (pre-potent response), and activate that response during each trial, including No-go trials. In No-go trials, there is conflict between the pre-potent but now incorrect response (Go) and the correct response (No-go). Error commission occurs when a participant fails to withhold a response. Notably, this task requires active inhibition of a motor response.

Erroneous responding during high cognitive interference trials may occur due to insufficient cognitive inhibition which results in responding to the task-irrelevant stimulus (e.g., in the Stroop task, responding to the word rather than the ink color; in the Flanker task, responding to the flankers and not the central letter), or failing to withhold a response (e.g., pressing the button in a No-go trial of the Go/No-go task).

Conflict Processing: ERP studies

Prior studies investigating the Stroop task and related tasks have described two ERP components, the N2 and N450, which appear to be related to cognitive inhibition (Figure 1). The N2 is a negative fronto-central deflection typically found between 200ms and 350ms of stimulus presentation. During high cognitive interference trials (e.g., incongruent rather than congruent trials) the N2 amplitude is typically greater (Gehring,

Gratton, Coles, & Donchin, 1992; Kopp, Mattler, Goertz, & Rist, 1996; Kopp, Rist, & Mattler, 1996). The N2 has been associated with conflict detection in the Stroop, Flanker and Go/No-go paradigms, and is believed to be related to the sensory processing stage (Van Veen & Carter, 2002b) of conflict processing, although some controversy exists (R. West, Jakubek, Wymbs, Perry, & Moore, 2005; R. West, Krompinger, Bowry, & Doll, 2004). The N450 component is a negative deflection beginning approximately 400 milliseconds following the presentation of an incongruent trial. This component has been consistently linked to the Stroop Interference effect in particular and is thought to index the detection of conflict at the response preparation stage (Hanslmayr et al., 2008; R. West, 2003; R. West et al., 2005). The anterior cingulate cortex has been identified as the potential generator of both the N2 (Van Veen & Carter, 2002b) and the N450 (R. West & Alain, 2000b).

Neural Networks Underlying the Conflict-Control Loop

The cerebral network thought to be responsible for conflict processing includes the anterior cingulate cortex (ACC) and the dorsolateral prefrontal cortex (DLPFC). These two structures are the hypothesized neural substrates of the conflict-control loop (Figure 1). The dorsal portion of the ACC (dACC) (Ridderinkhof, Ullsperger, Crone, & Nieuwenhuis, 2004) is thought to detect conflict between competing, simultaneously active representations. Subsequently, the dACC engages the DLPFC (Friedman, Nessler, Johnson, Ritter, & Bersick, 2008; van Veen & Carter, 2006), which reduces or resolves such conflict by selectively orienting attention towards task-relevant information and facilitating engagement of appropriate sensory cortices towards goal attainment (Carter & van Veen, 2007).

The dACC and DLPFC were identified as central to conflict-control processes based on neuroimaging evidence. Activation of the dACC was found during information processing conflicts on various versions of the Stroop, Flanker, and Go/No-go tasks (Botvinick et al., 2001; Botvinick et al., 2004; Ridderinkhof et al., 2004). The DLPFC has been implicated in the allocation of top-down attention to task-relevant stimuli and in inhibition of task-irrelevant stimuli features so that behavioral goals can be carried out (Botvinick et al., 2001; Botvinick et al., 2004; Carter & van Veen, 2007; Kerns et al., 2004; Mansouri et al., 2009). Furthermore, some ERP studies report functional coupling in the activation of ACC and prefrontal cortex (PFC) regions during cognitive inhibition (Hanslmayr et al., 2008; Markela-Lerenc et al., 2004).

Additional support for the role of the dACC and DLPFC in the conflict-control loop also comes from neuroimaging studies. Greater ACC activation has been observed on incongruent compared to congruent Stroop trials (Hanslmayr et al., 2008; MacDonald, Cohen, Stenger, & Carter, 2000); on conflict trials of the Flanker task (Botvinick, Nystrom, Fissell, Carter, & Cohen, 1999; Bunge, Hazeltine, Scanlon, Rosen, & Gabrieli, 2002; Durston et al., 2003); and on No-go trials of the Go/no-go task (Braver, Barch, Gray, Molfese, & Snyder, 2001; de Zubicaray, Andrew, Zelaya, Williams, & Dumanoir, 2000; Durston, Thomas, Worden, Yang, & Casey, 2002). Furthermore, dipole source modeling of ERP components believed to be related to conflict processing (N2, N450) were generated by the ACC, the conflict detector within this framework (Carter & van Veen, 2007; Van Veen & Carter, 2002b; Yeung, Botvinick, & Cohen, 2004). Increased interference was linked to increased activity in both the lateral PFC and the ACC during a Stroop task (Roberts & Hall, 2008). Specifically, DLPFC activation was observed

(Kerns et al., 2004) following high conflict trials in which ACC activation was demonstrated. In sum, this research provides evidence that the dACC plays a role in detecting conflict, and then conveying conflict related information to the DLPFC, which up-regulates attention to task-relevant responses thereby improving task performance (Figure 1).

Conflict-Control Processes in Aging

Advancing age is characterized by behavioral and neural manifestations of changes to the cognitive control network. Studies of neuropsychological function in aging indicate that older adults experience greater difficulty than younger adults in performing tasks requiring cognitive control (Hedden & Gabrieli, 2004; Treitz, Heyder, & Daum, 2007; R. L. West, 1996). Cognitive control functions show early declines with age (Mittenberg, Seidenberg, O'Leary, & DiGiulio, 1989) relative to other neuropsychological functions, and older adults perform poorly on tasks that necessitate conflict resolution (Andres, Guerrini, Phillips, & Perfect, 2008; Cohn, Dustman, & Bradford, 1984; Waszak, Li, & Hommel, ; West & Alain, 2000a; West & Baylis, 1998) relative to their younger counterparts.

Cognitive Inhibition in Aging

Theories of cognitive aging suggest that older adults may have intact attentional mechanisms relative to younger adults, but less efficient inhibition of irrelevant information (Hasher, Stoltzfus, Zacks, & Rypma, 1991; Hasher & Zacks, 1988). Several reasons for this inefficiency have been proposed, including a failure of executive control over inhibition of irrelevant information, resulting in an inability to suppress this information from working memory (Andres et al., 2008). Another possible explanation is

that inhibitory deficits may arise due to abnormal detection of a need to implement additional inhibitory control in service of goal attainment. In either case, a consequence of deficient inhibition may include increased availability of distracters and therefore, greater interference effects. Indeed, empirical investigations indicate that healthy older adults exhibit greater interference effects when compared to younger adults on the color-word interference trial of the Stroop task (e.g., older adults are more susceptible to reading the word rather than naming the color) (Treitz et al., 2007; R. West, 1999).

The decline in inhibition processing observed in aging may be related to structural and functional abnormalities in aspects of the conflict-control network. For instance, under-recruitment of the PFC during high conflict tasks has been found in normal aging relative to younger adults (Milham et al., 2002; Schulte et al., 2011), absent performance differences. Additionally, under-recruitment of the dACC in older relative to younger adults has been demonstrated in studies of conflict processing examining the N2 and N450 responses (West & Alain, 2000a; West et al., 2004). Furthermore, the N2 response declines with age, and the N2 latency is delayed in older relative to younger adults (Falkenstein, Hoormann, & Hohnsbein, 2001; Mager et al., 2007). The attenuation of response within the DLPFC and dACC suggests dysfunction in neural processing within structures of the conflict-control loop in aging.

Notably, commensurate task accuracy between young and older adults in the context of neural activation differences may reflect a shift towards compensatory processing mechanisms in aging (Paxton, Barch, Racine, & Braver, 2008). For instance, under-activation of LPFC in aging may be related to implementation of an accurate but less efficient strategy that depends more on attentional processes (Paxton et al., 2008).

Reports of activation in alternative networks relative to younger adults support the claim that attentional rather than conflict-resolution processes compensate for poor neural recruitment (Cabeza, Anderson, Locantore, & McIntosh, 2002; DiGirolamo et al., 2001). Therefore, differential activation of structures within the conflict-control loop in aging, absent performance differences, may be related to compensatory neural mechanisms that may result in accurate but neurally distinct performance than is observed in younger adults.

Cognitive Control and Depression: Focus on Late-life

A prominent feature of depression is difficulty focusing on goal-directed behavior while ignoring irrelevant stimuli and thoughts. Cognitive control is crucial for the successful cognitive inhibition of irrelevant thoughts, and therefore dysfunction of conflict-control processes may be relevant to the pathophysiology of depression.

Cognitive Inhibition in Depression

Patients with depression perform poorly relative to non-depressed comparison subjects on tasks engaging cognitive control and particularly, cognitive inhibition (Goeleven, De Raedt, Baert, & Koster, 2006; Gotlib et al., 2004; Joormann, Nee, Berman, Jonides, & Gotlib, 2010; Rogers et al., 2004). Greater interference effects on the Stroop task are frequently found in depressed patients when compared to healthy controls (Lemelin, Baruch, Vincent, Everett, & Vincent, 1997; Moritz et al., 2004; Ravnkilde et al., 2002). Depressed patients may not be more likely to commit errors in behavioral tasks recruiting cognitive inhibition (Elliott et al., 1996); however they display behavioral impairments in trials following error commission (Elliott et al., 1996).

There may be an association between poor cognitive inhibition and clinical symptoms of depression. Deficits in cognitive inhibition may be associated with the tendency of depressed individuals to ruminate, or engage in uncontrollable thinking about the causes and consequences of depressive symptoms (Nolen-Hoeksema, 1991; Nolen-Hoeksema, Wisco, & Lyubomirsky, 2008; Vanderhasselt & De Raedt, 2009). Increased interference effects during a high conflict task were strongly correlated to rumination, and reduced inhibition of negative material among depressed participants was associated with greater rumination (Levens, Muhtadie, & Gotlib, 2009).

Older depressed adults have even greater deficits in cognitive control than young adults with depression (Gualtieri & Johnson, 2008; Lockwood et al., 2002). Among elderly depressed subjects, deficits in cognitive inhibition have been found across several studies (Elderkin-Thompson et al., 2003; Fallgatter et al., 2004; Lockwood et al., 2002; Pisljar et al., 2008). Depressed older adults suffer performance decrements in interference trials of the Stroop Color Word Test (Pisljar et al., 2008), and on certain versions of the Go/No-go and Flanker tasks relative to non-depressed elderly controls (Katz et al., 2010).

Cognitive impairment in late life depression may represent trait and not state abnormalities. Observations from acute treatment trials (Butters et al., 2000; Nebes et al., 2001) and from longer-term follow-up of depressed elders receiving uncontrolled treatment (Murphy & Alexopoulos, 2004) suggest persistent, although milder, cognitive control impairments even after depressive symptoms subside. Further, deficits in cognitive inhibition processes may be related to poor treatment outcomes in older adults (Sneed et al., 2007) particularly when treated with pharmacotherapy (Sneed et al., 2010). Furthermore, geriatric depression with prominent cognitive control deficits may represent

a recently validated depression subtype with vascular etiology (Alexopoulos, Meyers, Young, Campbell et al., 1997; Krishnan, Hays, & Blazer, 1997; Sneed, Rindskopf, Steffens, Krishnan, & Roose, 2008).

Functional and Structural anomalies of the Conflict-Control Loop in Depression

Depression may be associated with dysfunction of frontolimbic brain structures. Among these structures, the dACC and DLPFC have also been linked to cognitive impairment (Drevets, 2000a, 2000b, 2001). Neuroimaging studies provide evidence of structural and functional anomalies of the dACC in young adults (Drevets, 2000b; Rogers et al., 2004) as well as in older adults (Alexopoulos et al., 2008; Murphy et al., 2007) with depression. Hypoactivity of the DLPFC in major depression has been found in younger as well as older adults performing cognitive control tasks (Elliott et al., 1996; Siegle, Thompson, Carter, Steinhauer, & Thase, 2007). Further, hypoactivation of the dACC, and reduced functional coupling of the dACC and DLPFC have been reported in geriatric depression (Aizenstein et al., 2009). Taken together, these findings suggest that the very structures that comprise integral aspects of the conflict-control loop are hypoactive in depressed individuals.

Processing Dysfunction of the Conflict-Control Loop in Depression

Although structural and functional investigations have reported dysfunction in the conflict-control network in depression, the temporal resolution of these methods does not allow for dissociation of the specific aspects of conflict processing. Therefore, although we have answered the "where?", we have yet to clarify the "how?" of conflict processing dysfunction.

Abnormalities in conflict processes and specifically conflict detection, as reflected by the N2 and N450 components, have been found in depressed relative to non-depressed individuals. Relatively few studies examining conflict processes utilizing ERP methodology have been conducted in geriatric depression. Furthermore, the majority of studies to date have focused on conflict processes related to response inhibition, rather than cognitive inhibition.

Electrophysiological studies of cognitive inhibition thus far are equivocal. In young adults, studies have found larger and smaller amplitudes of conflict process components, or no differences between depressed and non-depressed subjects. In one study utilizing the Stroop paradigm, depressed subjects exhibited a larger Stroop interference effect and reduced N2 amplitudes relative to healthy controls in incongruent compared to congruent trials (Holmes & Pizzagalli, 2008). Furthermore, in the same study, depressed subjects with stronger dACC recruitment did not differ from controls in interference effects, indicating that increased engagement of the dACC may reduce competition among different response options and facilitate cognitive inhibition. In one study, no differences were observed in N2 amplitude during No-go trials in depressed relative to non-depressed subjects. This study used a combined Flanker Go/No-go task where subjects had to press a key to a central target letter flanked by distracter letters, and suppress that response when presented with a central non-target letter (Ruchsow et al., 2008). The added complexity of stimulus discrimination in this task may have involved recruitment of other sensory processes, making conclusions about the meaning of the N2 in this task unclear. In another study, the N450 in remitted depressed patients was

significantly reduced relative to healthy controls, and was related to number of prior depressive episodes (Vanderhasselt & De Raedt, 2009).

In late life depression, two studies have examined differences in the N2 amplitudes between depressed and healthy participants. Both of these studies utilized the Go/No-go task. Larger N2 in depressed relative to non-depressed older adults was observed during No-go trials, when response inhibition was implemented (Zhang, Zhao, & Xu, 2007). Severity of depression in the patient group was also significantly correlated to the N2 component. The authors suggested that depressed elderly patients over-recruit ACC function to bolster response inhibition during conflict trials relative to healthy comparison subjects. The second study examined the difference in N2 between Go and No-go trials in a small sample of elderly depressed and healthy control subjects. The authors reported that the N2 effect (difference between Go and No-Go in N2 amplitude), was attenuated in depressed subjects. Furthermore, the depressed subjects had greater commission errors, suggesting that that reduced motor response inhibition is related to a smaller N2 effect these subjects.

With the exception of one study (Holmes & Pizzagalli, 2008), most of the ERP studies in examining conflict processing in depression have utilized a version of the Go/No-go task, thus limiting conclusions regarding conflict processes to this paradigm. The present study utilized a Stroop task in order to examine conflict processing at the cognitive inhibition level.

Summary

Structures that underlie the conflict-control loop are functionally impaired in aging and in depression. Although fMRI studies have provided some evidence of

abnormal processing within the conflict-control loop in older depressed adults, the poor temporal resolution of this method makes it less than ideal for investigating rapidly changing neural responses to stimuli. Studies utilizing ERP methodology, a more temporally precise alternative, reveal that there is a burgeoning area of empirical research beginning to outline the role of the conflict-control system in an important and prevalent psychopathology: Major depressive disorder. Geriatric depression lends itself to the study of cognitive control processes for several reasons, including the influence of depression and advancing age on brain structures implicated in conflict-control processes.

However, very few studies have yet examined conflict-control processes in this population. Furthermore, the few existing studies focused on conflict processing related to response inhibition, rather than to cognitive inhibition. The present study aims to characterize conflict processes related to cognitive inhibition in late life depression and in normal aging. Differences in conflict processing between these groups will be examined by evaluating the N2 waveform elicited by a computerized Stroop Color Word paradigm. Furthermore, the functional significance of the N2 will be evaluated by examining its relationship to neuropsychological measures of cognitive control. Identification of an association between N2 dysfunction and depression in late life may provide evidence that will help in clarifying the mechanisms of depression in this cohort. Further, associations between the N2 and specific measures of executive function may help characterize cognitive symptoms of depression, related to conflict-control processing.

Methods

Participants

Participants were 75 individuals recruited from the Westchester, NY community as part of a larger treatment study. All individuals were right-handed (Chapman & Chapman, 1987) and were sixty years of age or older. Subjects provided written informed consent to a research protocol approved by the Weill Cornell Medical College Institutional Review Board (IRB). The data obtained from this experiment for was approved for analysis for the current study by the City University of New York Graduate School IRB.

Patients with depression were included if they had unipolar, non-psychotic depression without dementia or mild cognitive impairment. Inclusion criteria for depressed subjects included 1) Age >60 years old, 2) Unipolar Major Depression by DSM-IV criteria, as established by the Structured Clinical Interview for DSM-IV, Patient Edition (SCID-P; First, 2002), 3) At least mild severity of depression (Hamilton Depression Rating Scale-24 items score $\geq$ 17). Exclusion criteria for depressed subjects included: 1) Psychotic Depression by DSM-IV criteria, 2) High suicide risk, 3) Presence of any other Axis I disorder or substance abuse, 4) Axis II diagnosis of antisocial personality, 5) History of psychiatric disorders other than unipolar major depression or generalized anxiety disorder or electroconvulsive treatment, 6) Dementia, 7) Medical or neurological illness, 8) Inability to perform any ADLs even with assistance, 9) Inability to speak English,10) Aphasia, 11) corrected visual acuity <20/70 or color blindness.

Seven participants (3 depressed, 4 non-depressed) were excluded due to poor quality of EEG recording. The final sample consisted of 44 depressed subjects (ranging in

age from 62 - 92 years old) with unipolar, non-psychotic major depression without dementia or mild cognitive impairment and 24 non-depressed comparison subjects within the same age range (61-85 years old).

Procedure

Upon study entry, subjects participated in an ERP session during which behavioral task data and EEG recordings were obtained. A corresponding baseline clinical assessment was conducted on the same date which included collection of affective and neuropsychological data. All participants in the depressed group were determined to have an HDRS-24 total score of ≥17 within a week of the EEG recording session. In order to ensure that depressed subjects were antidepressant-free at the time of the ERP recording, they underwent a 2-week placebo wash out period and were re-assessed for depression severity at the end of that period. Those that continued to meet the depression severity eligibility criterion (Hamilton Depression Rating Scale-24 items score ≥ 17) after the placebo phase underwent ERP recording. Participants were compensated 45$ for the EEG administration, and 50$ for the baseline assessment battery. ERP recording and clinical research assessments occurred at the Electrophysiology Laboratory of Weill-Cornell Medical College Institute of Geriatric Psychiatry.

ERP Recording

The task was presented on a Dell 3.1 Ghz computer using E-prime software (Psychology Software Tools, Inc., Pittsburgh, Pennsylvania) integrated with the EGI GES 200 high-density event-related potential (ERP) system. The system includes the Net Amps 200 high input impedance dense array amplifier that is capable of processing and

digitizing 128 channels at up to 1000 samples per second and the 128-lead HydroCell Geodesic Sensor Net (HCGSN; Electrical Geodesic, Inc. Oregon, WA) which allows for recordings at high impedance levels. Participant responses were collected via a three-button box. The study task was presented in counterbalanced order on a 17-inch LCD screen. Participants were seated two feet from an LCD screen which presented the stimuli and were instructed to remain still and to minimize their eye blinks. Impedances of all channels were maintained below 70 kΩ before recording. All channels were referenced to the Cz lead during recording, digitized at 500 Hz, with a 0.1 to 100 Hz bandwidth filter. Horizontal extra-occular movements were recorded using electrodes to the left and right of each eye. Vertical extra-occular movements were recorded using electrodes above and below the orbital regions of each eye.

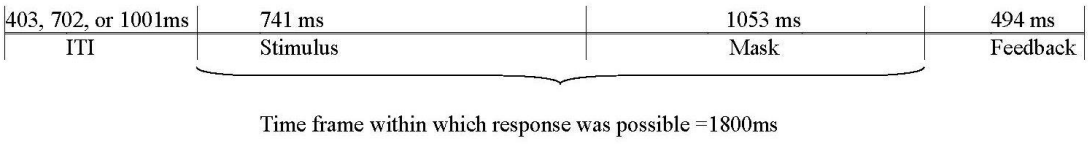
Computerized Stroop Task

A computerized variant of the Stroop Color Word Interference Task consisting of equal numbers of the words RED, BLUE, and GREEN (420 words) printed in one of three different colors of ink (RED, BLUE and GREEN). Trials were either congruent (i.e., the word matched the color of ink) or incongruent.

The subjects were familiarized with the task before recording of EEG in the following manner: Verbal instructions and manual training was provided. A practice session with a total of 87 stimuli was used and included a feedback signal delivered each time subjects made an erroneous response, or failed to generate a response within 1.8 sec from the stimulus. The initial practice block consisted of 50 untimed trials of color words printed in white ink, and the participant was asked to read and respond to the word. This initial trial was meant to familiarize participants with the three button response pad. The

second practice block consisted of 12 untimed incongruent color words and the participants were instructed to respond to the color of ink presented rather than read the word. The final practice block consisted of 25 trials that determined the level of difficulty (Easy, Medium, Difficult) for the rest of the experiment. During the final practice block the stimulus was presented for 741ms followed by a fixation cross for 1053ms and a jittered inter stimulus interval (ITI) of 403, 702, or 1001ms (Figure 2). Participants could respond at any point during stimulus presentation or during the fixation cross. At the conclusion of the practice session, the difficulty level (easy – total stimulus response time=2041ms, medium- total stimulus response time=1800ms, difficult – total stimulus response time=1248ms) of the subsequent experiment was determined by assessing the accuracy and speed of reaction time of each participant to ensure that participants were completing a task that was of adequate difficulty to elicit waveform responses. For each of the difficulty levels in the experiment proper, the Stroop stimulus was presented for 741ms. However, to increase or decrease the difficulty, the time window within which the participant could respond following stimulus presentation was 1300ms in the "easy" condition, 1053ms in the "medium" condition and 507ms in the "difficult" condition. All conditions had the same jittered inter-trial interval (ITI; 403-1001ms). Participants performed six blocks in total separated by a brief rest period. Reaction time and accuracy measures were collected throughout the experiment.

Figure 2. Schematic example of timing of Stroop stimulus presentation during training within the "Medium" difficulty condition.



Feedback was not provided during the experiment proper. The color words were presented in 6 blocks of 70 stimuli per block. In each block, the ratio of color-incongruent (word 'BLUE' displayed in red) to color-congruent (word 'BLUE' in blue) words was approximately 1:1.The range of congruent stimuli per block varied from 37% to 59%, so as to prevent expectancy of incongruent stimuli, as there is some evidence that increased expectancy of conflict may reduce the experience of conflict during the task (Gratton, Coles, & Donchin, 1992). The order of stimulus presentation in each block was randomized for each experiment. Participants were instructed to respond, as quickly and as accurately as possible to the color of the stimulus, and to respond with a key-press on a color-coded keypad corresponding to the color they saw. Prior to the onset of a new block, a reminder screen with the task instructions and the order of the keys to be pressed was presented to the participants.

Clinical Assessment

An initial screening assessment to evaluate depression severity and cognitive status (HDRS, MADRS, MMSE, DRS) was conducted. Following the 2-week placebo lead in period, a longer baseline evaluation was conducted which included a re-evaluation of affective status to ensure that subjects were depressed as ERP administration was conducted during depressed state. Executive function instruments administered at this time-point consisted of the Stroop Color Word Interference Test (Stroop CW), and the Trail Making Test (TMT).The Hopkins Verbal Learning Test- revised (HVLT-R) was administered at this time as well, and was chosen as an instrument in the analysis as a comparator scale for specificity analyses as this is a measure of learning and memory.

Data Reduction

Behavioral Data

Behavioral performance patterns were evaluated to ensure participant adherence to task instructions. Outlier response trials, defined as responses that occur less than 100ms after stimulus presentation or that have a reaction time of ≤ or ≥ 3 standard deviations of the mean of correct responses by trial type within each block, were excluded.

Electrophysiological Data

Data were processed using Net Station 5.1 software (EGI, Oregon). Waveform data was re-referenced to an average reference. The ERP data were then bandpass filtered (0.03–30 Hz). Stimulus locked data was then epoched from 100ms before, to 500ms post-stimulus presentation for correct congruent and incongruent response trials to allow for extraction of the N2 waveform. Semiautomatic artifact detection was performed to identify and remove remaining artifacts (within segment absolute amplitude difference, 150 μv). Channels were marked bad if they exceeded this threshold for more than 20 percent of the recording. Bad channels were automatically interpolated from surrounding leads. Segments were marked bad if they contained more than 10 bad channels. Similarly, segments that included outlier trials, eye blinks and eye movement artifacts (threshold 55 μV), signals exceeding 140 μV were excluded. ERPs to correct responses were computed for incongruent and congruent trials. A baseline derived from the 100ms prior to response was calculated and subtracted from each channel. Artifact free segments from each subject were averaged for the correct congruent and incongruent stimulus response type for each subject. A minimum of 30 artifact-free segments were required for individual

average waveforms. Grand mean ERP waveforms were calculated by averaging ERPs across conditions and groups. The mean number of segments available for the ERP analysis did not statistically differ between patients with depression (Congruent Mean Segments= 137, Standard Deviation=39; Incongruent Mean Segments=125, Standard Deviation=40) and comparison subjects (Congruent Mean Segments=129, Standard Deviation =49; Incongruent Mean Segments=112, Standard Deviation=49).

The ERP analyses focused on the N2 waveform which was obtained by extracting the N2 amplitudes and latencies within 200ms-310ms after stimulus presentation from midline (11, 6, Cz) lead sites. The peak amplitude was obtained across the three lead sites to improve the accuracy of the signal to noise ratio. Selection of this frontocentral lead group was based on the orientation of the dipole source (Luck, 2005) of the theoretical generator of the N2, the ACC (Van Veen & Carter, 2002b). The N2 was quantified as the second peak waveform of lowest amplitude within 310ms after the stimulus presentation of correct response trials.

Latency and amplitude were quantified with Netstation 5.1 software. Minimum peaks were extracted from each lead within the time frame (200-310 ms post-stimulus presentation) where the N2 was expected to appear. The presence of the N2 peak within this timeframe was confirmed by visual inspection for each individual participant as well as for the grand-averaged waveform within each subject group. Finally, the average N2 minimum peak amplitude was obtained by calculating the arithmetic mean of minimum peaks of the midline lead group.

Statistical Analysis

ERP Experiment Reaction Time and Accuracy

Exploratory analyses found no significant differences between groups in ethnicity, education, gender, or age (Table 1). Furthermore, there were no between-group differences in task difficulty level (Table 2) Easy/Medium/Difficult Stroop Task by Group χ^2 =3.5, df=2, p=0.18). These variables were therefore not included in subsequent analyses. For reaction time and accuracy scores, separate repeated analysis of variance (ANOVA) with group (patients with depression vs. comparison subjects) as the between-subject factor and condition (congruent vs. incongruent) as the repeated measure were conducted.

Table 1. Baseline Characteristics of Older Patients with Major Depression and Non-Depressed Older Adults

	Depressed (N=44)		**Non-Depressed (N=24)**	
	Mean	SD	Mean	SD
Gender (F:M)	1.9:1		1.2:1	
Age	72.5	8.0	73.1	6.2
Education	16.4	2.7	16.3	2.3
24-item HDRS Total	24.4	5.7	0.5	0.9
Mini-Mental State Exam Total	28.7	1.4	28.6	0.8
DRS Total	136.4	3.9	137.8	3.8
Trails A	36.3	11.2	33.8	9.4
Trails B	97.0	48.4	95.6	57.0
Trails B-A	60.7	42.7	61.8	52.1
Stroop Interference	-2.9	6.5	-4.0	8.1
Stroop Word	95.8	13.9	90.5	13.9
Stroop Color	63.4	9.7	65.7	10.8
Stroop Color- Word	35.1	7.9	33.9	8.1
HVLT-R Immediate Recall	23.4	5.5	25.6	4.7
HVLT-R Delayed Recall	8.7	2.1	9.7	1.9
Age of Onset of First Depressive Episode	48.3	24.9	-	-

Table 2. Frequency of Tasks Administered by Difficulty Level and Group.

Task Difficulty	Non-Depressed	% of Total	Depressed	% of Total
Easy	2	8.3	5	11.4
Medium	5	20.8	18	40.9
Difficult	17	70.8	21	47.7

χ^2=3.5, df=2, p=0.18

Scalp ERP Waveform Latency

The N2 latency was examined using repeated measures ANOVAs with group (patients with depression vs. non-depressed subjects) as the between subjects factor and condition (congruent vs. incongruent) as the repeated measure. The Bonferroni correction was applied where applicable. Post hoc paired t-tests were performed in case of significant ANOVA findings.

Scalp ERP Waveform Peak Amplitude

The N2 waveform peak amplitude was examined using repeated measures ANOVAs with group (patients with depression vs. comparison subjects) as the between subjects factor and condition (congruent vs. incongruent) as the repeated measure. The Bonferroni correction was applied where applicable. Post hoc paired t-tests were performed in case of significant ANOVA findings.

Tests of Specificity- Analysis of Occipital Lead groups:

In order to examine the specificity of the N2 to the selected sites, a theoretically unrelated generator site, the occipital lobe, was selected. The analyses that were implemented on midline sites were repeated for left (65,66,70,71,72,74,75) and right (77,83,84,85,89,90,91) occipital lobe leads. The minimum negative peak amplitude

during the time window within which the N2 waveform amplitude was expected (200-310ms) was examined using repeated measures ANOVAs with group (patients with depressed vs. comparison subjects) as the between subjects factor and condition (congruent vs. incongruent) as the repeated measure. Separate analyses were run on amplitude for the average of each set of sites (left occipital, right occipital). The Bonferroni correction was applied where applicable. Post hoc paired t-tests were performed in case of significant ANOVA findings.

Relationship of N2 to Neuropsychological Measures

Hierarchical (sequential) multiple regressions were conducted to assess the predictive contribution of N2 peak amplitude, over and above demographic and clinical variables, to measures of neuropsychological functioning. According to the study hypotheses, it was expected that N2 peak amplitude to incongruent stimuli would be related to measures of executive function. In order to ascertain the specificity of any findings, measures not exclusively related to executive functions including processing speed and memory were also included as dependent variables in separate models. Hierarchical multiple regression was chosen due to the cumulative explanatory power of the model as additional sets of predictor variables are entered. In order to investigate the predictors neuropsychological functioning within each subject group, separate regressions were conducted by participant group (depressed vs. non-depressed). These analyses were conducted using the IBM Regression procedure.

Within the hierarchical regression, the neuropsychological measures were used as dependent variables individually. The predictor variables were grouped according to categories at each step of entry into the model. In the initial step clinical and demographic

variables were entered into the model. In the second step, N2 elicited by congruent stimuli was entered, and in the third and final step, N2 elicited by incongruent stimuli was entered last as the last position in a hierarchical regression constitutes the most conservative place for a predictor variable. To reduce the possibility of Type I error due to multiple analyses, $p<0.01$ was applied to test statistical significance at each step of the model.

Demographic variables were defined as age (in years), education (in years), and gender (male, female). Clinical variables included 24-item HDRS total at the time of the EEG recording for non-depressed subjects, whereas the variables of age of onset of first depressive episode (in years), and number of previous depressive episodes were also included for depressed subjects.

Neuropsychological measures included a) Executive function measures of Stroop Color Word Interference and Trails B- Trails A from the TMT. These measures were calculated so as to control for the influence of processing speed on executive function; b) processing speed measures of Trails A from the TMT, and Stroop Color and Word Total Correct score; c) Memory measures of HVLT-R Immediate Recall Total and Delayed Recall Total.

Power Analysis

To ensure that the sample size of the current study was adequate for rejection of the null hypothesis, a power analysis was conducted. With α set at 0.05 and using data from 68 participants, a two level repeated measures within-between interaction ANOVA with a 2 level within variable (congruency), and a 2 level between variable (group), if a small effect (f= 0.1) is expected, power would be 0.71. If a medium effect (f= 0.25) is

expected, power would be 0 .97, which is sufficient to undertake the present analysis. If a large effect size (*f*= 0.4) is expected, statistical power would reach 0.99. Based on this power analysis and review of the literature, in order to have adequate power (0.25) a total of 68 participants would be sufficient for repeated measures within-between interaction ANOVA. A medium to large effect size was expected for this study (Cohen, 1988).

Results

Demographic and clinical characteristics of the sample

Sixty-eight individuals participated in the study. All individuals were right-handed. Of these, 44 subjects (ranging in age from 62 - 92 years old) had unipolar, non-psychotic major depression without dementia or mild cognitive impairment. The remaining 24 subjects were non-depressed individuals within the same age range (61-85 years old). Groups did not differ with respect to ethnicity, sex, age or educational level (Table 1). Depressed subjects reported significantly increased levels of depressive symptoms on the HAMD-24.

ERP Experiment Accuracy and Reaction Time

Higher task accuracy for congruent than for incongruent trials was found across both groups. There was a significant main effect of condition (congruent vs. incongruent, $F_{(1,63)}$=99.43, p=0.000, partial η^2=0.61) due to higher accuracy for congruent (Mean=92.9, Standard Deviation= 5.38) as compared to incongruent (Mean=83.6, Standard Deviation= 7.9) stimuli (Figure 3). There was no main effect of group ($F_{(1,63)}$=0.023, p=0.88) as depressed subjects (Mean=88.3, Standard Deviation=6.4) and comparison subjects (mean=87.9, SD=4.8) did not differ in overall accuracy. Furthermore, the condition x group interaction ($F_{(1,63)}$=0.001, p=0.975) was not statistically significant.

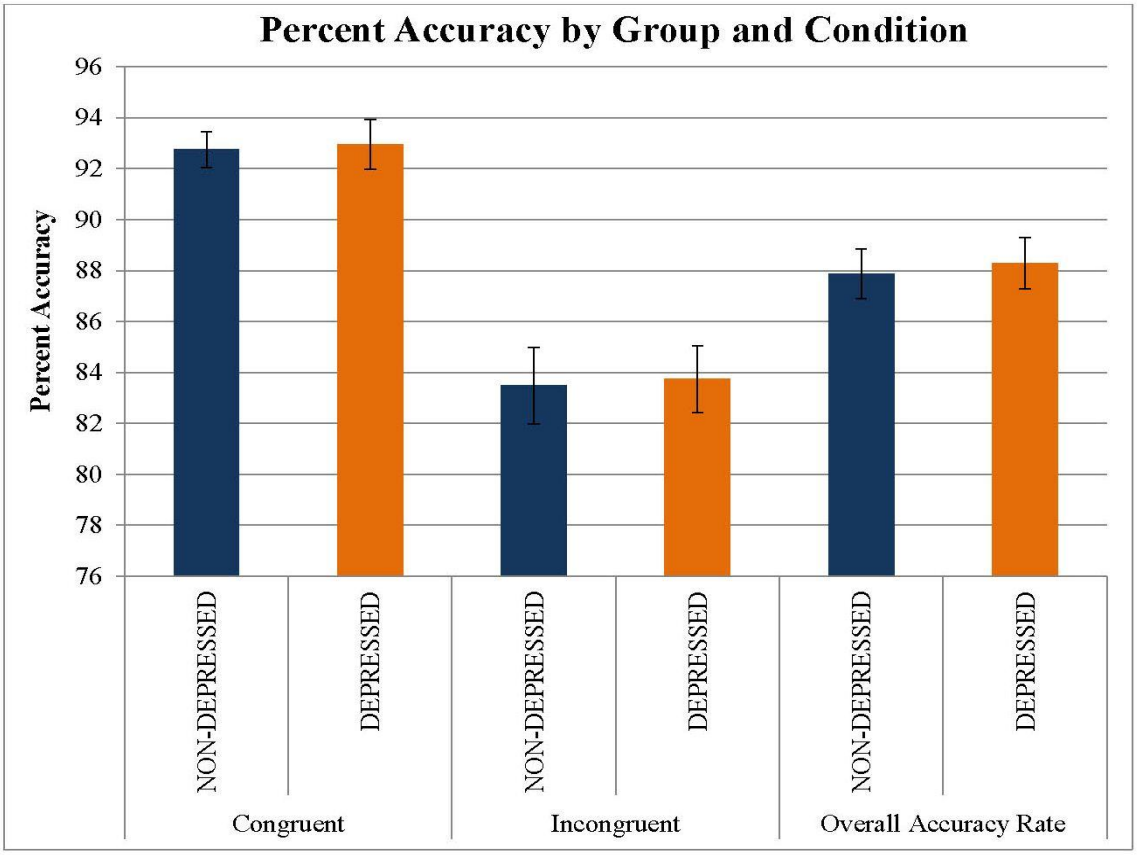


Figure 3. Computerized Stroop Task: Accuracy rate according to group, and congruency condition.

Reaction time was faster for congruent than for incongruent stimuli across both groups. There was a significant main effect of condition (congruent vs. incongruent $F_{(1,63)}$=167.05, p=0.000, partial η^2=0.73) due to a faster mean reaction time for congruent stimuli (Mean=649.6, Standard Deviation =122.22) when compared to incongruent stimuli (Mean=784.6, Standard Deviation=185.0). The main effect of group ($F_{(1,63)}$=0.441, p=0.51) and the condition x group interaction ($F_{(1,63)}$=0.22, p=0.64) were not statistically significant. Depressed subjects (Mean=723.66, Standard Deviation =144.9) did not differ significantly from comparison subjects (Mean=698.66, Standard Deviation =128.4) in overall reaction time to correct trials (Figure 4).

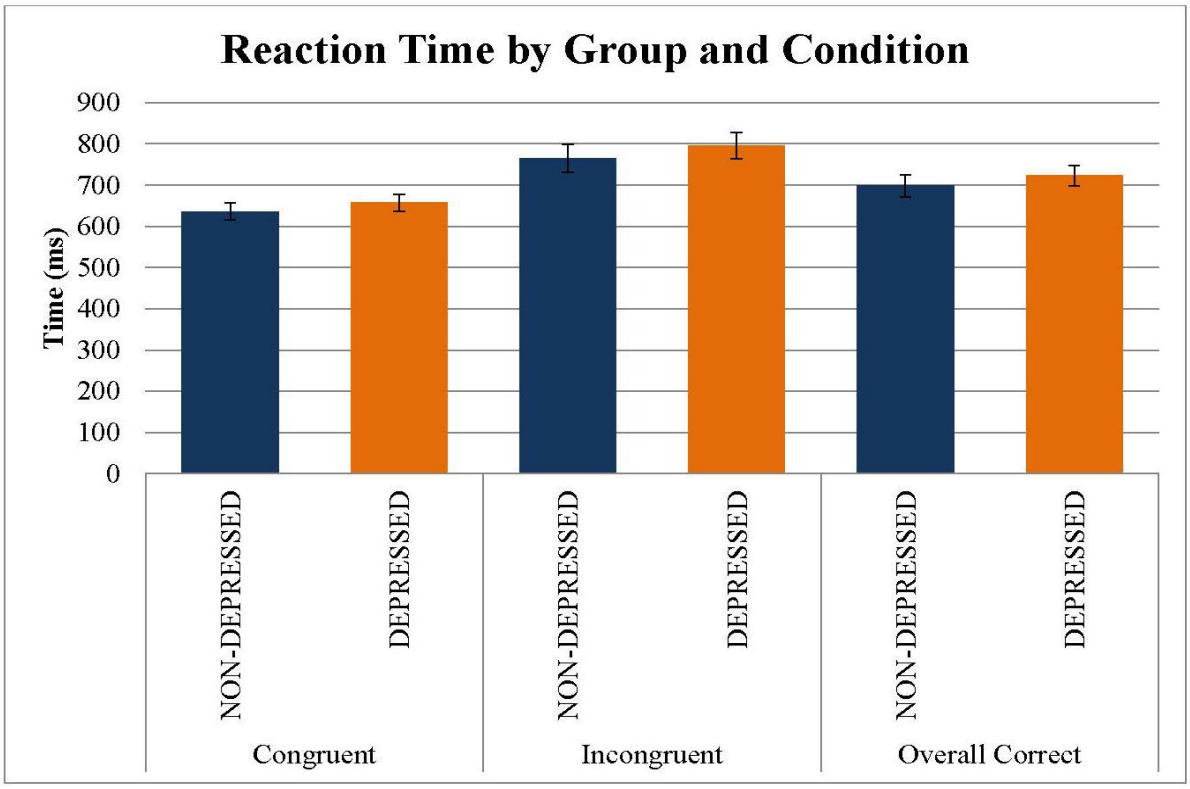


Figure 4. Computerized Stroop Task-Accuracy: Reaction Time (ms) by group, and congruency condition.

Scalp Waveform Latency

There was no significant difference in the latency of the N2 waveform between groups or across conditions. There was no main effect of group (depressed vs. non-depressed: $F_{(1,66)}$ =0.002, p=0.965) or condition (congruent vs. incongruent: $F_{(1,66)}$ =0.64, p=0.427) on N2 latency. Furthermore, the interaction ($F_{(1.66)}$ =3.95, p=0.051) between group (depressed vs. non-depressed) and condition (congruent vs. incongruent) on N2 latency did not reach statistical significance. It should be noted however, that although the interaction did not reach statistical significance, the data suggest that non-depressed subjects had a longer latency for incongruent stimuli (Mean =251.00, Standard Deviation =8.0) than for congruent stimuli (Mean= 244.22, Standard Deviation =7.7) when compared with depressed subjects who did not differ in latency of incongruent (Mean

=248.64, Standard Deviation =5.7) as opposed to congruent (Mean =245.74, Standard Deviation =5.9) stimuli (Figure 5).

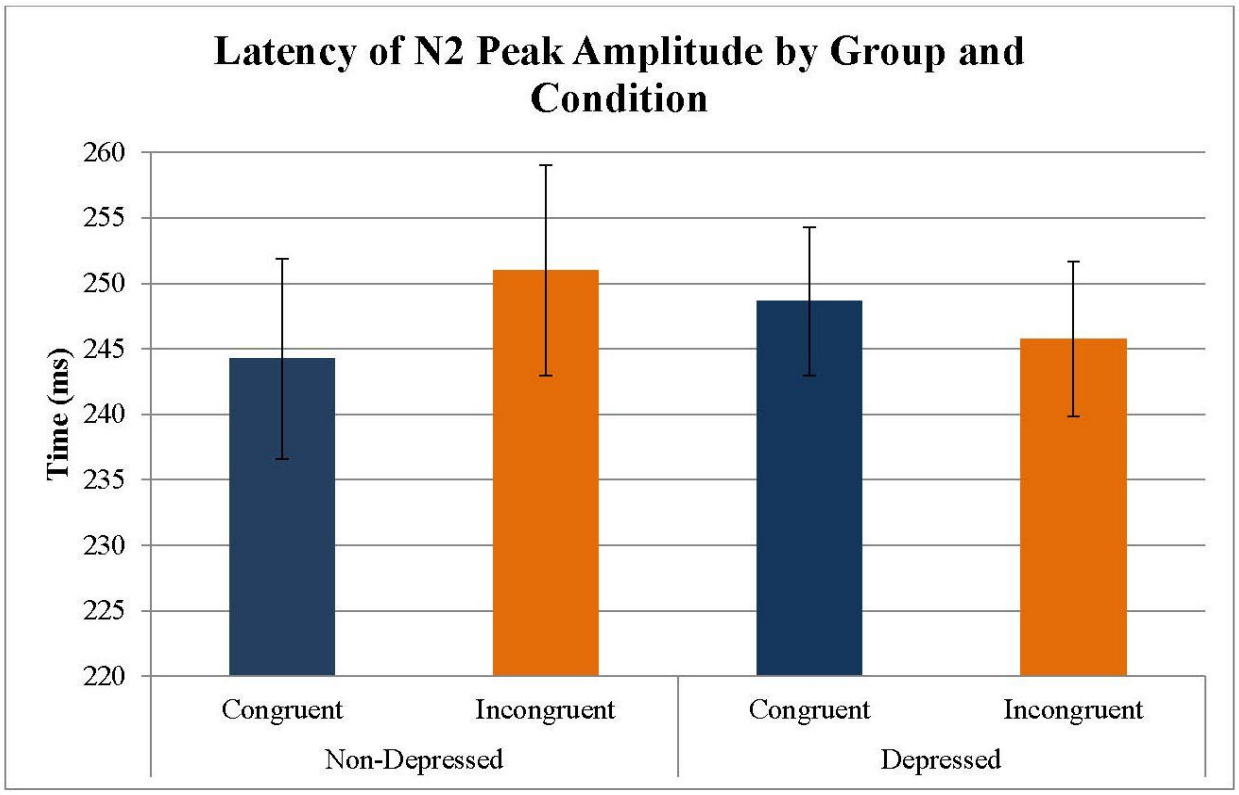


Figure 5. Average waveform latency of minimum peak N2 across midline sites by group, and congruency condition.

Scalp N2 Waveform Minimum Peak Amplitude

N2 Peak Amplitude at Midline Sites

Depressed subjects exhibited a smaller N2 peak amplitude in response to incongruent compared to congruent conditions of the Stroop task, whereas there was no difference by condition in normal subjects (Figure 6). In a repeated measures ANOVA there was no main effect of group (depressed vs. non-depressed) or condition (congruent

vs. incongruent) on N2 peak amplitude. However, there was a significant interaction ($F_{(1.66)}$ =10.2, p=0.002, η^2=0.13) between group (depressed vs. non-depressed) and condition (congruent vs. incongruent). Post-hoc paired t-tests were conducted to investigate the relationship of variables within the interaction. Within the non-depressed group, there was no difference in N2 minimum amplitude of the congruent (Mean=-0.20, Standard Deviation= 1.6) and incongruent (Mean=-0.40, Standard Deviation= 1.9) conditions (paired t=1.0, df = 23, p=0.32). However, within the depressed group, the N2 minimum peak amplitude was smaller for the incongruent condition (Mean: 0.24, SD: 1.3) than for the congruent condition (Mean=-0.28, Standard Deviation= 1.0; paired t=-4.1, df =43, p=0.00).

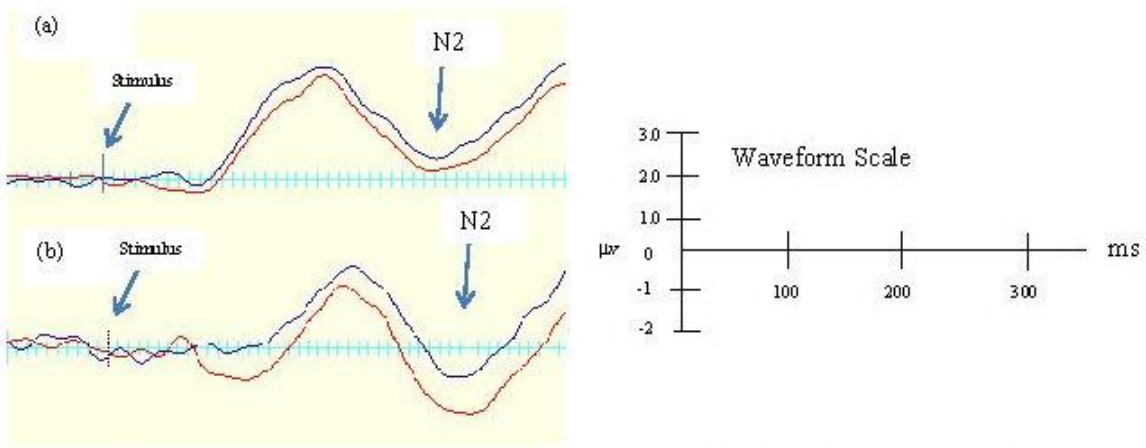


Figure 6. Patient (a) and control (b) grand average waveforms following stimulus presentation of incongruent (red) and congruent (blue) stimuli.

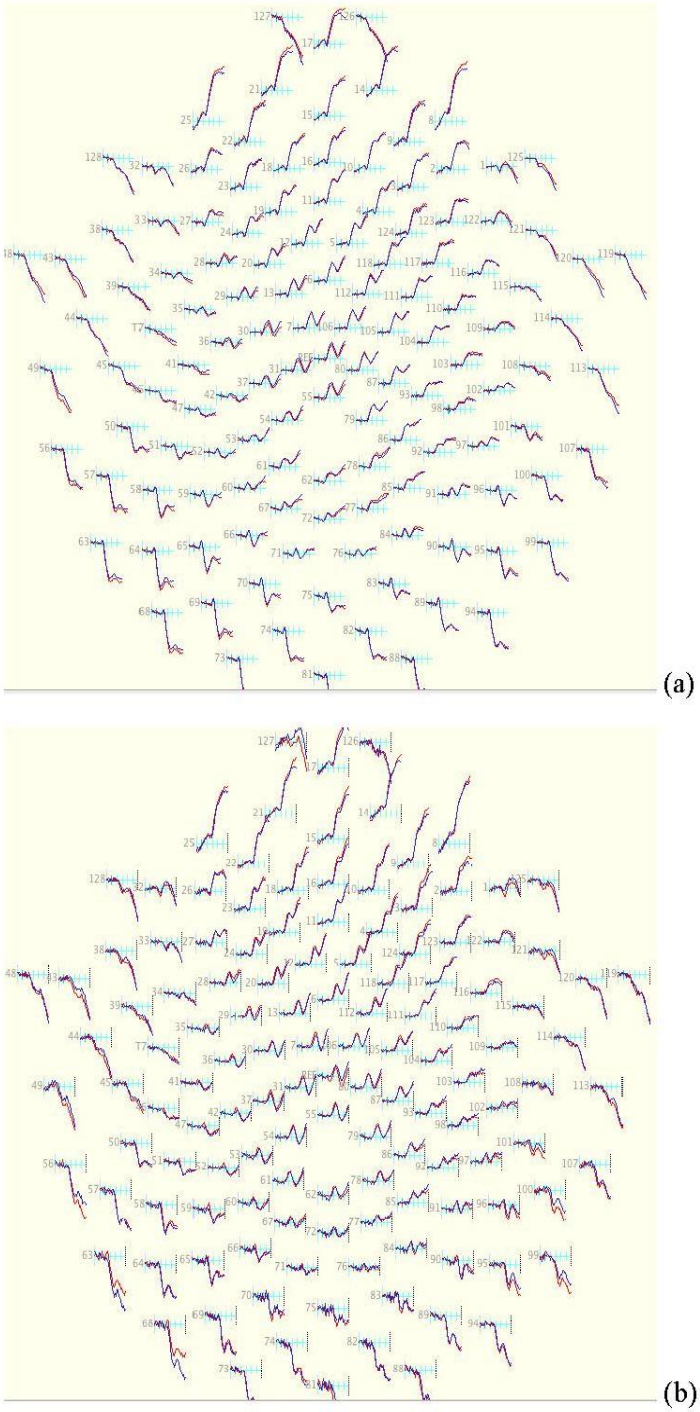


Figure 7. Grand average waveform distribution for (a) depressed patients and (b) controls. Blue lines represent congruent segments; red lines represent incongruent segments.

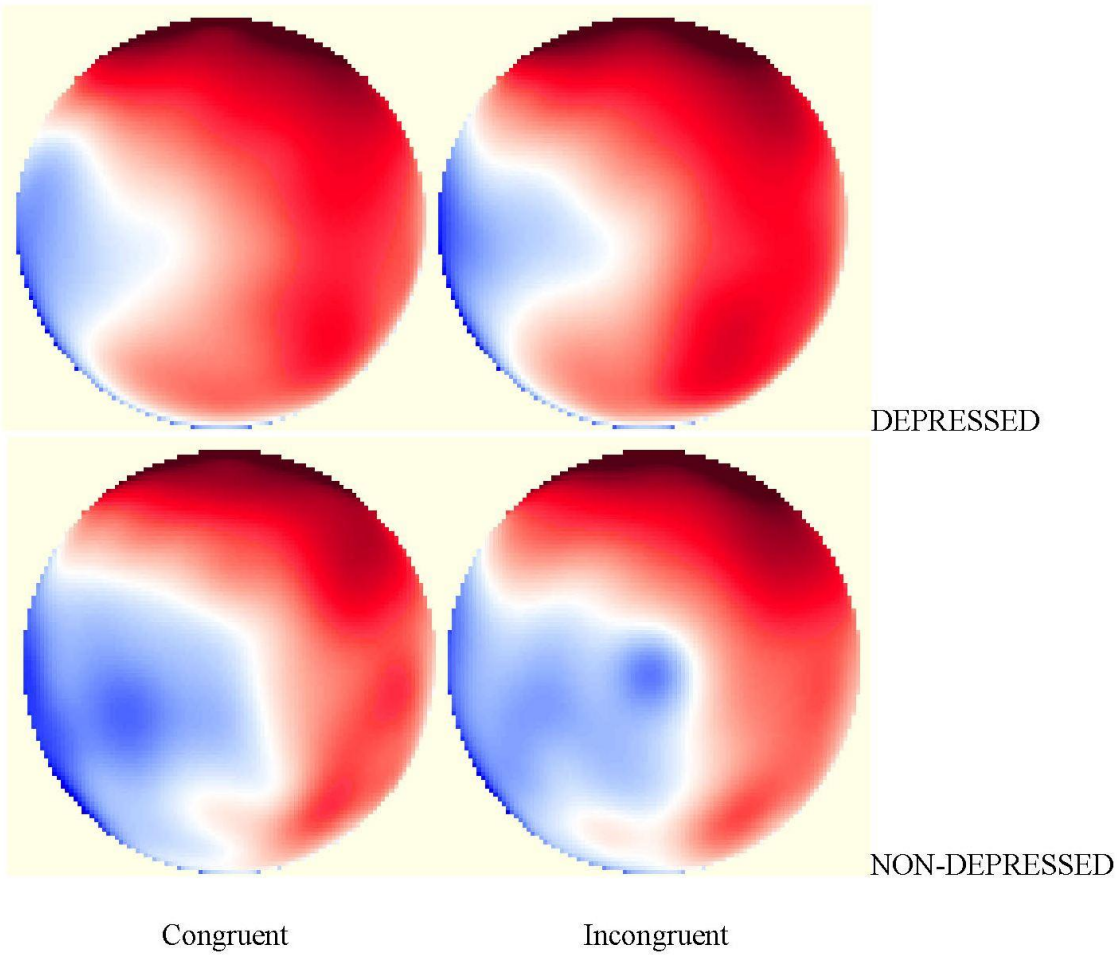


Figure 8. Topographic maps of congruent and incongruent conditions across groups.

Tests of Specificity- Analysis of Occipital Lead Sites

In order to test the specificity of the above findings, the N2 minimum amplitude from two sets of leads unrelated to the location of the anterior cingulate cortex, the hypothesized generator of the N2, were selected and the analysis was repeated. Specificity analyses indicated that the above findings were specific to midline (11, 6, Cz) sites as repeating the analyses utilizing occipital leads did not yield a similar pattern.

Left Occipital Lobe Leads (65,66,70,71,72,74,75)

The average of the peak minimum amplitude of the left occipital lobe leads was computed and there was no evidence of difference in N2 peak amplitude at these lead sites by condition or group. There were no main effects of condition ($F_{(1,66)} = 0.316$, p=0.58), group ($F_{(1,66)} = 0.054$, p=0.82), and there was no significant interaction of condition and group in the left occipital lobe ($F_{(1,66)} = 0.060$, p=0.81).

Right Occipital Lobe Leads (77,83,84,85,89,90,91)

The average of the peak minimum amplitude of the right occipital lobe leads was computed and there was no evidence of difference in N2 peak amplitude at these lead sites by condition or group. There were no main effects of condition ($F_{(1,66)} = 0.003$, p=0.96), group ($F_{(1,66)} = 0.000$, p=0.98), and there was no significant interaction of condition and group in the right occipital lobe ($F_{(1,66)} = 0.020$, p=0.89).

N2 Relationship with Demographic, Clinical and Neuropsychological Measures

The results of the hierarchical (sequential) multiple regression showing the predictive contribution of the N2 peak amplitude elicited by incongruent stimuli to neuropsychological variables over and above the influence of demographic and clinical variables are given in Table 3.

Among non-depressed subjects, the overall model predicting Trails B-Trails A performance was significant when the N2 peak amplitude to incongruent stimuli was added as a predictor ($F_{(6,23)}$=8.86, p=0.000). N2 peak amplitude to incongruent stimuli (β=-1.74, p=0.000) added 68.4% to the explanatory variance of the previous step in the model which included age, education, gender, depression severity, and N2 peak

amplitude to congruent stimuli (change in R^2=0.684, F_{change}=47.97, p=0.000). No other regression models were significant among non-depressed individuals.

Among depressed subjects, clinical and demographic factors were predictive of Trails A, and HVLT-R Immediate and Delayed recall (Table 3). However, N2 peak amplitude (congruent or incongruent) did not significantly add to the predictive variance of these models over and above the influence of clinical and demographic factors. Specifically, age (β=0.64, p=0.000) and baseline 24-item HDRS total (β=0.33, p=0.025) were predictive of 45.6% of the variance in Trails A performance ($F_{(5,37)}$=5.37, p=0.001) in a model which also included age, education, and age of depression onset. Although the overall model remained significant when N2 peak amplitude to congruent stimuli ($F_{(6,37)}$=4.82, p=0.001) and to incongruent stimuli ($F_{(7,37)}$=4.25, p=0.002) were added, the additional variance explained by either of these variables was not significant (Change in R^2 due to N2 congruent=0.027, F_{change}=1.60, p=0.216; Change in R^2 due to N2 incongruent=0.015, F_{change}=0.90, p=0.350). No additional variables were predictive of performance on neuropsychological variables amongst depressed patients.

Table 3. Hierarchical Regression Analyses with Neuropsychological Measures as Individual Dependent Variables.

	Non-Depressed			**Depressed**		
	Predictor Variables					
	Step 1	**Step 2**	**Step 3**	**Step 1**	**Step 2**	**Step 3**
ependent Variables	Age, Gender, Education, Depression Rating[1]	N2 Peak Amplitude - Congruent Stimuli	N2 Peak Amplitude - Incongruen t Stimuli	Age, Gender, Education, Depression Rating[1], Age of Onset[2]	N2 Peak Amplitude - Congruent Stimuli	N2 Peak Amplitude - Incongruen t Stimuli
Executive Function						
Stroop Color Word Interference	0.032	0.032	0.224	0.137	0.381	0.395
Trails B - Trails A	0.072	0.072	0.758[+]	0.254	0.254	0.273
Processing Speed						
Trails A	0.059	0.06	0.107	0.456[+]	0.483[+]	0.498
Stroop Color Total	0.184	0.184	0.216	0.211	0.222	0.233
Stroop Word Total	0.372	0.426	0.447	0.095	0.199	0.201
Memory						
HVLT-R Immediate Recall	0.257	0.309	0.48	0.325	0.325	0.365
HVLT-R Delayed Recall	0.244	0.306	0.429	0.319	0.319	0.347

The results are expressed as proportions of total variance R^2 explained by the regression models.

+ Statistical Significance $p<0.001$ represents the incremental explanatory power at each step.

1. 24 - Item Hamilton Depression Scale Total
2. Age of Onset of First Depressive Episode

Discussion

The principal finding of this study is that depressed subjects exhibit a smaller N2 when responding to incongruent as compared to congruent stimuli, and this difference in N2 amplitude was not observed in non-depressed subjects. These results may suggest that deficient neural recruitment of conflict processing could manifest in non-depressed older adults, and may be exaggerated in geriatric depression. These findings build on the available functional neuroimaging literature by providing a time point at which neural processing within the conflict-control network deteriorates; that is, degradation begins early on at the point where discrimination of relevant and irrelevant features of the stimulus are being processed. However, these findings were not accompanied by differences in behavioral performance between groups, limiting the conclusions that can be drawn to the characterization of neural aspects of conflict processing.

Abnormalities in cognitive inhibition of both depressed and non-depressed older adults are well documented. When compared to younger adults, older adults exhibit impairments in conflict processing tasks (West, 2003). Depressed older adults exhibit greater interference effects across a variety of cognitive control tasks, including tasks eliciting cognitive inhibition (Gualtieri & Johnson, 2008; Lockwood et al., 2002; Pisljar et al., 2008), when compared to their non-depressed peers. The current study presents a possible mechanism by which cognitive inhibition is affected in both depressed and non-depressed older adults.

Healthy older adults exhibit neural conflict processing abnormalities relative to their younger counterparts. Aging may impact conflict processing, as smaller N2 amplitudes and longer N2 latencies have been observed in older as compared to younger

adults (Falkenstein, 2003). The results of this study are consistent with observations of smaller N2 amplitude in older adults, as there was no difference between congruent and incongruent N2 amplitudes within this group.

Depressed individuals across the lifespan may under-recruit neural resources required for conflict processing. For instance, depressed younger adults exhibit smaller N2 amplitudes during cognitive inhibition (Holmes & Pizzagalli, 2008), and response inhibition paradigms (Kaiser et al., 2003) when compared to controls. Furthermore, smaller N2 amplitudes have also been observed during response inhibition in geriatric depression (Katz et al., 2010; Zhang et al., 2007). The present study provides evidence of neural under-recruitment during a cognitive inhibition task. Taken together, these findings suggest that depressed individuals may not adequately activate aspects of the neural network underlying cognitive control. However, these neural differences may not manifest in behavioral performance discrepancies.

In the current study, older depressed subjects performed as accurately as non-depressed subjects, suggesting perhaps that an alternate neural network may underlie successful performance. Recent investigations have posited that aspects of the DLPFC may be connected to a posterior parietal network, and that this posterior network is also involved in upregulation of cognitive control (Shomstein, 2012). These studies suggest that while frontal cognitive control networks are associated with cognitive inhibition and attention, posterior networks are involved in working memory and action execution (Cieslik et al., 2012). Although the current study did not examine processing within the posterior network, it is possible that under-recruitment of the frontal conflict-control network may have corresponded to up-regulation of the posterior networks for regulation

of behavioral responses to conflict. Overall the lack of difference in behavioral performance between groups may point towards implementation of possible compensatory mechanisms to assist performance.

Smaller N2 is related to poor conflict detection

Smaller N2 amplitude has been found to be related to dysfunction of the dorsal anterior cingulate (dACC), the structure thought to underlie conflict detection. Once the dACC is activated by cognitive interference, it signals structures such as the dorsolateral prefrontal cortex (DLPFC) that there is a need for increased neural resources for goal attainment. Dysfunction of the dACC may result in poor conflict detection, and thereby poor signaling for additional neural resources (Carter & vanVeen, 2007).

The results of the current study suggest that aging may be related to abnormal activation of conflict detection mechanisms. Our findings are inconsistent with the younger adult literature citing differences in N2 magnitude according to conflict condition. In the current study, there were no significant differences in amplitude between high and low conflict conditions. However, some studies suggest that the N2 response to incongruent stimuli declines with age (Falkenstein, 2003). Therefore one possible explanation for the lack of differentiation in amplitude by congruency in the non-depressed group is that aging reduces the N2 response to conflict. However, this claim cannot be fully examined in the current study due to the lack of a younger non-depressed comparison group. Nonetheless, the influence of aging on conflict processing and conflict detection in particular is an intriguing prospect for future research.

Depressed individuals exhibit decreased activation of the dACC and the DLPFC during fMRI cognitive control tasks (Fitzgerald, Laird, Maller, & Daskalakis, 2008).

Relative to controls, older depressed individuals exhibit decreased activation of the dACC (Aizenstein et al., 2009). The findings of the current study may suggest reduced engagement of the dACC in depressed adults on high conflict trials above and beyond that seen in non-depressed older adults. Since the dACC is useful in resolving interference caused by competing stimuli (Holmes & Pizzagalli, 2008), decreased activity in the dACC may lead to increased interference effects. In turn, increased interference caused by poor conflict detection may lead to abnormal cognitive inhibition in depressed older adults. However, this relationship was not fully supported by our data, as neural processing abnormalities did not manifest into behavioral performance differences.

Hypoactivation of the dACC may be related to some of the clinical and affective symptoms of geriatric depression. Dysfunction of the dACC may lead to enhanced attention to negative emotional stimuli or inability to suppress emotionally valenced distractions (Ochsner & Gross, 2005). Symptoms such as reduced concentration, rumination, and suicidal ideation may reflect a failure of cognitive inhibition processes leading to uncontrolled and maladaptive thinking. Increased processing of irrelevant or negative stimuli, may predispose and perpetuate depressive syndromes in older individuals (Fales et al., 2008).

Furthermore, reduced conflict processing within the dACC may contribute to the affective symptoms that are characteristic of geriatric depression. For instance, apathy, a symptom more commonly seen in geriatric depression than in younger adult depression, is associated with lower functional connectivity between the dACC and DLPFC (Alexopoulos et al., 2012). Furthermore, apathy is closely related to executive dysfunction (Feil et al., 2003), signifying that dysfunction in conflict-control networks is

related to both cognitive and emotional dysregulation. The results of this study suggest that one mechanism by which cognitive and affective dysregulation occurs may involve failure of early conflict detection processing of the dACC.

Slowed N2 latency in non-depressed older adults may be related to enhanced conflict processing

The N2 latency was slower for incongruent than congruent stimuli in the non-depressed group only; however, there may not have been enough power to see an effect, and this interaction did not reach statistical significance. Slowed N2 latency in response to incongruent stimuli is indicative of slowed neural processing in response to conflict (Ridderinkhof et al., 2004; Yeung et al., 2004). This finding is consistent with previous studies reporting increased waveform latency in response to high conflict stimuli in normal older adults. Healthy older adults display a slower N2 latency during high conflict tasks (Wascher, Schneider, Hoffmann, Beste, & Sanger) and a delay in N2 latency relative to younger adults (Falkenstein et al., 2001). Slowed N2 latency in normal aging may reflect the strategic use of increased time to process high conflict stimuli (Vallesi, Stuss, McIntosh, & Picton, 2009).

Unlike normal controls, depressed older adults did not exhibit slowed N2 latency for incongruent stimuli, perhaps indicating that abnormalities in conflict processing may exist in neural speed of processing. An alternative explanation is that rather than processing conflict within the conflict-control loop, depressed individuals may have depended on additional recruitment of posterior attentional networks to meet task demands. In either case, depressed older adults may not process conflict in the same manner as their healthy counterparts. The confluence of smaller N2 amplitude and

absence of a delay in latency suggests that depressed individuals may have early and defective neural recruitment in conflict-control networks when they engage in conflict processing. However, the implications of these differences in neural recruitment require further examination, as they were not related to behavioral deficits in the current study.

Executive Function in Non-depressed Adults is Associated with Larger N2

An additional finding of this study was that larger N2 elicited by high conflict stimuli was associated with better performance on an aspect of executive function, but only in non-depressed subjects. This relationship was specific to the set-shifting aspect of executive function, as performance on measures of processing speed, cognitive inhibition, and memory was not correlated with N2 amplitude. Therefore, in this study, greater recruitment of neural resources in healthy controls was related to better set-shifting when controlling for processing speed.

This finding suggests that in non-depressed older adults, greater activation of neural structures within the conflict-control loop may represent an attempt to recruit greater cognitive control (Schulte et al., 2009). Greater recruitment of conflict-control neural resources may reflect increased engagement of compensatory neural mechanisms in an attempt to overcome aging related cognitive deficits (Falkenstein, 2003) that occur within this network. The absence of a relationship in the depressed group suggests that increased activation of the conflict-control loop to improve performance on an executive task is unique to aging without affective dysregulation. Future studies should examine the role of other networks that may be involved in successful cognitive inhibition (e.g., fronto-parietal networks) among depressed older adults.

Limitations

While the results of this study suggest early neural manifestations of conflict processing abnormalities in geriatric depression, several limitations should be noted. First, due to the small size of the sample, further investigation of depression subgroups based on symptomatology was not possible. Second, since all depressed subjects were unmedicated, the influence of antidepressant medication usage on conflict detection and resolution processes could not be assessed. Third, the sample of depressed individuals in this study exhibited depression of moderate severity. As such, these results may not be generalizable to individuals with other levels of depression. It is also possible that use of different ERP paradigms of conflict-control processes (e.g., Flanker tasks) may have elicited different electrophysiological responses. However, the Stroop task was chosen so as to examine resistance to interference embedded within a stimulus, in order to minimize the contribution of attention shifting that is necessary in tasks like the Flanker task. Further, although the cognitive paradigm used to elicit the N2 waveform was tailored to each individual to ensure an adequate level of difficulty it is possible that the task was not rigorous enough to elicit the magnitude of N2 response observed among younger adults. Future studies may perhaps examine N2 response in cognitive inhibition using more rigorous paradigms. Furthermore, paradigms that utilize emotional interference may be of particular interest in examining whether the cognitive conflict processing response is related to activation in emotional processing networks. Additionally, the cognitive battery administered to subjects was somewhat limited; it is possible that given a more extensive battery, behavioral aspects of cognitive control and their relationship to conflict processing could have been explored more thoroughly. Finally, some methodological

limitations were imposed by the physiological effects of age (e.g., use of glasses, hearing aids, alopecia, benign tremors) which resulted in the elimination of several research subjects due to data that was contaminated.

Conclusions

Older non-depressed and depressed older adults exhibit neural conflict processing abnormalities during a cognitive inhibition task. Conflict processing abnormalities manifested as smaller than expected N2 in response to high conflict tasks. Within the non-depressed group, although a normative delay in N2 latency emerged, there was no clear differentiation of N2 according to congruency, as the literature on N2 response in young adults would suggest. However, attenuation in the N2 has been observed in aging studies of conflict processing, and therefore the absence of a distinction in magnitude of the N2 according to conflict intensity may perhaps be developmentally appropriate within this group. Within the depressed group, the absence of an age-appropriate delay in latency of the N2 waveform, and smaller N2 response to high conflict stimuli, perhaps points towards an exacerbation of the effects of aging on the N2 component in this group. Notably, among depressed individuals, the high conflict N2 was smaller than the N2 to congruent stimuli, which is the opposite of what would be expected in young non-depressed adults, and smaller than what would be expected of non-depressed older adults.

These results suggest possible neural processing dysfunction of conflict-control networks in geriatric depression. However, the significance of these finding is limited by the lack of between- group behavioral performance differences. To overcome these limitations, in addition to using more rigorous interference tasks, future studies should include younger depressed and non-depressed comparator groups as part of the study

design. Including these groups may allow for a more robust investigation of the influence of aging versus depression on conflict processing.

An additional finding of the current study was that non-depressed older adults with a larger N2 to high conflict stimuli, exhibit better performance on an executive task. It is possible that these individuals over-recruit neural resources within the conflict-control loop to address high conflict stimuli. This relationship was not observed among depressed older adults, suggesting perhaps that depressed individuals may recruit alternate neural networks towards the resolution of conflict. However, the scope of the current study did not allow for a full examination of alternate networks. Nonetheless, this possibility is intriguing and should be evaluated in future studies.

Abnormal neural activity in the conflict-control loop may be part of a larger disconnection syndrome of frontolimbic structures responsible for top-down control of affective and cognitive information. Disruption of this network may lead to, and perpetuate the depressive syndrome by biasing incoming information processing and by preventing proper inhibition of maladaptive negative thoughts. Frontolimbic abnormalities have been found to predispose older individuals to depression. Characterization of dysfunction among frontolimbic structures can provide a greater understanding of geriatric depression. Furthermore, identifying neural abnormalities in specific networks can provide targets for novel pharmacological and psychotherapeutic interventions.

Late-life depression is a suitable model for exploring how dysfunction in neural networks relates to treatments for the depressive illness. First, aging related brain changes in frontolimbic systems increase vulnerability to depression. Also, frontolimbic

abnormalities are common in geriatric depression and may be associated with poor treatment response. Finally, inefficiency in conflict-control systems may be responsible for some of the core symptoms of geriatric depression. Specifically, dysfunction in frontolimbic structures critical for detection of conflict (dACC) and resolution of that conflict (DLPFC) may contribute to the development of symptoms that are more often seen in late life depression such as poor concentration and apathy.

This study is an initial step towards characterizing electrophysiological abnormalities underlying cognitive inhibition deficits in late life depression. Future investigations should also focus on the influence of features related to the presentation and course of geriatric depression on neural processing of conflict. For instance, the relationship between conflict processing and severity of depression, age of symptom onset, number of previous episodes, duration of symptoms or history of antidepressant treatment response has not been fully explored. It is possible that the course and characteristics of depressive illness may influence structures of the cognitive control network, and degrade conflict processing. Furthermore, the question of whether abnormal conflict processing relates to state or trait abnormalities remains unanswered. Future investigations should explore whether abnormalities in early conflict detection and resolution processes are related to specific genotypes, and whether abnormalities persist when older depressed individuals remit with pharmacological or psychotherapeutic treatment.

In summary, depressed older adults exhibit a neural response to high conflict stimuli that is different than non-depressed older adults. Furthermore, non-depressed older adults with executive dysfunction may activate the conflict-control network to a

greater degree than older individuals with depression. The current study adds to the existing literature by providing electrophysiological evidence of neural dysfunction in the selection of competing stimuli during initial aspects of conflict processing in depressed older adults. The results of this study however, are tempered by the lack of behavioral manifestations of conflict processing dysfunction between groups. The extent to which neural processing dysfunction could contribute to poor outcomes in geriatric is not fully known. Therefore, further research should evaluate the relevance of neural manifestations of conflict processing abnormalities to the course of normal aging, and compare it to the course and treatment of depression across the life span. The definition of neural and behavioral endophenotypes of depression using well designed paradigms may ultimately aid in characterizing psychiatric symptoms and response to treatment in this heterogeneous disorder.

References

American Psychiatric Association. (2000). *Diagnostic and Statistic Manual of Mental Disorders.* (4th edition text revision). Washington, DC: Author.

Baddeley, A.D. & Hitch, G.J. (1994). Developments in the concept of working memory. *Neuropsychology*, 8, 485–493.

Aizenstein, H. J., Butters, M. A., Wu, M. J., Mazurkewicz, L. M., Stenger, V. A., Gianaros, P. J. (2009). Altered Functioning of the Executive Control Circuit in Late-Life Depression: Episodic and Persistent Phenomena. *American Journal of Geriatric Psychiatry*, *17*(1), 30-42.

Alexopoulos, G. S., Gunning-Dixon, F. M., Latoussakis, V., Kanellopoulos, D., & Murphy, C. F. (2008). Anterior cingulate dysfunction in geriatric depression. *International Journal of Geriatric Psychiatry, 23*(4), 347-355.

Alexopoulos, G. S., Hoptman, M. J., Kanellopoulos, D., Murphy, C. F., Lim, K. O., & Gunning, F. M. (2012). Functional connectivity in the cognitive control network and the default mode network in late-life depression. *Journal of Affective Disorders, 139*(1), 56-65.

Alexopoulos, G. S., Meyers, B. S., Young, R. C., Campbell, S., Silbersweig, D., & Charlson, M. (1997). 'Vascular depression' hypothesis. *Archives of General Psychiatry, 54*(10), 915-922.

Alexopoulos, G. S., Meyers, B. S., Young, R. C., Kakuma, T., Silbersweig, D., & Charlson, M. (1997). Clinically defined vascular depression. *American Journal of Psychiatry, 154*(4), 562-565.

Andres, P., Guerrini, C., Phillips, L. H., & Perfect, T. J. (2008). Differential effects of aging on executive and automatic inhibition. *Developmental Neuropsychology, 33*(2), 101-123.

Aron, A. R. (2007). The neural basis of inhibition in cognitive control. *Neuroscientist, 13*(3), 214-228.

Baxter, L. R., Jr., Schwartz, J. M., Phelps, M. E., Mazziotta, J. C., Guze, B. H., Selin, C. E. (1989). Reduction of prefrontal cortex glucose metabolism common to three types of depression. *Archives of General Psychiatry, 46*(3), 243-250.

Beats, B. C., Sahakian, B. J., & Levy, R. (1996). Cognitive performance in tests sensitive to frontal lobe dysfunction in the elderly depressed. *Psychological Medicine, 26*(3), 591-603.

Botvinick, M., Braver, T., Barch, D., Carter, C., & Cohen, J. (2001). Conflict monitoring and cognitive control. *Psychological Review, 108*(3), 624-652.

Botvinick, M., Cohen, J., & Carter, C. (2004). Conflict monitoring and anterior cingulate cortex: an update. *Trends in Cognitive Sciences, 8*(12), 539-546.

Botvinick, M., Nystrom, L. E., Fissell, K., Carter, C. S., & Cohen, J. D. (1999). Conflict monitoring versus selection-for-action in anterior cingulate cortex. *Nature, 402*(6758), 179-181.

Braver, T. S., Barch, D. M., Gray, J. R., Molfese, D. L., & Snyder, A. (2001). Anterior cingulate cortex and response conflict: effects of frequency, inhibition and errors. *Cerebral Cortex, 11*(9), 825-836.

Broomfield, N. M., Davies, R., MacMahon, K., Ali, F., & Cross, S. M. (2007). Further evidence of attention bias for negative information in late life depression. *International Journal of Geriatric Psychiatry, 22*(3), 175-180.

Bunge, S. A., Hazeltine, E., Scanlon, M. D., Rosen, A. C., & Gabrieli, J. D. (2002). Dissociable contributions of prefrontal and parietal cortices to response selection. *Neuroimage, 17*(3), 1562-1571.

Bush, G., Luu, P., & Posner, M. I. (2000). Cognitive and emotional influences in anterior cingulate cortex. *Trends in Cognitive Science, 4*(6), 215-222.

Butters, M. A., Becker, J. T., Nebes, R. D., Zmuda, M. D., Mulsant, B. H., Pollock, B. G. (2000). Changes in cognitive functioning following treatment of late-life depression. *American Journal of Psychiatry, 157*(12), 1949-1954.

Butters, M. A., Whyte, E. M., Nebes, R. D., Begley, A. E., Dew, M. A., Mulsant, B. H. (2004). The nature and determinants of neuropsychological functioning in late-life depression. *Archives of General Psychiatry, 61*(6), 587-595.

Cabeza, R., Anderson, N. D., Locantore, J. K., & McIntosh, A. R. (2002). Aging gracefully: compensatory brain activity in high-performing older adults. *Neuroimage, 17*(3), 1394-1402.

Carter, C. S., & van Veen, V. (2007). Anterior cingulate cortex and conflict detection: an update of theory and data. *Cognitive, Affective & Behavioral Neuroscience, 7*(4), 367-379.

Chapman, L. J., & Chapman, J. P. (1987). The measurement of handedness. *Brain and Cognition, 6*(2), 175-183.

Cieslik, E. C., Zilles, K., Caspers, S., Roski, C., Kellermann, T. S., Jakobs, O. (2012). Is There "One" DLPFC in Cognitive Action Control? Evidence for Heterogeneity From Co-Activation-Based Parcellation. *Cerebral Cortex*.

Cohen, J. (1988). *Statistical power analysis for the behavioral sciences* (2nd ed.). Hillsdale, NJ: Earlbaum.

Cohn, N. B., Dustman, R. E., & Bradford, D. C. (1984). Age-related decrements in Stroop Color Test performance. *Journal of Clinical Psychology, 40*(5), 1244-1250.

Compton, R. J., Lin, M., Vargas, G., Carp, J., Fineman, S. L., & Quandt, L. C. (2008). Error detection and posterror behavior in depressed undergraduates. *Emotion, 8*(1), 58-67.

Dai, Q., & Feng, Z. (2011). Deficient interference inhibition for negative stimuli in depression: an event-related potential study. *Clinical Neurophysiology, 122*(1), 52-61.

de Zubicaray, G. I., Andrew, C., Zelaya, F. O., Williams, S. C., & Dumanoir, C. (2000). Motor response suppression and the prepotent tendency to respond: a parametric fMRI study. *Neuropsychologia, 38*(9), 1280-1291.

DiGirolamo, G. J., Kramer, A. F., Barad, V., Cepeda, N. J., Weissman, D. H., Milham, M. P. (2001). General and task-specific frontal lobe recruitment in older adults during executive processes: a fMRI investigation of task-switching. *Neuroreport, 12*(9), 2065-2071.

Dillon, D. G., & Pizzagalli, D. A. (2007). Inhibition of Action, Thought, and Emotion: A Selective Neurobiological Review. *Applied and Preventative Psychology, 12*(3), 99-114.

Drevets, W. C. (2000a). Functional anatomical abnormalities in limbic and prefrontal cortical structures in major depression. *Progress in Brain Research, 126*, 413-431.

Drevets, W. C. (2000b). Neuroimaging studies of mood disorders. *Biological Psychiatry, 48*(8), 813-829.

Drevets, W. C. (2001). Neuroimaging and neuropathological studies of depression: implications for the cognitive-emotional features of mood disorders. *Current Opinion in Neurobiology, 11*(2), 240-249.

Durston, S., Davidson, M. C., Thomas, K. M., Worden, M. S., Tottenham, N., Martinez, A. (2003). Parametric manipulation of conflict and response competition using rapid mixed-trial event-related fMRI. *Neuroimage, 20*(4), 2135-2141.

Durston, S., Thomas, K. M., Worden, M. S., Yang, Y., & Casey, B. J. (2002). The effect of preceding context on inhibition: an event-related fMRI study. *Neuroimage, 16*(2), 449-453.

Elderkin-Thompson, V., Kumar, A., Bilker, W. B., Dunkin, J. J., Mintz, J., Moberg, P. J. (2003). Neuropsychological deficits among patients with late-onset minor and major depression. *Archives of Clinical Neuropsychology, 18*(5), 529-549.

Elliott, R., Sahakian, B. J., McKay, A. P., Herrod, J. J., Robbins, T. W., & Paykel, E. S. (1996). Neuropsychological impairments in unipolar depression: the influence of perceived failure on subsequent performance. *Psychological Medicine, 26*(5), 975-989.

Eriksen, B., & Eriksen, C. (1974). Effects of noise letters upon the identification of a target letter in a nonsearch task. *Perception & Psychophysics, 16*(1), 143-149.

Fales, C. L., Barch, D. M., Rundle, M. M., Mintun, M. A., Mathews, J., Snyder, A. Z. (2009). Antidepressant treatment normalizes hypoactivity in dorsolateral prefrontal cortex during emotional interference processing in major depression. *Journal of Affective Disorders, 112*(1-3), 206-211.

Fales, C. L., Barch, D. M., Rundle, M. M., Mintun, M. A., Snyder, A. Z., Cohen, J. D. (2008). Altered emotional interference processing in affective and cognitive-control brain circuitry in major depression. *Biological Psychiatry, 63*(4), 377-384.

Falkenstein, M., Hoormann, J., & Hohnsbein, J. (2001). Changes of error-related ERPs with age. *Experimental Brain Research, 138*(2), 258-262.

Fallgatter, A. J., Herrmann, M. J., Roemmler, J., Ehlis, A. C., Wagener, A., Heidrich, A. (2004). Allelic variation of serotonin transporter function modulates the brain electrical response for error processing. *Neuropsychopharmacology, 29*(8), 1506-1511.

Feil, D., Razani, J., Boone, K., & Lesser, I. (2003). Apathy and cognitive performance in older adults with depression. *International Journal of Geriatric Psychiatry, 18*(6), 479-485.

Fitzgerald, P. B., Laird, A. R., Maller, J., & Daskalakis, Z. J. (2008). A meta-analytic study of changes in brain activation in depression. *Human Brain Mapping, 29*(6), 683-695.

Folstein, J. R., & Van Petten, C. (2008). Influence of cognitive control and mismatch on the N2 component of the ERP: a review. *Psychophysiology, 45*(1), 152-170.

Friedman, D., Nessler, D., Johnson, R., Jr., Ritter, W., & Bersick, M. (2008). Age-related changes in executive function: an event-related potential (ERP) investigation of task-switching. *Neuropsychology Development & Cognition. Section B, Aging Neuropsychology & Cognition, 15*(1), 95-128.

Gehring, W. J., Gratton, G., Coles, M. G., & Donchin, E. (1992). Probability effects on stimulus evaluation and response processes. *Journal of Experimental Psychology: Human Perception and Performance, 18*(1), 198-216.

Goeleven, E., De Raedt, R., Baert, S., & Koster, E. H. (2006). Deficient inhibition of emotional information in depression. *Journal of Affective Disorders, 93*(1-3), 149-157.

Gohier, B., Ferracci, L., Surguladze, S. A., Lawrence, E., El Hage, W., Kefi, M. Z. (2009). Cognitive inhibition and working memory in unipolar depression. *Journal of Affective Disorders, 116*(1-2), 100-105.

Golden, C. J. (1978). *The Stroop Color and Word Test (Manual)*. Chicago: Stoetling.

Gotlib, I. H., Krasnoperova, E., Yue, D. N., & Joormann, J. (2004). Attentional biases for negative interpersonal stimuli in clinical depression. *Journal of Abnormal Psychology, 113*(1), 121-135.

Gratton, G., Coles, M. G., & Donchin, E. (1992). Optimizing the use of information: Strategic control of activation of responses. *Journal of Experimental Psychology, 121*(4), 480-506.

Gualtieri, C. T., & Johnson, L. G. (2008). Age-related cognitive decline in patients with mood disorders. *Progress in Neuropsychopharmacology and Biological Psychiatry, 32*(4), 962-967.

Hanslmayr, S., Pastotter, B., Bauml, K. H., Gruber, S., Wimber, M., & Klimesch, W. (2008). The electrophysiological dynamics of interference during the Stroop task. *Journal of Cognitive Neuroscience, 20*(2), 215-225.

Hasher, L., Stoltzfus, E. R., Zacks, R. T., & Rypma, B. (1991). Age and inhibition. *Journal of Experimental Psychology: Learning, Memory and Cognition, 17*(1), 163-169.

Hasher, L., & Zacks, R. (1988). Working memory, comprehension,and aging: A review and a new view. In G. Bower (Ed.), *The psychology of learning and motivation* (Vol. 22, pp. 193-225). San Diego, CA: Academic Press.

Hedden, T., & Gabrieli, J. D. (2004). Insights into the ageing mind: a view from cognitive neuroscience. *Nature Reviews Neuroscience, 5*(2), 87-96.

Hertel, P. (2004). Memory for emotional and nonemotional events in depression: a question of habit? In D. Reisberg & P. Hertel (Eds.), *Memory and Emotion* (pp. 186-216). New York: Oxford University Press.

Holmes, A. J., & Pizzagalli, D. A. (2008). Response conflict and frontocingulate dysfunction in unmedicated participants with major depression. *Neuropsychologia, 46*(12), 2904-2913.

Joormann, J., & Gotlib, I. H. (2006). Is this happiness I see? Biases in the identification of emotional facial expressions in depression and social phobia. *Journal of Abnormal Psychology, 115*(4), 705-714.

Joormann, J., & Gotlib, I. H. (2010). Emotion regulation in depression: relation to cognitive inhibition. *Cognition & Emotion, 24*(2), 281-298.

Joormann, J., Nee, D. E., Berman, M. G., Jonides, J., & Gotlib, I. H. (2010). Interference resolution in major depression. *Cognitive, Affective & Behavioral Neuroscience, 10*(1), 21-33.

Kaiser, S., Unger, J., Kiefer, M., Markela, J., Mundt, C., & Weisbrod, M. (2003). Executive control deficit in depression: event-related potentials in a Go/Nogo task. *Psychiatry Research, 122*(3), 169-184.

Katz, R., De Sanctis, P., Mahoney, J. R., Sehatpour, P., Murphy, C. F., Gomez-Ramirez, M. (2010). Cognitive control in late-life depression: response inhibition deficits and dysfunction of the anterior cingulate cortex. *American Journal of Geriatric Psychiatry, 18*(11), 1017-1025.

Kerns, J. G., Cohen, J. D., MacDonald, A. W., 3rd, Cho, R. Y., Stenger, V. A., & Carter, C. S. (2004). Anterior cingulate conflict monitoring and adjustments in control. *Science, 303*(5660), 1023-1026.

Kindermann, S. S., Kalayam, B., Brown, G. G., Burdick, K. E., & Alexopoulos, G. S. (2000). Executive functions and P300 latency in elderly depressed patients and control subjects. *American Journal of Geriatric Psychiatry, 8*(1), 57-65.

Kopp, B., Mattler, U., Goertz, R., & Rist, F. (1996). N2, P3 and the lateralized readiness potential in a nogo task involving selective response priming. *Electroencephalogr Clinical Neurophysiology, 99*(1), 19-27.

Kopp, B., Rist, F., & Mattler, U. (1996). N200 in the flanker task as a neurobehavioral tool for investigating executive control. *Psychophysiology, 33*(3), 282-294.

Kramer, A. F., Hahn, S., & Gopher, D. (1999). Task coordination and aging: explorations of executive control processes in the task switching paradigm. *Acta Psychologica (Amsterdam), 101*(2-3), 339-378.

Krishnan, K. R., Hays, J. C., & Blazer, D. G. (1997). MRI-defined vascular depression. *American Journal of Psychiatry, 154*(4), 497-501.

Lemelin, S., Baruch, P., Vincent, A., Everett, J., & Vincent, P. (1997). Distractibility and processing resource deficit in major depression. Evidence for two deficient attentional processing models. *J Nerv Ment Dis, 185*(9), 542-548.

Levens, S. M., Muhtadie, L., & Gotlib, I. H. (2009). Rumination and impaired resource allocation in depression. *Journal of Abnormal Psychology, 118*(4), 757-766.

Lockwood, K. A., Alexopoulos, G. S., & van Gorp, W. G. (2002). Executive dysfunction in geriatric depression. *American Journal of Psychiatry, 159*(7), 1119-1126.

Luck, S. (2005). *An introduction to the event-related potential technique*. Cambridge, Massachusetts: The MIT Press.

MacDonald, A. W., 3rd, Cohen, J. D., Stenger, V. A., & Carter, C. S. (2000). Dissociating the role of the dorsolateral prefrontal and anterior cingulate cortex in cognitive control. *Science, 288*(5472), 1835-1838.

Mager, R., Bullinger, A. H., Brand, S., Schmidlin, M., Scharli, H., Muller-Spahn, F. (2007). Age-related changes in cognitive conflict processing: an event-related potential study. *Neurobiology of Aging, 28*(12), 1925-1935.

Mansouri, F. A., Tanaka, K., & Buckley, M. J. (2009). Conflict-induced behavioural adjustment: a clue to the executive functions of the prefrontal cortex. *Nature Reviews Neuroscience, 10*(2), 141-152.

Markela-Lerenc, J., Ille, N., Kaiser, S., Fiedler, P., Mundt, C., & Weisbrod, M. (2004). Prefrontal-cingulate activation during executive control: which comes first? *Brain Research: Cognitive Brain Research, 18*(3), 278-287.

Milham, M. P., Erickson, K. I., Banich, M. T., Kramer, A. F., Webb, A., Wszalek, T. (2002). Attentional control in the aging brain: insights from an fMRI study of the stroop task. *Brain and Cognition, 49*(3), 277-296.

Mittenberg, W., Seidenberg, M., O'Leary, D. S., & DiGiulio, D. V. (1989). Changes in cerebral functioning associated with normal aging. *Journal of Clinical Experimental Neuropsychology, 11*(6), 918-932.

Moritz, S., Jacobsen, D., Kloss, M., Fricke, S., Rufer, M., & Hand, I. (2004). Examination of emotional Stroop interference in obsessive-compulsive disorder. *Behaviour Research and Therapy, 42*(6), 671-682.

Murphy, C., Gunning-Dixon, F., Hoptman, M., Lim, K., Ardekani, B., Shields, J. (2007). White-matter integrity predicts stroop performance in patients with geriatric depression. *Biological Psychiatry, 61*(8), 1007-1010.

Murphy, C. F., & Alexopoulos, G. S. (2004). Longitudinal association of initiation/perseveration and severity of geriatric depression. *American Journal of Geriatric Psychiatry, 12*(1), 50-56.

Murphy, C. F., Gunning-Dixon, F. M., Hoptman, M. J., Lim, K. O., Ardekani, B., Shields, J. K. (2007). White-matter integrity predicts stroop performance in patients with geriatric depression. *Biological Psychiatry, 61*(8), 1007-1010.

Murphy, F. C., Michael, A., Robbins, T. W., & Sahakian, B. J. (2003). Neuropsychological impairment in patients with major depressive disorder: the effects of feedback on task performance. *Psychol Med, 33*(3), 455-467.

Nakano, Y., Baba, H., Maeshima, H., Kitajima, A., Sakai, Y., Baba, K. (2008). Executive dysfunction in medicated, remitted state of major depression. *Journal of Affective Disorders, 111*(1), 46-51.

Nebes, R. D., Butters, M. A., Houck, P. R., Zmuda, M. D., Aizenstein, H., Pollock, B. G. (2001). Dual-task performance in depressed geriatric patients. *Psychiatry Research, 102*(2), 139-151.

Nolen-Hoeksema, S. (1991). Responses to depression and their effects on the duration of depressive episodes. *Journal of Abnormal Psychology, 100*, 569-582.

Nolen-Hoeksema, S., Wisco, B. E., & Lyubomirsky, S. (2008). Rethinking Rumination. *Perspectives on Psychological Science, 3*(5), 400-424.

Ochsner, K. N., & Gross, J. J. (2005). The cognitive control of emotion. *Trends in Cognitive Science, 9*(5), 242-249.

Paxton, J. L., Barch, D. M., Racine, C. A., & Braver, T. S. (2008). Cognitive control, goal maintenance, and prefrontal function in healthy aging. *Cerebral Cortex, 18*(5), 1010-1028.

Pisljar, M., Pirtosek, Z., Repovs, G., & Grgic, M. (2008). Executive dysfunction in late-onset depression. *Psychiatria Danubina, 20*(2), 231-235.

Porter, R. J., Gallagher, P., Thompson, J. M., & Young, A. H. (2003). Neurocognitive impairment in drug-free patients with major depressive disorder. *British Journal of Psychiatry, 182*, 214-220.

Ravnkilde, B., Videbech, P., Clemmensen, K., Egander, A., Rasmussen, N. A., & Rosenberg, R. (2002). Cognitive deficits in major depression. *Scandinavian Journal of Psychology, 43*(3), 239-251.

Ridderinkhof, K. R., Ullsperger, M., Crone, E. A., & Nieuwenhuis, S. (2004). The role of the medial frontal cortex in cognitive control. *Science, 306*(5695), 443-447.

Roberts, K. L., & Hall, D. A. (2008). Examining a supramodal network for conflict processing: a systematic review and novel functional magnetic resonance imaging data for related visual and auditory stroop tasks. *Journal of Cognitive Neuroscience, 20*(6), 1063-1078.

Rogers, M. A., Kasai, K., Koji, M., Fukuda, R., Iwanami, A., Nakagome, K. (2004). Executive and prefrontal dysfunction in unipolar depression: a review of neuropsychological and imaging evidence. *Neuroscience Research, 50*(1), 1-11.

Ruchsow, M., Groen, G., Kiefer, M., Beschoner, P., Hermle, L., Ebert, D. (2008). Electrophysiological evidence for reduced inhibitory control in depressed patients in partial remission: a Go/Nogo study. *International Journal of Psychophysiology, 68*(3), 209-218.

Schulte, T., Muller-Oehring, E. M., Chanraud, S., Rosenbloom, M. J., Pfefferbaum, A., & Sullivan, E. V. (2011). Age-related reorganization of functional networks for successful conflict resolution: a combined functional and structural MRI study. *Neurobiological Aging, 32*(11), 2075-2090.

Shomstein, S. (2012). Cognitive functions of the posterior parietal cortex: top-down and bottom-up attentional control. *Frontiers in Integrative Neuroscience, 6*, 38.

Siegle, G. J., Thompson, W., Carter, C. S., Steinhauer, S. R., & Thase, M. E. (2007). Increased amygdala and decreased dorsolateral prefrontal BOLD responses in unipolar depression: related and independent features. *Biological Psychiatry, 61*(2), 198-209.

Sneed, J. R., Culang, M. E., Keilp, J. G., Rutherford, B. R., Devanand, D. P., & Roose, S. P. (2010). Antidepressant medication and executive dysfunction: a deleterious interaction in late-life depression. *American Journal of Geriatric Psychiatry, 18*(2), 128-135.

Sneed, J. R., Rindskopf, D., Steffens, D. C., Krishnan, K. R., & Roose, S. P. (2008). The vascular depression subtype: evidence of internal validity. *Biological Psychiatry, 64*(6), 491-497.

Sneed, J. R., Roose, S. P., Keilp, J. G., Krishnan, K. R., Alexopoulos, G. S., & Sackeim, H. A. (2007). Response inhibition predicts poor antidepressant treatment response in very old depressed patients. *American Journal of Geriatric Psychiatry, 15*(7), 553-563.

Treitz, F. H., Heyder, K., & Daum, I. (2007). Differential course of executive control changes during normal aging. *Neuropsychology, Development, and Cognition. Section B: Aging Neuropsychology and Cognition, 14*(4), 370-393.

Vallesi, A., Stuss, D. T., McIntosh, A. R., & Picton, T. W. (2009). Age-related differences in processing irrelevant information: evidence from event-related potentials. *Neuropsychologia, 47*(2), 577-586.

van Veen, V., & Carter, C. S. (2002a). The anterior cingulate as a conflict monitor: fMRI and ERP studies. *Physiology & Behavior, 77*(4-5), 477-482.

Van Veen, V., & Carter, C. S. (2002b). The timing of action-monitoring processes in the anterior cingulate cortex. *Journal of Cognitive Neuroscience, 14*(4), 593-602.

van Veen, V., & Carter, C. S. (2006). Error detection, correction, and prevention in the brain: a brief review of data and theories. *Clinical EEG & Neuroscience, 37*(4), 330-335.

Vanderhasselt, M. A., & De Raedt, R. (2009). Impairments in cognitive control persist during remission from depression and are related to the number of past episodes: an event related potentials study. *Biological Psychology, 81*(3), 169-176.

Wascher, E., Schneider, D., Hoffmann, S., Beste, C., & Sanger, J. When compensation fails: attentional deficits in healthy ageing caused by visual distraction. *Neuropsychologia, 50*(14), 3185-3192.

Waszak, F., Li, S. C., & Hommel, B. The development of attentional networks: cross-sectional findings from a life span sample. *Developmental Psychology, 46*(2), 337-349.

Watters, A. J., & Williams, L. M. (2011). Negative biases and risk for depression; integrating self-report and emotion task markers. *Depress Anxiety, 28*(8), 703-718.

West, R. (1999). Age differences in lapses of intention in the Stroop task. *The Journals of Gerontology. Series B, Psychological Sciences and Social Sciences, 54*(1), P34-43.

West, R. (2003). Neural correlates of cognitive control and conflict detection in the Stroop and digit-location tasks. *Neuropsychologia, 41*(8), 1122-1135.

West, R. (2004). The effects of aging on controlled attention and conflict processing in the Stroop task. *Journal of Cognitive Neuroscience, 16*(1), 103-113.

West, R., & Alain, C. (2000a). Age-related decline in inhibitory control contributes to the increased Stroop effect observed in older adults. *Psychophysiology, 37*(2), 179-189.

West, R., & Alain, C. (2000b). Effects of task context and fluctuations of attention on neural activity supporting performance of the stroop task. *Brain Research, 873*(1), 102-111.

West, R., & Baylis, G. C. (1998). Effects of increased response dominance and contextual disintegration on the Stroop interference effect in older adults. *Psychology and Aging, 13*(2), 206-217.

West, R., Jakubek, K., Wymbs, N., Perry, M., & Moore, K. (2005). Neural correlates of conflict processing. *Experimental Brain Research, 167*(1), 38-48.

West, R., Krompinger, J., Bowry, R., & Doll, R. (2004). Neural correlates of conflict monitoring and error processing. *Brain and Cognition, 54*(2), 168-170.

West, R. L. (1996). An application of prefrontal cortex function theory to cognitive aging. *Psychological Bulletin, 120*(2), 272-292.

Yeung, N., Botvinick, M. M., & Cohen, J. D. (2004). The neural basis of error detection: conflict monitoring and the error-related negativity. *Psychological Review, 111*(4), 931-959.

Zhang, B. W., Zhao, L., & Xu, J. (2007). Electrophysiological activity underlying inhibitory control processes in late-life depression: a Go/Nogo study. *Neuroscience Letters, 419*(3), 225-230.