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Cognitive Control in Late-Life Depression: Response inhibition deficits and dysfunction of the Anterior Cingulate Cortex

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Abstract

Objectives—Geriatric depression is associated with frontolimbic functional deficits, and this frontal dysfunction may underlie the marked executive control deficits often seen in this population. Our goal was to assess the integrity of frontal cortical functioning in geriatric depression while these individuals performed a standard cognitive control task. The N2 component of the event-related potential (ERP), an evoked response generated within the anterior cingulate cortex (ACC), is significantly enhanced when non-depressed individuals successfully inhibit a response, providing an excellent metric of frontal inhibitory function.

Design—We used a variant of a demanding Go/NoGo task-switching paradigm that required participants to inhibit response execution during NoGo trials by overcoming a potent response tendency established by frequent Go trials.

Participants—We compared a cohort of depressed geriatric outpatients (n=11) with a similarly aged group of non-depressed participants (n=11).

Measurements—Reaction times, accuracy and high-density ERP recordings from a 64-channel electrode montage were obtained.

Results—A significantly enhanced N2 to NoGo trials was observed in non-depressed elderly participants, with generators localized to the ACC. In contrast, this enhancement was strongly reduced in the depressed sample. Source-analysis and topographic mapping pointed to a

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displacement of N2 generators towards more posterior areas of the middle frontal gyrus in depressed subjects.

Conclusions—Findings confirm previous reports of an inhibitory control deficit in depressed elderly who show significantly increased rates of commission errors (i.e., failures to inhibit responses on NoGo trials). Electrophysiological data suggest underlying dysfunction in ACC as the basis for this deficit.

Keywords

Aging; Geriatric; Elderly; Depression; N2 component; ERP; Executive control; Anterior Cingulate Cortex; ACC; EEG; Response Inhibition

Introduction

Geriatric depression has been associated with fronto-striatal abnormalities that are thought to lead to the executive control deficits often observed in this population^{1,2}. Neuroimaging studies have shown structural abnormalities in fronto-striatal regions in depressed elderly with executive control deficits³⁻⁵. For example, Murphy et al.³ reported white-matter integrity deficits in the general vicinity of the cingulate cortex and nearby prefrontal regions that predicted performance deficits on the Stroop task in patients with geriatric depression. Functional neuroimaging studies have suggested that activation of the anterior cingulate cortex (ACC), a major node of the executive control circuit, may be particularly affected in geriatric depression^{6,7}. Various neural models of executive functioning implicate the ACC in cognitive control^{8,9} and it has been consistently shown to play a central role in response inhibition^{10, 11, 12}. In turn, deficits in response inhibition have been linked to poor treatment response to antidepressant medications in depressed elders¹³.

Variants of the Go/NoGo task paradigm are among the tasks used to interrogate the integrity of these response inhibition mechanisms in clinical populations. The Go/NoGo task requires subjects to overcome a potent response tendency established by frequent Go trials in order to successfully inhibit response execution during NoGo-trials. When non-depressed participants make successful inhibitions to NoGo trials, the N2 component of the event-related potential (ERP) is significantly enhanced compared to Go-trials¹⁴⁻¹⁶. This relative difference in N2 amplitude (termed the *N2-effect* hereafter) is used as an index of the integrity of inhibitory control mechanisms. Further, as human studies¹⁷ and intracranial recordings in non-human primates¹⁸ suggest that the ACC is a major generator of the N2, the *N2-effect* can also be interpreted as an index of ACC functional integrity.

Although the neuroimaging results detailed above suggest that there are both structural and functional deficits in ACC in geriatric depression, the few electrophysiological studies of depression using Go/NoGo tasks have not yielded a consistent pattern of results¹⁹⁻²¹ despite behavioural results that show clear deficits in inhibitory control in this population²². For example, Zhang et al.²⁰ reported a robust N2-enhancement of similar amplitude in both patients suffering from late-life depression and non-depressed subjects. Ruchow et al.²¹ investigated a middle-aged group (mean age = 40.1 years) of depressed patients in partial remission and found larger absolute N2 amplitude for NoGo-trials in their depressed cohort. A key distinction here though is between absolute N2 amplitude and the relative difference in N2-amplitude between Go and NoGo trials (i.e. the *N2-effect*). In this regard, Ruchow and colleagues found that the *N2-effect* was minimal, if not absent, in both their depressed and non-depressed participants. Kaiser et al.¹⁹, conversely, found decreased absolute N2 amplitude for NoGo-trials in depressed middle-aged participants (mean age = 40 years). Differences in age and severity of depression may have contributed to the conflicting results across these three studies and thus there is a clear need for clarification.

The present study used high-density electrical mapping of event-related potentials (ERP) to test for deficits in inhibitory control in late-life depression. A task-switching paradigm was implemented involving response execution (Go) and response withholding (NoGo). Topographical mapping and source localization were used to investigate the spatiotemporal characteristics and neural generators of the *N2-effect* in late-life depression.

Methods

Participants

Eleven non-demented, depressed patients (six male) with non-psychotic major depression (by SCID, DSM-IV; and a 24-item baseline Hamilton Depression Rating Scale [HDRS; score of 17 or higher]) participated in this study. Of the eleven patients diagnosed with MDD, four were taking selective serotonin reuptake inhibitors. Mean age of the patient group was 73.4 years. Eleven non-depressed community dwelling participants (five male) without a history of psychiatric illness served as a comparison group (average age of 73.1 years). The non-psychiatric comparison group was screened with the Geriatric Depression Scale (GDS)²³ and an exclusion criterion was set at a GDS score > 6. These participants were not assessed with the HDRS. Cognitive function in the depressed and non-depressed comparison group was assessed with the Mini-Mental Status Exam (MMSE)²⁴. Exclusion criteria included a MMSE score < 26 and corrected vision that was worse than 20/40. All subjects signed informed consent and the Institutional Review Board of the Nathan Kline Institute for Psychiatric Research approved all the procedures in accordance with the tenets of the Declaration of Helsinki.

Stimuli

We presented letter-number pairs as stimuli in this experiment, identical to those employed by Wylie and colleagues²⁵⁻²⁷. The letters were drawn from a set containing four vowels (A E I U) and four consonants (G K M R). The numbers were drawn from a set containing four even numbers (2 4 6 8) and four odd numbers (3 5 7 9). On every trial, one letter and one number were randomly chosen with the constraint that neither the letter nor the number was the same as those presented on the previous trial. One of these characters was presented 1° to the left of central fixation and the other was presented 1° to the right of fixation (this was randomly determined). All stimuli subtended 1.6° in the horizontal plane and 1° in the vertical plane (duration = 120 ms). The stimulus onset asynchrony (SOA) was 2000 ms. The stimuli were colored: for three trials in a row, they were red, for the next three they were purple, for the next three they were red, and so on. In total, 150 stimuli were presented in a single block of trials.

Behavioral Task & Analysis

The experimental paradigm used in this study was originally instituted to investigate another aspect of cognitive control, namely task-switching, but this task allows for a straightforward assessment of response-inhibition mechanisms without any explicit modification. For three trials in succession, the stimuli were colored red, and for the next three they were colored purple. This triple-alternating sequence was repeated throughout the experiment. When the stimuli were presented in red, participants were instructed to attend to the letter and respond (Go) when a vowel was present. When the stimuli were purple, participants were instructed to attend to the number and respond (Go) when an even number was present. Otherwise, they were instructed to withhold a response (NoGo).

The colors of the alphanumeric stimuli were counterbalanced (50/50) throughout the experiment. Participants responded by pressing a button with their right forefinger. As participants responded, accuracy (in the form of hits and correct rejection) and response time

were recorded. Accuracy and response time were analyzed using independent-sample *t*-tests between groups.

ERP Recordings & Analysis

High-density event-related brain potentials (ERPs) were acquired using the Neuroscan Synamp I system from a 64 channel scalp montage (impedances $<5\text{ k}\Omega$), referenced to an electrode on the nosetip, band-pass filtered (between 0.05 and 100 Hz), and digitized at 500 Hz. Epochs of 700 ms were employed including a 100 ms pre-stimulus baseline. Trials with blinks and eye movements were rejected offline on the basis of vertical and horizontal EOG. An automatic artefact rejection criterion of $\pm 70\mu\text{Vs}$ was used for all other scalp recordings. The grand average was subsequently low-pass filtered at 40 Hz (48dB/Octave) and high-pass filtered at 1.6 Hz (6 dB/Octave). N2 amplitude was measured at electrode position AFz, AF3/AF4, and FP1/FP2. The *N2-effect* was statistically assessed by applying Analysis of Variance (ANOVA) to peak amplitude measures in a time window spanning from 250-350 ms and derived from the fronto-central scalp site AFz where visual inspection showed that the *N2-effect* was at its strongest in our data. The ANOVA was calculated with the between-subject factor *Group* (depressed versus non-depressed participants) and the within-subject factor *Trial* (Go versus NoGo). It is important to note that only trials on which subjects performed successfully were included in the ERP analysis. That is, trials upon which commission errors were made or targets missed were excluded from this analysis.

Topographic voltage maps

Scalp topographic maps in the present study represent interpolated voltage distributions, derived from 64-scalp measurements. These interpolated potential maps are displayed on the 3-D reconstruction of a rendered scalp surface (derived from an anatomical MRI) as implemented in the BESA2000 (Ver. 5.0) multimodal neuroimaging analysis software package (MEGIS Software GmbH, Munich, Germany).

Statistical cluster plot

For exploratory purposes, point-wise two-tailed *t*-tests for the Go-ERP and NoGo-ERP (between groups) and between Go-ERP and NoGo-ERP (within groups) were calculated at each time-point for all electrodes. The results of the point-wise *t*-tests from 64 electrodes are displayed as an intensity plot to efficiently summarize and facilitate identification of differences within and between groups in the onset and general topographic distribution of differential activation associated with the Go-ERP and NoGo-ERP. The x-, y-, and z- axes, respectively, represent time, electrode location, and *t* test result (indicated by a color value) for each data point. This approach offers a statistical cluster plot^{28,29} identifying differences between depressed and non-depressed participants in general scalp distribution and onset of differential ERP-response across the entire epoch. We are aware that conclusions based on statistical cluster plots are undermined due to the large number of *t* tests calculated across the electrode montage and recording epoch. In the present data treatment, periods of significant difference were only plotted if an alpha criterion of 0.05 or less was obtained and then only if this criterion was obtained for at least 11 consecutive data points ($> 22\text{ms}$ at a 500Hz digitization rate - see^{30,31} for similar approaches).

Source model

We used Brain Electric Source Analysis software (BESA 5.1. software^{32,33}) for source modeling. The main premise of this software is that an observable deflection in the EEG recording is related to a change in the local activity of a particular brain region. Therefore, a component can be defined as the part of the scalp waveform that results from the compound

local activity of a circumscribed brain region³². BESA employs a least squares fitting algorithm, over which the user has interactive control. Source localization involves searching within the head model for a location where the sources can explain a maximal amount of variance³⁴. Here, we proceeded by using dipoles that were freely fitted. Note, that in dipole source analysis the modeled dipoles represent an oversimplification of the activity in the areas and should be considered as representative of centers of gravity of the observed activity rather than an exact localizations of generators^{17,29,35}.

Results

Table 1 shows reaction time (RT) and accuracy (hits and false alarms) data for both groups. Mean RT for depressed (766 ms) and non-depressed participants (789 ms) in Go trials did not differ from each other ($t_{20} = 0.82$, $p = 0.96$). However, the depressed participants showed a significantly reduced hit rate ($t_{20} = 9.7$, $p < .0001$) and increased false alarm rate ($t_{20} = -3.1$, $p < .01$) when compared to the non-depressed subjects.

Figure 1 displays the ERP in Go and NoGo trials for both depressed and non-depressed groups at frontal electrode sites. The earliest difference in ERP activity between Go and NoGo trials can be seen within the N2 time frame from 250 to 350 ms. Here, an enhanced N2 amplitude in NoGo trials compared to Go trials was evident for the non-depressed group. In contrast, for the depressed group this N2-difference was minimal at best. A 2-way ANOVA assessing the N2-effect at electrode site AFz confirmed a significant Group by Trial interaction ($F_{1,19} = 6.94$, $p < .016$).

A pair of protected follow-up t-tests revealed significantly enhanced N2 amplitude to NoGo trials for the non-depressed group ($t_{10} = 6.3$, $p < .0001$). In contrast, there was no such N2-effect for the depressed group ($t_{10} = 1.3$, $p = .42$). Figure 2 presents a statistical cluster plot marking onset and topographical distribution of ERP modulations between Go and NoGo trials in depressed and non-depressed participants. Only the non-depressed group demonstrated the N2-effect seen as a first cluster of differential activation (onset marked by a vertical white line) at approximately 310 ms over frontal scalp region. A second cluster of activation starting at approximately 400 ms and extending to fronto-parietal areas is evident in both depressed and non-depressed participants, although much attenuated in the latter.

Figure 3 (upper panel) illustrates scalp potential maps for the N2-effect at peak latency for geriatric depressed and non-depressed participants. The distribution in non-depressed participants revealed a confined maximum over fronto-polar scalp regions. In contrast, the depressed group showed a far less defined topography with a broader maximum spreading over central scalp regions.

Figure 3 (lower panel) illustrates source localization analysis in each group carried out over the maximal N2 time-window from 250 to 350 ms, where significant differences between Go and NoGo conditions were observed in non-depressed participants. Source analysis was performed for the N2 component in NoGo trials and not on the N2-effect. This was done because there was no significant N2-effect in our depressed sample. To be able to perform source analysis in both groups we chose to localize the N2 component. Source analysis was achieved with three dipoles in each group (Figure 3). The first step of the fitting procedure required the use of a pair of symmetric dipoles. A freely fitted third dipole was added to the model in the second step. The entire model was then tested for stability. The positions of the symmetric dipoles in both samples indicated a similar location in bilateral medial temporal gyrus (MTG). The location of the third dipole was however different in the two groups: for the non-depressed group, this dipole was located in the ACC, while for the depressed group this third dipole was located in the medial frontal gyrus (MFG) in Brodmann's Area 6, near

the posterior cingulate gyrus and in the vicinity of the Supplementary Motor Area (SMA). The Source Analysis procedure for the depressed group produced a goodness-of-fit value of 98.6% (residual variance = 1.4%) across the specified time window. The model derived for the non-depressed group produced a goodness-of-fit value of 90% (residual variance = 10%). The addition of a test dipole to the original dipole solution did not significantly affect the explained variance, suggesting that three dipole sources provided an optimal solution across the epoch.

Discussion

The principal finding of the current study is that patients suffering from geriatric depression displayed a much-attenuated *N2-effect* when compared to non-depressed elders. Source-analysis and topographic mapping pointed to a predominantly midline frontal generator of this *N2-effect*, which was localized to the Anterior Cingulate Cortex (ACC) in the non-depressed group. In contrast, there was an apparent displacement of N2 generators towards more posterior areas of the middle frontal gyrus in the depressed group. There is substantial support from source-localization studies^{17,36,37} and from intracranial recordings in non-human primates¹⁸ that the N2 is generated in large part within the ACC, and as such, the results here suggest a specific involvement of the ACC in the inhibitory response deficits seen in depressed elders. The presence of a deficit in inhibitory control in this depressed elderly group was also evidenced by their significantly increased rate of commission errors. Our data suggest that the deficit might be attributed to a diminished contribution of specialized brain regions, with the depressed group less able to engage the relevant neural circuits associated with inhibitory control^{16,38-40}.

As outlined in the introduction, electrophysiological studies of inhibitory control deficits in midlife and late-life depression using the Go/NoGo task have provided inconsistent results¹⁹⁻²¹. Previous studies have either found significant *N2-effects* of similar amplitude between groups²⁰ or diminished, non-significant ones in both, depressed and non-depressed participants²¹. Here we report a strongly reduced *N2-effect* in geriatric depressed compared to non-depressed participants. It is possible that some of this inconsistency stems from design differences between studies. For instance, one major difference in the present study is that we asked participants to perform a Go/NoGo-task in the context of an ongoing task-switching paradigm. Given the second level of task-demand inherent in our study, there is significantly greater cognitive “overhead” under the present design than in the previous studies and this is borne out if one examines the average RTs reported in each of those studies. That is, in comparison to previous studies, RTs here are approximately 400 ms longer and P300 latency is also about 100 ms later in the present study, bearing out the fact that task-load under the current design was considerably higher. As such, control processes were likely taxed to a much greater degree in this study and this may have resulted in a relative unmasking of the inhibitory deficits in the depressed group. The only other ERP study using a Go-NoGo task with a focus on geriatric depression found a robust *N2-effect* of similar amplitude in both depressed and non-depressed participants²⁰. The groups of geriatric depressed in both studies are comparable in age and severity of depression. However, Zhang and colleagues²⁰ used a very basic visual Go-NoGo task that had only a single task-dimension. Average RTs in their study were approximately 370 ms for both groups as opposed to 750 ms here. One clear implication is that response inhibition circuits may operate normally or near-normally under low-task demands in depressed elderly but that they are highly susceptible to failure when task demands increase. A systematic study of the effects of task-demand will be needed to assess this hypothesis.

In addition to the well-established role of the ACC in cognitive control, there is also accumulating evidence for a role for the ACC in mediating antidepressant treatment

response of depression^{2,41,42}. For example, in a pre/post antidepressant treatment trial where escitalopram was administered over a 12-week controlled period, Gunning et al.⁴² reported that patients who failed to remit also had smaller dorsal and rostral ACC gray matter volumes. Aizenstein et al.⁴¹ also showed pretreatment diminished activity in the dorsolateral PFC and diminished functional connectivity between dorsolateral PFC and dorsal ACC. In a similar vein, Alexopoulos et al.² studied evoked potentials related to error commission in a depressed sample of older adults and reported patients who remained symptomatic after 8 weeks of treatment showed significantly larger baseline error-related negativity (ERN) and diminished Error Positivity (Pe) relative to those patients who achieved remission after a treatment trial of 10 mg of escitalopram daily. The two response-locked evoked potentials were studied during an emotional go/no-go challenge, a task known to activate the rostral anterior cingulate. The ERN is thought to be elicited during conflict detection and the Pe in turn is thought to reflect the subsequent emotional evaluation/reaction to an error. Thus, these findings suggest that two distinct conflict-processing functions of the anterior cingulate are important for antidepressant response in geriatric depression, and that dysfunction in the ACC may underlie the common finding that many patients with late-life depression are resistant to standard antidepressant treatments.

Conclusions

While structural neuroimaging studies have consistently pointed to dysfunction in the ACC as an important neural substrate in geriatric depression, electrophysiological studies of ACC function have been considerably less consistent in their findings. Here, using a well-characterized and highly challenging task-switching design, we assessed response inhibition mechanisms in the ACC as reflected by the N2 ERP component and the *N2-effect*. Our data suggest clear differences between non-depressed elderly participants and those suffering from late-life depression, in that non-depressed participants showed a robust *N2-effect* whereas this effect was absent in the depressed cohort. These data suggest functional deficits in the ACC during response inhibition processes and suggest that these deficits in depressed subjects may only become apparent under high-load conditions when this system is particularly taxed.

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Figure 1. Grand mean ERPs for depressed and non-depressed groups at electrode sites AFz, AF3, AF4, FP1 and FP2. The N2 enhancement seen in the non-depressed group (left, bottom panel) is substantially reduced for the depressed group (right, bottom panel).

Figure 2.

Statistical Cluster Plots. Color values indicate the result of pointwise, t -tests evaluating differences between Go- and NoGo-trials evoked activity across time (x -axis) and electrode positions (y -axis) for the entire 64-electrode montage. For clarity, only p values $< .05$ are color encoded. An early cluster at about 300 ms over the anterior frontal region indicating the N2 enhancement is present in non-depressed participants and absent for the geriatric depressed. A second cluster starting at about 400 ms spreading across frontal to occipital regions is seen in non-depressed participants and also in an attenuated form in the depressed group.

Figure 3.

Topographic mapping of spline-interpolated potential distributions are plotted at the peak of the N2 effect for non-depressed comparison and geriatric depressed groups. A clear defined distribution with a maximum over fronto-polar scalp region is evident in non-depressed participants. In contrast, geriatric depressed show a broader less defined maximum spreading over central scalp regions. Source solutions for a 250-350 ms time window for both the non-depressed and depressed groups are displayed. The middle row shows a coronal view of two free-fitting dipoles (in red and blue) for non-depressed participants and patients, respectively. Dipoles were localized to the Medial Temporal Gyrus (MTG) within 3mm circumference of nearest grey matter for both groups. The bottom row displays the sagittal view of the third dipole moment (green) for non-depressed and depressed groups. The dipole for the non-depressed group was localized to the anterior cingulate cortex (ACC) whereas the dipole for the depressed group was localized more posteriorly within the medial frontal gyrus (MFG), in the vicinity of the Supplementary Motor Area (SMA).

Table 1
Demographics, Screening Test Scores, and Performance Measures

Characteristic	<i>Health Non Depressed (N=11)</i>		<i>Geriatric Depressed (N=11)</i>	
	Means	SD	Mean	SD
Age (years)	73.1	5.36	73.4	7.04
Education (years)	15.1	2.47	16.4	2.61
HDRS *	N/A	N/A	20	4.51
GDS **	4.2	0.9	N/A	N/A
MMSE ***	28	1.21	28	2.91
False A. in %	3.86	2.2	11.1	8.3
Hits in %	65.4	7.8	43.4	5.8
RT in ms	789	88.0	766	117.1

* 24 item Hamilton Depression Rating Scale

** Geriatric Depression Scale

*** Mini-Mental Status Exam