Prefrontal and Striatal Activation During Sequence Learning in Geriatric Depression

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Background: *Frontostriatal dysfunction is a primary hypothesis for the neurocognitive changes of depression in late life. The aim of the present study was to test this hypothesis with the use of functional magnetic resonance imaging (fMRI) tasks that are known to engage the prefrontal and neostriatal cognitive circuits.*

Methods: *Twenty-three elderly subjects (mean age, 69.9 years) participated: 11 subjects with a current major depressive episode and 12 nondepressed elderly control subjects. Subjects underwent fMRI while performing a concurrent implicit and explicit sequence learning task. Region of interest (ROI)-based analyses were conducted, focusing on the dorsal anterior cingulate cortex, the dorsolateral prefrontal cortex, and the neostriatum.*

Results: *As expected, both the control and depressed subjects learned the sequence during both implicit and explicit conditions. During explicit learning, decreased prefrontal activation was found in the depressed subjects, along with increased striatal activation. The increased striatal activity in the depressed subjects was due to increased activity on the trials that violated the sequence. During implicit learning, no significant differences were found between the groups in the identified ROIs.*

Conclusions: *The increased striatal activation on trials that violated the sequence demonstrates a greater response to negative feedback for depressed compared with control subjects. Our observations of significant differences in both prefrontal and striatal regions in the depressed elderly subjects relative to elderly control subjects supports the frontostriatal dysfunction hypothesis of late-life depression.*

Key Words: fMRI, depression, aging, implicit learning, sequence learning, serial reaction time, striatum, prefrontal cortex

Geriatric depression is a major public health problem, affecting approximately 15% of individuals over the age of 65 years. For these individuals, current treatments have limited efficacy, with approximately 40%–50% of elderly individuals with depression having a delayed or partial response to first-line antidepressant treatment (Lebowitz et al 1997). A prominent theory for delayed or brittle response in late-life depression (LLD) is that the neuropathology in geriatric depression is distinguished by cerebrovascular and/or neurodegenerative changes that are associated with dysfunction in frontostriatal cognitive circuits.

Convergent evidence from structural neuroimaging, diffusion tensor imaging, cognitive assessment, and electrophysiologic studies supports the frontostriatal hypothesis of LLD (Alexopoulos et al 2002b). Structural magnetic resonance imaging (MRI), diffusion tensor imaging, and magnetic resonance spectroscopy studies (Alexopolous et al 2002a; Hickie 1997; Krishnan et al 1997; Kumar et al 2002; Taylor et al 2004) have shown that elderly depressed individuals have higher rates (compared with age-matched control subjects) of gray and white matter brain structural changes affecting frontal and subcortical areas, and consistent with small vessel ischemic disease. Cognitive assessment in LLD shows a pattern of impairment in executive tasks and slowed information processing speed, also suggestive of dysfunction of frontal and striatal cognitive circuits (e.g., Butters et al 2004). Functional imaging studies in geriatric depression have shown decreased resting cerebral blood flow and glucose metabolism in prefrontal and anterior cingulate (reviewed in Nobler et al 1999); however, the relationship of functional changes in frontostriatal regions to cognitive function has not yet been demonstrated and is the focus of the present study.

The frontostriatal dysfunction hypothesis of LLD predicts that tasks that engage prefrontal cortex (PFC), anterior cingulate cortex, and neostriatum should show decreased activation in elderly depressed subjects relative to nondepressed comparison subjects. The present study tested this prediction with the use of an implicit and explicit sequence learning task, which was chosen because it is known to engage these regions in both young and elderly subjects (Aizenstein et al 2004; Aizenstein et al, in press). Studies have suggested that implicit and explicit learning use different neural systems (e.g., Nissen and Bullemer 1987) and thus provide a means of separately engaging prefrontal, medial temporal, and striatal brain regions. Recent functional imaging studies (Aizenstein et al 2004; Willingham et al 2002) have also emphasized the overlap of both striatal and prefrontal activation when the implicit and explicit tasks both involve sequential learning, such as in the present study.

Methods and Materials

Research Participants

Twenty-seven subjects completed MR scanning as part of this study; however, data from three subjects (one depressed subject and two control subjects) were unusable owing to computer malfunction, and evidence of a subcortical stroke was identified during the structural scan on one control subject. Data from the remaining 23 subjects were analyzed. These included 12 elderly control subjects (6 male, aged 68.7 ± 6.0 years [mean ± SD]) and 11 elderly subjects with major depressive disorder (MDD), currently in a major depressive episode (Hamilton Rating Scale for Depression score = 18.5 ± 4.8) (5 male, aged 71.3 ± 6.3 years). The Structured Clinical Interview for DSM-IV Diagnosis (SCID-IV) was used to standardize the inclusion criteria for MDD

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Table 1. Demographic Data for Depressed and Nondepressed (Control) Elderly Subjects

	Elderly Control Subjects	Depressed Subjects
n	12	11
Age (y)	68.7 (6.00)	71.3 (6.26)
Gender	6 M, 6 F	5 M, 6 F
Race	10 C, 2 AA	11 C
Handedness	12 R	11 R
17-Item Hamilton Rating Scale for Depression Rating Score	1.6 (1.7)	18.5 (4.8)
Age of Depression Onset (y)	N/A	67.6 (7.2)
Mini-Mental Status Examination Score	29.3 (1.15)	27.45 (3.72)

Numbers in parentheses are SD. M, male; F, female; C, Caucasian; AA, African American; R, right; N/A, not applicable.

and the age of depression onset. All subjects (control and depressed) received a SCID-IV evaluation, which was reviewed in a diagnostic consensus conference. Other than MDD (for subjects in the depressed group) and the anxiety disorders, all other Axis I psychiatric disorders were used as exclusion criteria. Subjects were also excluded for a prior history of stroke or significant head injury and Alzheimer's, Parkinson's, and Huntington's disease. We chose to include subjects with comorbid anxiety disorders owing to the high prevalence (48%) of anxiety disorders in subjects with LLD (Beekman et al 2000). Five of the eleven LLD subjects and 2 of the 12 control subjects met criteria for an anxiety disorder. In almost all cases the anxiety disorder was generalized anxiety disorder, but there were also individual cases of specific phobia, posttraumatic stress disorder, social phobia, and anxiety disorder not otherwise specified. All depressed subjects had late-onset LLD, with their first episode of depression starting after the age of 50 years (age of depression onset = 67.6 ± 7.2 years). All subjects were right-handed. Demographic data for the included subjects are shown in Table 1.

Both control and depressed elderly subjects were recruited through the Intervention Research Center for Late-Life Mood Disorders (Western Psychiatric Institute and Clinic, Pittsburgh, Pennsylvania). The depressed subjects were recruited from an ongoing treatment study of paroxetine for major depression (the second Pittsburgh study of maintenance therapies in LLD; described in Szanto et al 2003). Subjects underwent functional MRI (fMRI) scanning before starting antidepressant medication. The Mini-Mental State Examination (MMSE; Folstein et al 1975) score for the elderly control subjects was 29.3 ± 1.15 and for the depressed subjects was 27.45 ± 3.72. There was not a significant difference in MMSE scores between the groups [$t(21) = 1.66$, $p = .11$]. Informed consent was obtained before scanning through procedures approved by the University of Pittsburgh Institutional Review Board. Each subject was paid $50 for his or her participation. Subjects were excluded if they were taking psychotropic medications. Subjects were psychotropic free for at least 2 weeks before imaging. Medications other than antidepressants were acceptable, because medication use is common in the elderly population. Medication use included antihypertensives, thyroid replacement medication, hormone replacement therapy, cholesterol-lowering medication, and gingko biloba. Medication use was distributed similarly between the depressed and control subjects.

Procedure

The sequence learning task involved concurrent implicit and explicit components. The task is a variation of the serial reaction time (RT) task, similar to that described by Howard and Howard (1997) and Jiminez and Mendez (1999). The sequence learning task is briefly described below; further details are provided elsewhere (Aizenstein et al 2004; Aizenstein et al, in press).

Sequence Learning Stimuli

Each subject viewed eight different sequences of 85 colored shapes. Three colors (red, green, and blue) and three shapes (circle, square, and triangle) were used. The sequence of colors and shapes was determined independently with two different first-order Markov chains (i.e., the probability distribution of states at time $i+1$ is completely determined by the state at time i; see Figure 1). At each state in the Markov chain, the next color had a 70% chance of following in the set order (e.g., red, green, blue) and a 30% chance of violating the set order (i.e., either repeating or skipping a position). Similarly, the next shape had a 70% chance of following a set order of shapes and a 30% chance of violating the order.

Sequence Learning Procedure

Each stimulus appeared in the center of the screen. After 750 msec, the red, green, or blue stimulus changed to white (i.e., a white circle, square, or triangle on a black background). The subject was instructed to look at each colored shape and respond to the color as quickly and accurately as possible by pressing the button corresponding to the color. The white shape stayed on the screen for an additional 750 msec. A fixation stimulus was then displayed on the screen for 500 msec, until the onset of the next trial.

Participants were instructed that although they were to respond as quickly as possible to the color, they were also to look for a sequential pattern in the shapes. They were told that the sequential pattern did not always hold but that they should look for one and report this after each of the learning blocks. As described, the shapes did follow a sequence determined by the Markov chain (Figure 1B). Learning the sequence in shapes was the explicit learning component of the task. Unbeknownst to the

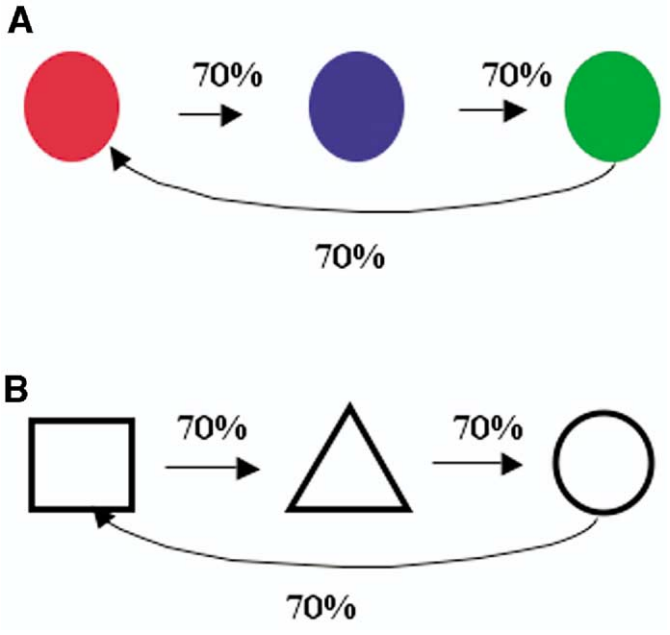

Figure 1. Markov chains that generate the color **(A)** and shape **(B)** sequences.