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Differential associations between types of verbal memory and prefrontal brain structure in healthy aging and late life depression

Melissa Lamar*, Rebecca Charlton, Aifeng Zhang, Anand Kumar

University of Illinois at Chicago, Department of Psychiatry, 1601 West Taylor Street (MC912), Chicago, IL 60612, USA

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ABSTRACT

Verbal memory deficits attributed to late life depression (LLD) may result from executive dysfunction that is more detrimental to list-learning than story-based recall when compared to healthy aging. Despite these behavioral dissociations, little work has been done investigating related neuroanatomical dissociations across types of verbal memory performance in LLD. We compared list-learning to story-based memory performance in 24 non-demented individuals with LLD (age$\sim$66.1 $\pm$ 7.8) and 41 non-demented/non-depressed healthy controls (HC; age$\sim$67.6 $\pm$ 5.3). We correlated significant results of between-group analyses across memory performance variables with brain volumes of frontal, temporal and parietal regions known to be involved with verbal learning and memory. When compared to the HC group, the LLD group showed significantly lower verbal memory performance for spontaneous recall after repeated exposure and after a long-delay but only for the list-learning task; groups did not differ on story-based memory performance. Despite equivalent brain volumes across regions, only the LLD group showed brain associations with verbal memory performance and only for the list-learning task. Specifically, frontal volumes important for subjective organization and response monitoring correlated with list-learning performance in the LLD group. This study is the first to demonstrate neuroanatomical dissociations across types of verbal memory performance in individuals with LLD. Results provide structural evidence for the behavioral dissociations between list-learning and story-based recall in LLD when compared to healthy aging. More specifically, it points toward a network of predominantly anterior brain regions that may underlie the executive contribution to list-learning in older adults with depression.

1. Introduction

Late-life depression (LLD) is the most commonly diagnosed psychiatric disorder in adults over 60 years of age, affecting upwards of 16% of this aging population. LLD has significant implications for quality of life and independent living (Blazer, 2003) given that it may increase vulnerability to and exacerbation of existing age-related cognitive deficits. Although there is some debate over the profile and significance of the cognitive deficits, lower performance across episodic memory, information processing, executive functioning and visuospatial abilities have been reported when compared to healthy controls (see McClintock, Husain, Greer, & Cullum, 2010 for review). After treatment, some of these deficits resolve; however, deficits in executive functioning have been shown to persist following both treatment and remission of LLD (Alexopoulos et al., 2000, 2005; Kalayam & Alexopoulos, 1999) suggesting that there are residual executive deficits associated with LLD that may negatively impact other cognitive processes.

Verbal memory deficits attributed to LLD may result from these residual executive deficits, negatively impacting specific forms of recall performance. For example, impaired semantic organization – a skill often associated with executive functioning (Delis, Kramer, Kaplan, & Ober, 2000) – mediated performance on verbal list-learning from the California Verbal Learning Test (CVLT) in LLD but not healthy aging (Elderkin-Thompson, Mintz, Haroon, Lavretsky, & Kumar, 2006). The contribution of executive functioning to verbal memory performance was not replicated when tested via story-based recall as measured by the Logical Memory subtest (LM) of the WMS-III across aging populations with depression (Keiski, Shore, & Hamilton, 2007). In fact, successful performance on LM predicts successful treatment response in LLD (Story, Potter, Attix, Welsh-Bohmer, & Steffens, 2008) whereas executive dysfunction negatively impacts treatment response and remission rates in LLD (Alexopoulos et al., 2000). Taken together this would suggest that story-based verbal recall is not contingent upon executive function or dysfunction in LLD. Thus, executive deficits in LLD appear more detrimental to list-learning given the heavier (executive)

* Corresponding author. Tel.: +1 312 996 5779; fax: +1 312 996 7658.
E-mail address: mlamar@psych.uic.edu (M. Lamar).

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burden placed on individuals during list-learning tasks (e.g., the subjective organization of individually presented items heavily reliant on executive processes; Moscovitch & Winocur, 2002) when compared to story-based recall that provides contextually-based information (Rabin et al., 2009).

While this behavioral dissociation may have implications for predicting treatment response and facilitating learning and memory in older adults with LLD, identifying individuals for treatment or determining the best time to implement compensation strategies remains difficult. Investigating the underlying neuro anatomical dissociations of previously determined behavioral dissociations in verbal memory performance in LLD may assist clinicians in timing and targeting specific remediation techniques in this vulnerable population. To our knowledge, little to no work has been done examining the neuroanatomical dissociations associated with verbal memory performance in LLD compared to healthy aging despite the literature exploring neuroanatomical alterations within and between these groups of older adults.

Cerebral gray and white matter of individuals with LLD as well as healthy older adults shows age-related change; however, individuals with LLD also show disease-specific differences when compared to their healthy aging counterparts. Briefly, individuals with LLD show volumetric changes in gray matter structures including the orbitofrontal and dorsolateral prefrontal regions (Ballmaier et al., 2004; Chang et al., 2011; Taylor et al., 2007) as well as in temporal and subcortical structures including the hippocampus and anterior cingulate (Ballmaier et al., 2004, 2008; Dotson, Davatzikos, Kraut, & Resnick, 2009; Lavretsky, Ballmaier, Pham, Toga, & Kumar, 2007) when compared to healthy controls. In addition, individuals with LLD show added white matter burden when compared to healthy controls (O'Brien et al., 2006) and regional vulnerability within prefrontal white matter regions (Bae et al., 2006) when compared to healthy controls. The degree to which alterations in brain volume – particularly gray matter structures known to play an important role in learning and memory such as the hippocampus, orbitofrontal and dorsolateral prefrontal regions (see Blumenfeld & Ranganath, 2007; Squire, Stark, & Clark, 2004 for review) – contribute to list-learning versus story-based recall performance in LLD when compared to healthy controls (HC) is unknown.

The aim of the current research was to combine behavioral measures of verbal memory with neuroanatomical measures of gray matter volumes to investigate the dissociations between structure and function of verbal memory performance in LLD and HC groups. Thus, we combined previously applied and well known clinical measures of list-learning (i.e., the CVLT) and story-based (i.e., LM) verbal recall performance with MRI-derived volumes of cerebral gray matter regions chosen based on their documented involvement in learning and memory (see Blumenfeld & Ranganath, 2007; Squire et al., 2004 for review). In addition to temporal regions targeted for their role in encoding and consolidation of information for long term memory stores (e.g., hippocampal regions including the entorhinal cortex), we included more anterior regions of prefrontal and cingulate cortices associated not only with memory processes (see Blumenfeld & Ranganath, 2007; Squire et al., 2004 for review) but also LLD (e.g., Ballmaier et al., 2004). This study is one of, if not the first of its kind to investigate the neuroanatomy associated with verbal memory performance dissociations in LLD.

Previous work in healthy older adults (Van Petten et al., 2004) has shown patterns of negative correlations between episodic memory performance (i.e., list-learning and story-based recall) and gray matter volumes (i.e., middle frontal and most temporal regions); however, we hypothesize that specific patterns of associations will exist for list-learning compared to story-based recall of verbally mediated information within the LLD group when compared to the HC group. More specifically, the LLD group will show lower levels of performance when compared to the HC group on the list-learning task only. Additionally, regions of the prefrontal cortex will correlate more strongly with list-learning than story-based recall in the LLD group when compared to the HC group.

2. Methods

2.1. Participants

Data were collected as part of a larger research study investigating late life depression (LLD) at the University of Illinois at Chicago (UIC). Individuals age 60 and older were recruited via community outreach (e.g., newspaper, radio, and television advertisements) and relevant outpatient clinics within the School of Medicine (e.g., mood and anxiety, geriatrics). The study was approved by the UIC Institutional Review Board and conducted in accordance with the Declaration of Helsinki.

All participants underwent a preliminary telephone screen. Exclusion criteria consisted of current or past history of brain disorders (i.e., dementia, stroke, seizure, etc.), a history of head injury or loss of consciousness, a present or past history of substance abuse or dependence, an Axis I disorder other than major depression (i.e., bipolar disorder), psychotropic medication use including anti-depressant medication and the presence of metallic implant(s) that would preclude magnetic resonance imaging (MRI). Thus, all study participants, including those diagnosed with major depression (see below) were free of anti-depressant medication for at least two weeks in order to study depressed mood in an untreated state.

After passing the telephone screen, participants were scheduled for a more detailed evaluation which included cognitive, i.e., Mini-Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975) and affective, i.e., Structured Clinical Interview for DSM-IV (SCID; Spitzer, Williams, Gibbon, & First, 1992) screens for final inclusion and exclusion determination. Screening measures were administered by a trained research assistant and followed by an evaluation by a board certified (AK) or board eligible (OA) psychiatrist who completed the Hamilton Depression Rating Scale (HDRS; Hamilton, 1960). All raters were blind to telephone screen information.

Final inclusion criteria for adults with LLD included a diagnosis of major depressive disorder based on the SCID and a score ≥ 15 on the 17-item HDRS. Thus, at the time of the study, individuals with LLD were in a major depressive episode and at the moderately depressed level or higher given the average HDRS score for this group (18.6 ± 3.1). Inclusion criteria for healthy control (HC) participants included an absence of symptoms of depression based on the SCID and a score ≤ 8 on the HDRS. All subjects, regardless of group, had an MMSE score ≥ 24 and were native English speakers. All study participants completed the Center for Epidemiological Studies Depression scale (CESD; Radloff, 1977; Radloff & Teri, 1986) for a more subjective measure of depressive symtomatology independent of diagnostic criteria.

Participants also received an assessment of vascular risk using the criteria provided by the Framingham Heart Study's Stroke Risk Profile (Wolf, D'Agostino, Belanger, & Kannel, 1991) given the impact of vascular risk on aging, cognition and depressive symptomatology (Alexopoulos et al., 1997; Au et al., 2006). The Framingham Stroke Risk Profile (FSRP) determines stroke risk based on data from the Framingham Heart Study using age, systolic blood pressure, anti-hypertensive therapy, diabetes mellitus, current cigarette smoking, cardiovascular disease, atrial fibrillation, and left ventricular hypertrophy. Laboratory testing documented levels of health related variables (i.e., hypercholesterolemia and glucose levels) and an electrocardiogram assessed for atrial fibrillation and left ventricular