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Selective verbal recognition memory impairments are associated with atrophy of the language network in non-semantic variants of primary progressive aphasia

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ABSTRACT

Primary progressive aphasia (PPA) is clinically defined by an initial loss of language function and preservation of other cognitive abilities, including episodic memory. While PPA primarily affects the left-lateralized perisylvian language network, some clinical neuropsychological tests suggest concurrent initial memory loss. The goal of this study was to test recognition memory of objects and words in the visual and auditory modality to separate language-processing impairments from retentive memory in PPA. Individuals with non-semantic PPA had longer reaction times and higher false alarms for auditory word stimuli compared to visual object stimuli. Moreover, false alarms for auditory word recognition memory were related to cortical thickness within the left inferior frontal gyrus and left temporal pole, while false alarms for visual object recognition memory was related to cortical thickness within the right-temporal pole. This pattern of results suggests that specific vulnerability in processing verbal stimuli can hinder episodic memory in PPA, and provides evidence for differential contributions of the left and right temporal poles in word and object recognition memory.

1. Introduction

Primary progressive aphasia (PPA) is a neurodegenerative dementia syndrome clinically characterized by the selective loss of language and initial preservation of other cognitive abilities, including episodic memory (Mesulam, 2003). Despite the prevailing notion that PPA primarily affects language, some studies have reported initial memory deficits (Hutchinson and Mathias, 2007; Zakzanis, 1999). However, the verbal assessment methods used in these studies could not determine whether the problem was secondary to the aphasia or also indicative of a general episodic memory failure.

Episodic memory depends on effective stimulus processing and successful binding into a durable representation (Eichenbaum, 2000). Poor verbal memory in PPA could therefore be due to upstream deficiencies in stimulus processing (a language-driven impairment) or due to more downstream deficiencies in relational binding (a memory-driven impairment) (Neary and Snowden, 1996; Osher et al., 2007).

Based on the nature of the language impairment, PPA has been subdivided into three clinical variants (Gorno-Tempini et al., 2011). Relative to individuals with semantic PPA, non-semantic variants of PPA (agrammatic and logopenic subtypes) have preserved single word comprehension. Individuals with non-semantic PPA can exhibit agrammatism, loss of fluency, and poor repetition (Gorno-Tempini et al., 2011; Grossman, 2012; Mesulam et al., 2009; Weintraub et al., 1990). In concert with these language impairments, individuals with non-semantic PPA often show peak cortical atrophy within the left inferior frontal gyrus (IFG) or temporal parietal junction (TPJ). As the disease progresses, atrophy spreads to other components of the language network (Rogalski et al., 2011, 2014). The hippocampus is not an initial site of peak atrophy in PPA.

The left IFG, known as Broca's area, is specialized for phonological encoding and fluency (Hickok and Poeppel, 2007; Xiang et al., 2010). The left IFG is structurally connected via the arcuate fasciculus to the left temporal parietal junction, a site that is likely to be important for integrating visual and auditory information (Raij et al., 2000). The adjacent superior temporal gyrus acts as an auditory association area,

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serving the phonological loop and auditory working memory (Leff et al., 2009). The inclusion of these areas within the regions of peak atrophy in non-semantic PPA suggests that individuals with PPA may have vulnerability in processing auditory stimuli in the verbal modality.

The role of the temporal poles in object and language processing is debated. Studies of patients with semantic dementia (with bilateral anterior temporal lobe atrophy), have proposed that both the left and right temporal lobe contain domain-independent object representations (Patterson et al., 2007; Pobric et al., 2007, 2010). In contrast, other studies have dissociated verbal from non-verbal markers of object knowledge and suggest disparate domain-specific roles for the temporal poles. This model suggests that the left temporal pole acts in part with the left lateralized language network and is critical for verbal and semantic associations of objects; whereas the right temporal pole acts within the predominantly right-lateralized or bilateral object recognition network (Hurley et al., 2012; Mesulam et al., 2015, 2013).

Our group has previously studied recognition memory in PPA. We found a higher incidence of false alarms for visually presented words compared to objects, especially among semantically related foils (Rogalski et al., 2007). The present study aims to extend these findings by examining the anatomical substrates related to language processing and subsequent memory performance using object and word stimuli in both the visual and auditory modalities. The goal was to dissociate language-processing impairments from episodic memory impairments in mild non-semantic PPA.

2. Methods

2.1. Participants

Twenty-two participants with PPA and fourteen age-matched cognitively normal controls participated in this experiment. All participants were right-handed.

PPA participants were recruited from the PPA Research Program at the Cognitive Neurology and Alzheimer's Disease Center (CNADC) at Northwestern University. PPA participants were clinically diagnosed by a neurologist (MMM), and subtyped as non-semantic by established criteria (Gorno-Tempini et al., 2011). Eight participants were characterized as logopenic, 12 participants were characterized as agrammatic, and 2 participants were unclassifiable as either strictly agrammatic or logopenic. All PPA participants therefore had prominent deficits in grammatical processing or fluency with preserved single word comprehension. Participation in the research program included a series of neuropsychological tests assessing overall cognition, and structural neuroimaging. Normal controls were recruited from the Clinical Core at the Northwestern University Alzheimer's Disease Center. All control participants reported no history of neurologic or psychiatric condition. Through participation in the Clinical Core, control participants also received series of neuropsychological tests confirming normal cognitive functioning (defined as within 1 standard deviation of age normed scores) within 3 months of participation in this experiment. All participants gave written informed consent, and were monetarily compensated for their time. Northwestern University Institutional Review Board approved all study procedures.

2.2. Neuropsychological measures

To better characterize the participants included in this study, a series of neuropsychological tests were conducted during each study visit. To characterize aphasia, language specific measures were collected within the PPA cohort. Western Aphasia Battery - Aphasia Quotient (WAB) (Kertesz, 1982) is a composite measure of aphasia severity based on auditory comprehension, naming, repetition and spontaneous speech production. The 60-item Boston Naming Test (BNT) (Kaplan et al., 1983) was used to measure object naming. A subset of 36 moderately difficult items (#157–192) from PPVT (Peabody Picture Vocabulary Test) (Dunn, 2007) was also used to measure auditory lexical-semantic processing and verbal comprehension. Diadochokinetic rate (how quickly a participant can accurately repeat a series of phonetic sounds [puh/tuh/kuh] over 5 s), and deterioration in articulation with the increase of syllable word length [thick, thicken, thickening], were used to characterize the presence of motor speech impairments, based on standardized tests from an apraxia battery (Dabul, 2000; Wertz et al., 1984). In all study participants, the Mini Mental State Exam (MMSE) (Folstein et al., 1975) was used to measure overall dementia severity. Table 1 presents the neuropsychological data comparing and characterizing each diagnostic group. Two control participants received the Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005) rather than the MMSE, and their scores were accordingly converted (Roalf et al., 2012). Independent sample *t*-tests and chi-square tests were used to compare both groups where appropriate. Age between both groups ($t(1,34) = 0.08$, $p = 0.94$) and gender distribution ($\chi^2 = 0.77$, $p = 0.38$) were matched. As expected in an aphasic sample (Osher et al., 2007), MMSE was significantly lower for PPA patients ($t(1,34) = 6.35$, $p < 0.001$), as was performance on the PPVT ($t(1,34) = 3.52$, $p = 0.002$).

Table 1
Neuropsychological measures and participant demographics. Means ± standard deviations are reported for neuropsychological measures and participant demographics for controls and non-semantic primary progressive aphasia. Abbreviations: PPA = Primary progressive aphasia, MMSE = Mini Mental State Exam, PPVT = Peabody Picture Vocabulary Test, WAB-AQ = Western Aphasia Battery Aphasia Quotient, BNT = Boston Naming Test.

	PPA (n = 22)	Control (n = 14)
Age (years)	65.81 ± 7.26	65.64 ± 6.40
Gender	14M:8F	6M:8F
Symptom duration (years)	2.90 ± 1.20	–
MMSE	25.95 ± 2.40	29.53 ± 0.97
PPVT	33.55 ± 2.13	35.29 ± 0.73
WAB-AQ	86.55 ± 7.63	–
BNT	58.9 ± 2.18	–
Diadochokinetic Rate	4.27 ± 2.73	–
Deterioration Articulation	0.15 ± 0.28	–

2.3. Stimuli

This study examined recognition memory performance over three modality conditions: auditory words, visual words, and visual objects. All stimuli were high-frequency concrete namable items presented via SuperLab Pro v2.0.3. Frequency was matched for each condition. Mean frequency was 15.710 as measured by the Corpus of Contemporary American English (Davies, 2008).

Visual stimuli were presented at the center of the screen (1920 × 1080 pixel resolution) for 2000 ms. Objects were a subset of color-line drawings (derived from (Rossion and Pourtois, 2004)). Words (6.25 ± 2.11 letters) were horizontally presented and appeared in 72-point font. Auditory words were presented in a male native English voice for variable times (723.086 ± 192.25 ms) depending on the length of the word (6.35 ± 2.19 letters). During the presentation of an auditory stimulus, a sound icon would visually appear at the center of the screen to indicate stimulus onset.

Each condition had distinct stimuli. For example, if a rooster appeared as a visual object, the visual word “rooster” and the auditory word “rooster” were not used. Stimulus presentation order within each modality was randomized.

2.4. Task design

Instructions were presented both visually and orally. The main task consisted of two phases: study phase and test phase. At the onset of each study phase, three stimuli were presented as practice trials. The practice