Verbal and Nonverbal Memory in Neurodegenerative and Stroke Aphasia: Evidence From the Turkish Version of the Three Words Three Shapes Test

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Background: Although language impairment is the most salient feature of cognitive impairment in both primary progressive aphasia (PPA) and stroke aphasia (SA), memory can also be impaired in both patient populations.

Objective: To identify distinctive features of verbal and nonverbal memory processing in individuals with PPA and those with SA.

Method: We gave individuals with PPA (n = 14), those with SA (n = 8), and healthy controls (HC; n = 13) a comprehensive neuropsychological test battery and the Turkish version of the Three Words Three Shapes Test (3W3S–Turkish). The 3W3S–Turkish Test includes five subtests: Copy, Incidental Recall, Acquisition, Delayed Recall, and Recognition. High-resolution brain scans were performed in a subset of individuals with PPA and those with SA. Lesion distribution was limited to the dorsal language areas in the SA group, whereas peak atrophy areas in the PPA group extended beyond the language network, including the medial temporal lobe, precuneus, and posterior/medial portions of the cingulate cortex.

Results: Both the PPA and SA groups showed impairment in incidental recall, and the PPA group showed additional impairment in delayed recall. Greater impairment for verbal stimuli suggestive of material-specific memory impairment was evident in the PPA group's scores on the Incidental Recall and Delayed Recall subtests. Both aphasia groups retained the acquired information regardless of material type.

Conclusion: Although both aphasia groups shared similarities in the involvement of the dorsal prefrontal working memory/attention network, the PPA group showed greater impairment in delayed recall compared with the SA group.

Key Words: memory, primary progressive aphasia, stroke aphasia, three words three shapes, Turkish

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3W3S–Turkish = Three Words Three Shapes Test—Turkish version. **AD** = Alzheimer disease. **lv** = logopenic variant. **nfv** = nonfluent variant. **PPA** = primary progressive aphasia. **SA** = stroke aphasia. **sv** = semantic variant.

Memory impairment presents as the most salient feature of progressive cognitive decline in typical Alzheimer disease (AD), also referred to as the amnestic presentation of probable AD (McKhann et al, 2011). However, in a subset of individuals with AD, language impairment is the most salient feature of progressive cognitive decline, and memory and other cognitive domains are relatively preserved (Lam et al, 2013; Rogalski et al, 2016). Individuals with non-Alzheimer pathologies such as frontotemporal lobar degeneration associated with TDP-43 or tau may also present with language-predominant cognitive decline (Mesulam et al, 2014b). This phenotype, with selective involvement of language functions in neurodegenerative disease, is known as *primary progressive aphasia* (PPA; Mesulam et al, 2009).

Three distinct variants of PPA have been described in the literature. In the semantic variant of PPA (svPPA), individuals have difficulty comprehending single words due to the disruption of lexicosemantic associations

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(Gorno-Tempini et al, 2011). In the other two variants, nonfluent/agrammatic PPA (nfvPPA) and logopenic variant PPA (lvPPA), individuals present with relatively preserved single-word comprehension; these two variants are also referred to as the nonsemantic variants of PPA (Christensen et al, 2015). nfvPPA is characterized by effortful, halting speech (apraxia of speech) and/or agrammatism (syntactical and/or morphological errors in spontaneous speech). lvPPA is characterized by speech that is frequently interrupted due to word-finding difficulty, and repetition is impaired, particularly for long phrases (Gorno-Tempini et al, 2011).

Recent studies have revealed that individuals with aphasia may also have compromised memory functions. For example, short-term memory impairment has been reported in individuals with stroke aphasia (SA), particularly due to cerebrovascular damage to the left prefrontal cortex (Fonseca et al, 2019). The short-term memory profiles of individuals with SA include auditory–verbal working memory impairment, as evidenced by poor scores on digit-span and alphabet span tasks, where participants are asked to rearrange series of presented digits or words in numerical and alphabetical order (Salis et al, 2018).

Individuals with PPA may also have impairments in short-term memory, particularly in incidental learning, which does not involve effortful encoding (Kielb et al, 2016). Foxe et al (2020) reported that individuals with PPA may have visuospatial and verbal short-term memory impairments. However, impairment in verbal retrieval memory may also be evident in individuals with PPA, particularly in cases with underlying AD pathology (Kielb et al, 2016).

Memory Processing

Intact perceptual processing is a prerequisite for the assessment of memory processing as perceptual impairment interferes with memory, particularly within the same modality (Allen et al, 2011; Barense et al, 2012; Quiñones et al, 2021). The stages of memory processing include effortless learning, effortful learning, retrieval, and retention (Weintraub et al, 2000). Incidental recall is associated with effortless learning that is inherent to working memory processing. During effortless learning, the information is encoded spontaneously and held online for immediate reproduction, whereas effortful learning includes the deliberate encoding of information (Weintraub et al, 2013). The contrast between the effortful learning and delayed recall stages reveals one's ability to retrieve messages. On the other hand, comparison of acquisition and recognition from multiple choice reveals one's ability to retain memories (Kielb et al, 2016). Another aspect of memory includes the type of material that is being remembered, such as verbal or nonverbal (ie, visual) information (Weintraub et al, 2013).

Prominent impairment in verbal memory compared with nonverbal memory (material-specific memory disorder) is typical in individuals with PPA (Weintraub et al, 2013). However, material-specific memory impairment has been insufficiently characterized in individuals with cerebrovascular lesions. Although it has been reported that individuals with a left hippocampal, anterior, and paramedian thalamic stroke presented with material-specific memory impairment, these individuals did not have aphasia (Carota et al, 2015; Ott and Saver, 1993).

To our knowledge, there are no studies that have included a detailed comparison of memory processing in individuals with neurodegenerative aphasia (ie, PPA) versus individuals with SA. Therefore, we decided to investigate how neurodegenerative versus cerebrovascular etiologies affect memory processing in individuals with aphasia using a head-to-head comparison of individuals with PPA and those with SA.

There are several limitations to the current battery of tests that are used to evaluate memory in individuals with aphasia. The majority of memory assessments rely on the ability to process verbal stimuli such as auditory-based word lists, including the Rey Auditory Verbal Learning Test (Rey, 1970) and the California Verbal Learning Test (Delis et al, 1987). On the other hand, some memory assessments rely on the ability to process nonverbal stimuli such as objects, faces, and spatial locations, including the Cambridge Face Memory Test (Duchaine and Nakayama, 2006) and the Complex Figure Test (Zhang et al, 2021). Still, few memory assessments contain both domain-specific stimuli, thus preventing the memory processing of verbal and nonverbal material to be compared. In addition, the level of heightened complexity and difficulty in nonverbal memory tests specifically may lead to a "floor effect" in individuals in the moderate to severe stages of neurodegenerative diseases (Blessed et al, 1968; Folstein et al, 1975; Weintraub et al, 2000).

Three Words Three Shapes Test

The Three Words Three Shapes Test (3W3S; Weintraub and Mesulam, 1985; Weintraub et al, 2000) was developed to overcome these limitations: It measures both verbal and nonverbal memory. The 3W3S Test consists of five subtests: *Copy*, *Incidental Recall*, *Acquisition*, *Delayed Recall*, and *Recognition*. These five subtests provide an opportunity for clinicians and researchers to evaluate the different stages of memory processing, including perceptual processing of the input material (Copy), effortless learning (Incidental Recall), effortful learning (Acquisition), and the retrieval (Delayed Recall) and retention (Recognition) of memory.

Because the 3W3S Test includes both verbal (three words) and nonverbal (three geometric shapes) stimuli, it allows for the assessment of material-specific (verbal vs nonverbal) memory. Furthermore, presenting stimuli in the same (visual) modality helps overcome the difficulty of comparing individual performances in verbal versus nonverbal tests (Weintraub et al, 2013). Such difficulty is particularly evident when a verbal memory test is presented in the auditory modality but the nonverbal test is presented in the visual modality (Kielb et al, 2016).

Originally developed as a practical bedside memory test by Weintraub and Mesulam in 1985, the 3W3S Test has been used successfully to discriminate patterns of memory impairment in individuals with Korsakoff amnesia and probable AD (Weintraub et al, 2000). In the first study using the 3W3S Test to outline the memory profiles of individuals

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with PPA (Weintraub et al, 2013), the individuals with PPA performed poorly on the Incidental Recall and Delayed Recall subtests, exhibiting impairment in the effortless learning and retrieval stages of memory processing. Impairment in these memory stages was more prominent for words than it was for shapes. However, perceptual processing, effortful learning, and memory retention were relatively preserved for both words and shapes.

In another study, individuals with probable AD showed additional impairments in the effortful learning and retention stages without consistent errors for material specificity (Weintraub et al, 2000). Cortical distribution of the lesions in individuals with PPA may cause verbal memory impairment because the left anterior temporal lobe and the limbic/paralimbic areas are involved in addition to the left perisylvian regions due to the neurodegenerative nature of the disease (Nilakantan et al, 2017).

In a more recent study, group differences in the 3W3S Test were found in individuals with autopsy-confirmed PPA with two distinct pathologies: AD and the tau variant of frontotemporal lobar degeneration (Kielb et al, 2016). The PPA with AD group had greater impairment in effortless learning (a metric calculated by the within-group comparison of the Incidental Recall and Copy subtest scores) and delayed retrieval (a metric calculated by the within-group comparison of the Delayed Recall and Acquisition subtest scores) compared with the group with the tau variant of frontotemporal lobar degeneration. However, the 3W3S Test has never been used to assess memory processing in individuals with SA.

The structure of the 3W3S Test allows for easy adaptation to other languages, offering a feasible and reliable memory test in international, multicentered, and comparative studies. Successful international versions of the 3W3S Test have been reported. The Brazilian version of the 3W3S Test was used to reveal memory patterns in a cognitively healthy elderly population, and education level was found to be related to test performance, particularly for nonverbal stimuli (Armentano and Quayle, 2007). The Turkish version of the 3W3S Test (3W3S–Turkish) was developed and successfully validated in a cognitively healthy elderly population of 236 individuals (Kudiaki and Aslan, 2007). Recently, a parallel form of the 3W3S–Turkish Test was also introduced (Kudiaki et al, 2018).

In this study, our goal was to examine the ability of the 3W3S–Turkish Test to identify the characteristics of memory impairment in two Turkish-speaking groups of individuals with aphasia of different etiologies (neurodegenerative vs cerebrovascular). We hypothesized that the individuals with PPA would have more severe impairment in verbal memory compared with the individuals with SA due to more widespread involvement of the language and left hemispheric portions of the memory network.

METHOD

Participants

All of the participants were right-handed native Turkish speakers. We recruited individuals with PPA from the patient cohort of the behavioral neurology and movement disorders unit at the Istanbul Faculty of Medicine in Istanbul, Turkey. We recruited individuals with SA from the stroke unit at the same institute.

We invited individuals to participate in the study during routine clinic visits or reached out to individuals in the database via phone calls. Sixteen volunteers with no history of neurologic disease or cognitive complaints and with at least 11 years of education were recruited as healthy controls (HC) in response to advertisements we posted on social media and posters we hung on the advertisement boards in the neurology department. No incentive other than the opportunity for a comprehensive cognitive screening was offered to the participants.

All of the individuals in the PPA group, by definition, had progressive language impairment as the most salient feature of their cognitive decline for at least the first 2 years of disease onset (Mesulam et al, 2009) and met the core diagnostic criteria of PPA (Gorno-Tempini et al, 2011). All of the individuals in the SA group had a history of acute ischemic cerebrovascular disease at least 4 months ($M = 15.9 \pm 9.3$) before the cognitive examination. Two stroke specialists (N.Y. and O.Ç.) and an experienced speech-language pathologist (Ö.Ö.) conducted the initial evaluation of the individuals with stroke at the stroke unit. Individuals with acute cerebrovascular damage to the perisylvian language areas resulting in language impairment (Godefroy et al, 2002) qualified for the diagnosis of SA.

Visual acuity and possible visual field defects were evaluated by two behavioral neurologists (M.S. and H.G.). All of the participants (PPA, SA, and HC groups) had normal or corrected to normal vision. None of the participants had hand paresis that could affect their writing abilities.

The study protocol was approved by the ethics committee of Istanbul University and was performed according to the ethical guidelines of the Declaration of Helsinki and its later amendments. All individuals provided informed written consent before enrolling in the study.

Assessments

Neurocognitive Assessment

M.S. and H.G. conducted neurocognitive assessments and neurologic examinations of the individuals with PPA at the neurobehavior clinic at the Istanbul Faculty of Medicine. Assessments were performed on consecutive patients individually in the examination offices. Clinical diagnosis and classification were made based on the most recent criteria proposed by Gorno-Tempini et al (2011).

Neuropsychological Assessment

A neuropsychologist (İ.D.) administered a comprehensive neuropsychological assessment to the individuals in all three groups in the neuropsychological testing room at the behavioral neurology and movement disorders unit at the Istanbul Faculty of Medicine. All data were collected prospectively between 2017 and 2019 by direct examination of the participants, and additional information

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about medical history was obtained via interviews with the study partners (ie, spouses of the patients mostly).

Cognitive Assessment

İ.D. administered a comprehensive cognitive testing battery including a detailed assessment of linguistic and nonlinguistic domains to all three groups. The linguistic assessment included tests for fluency, naming, repetition, comprehension, reading, writing, and motor planning of speech.

- We used the number of words produced per minute during a picture description task and the Boston Naming Test (31-item Turkish adaptation; Soylu and Cangöz, 2018) to assess fluency and confrontation naming.
- We used an 18-item battery that included 10 items from the Turkish Language Assessment Test for Aphasia (Toğram and Maviş, 2012) and 8 items from the Istanbul Faculty of Medicine Aphasia Assessment Battery (unpublished) to assess repetition.
- We used a 10-item battery of yes–no questions that included 5 items from the Turkish Language Assessment Test for Aphasia and 5 items from the Istanbul Faculty of Medicine Aphasia Assessment Battery to assess comprehension.
- We used 5 items from the Turkish Language Assessment Test for Aphasia to assess reading and 5 items to assess writing to dictation. Participants received a score of 1 for phonologic or orthographic errors that consisted of <50% of an item produced and a full score of 2 when the response included no error(s).
- We used the 5-item Screening of Apraxia of Speech Test to assess the integrity of each individual's motor planning of speech. In this test, participants' ability to repeat sequences of the syllables "puh" (pa), "tuh" (ta), and "kuh" (ka) compared to single syllables reveals praxis of speech (Rohrer et al, 2010).

The nonlinguistic assessment included Turkish translations of tests for attention, visuospatial, and executive functions.

- We used Part A of the Trail-Making Test (Reitan and Wolfson, 1993) to assess sustained attention.
- We used three distinct tests to assess visuospatial functioning: Benton Facial Recognition Test (Benton et al, 1994; Keskinkılıç, 2008), Judgment of Line Orientation Test (Karakaş et al, 2013; Randolph, 1998), and Visual Target Cancellation Test (Karakaş et al, 2013; Mesulam, 2000; Weintraub and Mesulam, 1987).
- We used Part B of the Trail-Making Test to assess executive functions.

3W3S–Turkish Test

The 3W3S–Turkish Test consists of three verbal (words) and three nonverbal (shapes) stimuli. The words in the 3W3S–Turkish Test consist of *saygi, yemek,* and *kamyon*: *respect, meal,* and *truck*, respectively (Kudiaki and Aslan, 2007). The shapes in the 3W3S–Turkish Test are identical to the shapes in the follow-up form that was used in the original version of the 3W3S Test (Weintraub et al, 2000). The task and the scoring procedure are also based on the study design that was used in the original version of the 3W3S Test, with minor modifications (Weintraub et al, 2000, 2013).

During the test, we provided a paper to each individual and asked him or her to copy the shapes and words that appeared on the paper (Copy). Next, without warning about the next step, we removed the paper and asked the individual to reproduce the items he or she had just copied (Incidental Recall). Individuals who were unable to reproduce all six stimuli correctly were presented with the original stimuli for ~30 seconds and were asked to study and remember the six stimuli with all of the details and then to draw them from memory. If all of the stimuli were not reproduced correctly (Acquisition), we repeated the study trial up to 3 times. We used the score from the last study trial as the Acquisition subtest score.

We tested the three groups' retrieval ability (Delayed Recall) ~10 minutes after the last study trial of the Acquisition subtest. Between the Acquisition and Delayed Recall subtests, we had the individuals complete nonmemory tests, including Clock Drawing (Wolf-Klein et al, 1989), Luria's Alternating Sequences (Mesulam, 2000), and Parts A and B of the Trail-Making Test. The Clock Drawing and Luria's Alternating Sequences Tests were used as distractors only; therefore, they were not scored.

During the Delayed Recall subtest, we asked the individuals to reproduce the six stimuli again. In cases where all six stimuli were not reproduced correctly, we administered a multiple-choice paradigm to test memory retention (Recognition). The Recognition subtest included 10 shapes and 10 words, including the original stimuli (ie, 3 targets and 7 foils for each stimuli type).

Scoring. Participants received a maximum score of 5 for each stimulus, which summed up to a maximum score of 15 for words and 15 for shapes in each subtest. We used the details of the orthographic properties of the words and the configuration of the shapes as references for scoring the Copy, Incidental Recall, Acquisition, and Delayed Recall subtests as explained previously in the original versions of the test (Weintraub et al, 2000, 2013).

For each word, participants received a score of 4 if the "word was spelled correctly," 1 if the "word was semantically related," 2 if "3 consecutive letters were correct," and 3 if "4 consecutive letters were correct." An additional score of 1 was given for each word if the "word was in correct position relative to other words" (Weintraub et al, 2000). For the first shape, participants received a score of 2 for "circle," 1 for "double line horizontally through the center of circle," and 1 for "box shape close to the center of the circle." For the second shape, participants received a score of 2 for "vertical rectangle," 1 for "horizontal line bisecting the rectangle," and 1 for "diagonal line from the upper left to bottom right corner." Finally, for the third shape, participants received a score of 2 for "triangle," 1 for "arc in upper left corner," and 1 for "bisecting line from arc to opposite side of triangle." An additional score of 1 was given for each figure if the "figure was in correct position relative to other figures." One point was subtracted if a figure was correct but had superfluous lines or if

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all elements were there but it was not identical to the target. Table 1 in the supplementary digital content (SDC, http://links.lww.com/CBN/A107) provides the individual scores obtained by each group on each subtest.

For the Recognition subtest, individuals received a full score for the items they had already reproduced correctly during the Delayed Recall subtest. We also took false-positive answers into account during the Recognition subtest and subtracted them from the total score obtained from the correct responses. We used the following formula to calculate the corrected score for Recognition: $(5xn_{CR}) - n_{FP}$, where CR = correct responses and FP = false positives. For example, a participant who recognized two of three words correctly but had one false-positive answer would score 9 out of 15, which was calculated as $(5 \times 2) - 1$.

The representative performance of an individual with PPA on the 3W3S–Turkish Test is presented in Figure 1. The individual was biomarker positive for AD (heterozygous "pathogenic variant" in *PSEN1*), which might have caused greater difficulty, particularly on the Delayed Recall and Recognition subtests. Additional scores were calculated using the scores obtained from consequent study trials in the Acquisition subtest. On each study trial, individuals received a maximum score of 30 (15 for words and 15 for shapes). The sum of the scores from each study trial indicated a total learning score. In cases where individuals reproduced all six stimuli correctly in the first or second study trial, they received a full score for the following trial(s). Besides the total learning score (out of 90), subscores for learning words and shapes (out of 45 for each type of stimuli) were calculated separately. The Turkish version of the full scoring sheet is presented in the SDC as Figure 1 (http://links.lww.com/CBN/A108). The representative performances of an individual with svPPA and an individual with Broca aphasia are presented in the SDC as Figure 2 (http://links.lww.com/CBN/A109).

MRI Acquisition

Imaging was performed at Istanbul University Hulusi Behçet Life Sciences Center's neuroimaging laboratory in Istanbul, Turkey, using a Phillips-Achieva 3.0 Tesla scanner. T1-weighted 3D MPRAGE (magnetization-prepared rapid acquisition with gradient echo) sequences (repetition time = 8.2 ms; echo time = 3.2 ms; field of view = 256 × 256; flip angle = 7 degrees; 176

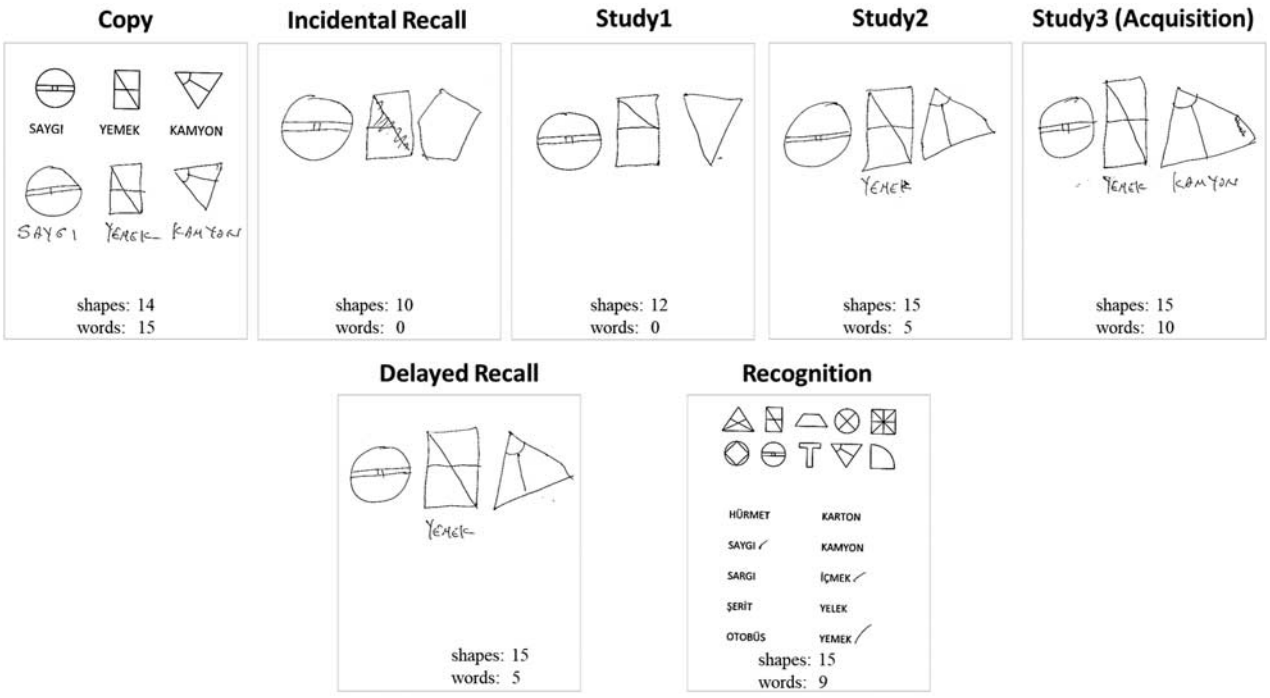


FIGURE 1. Representative performance of a 69-year-old male with PPA on the 3W3S–Turkish Test (individual P6 in Tables 1 and 2). The scores obtained for each subtest are presented at the bottom of the test forms (rectangles). On the Copy subtest, the patient copied two shapes correctly but missed one detail on the first shape—one of the lines of the box shape close to the center of the circle (score received: 14/15). The patient copied all three words correctly (score received: 15/15). On the Incidental Recall subtest, he reproduced one shape correctly but missed details on the other two shapes (score received: 10/15). He was unable to reproduce any of the words (score received: 0/15). Across three study trials, he was able to learn all three shapes (score received: 15/15) and two of the words (score received: 10/15), and the score from the third study trial was noted as the Acquisition score. On the Delayed Recall subtest (after a 10-minute delay after the last study trial of the Acquisition subtest), he reproduced three shapes correctly (score received: 15/15) but only one word (score received: 5/15). During the Recognition subtest, he received a full score of 15 out of 15 for recognizing shapes because of the correct drawings on the Delayed Recall subtest, but for words, he gave two correct responses and one false-positive response (score received: 9/15). **3W3S–Turkish** = Three Words Three Shapes Test—Turkish version. **PPA** = primary progressive aphasia.

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slices; slice thickness = 1 mm; voxel size = 1 × 1 × 1 mm) were acquired using a 32-channel head coil during the same week that the neuropsychological data were collected.

Cortical Atrophy in the PPA Group

We used the FreeSurfer image analysis suite (version 6.0.0; http://surfer.nmr.mgh.harvard.edu/) to measure cortical thickness in the PPA group. MRI data were available for 12 of the 14 individuals with PPA (a new scan could not be performed for P2 and P14). Cortical thickness estimates were calculated based on the distance between white–gray and pial–CSF boundaries across each point of the cortical surface (Fischl, 2012).

A general linear model was used to generate statistical surface maps by contrasting the thickness values at each vertex of the cortex from 29 healthy adults (including 13 controls from the current study and an additional 16 controls with similar demographic properties from the Hulusi Behçet Life Sciences Center's neuroimaging laboratory database). Areas of peak cortical thinning in the PPA group were calculated using a false discovery rate of 0.05 (Genovese et al, 2002). This method has been used previously as a reliable approach for calculating the magnitude of atrophy in individuals with PPA (Mesulam et al, 2009, 2015; Rogalski et al, 2011a).

Figure 2 shows the cortical thinning patterns in the PPA group that were obtained from the general linear model analysis. The figure provides a detailed presentation of the regional distribution of cortical atrophy in the PPA group on the cortical thickness map. The left hemisphere perisylvian language areas were selectively involved, which is consistent with earlier studies (Mesulam et al, 2014a; Rogalski et al, 2011a). Some portions of the medial temporal and cortical midline structures were also involved. Atrophy in the right hemisphere was less pronounced compared with the left hemisphere.

The total size of the atrophied area on the left hemisphere was 35603.57 mm^2; the total size of the atrophied area on the right hemisphere was 7606.27 mm^2. A cluster-based classification of cortical areas revealed 21 clusters with an average size of 1695.4 mm^2 in the left hemisphere and 38 smaller clusters with an average size of 200.2 mm^2 in the right hemisphere. Table 2 in the SDC (http://links.lww.com/CBN/A110) provides cluster-based distribution of cortical atrophy with significant differences in cortical thickness across the PPA and HC groups.

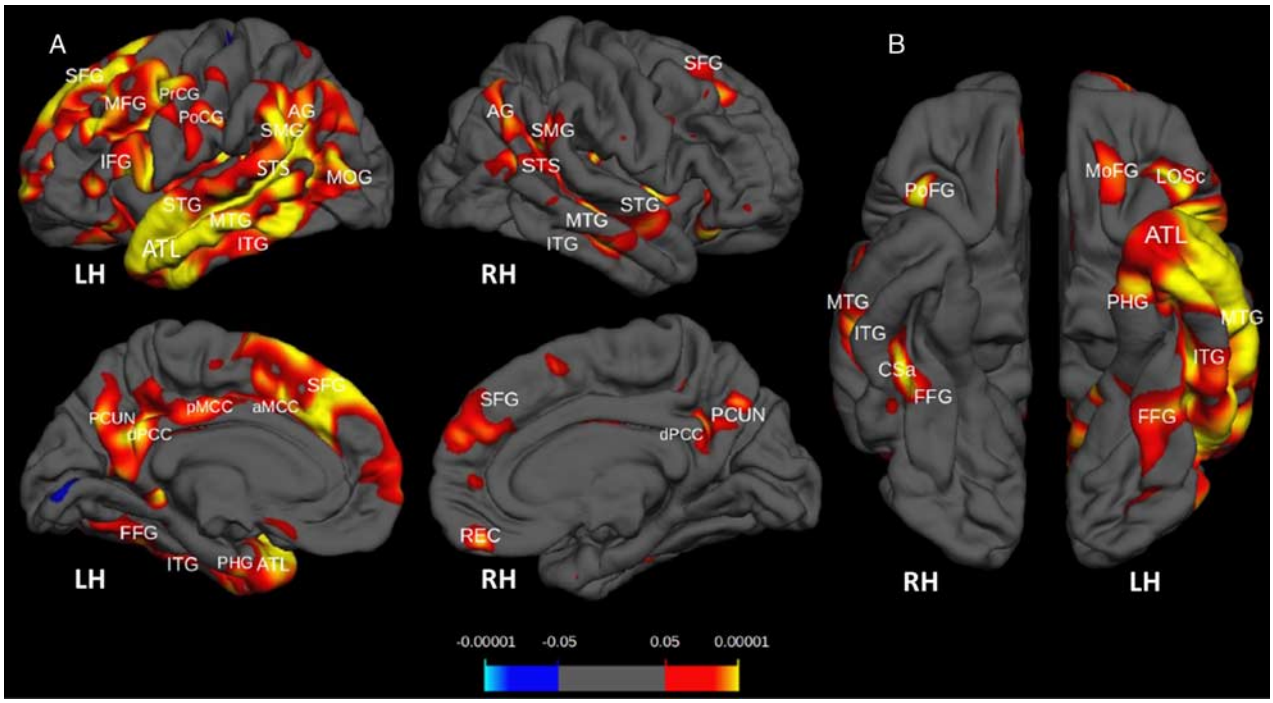


FIGURE 2. Regional distribution of cortical atrophy in the PPA group. Significantly thinner areas of the cortex compared with the healthy controls are presented in a red–yellow scale where yellow indicates the peak atrophy sites. **A.** Lateral (top) and medial (bottom) views of the cortical areas. **B.** Inferior frontal and temporal cortical structures. **AG** = angular gyrus. **aMCC** = middle-anterior part of the cingulate cortex and sulcus. **ATL** = anterior temporal lobe. **CSa** = anterior collateral sulcus. **dPCC** = posterior-dorsal part of the cingulate cortex. **FFG** = fusiform gyrus. **IFG** = inferior frontal gyrus. **ITG** = inferior temporal gyrus. **LH** = left hemisphere. **LOSc** = caudal lateral orbital sulcus. **MFG** = middle frontal gyrus. **MoFG** = middle orbitofrontal gyrus. **MOG** = middle occipital gyrus. **MTG** = middle temporal gyrus. **PCUN** = precuneus. **PHG** = parahippocampal gyrus. **pMCC** = middle-posterior part of the cingulate cortex and sulcus. **PoCG** = postcentral gyrus. **PoFG** = posterior orbitofrontal gyrus. **PPA** = primary progressive aphasia. **PrCG** = precentral gyrus. **REC** = gyrus rectus. **RH** = right hemisphere. **SFG** = superior frontal gyrus. **SMG** = supramarginal gyrus. **STG** = superior temporal gyrus. **STS** = superior temporal sulcus.

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Visualization of Lesion Sites in the SA Group

MRI data were available for six of the eight individuals with SA. T1W-3D MPRAGE images were processed on a Siemens, Syng.Via workflow workstation using Syngo.Via software (VB 40B). Brain gray–white matter was marked, special thresholds were adjusted (Via, region growing on mmReading toolbox), and rendered sections with 3D cinematic volume images were obtained.

Reconstruction of brain scans using T1W-3D MPRAGE images provided 3D visualization of the lesion sites in a subset of the SA group. Lesions sites are presented using both the lateral view of the 3D images and the corresponding slices of the coronal T1 images. Please note that in all of the individuals with SA, the dorsal language areas were involved due to the cerebrovascular damage of the middle cerebral artery, whereas the anterior temporal lobe and the medial temporal areas were spared. Figure 3 shows the lesion sites of each of the six individuals.

Statistical Analysis

During the statistical analysis, we added age as a covariate in all of the between-group analyses. First, we calculated the main effect for the group (PPA, SA, and HC), subtest (Copy, Incidental Recall, Acquisition, Delayed Recall, and Recognition), and stimuli type (words and shapes) in a 3 × 5 × 2 repeated measures mixed factorial design to identify a significant interaction between the variables. Then, we calculated the interaction between group and subtest followed by the analysis of each subtest separately to understand how different stages of memory processing are affected in different aphasia groups.

We used an analysis of covariance to determine whether the groups differed from each other on different subtests while controlling for age and used Bonferroni corrections for multiple pairwise comparisons to interpret the significance levels. Observed power for all of the between-subject comparisons ranged between 0.12 and 0.998, with three out of 12 results achieving >0.80.

We calculated the interaction between subtest and stimuli type for each group to examine material-specific memory impairments and used paired samples *t* tests for within-group comparisons of performances between the words and shapes stimuli of the 3W3S–Turkish Test (Weintraub et al, 2013). We calculated additional metrics, including effortless learning, retrieval, and retention, as part of the within-group analysis. To calculate the effortless learning scores, we used the within-group comparison of the Incidental Recall and Copy subtests, and to calculate the retrieval scores, we used the within-group comparison of the Acquisition (last study trial) and Delayed Recall subtests (Kielb et al, 2016). Finally, a within-group comparison of the Acquisition and Recognition subtests revealed the retention scores (Weintraub et al, 2013).

We used a two-step analysis to delineate effortful learning. First, we included total learning scores and the subscores for words and shapes in an analysis of covariance separately. Second, we used one-way repeated measures ANOVAs for learning trials in each aphasia group in order to show if a trend of improvement existed during the study trials in the Acquisition subtest (effortful learning), which was followed by paired samples *t* tests to reveal the study trial(s) where learning improved significantly.

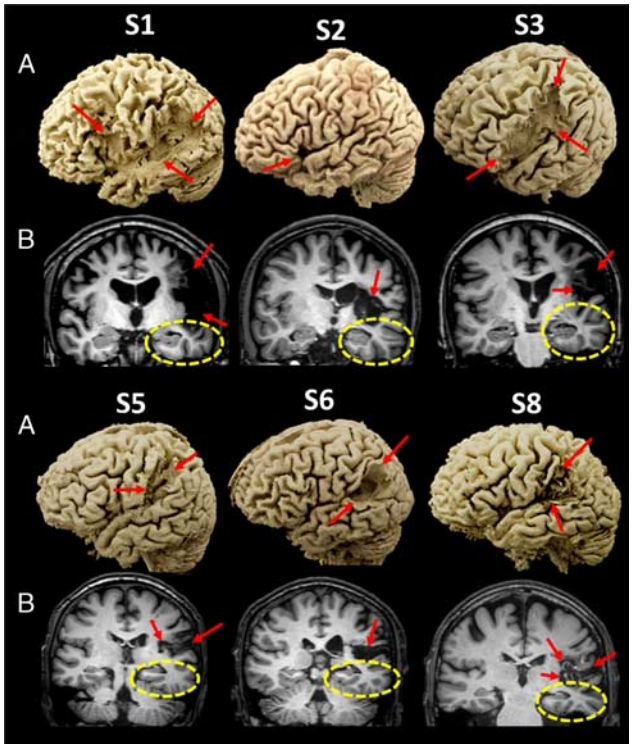


FIGURE 3. Lesion sites of six of the individuals with SA indicated by red arrows and presented as 3D-rendered images **A.** from the left lateral view and **B.** the corresponding slices in the coronal plane T1 images. Yellow dotted circles indicate intact temporal lobe structures. Note that the lesions are limited to the dorsal language areas, sparing the temporal lobe structures. Distribution of regional lesions obtained from individual scans are as follows: IFG, TPJ, and STG in S1; IFG and dorsal striatal areas in S2; IFG, insula, and TPJ in S3; AG and SMG in S5; AG, SMG, and posterior portions of the STG in S6; and AG and SMG in S8. **AG** = angular gyrus. **IFG** = inferior frontal gyrus. **SA** = stroke aphasia. **SMG** = supramarginal gyrus. **STG** = superior temporal gyrus. **TPJ** = temporoparietal junction.

RESULTS

Participants

Of the 18 individuals with PPA that we screened, four could not complete the 3W3S–Turkish Test due to either severe impairment in writing and/or difficulty understanding the task. Of the 11 individuals with SA that we screened, three could not complete the 3W3S–Turkish Test due to severe impairment in either writing or comprehension. These seven individuals were excluded from the study. Of the eight individuals with SA that we screened, all but one had a single-episode, left-sided cerebrovascular accident. S1 had an additional lesion in the right parietal lobe that was outside the language area. Of the 19 volunteers who applied to participate in the study as HC, three qualified for the diagnosis of mild

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cognitive impairment (Petersen et al, 2014) after neuropsychological assessment and were excluded from the study. This left us with a total study group of 14 individuals with PPA, 8 with SA, and 16 HC.

Demographics, Biomarkers, and Clinical Test Results

The details of each group's demographics, history, and biomarkers are presented in Table 1. The details of each group's neuropsychological characteristics, including language and other cognitive domains, are presented in Table 2. The three groups were matched for education (M = 14.4 for PPA group, 13.1 for SA group, and 15.6 for HC; $F_{2,32} = 2.48$, $P = 0.099$). However, group differences were shown for age (M = 65.2 for PPA group, 44.6 for SA group, and 61.2 for HC; $F_{2,32} = 16.45$, $P < 0.001$). Post hoc comparisons showed that the SA group was significantly younger than the PPA and HC groups ($P < 0.001$). The PPA and HC groups were matched for age ($P = 0.664$).

Primary Progressive Aphasia. Of the 14 individuals with PPA, two were subtyped as svPPA and five as nfvPPA according to the current guidelines for the classification of PPA (Gorno-Tempini et al, 2011). Three individuals were predominantly logopenic, with frequent word-finding pauses and preserved single-word comprehension. However, these three individuals also had agrammatic errors and met the criteria for both nfvPPA and lvPPA. We kept these three individuals unclassified and labeled them as lvPPA/nfvPPA in order to highlight the difference from other unclassified cases. The remaining four individuals with PPA had mild to moderate agrammatism and also met the core criteria for PPA. However, they did not meet the criteria for any of the subtypes according to the Gorno-Tempini and colleagues (2011) classification; thus, we kept them unclassified as well. Because of the small sample size, we included all of the individuals with PPA in the analyses as a single group.

Neurodegeneration biomarkers were available for seven of the 14 individuals with PPA. Out of seven individuals with biomarker evidence, CSF analysis for Aβ 42, phospho-tau, and total tau was available for four of them. These four individuals were classified according to the AT(N) biomarker grouping, where A stands for "aggregated Aβ or associated

TABLE 1. Detailed Demographics, History, and Biomarkers of the Participants

Participant		Demographics			History		
ID	Aphasia Type	Age (Years)	Gender (M/F)	Education (Years)	Disease Duration (Years)	Biomarker	Poststroke Period (Months)
P1	nfvPPA	70	F	11	3.5	*ATP13A2,*† *PARK2*†	NA
P2	svPPA	72	F	14	5.0	—	NA
P3	lvPPA/nfvPPA	61	M	16	1.5	A + T + N[+]	NA
P4	lvPPA/nfvPPA	58	F	20	5.0	*NOTCH3*†	NA
P5	nfvPPA	52	F	12	2.5	A + T − N[+]	NA
P6	lvPPA/nfvPPA	69	M	15	3.5	*PSEN1*	NA
P7	nfvPPA	61	F	11	4.0	A − T − N[+]	NA
P8	Unclassified	61	M	12	5.0	—	NA
P9	svPPA	77	M	21	1.0	—	NA
P10	nfvPPA	67	M	11	2.5	—	NA
P11	nfvPPA	65	M	15	1.0	A − T + N[+]	NA
P12	Unclassified	66	M	15	4.5	—	NA
P13	Unclassified	67	M	15	3.0	—	NA
P14	Unclassified	67	F	13	1.5	—	NA
PPA avg.	—	65.2*‡	—	14.4	3.0	—	—
S1	Broca	38	M	15	NA	NA	26
S2	Broca	23	F	14	NA	NA	18
S3	Broca	54	M	11	NA	NA	31
S4	Broca	51	F	16	NA	NA	19
S5	Broca	54	M	10	NA	NA	4
S6	Broca	27	M	9	NA	NA	9
S7	Broca§	52	M	15	NA	NA	10
S8	Broca§	58	M	15	NA	NA	10
SA avg.	—	44.6*‖	—	13.1	NA	NA	15.9
HC avg.	—	61.2	—	15.6	NA	NA	NA

*Significant at $P < 0.05$.
†Future examination for possible deletions/duplications is required.
‡Significant vs SA group.
§Broca aphasia with accompanying mild comprehension impairment.
‖Significant vs HC.
A = amyloid. **avg** = average. **F** = female. **lv** = logopenic variant. **M** = male. **NA** = not applicable. **nfv** = nonfluent variant. **PPA** = primary progressive aphasia. **SA** = stroke aphasia. **sv** = semantic variant. **T** = tau.

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TABLE 2. Detailed Neuropsychological Characteristics of the Participants

Participant	Language Assessments							Other Cognitive Assessments				
ID	WPM	BNT (31)	Yes/No (10)	Repetition (18)	SAOS (5)	Reading (10)	Writing (10)	Line Orientation (30)	Face Recognition (54)	Target Cancellation (60)	TMT-A (24)	TMT-B (24)
P1	17.9	27	8	12	4	9	8	17	43	60	24	16
P2	45.8	NA	NA	13	4	10	9	NA	41	57	24	NA
P3	69.4	24	9	17	5	10	10	23	46	40	24	12
P4	36.9	29	9	9	4	10	10	12	50	57	23	NA
P5	72.2	19	6	13	4	10	9	6	39	46	24	NA
P6	69.4	13	10	15	5	10	10	18	45	44	24	16
P7	37.7	31	10	16	3	8	9	16	46	54	24	11
P8	29.6	14	8	13	4	6	8	NA	35	NA	20	NA
P9	41.6	15	9	16	5	10	8	24	45	60	24	24
P10	24.7	6	9	14	5	9	10	21	45	50	24	5
P11	13.0	21	5	14	4	7	10	20	34	25	24	NA
P12	44.5	31	10	17	5	7	10	26	43	59	24	24
P13	30.5	27	9	18	5	9	10	15	54	60	24	12
P14	46.8	13	8	16	5	10	10	22	39	35	NA	NA
PPA avg.	41.4*†	20.8*†	8.5*†	14.5*†‡	4.4	8.9	9.4*‡	18.3*†	43.2*†	49.8*†	23.6	15.0*†
S1	18.6	9	9	2	2	7	9	19	45	58	24	16
S2	55.5	23	9	16	4	10	10	27	45	60	24	24
S3	33.8	26	10	9	4	6	6	NA	42	59	24	10
S4	23.3	23	10	15	5	10	10	28	41	60	24	24
S5	46.5	23	10	13	2	0	0	10	45	58	24	14
S6	25.8	5	9	6	3	9	6	20	45	59	24	3
S7	34.9	2	5	3	3	8	10	22	43	60	24	10
S8	70.6	2	5	0	3	7	2	NA	56	NA	24	24
SA avg.	38.6*†	14.1*†	8.4	8.0*†	3.3*†	7.1†	6.6*†	21.0	45.3	59.1	24.0	15.6
HC avg.	88.0	30.2	10.0	18.0	5.0	9.9	10.0	25.4	49.5	58.7	24.0	24.0

The numbers in parentheses below the test titles indicate the maximum scores.
*Significant at $P < 0.05$.
†Significant vs HC.
‡Significant vs SA group.
avg = average. **BNT** = Boston Naming Test. **NA** = not applicable. **PPA** = primary progressive aphasia. **SA** = stroke aphasia. **SAOS** = Screening for Apraxia of Speech. **TMT** = Trail-Making Test.

pathologic state," T stands for "phospho-tau (neurofibrillary tangles) or associated pathologic state," and N stands for "neurodegeneration or neuronal injury" and/or CSF total tau (Jack et al, 2018, p. 538). In the remaining three PPA cases, positive biomarkers were based on the genetic analysis.

Stroke Aphasia. Of the eight individuals with SA, agrammatism and effortful (nonfluent) speech were the core features of linguistic impairment, and the nonlinguistic domains were relatively preserved, as described in Hsu and Thompson (2018). None of the individuals with SA had any visual impairment (ie, homonymous hemianopia) as a result of the cerebrovascular accident. All of the individuals with SA qualified for a diagnosis of Broca aphasia, and two of the individuals (S7 and S8) had additional impairment in comprehension, but it was not severe enough to qualify for mixed aphasia (Godefroy et al, 2002).

The majority of the PPA group and all of the SA group had agrammatism and effortful/nonfluent speech. A subset of individuals had comprehension deficits that did not affect their understanding of the task instructions of the 3W3S–Turkish Test.

Different Stages of Memory Processing on the 3W3S–Turkish Test

The interaction between group, subtest, and stimuli type was significant: $F_{5.2,\ 80.5} = 2.5$, $P = 0.035$, $\eta^2 = 0.139$. The interaction between group and subtest was also significant: $F_{5.13,79.5} = 6.14$, $P < 0.001$, $\eta^2 = 0.284$. The details of the group comparisons in each subtest of the 3W3S–Turkish Test are presented in Figure 4.

Copy

All three groups showed perfect or near-perfect scores on the Copy subtest. There were no significant differences between the groups for either shapes ($F_{2,31} = 0.473$, $P = 0.627$, $\eta^2 = 0.03$) or words ($F_{2,31} = 0.881$, $P = 0.424$, $\eta^2 = 0.054$).

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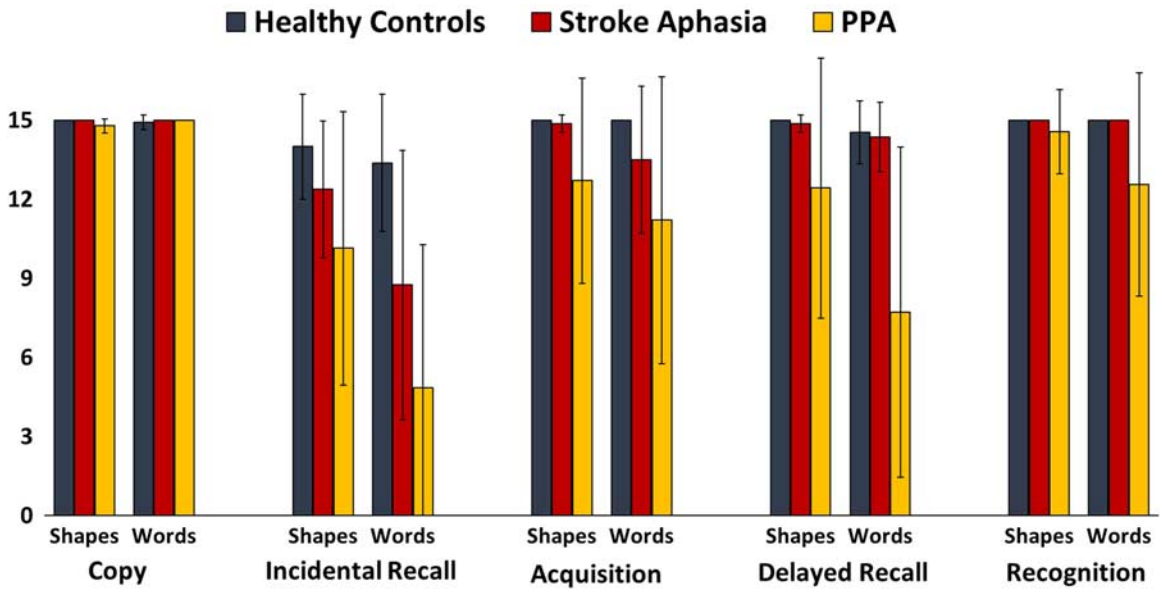


FIGURE 4. Distribution of group performances in each subtest of the 3W3S–Turkish Test. Data for shapes versus words are presented separately for each subtest. **3W3S–Turkish** = Three Words Three Shapes—Turkish version. **PPA** = primary progressive aphasia.

Incidental Recall

On the Incidental Recall subtest, the PPA, SA, and HC groups showed significant differences for shapes ($F_{2,31}$ = 3.415, P = 0.046, η^2 = 0.181) and for words ($F_{2,31}$ = 14.627, $P < 0.001$, η^2 = 0.486). Post hoc comparisons revealed that the SA group performed similarly to the PPA (P = 0.845) and HC ($P > 0.05$) groups for the shapes stimuli of the Incidental Recall subtest, whereas the PPA group had significantly lower scores on average compared with the HC (P = 0.041). For the words stimuli of the Incidental Recall subtest, the PPA and SA groups had significantly lower scores on average compared with the HC ($P < 0.001$ and $P = 0.002$, PPA vs HC and SA vs HC, respectively). The PPA and SA groups did not differ significantly from each other for the words stimuli of the Incidental Recall subtest ($P > 0.05$).

Acquisition

The score of the last study trial was used as the Acquisition subtest score. The PPA group had the lowest score on average. However, the group differences did not reach significance for either shapes ($F_{2,31}$ = 2.968, P = 0.066, η^2 = 0.161) or words ($F_{2,31}$ = 3.102, P = 0.059, η^2 = 0.167).

Delayed Recall

On the Delayed Recall subtest, there were no significant differences between the groups for shapes ($F_{2,31}$ = 2.409, P = 0.107, η^2 = 0.135). However, the groups differed significantly from each other for the words stimuli ($F_{2,31}$ = 8.024, P = 0.002, η^2 = 0.341), in particular when comparing the PPA group with the HC (P = 0.001). Although the PPA group had lower scores on average than the SA group, the pairwise comparison did not reach significance after adjustment for multiple comparisons (P = 0.176). The comparison of the SA and HC groups also was not significant ($P > 0.05$).

Although group averages did not show a significant difference between the PPA and SA groups on the Delayed Recall subtest, a classification based on the percentile scores was remarkable. Cross tabulation revealed that 71.4% of the PPA group performed <90th percentile in the Delayed Recall of words, but only 12.5% of the SA group performed <90th percentile. On the other hand, 92.8% of the PPA group and 75.0% of the SA group performed <90th percentile in the Incidental Recall of words. Figure 5 provides a representation of individual performances of the PPA and SA groups according to the percentile scores for words in the Incidental and Delayed Recall subtests.

Recognition

On the Recognition subtest, there were no significant differences between the groups for either shapes ($F_{2,31}$ = 0.836, P = 0.44, η^2 = 0.051) or words ($F_{2,31}$ = 2.241, P = 0.12, η^2 = 0.126).

Material-specific Memory

A repeated measures ANOVA in the PPA group yielded a significant interaction between subtest and stimuli type (words vs shapes): $F_{4,52}$ = 4.83, P = 0.002, η^2 = 0.271. The PPA group had significantly higher scores for shapes than words on the Incidental and Delayed Recall subtests (t_{13} = 3.351, P = 0.005 for Incidental Recall; t_{13} = 3.486, P = 0.004 for Delayed Recall), and the difference was close to significant for the Acquisition subtest (t_{13} = 2.071, P = 0.059). However, in the PPA group, scores for shapes and words in the Copy and Recognition subtests were equivalent (t_{13} = 1, P = 0.336 for Copy; t_{13} = 1.58, P = 0.136 for Recognition). In the SA and HC groups, a

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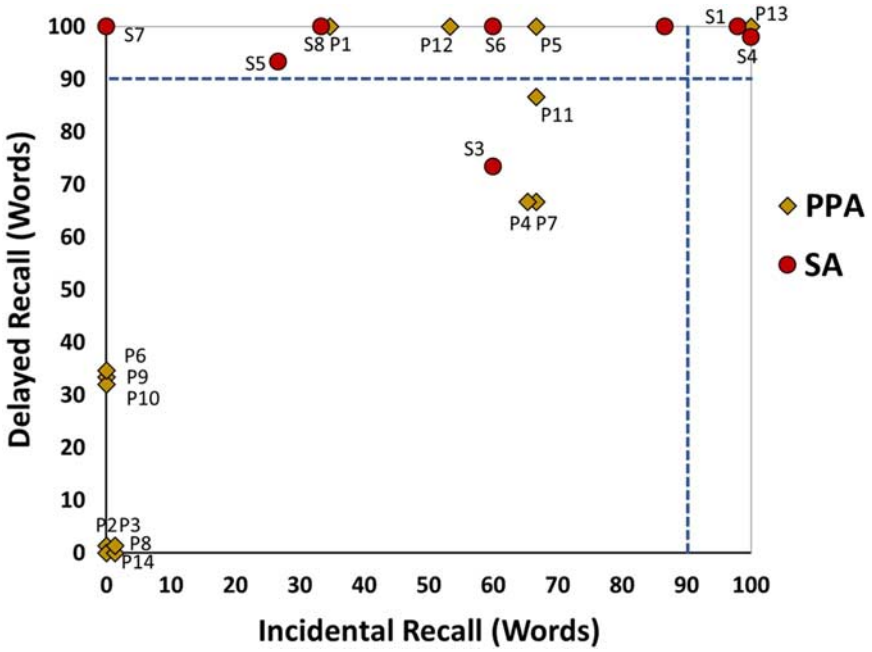


FIGURE 5. Representation of individual performances of the PPA and SA groups according to the percentiles in the effortless learning and retrieval of words. The ID of each participant is presented as a label next to each data point. Blue dotted lines representing the 90% threshold are used for both effortless learning and retrieval. **PPA** = primary progressive aphasia. **SA** = stroke aphasia.

repeated measures ANOVA showed no significant interaction between stimuli type and subtest ($F_{1.46,10.23} = 2.89$, $P = 0.11$, $\eta^2 = 0.293$ for the SA group; $F_{1.24,14.87} = 0.559$, $P = 0.503$, $\eta^2 = 0.045$ for the HC).

Effortless Learning of Shapes Versus Words

As a measure of effortless learning, a within-group comparison showed that the Incidental Recall subtest score was significantly lower than the Copy subtest score for both shapes and words in both the PPA group ($t_{13} = 3.45$, $P = 0.004$; $t_{13} = 6.98$, $P < 0.001$, for shapes and words, respectively) and the SA group ($t_7 = 2.67$, $P = 0.032$; $t_7 = 3.23$, $P = 0.014$, for shapes and words, respectively). In the HC, there was a slight decline in the Incidental Recall subtest score compared with the Copy subtest score, which did not reach significance for shapes ($t_{12} = 1.8$, $P = 0.097$) but did reach significance for words ($t_{12} = 2.21$, $P = 0.047$).

Retrieval of Shapes Versus Words

The within-group comparison revealed that the average score on the Delayed Recall subtest was significantly lower than that on the Acquisition subtest for words ($t_{13} = 2.73$, $P = 0.017$) but not shapes ($t_{13} = 0.37$, $P = 0.718$) in the PPA group, suggesting that the retrieval of words is impaired whereas the retrieval of shapes is relatively preserved. The SA group performed equally well on the Delayed Recall and Acquisition subtests for shapes (M ± SD = 14.85 ± 0.35 for both Delayed Recall and Acquisition). The comparison of the Delayed Recall and Acquisition subtest scores for words in the SA group was not significant ($t_7 = 1.26$, $P = 0.247$). The HC had perfect scores on the Delayed Recall and Acquisition subtests of shapes (M = 15 for both Delayed Recall and Acquisition) and near-perfect scores on the Delayed Recall subtest of words ($t_{12} = 1.4$, $P = 0.19$).

Retention of Shapes Versus Words

As a measure of retention, a within-group comparison in the PPA and SA groups showed that their Acquisition and Recognition subtest scores did not differ significantly from each other in either shapes ($t_{13} = 1.84$, $P = 0.09$ for PPA; $t_7 = 1.0$, $P = 0.351$ for SA) or words ($t_{13} = 1.15$, $P = 0.27$ for PPA; $t_7 = 1.43$, $P = 0.19$ for SA). A t test could not be computed in the HC because perfect scores were obtained on both the Acquisition and Recognition subtests.

Effortful Learning

Total Learning

The total learning scores obtained from the consequent study trials during the Acquisition subtest differed between the groups ($F_{2,31} = 5.269$, $P = 0.011$, $\eta^2 = 0.254$). The PPA group had significantly lower scores on average compared with the HC ($P = 0.009$). The SA group did not differ significantly from the PPA or HC group (vs PPA $P > 0.05$; vs HC $P = 0.73$).

The subscores for learning shapes and words differed significantly between the groups ($F_{2,31} = 3.996$, $P = 0.029$, $\eta^2 = 0.205$ for shapes; $F_{2,31} = 5.754$, $P = 0.007$, $\eta^2 = 0.271$ for words). The subscores for learning shapes and words were significantly lower for the PPA group compared with the HC ($P = 0.028$ for shapes; $P = 0.01$ for words). The subscores for learning shapes and words for the SA group did not differ significantly from the PPA ($P > 0.286$ for shapes; $P > 0.05$ for words) or HC group ($P > 0.05$ for shapes; $P = 0.257$ for words) (Figure 6A).

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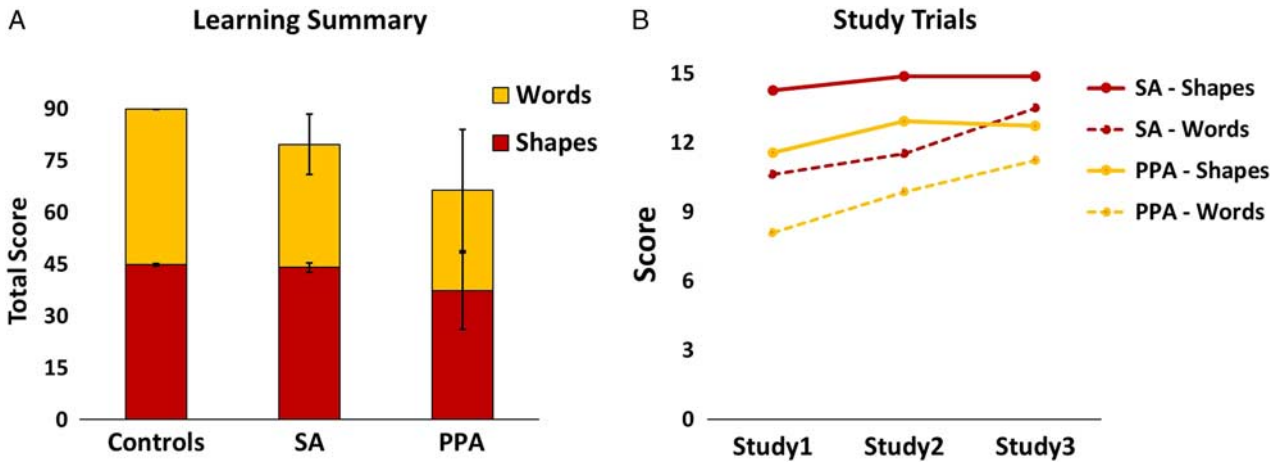


FIGURE 6. A. Summary of study trials on the Acquisition subtest presented as cumulative bar graphs. Each bar represents the cumulative scores out of a total score of 90 (45 for each component; shapes and words, respectively). **B.** Scores of each study trial for shapes versus words in the PPA and SA groups. While both groups reached the highest scores for learning shapes during the second study trial, the highest scores for learning words were reached during the third study trial. The learning trend for verbal material was more prominent in the PPA group compared with the SA group. **PPA** = primary progressive aphasia. **SA** = stroke aphasia.

Study Trial Outcomes

The three groups did not differ significantly from each other on the Acquisition subtest (last study trial), but a difference was observed in their total learning scores. One possible explanation is that the PPA group differed from the SA and HC groups at the first study trial, exhibiting significantly lower scores, and learning over time helped to improve their outcomes. To test this hypothesis, we conducted additional analyses of covariance including the scores of the first study trials. The results showed that the groups differed significantly from each other in the first study trial for both shapes ($F_{2,31} = 4.443$, $P = 0.02$, $\eta^2 = 0.223$) and words ($F_{2,31} = 6.276$, $P = 0.005$, $\eta^2 = 0.288$). Post hoc pairwise comparisons revealed that the PPA group had significantly lower scores compared with the HC in both shapes ($P = 0.018$) and words ($P = 0.01$) in the first study trial. The SA group did not differ significantly from the PPA and HC groups for either shapes (vs PPA group $P > 0.05$; vs HC, $P = 0.116$) or words (vs PPA group, $P > 0.05$; vs HC, $P = 0.116$) in the first study trial.

Group performances in each study trial were analyzed separately to determine the change in the level of information that was acquired over time (Figure 6B). In the PPA group, a one-way repeated measures ANOVA for consequent study trials in the Acquisition subtest was significant for learning words ($F_{1.42,\ 18.45} = 4.054$, $P = 0.047$, $\eta^2 = 0.237$) but not shapes ($F_{1.04,\ 13.51} = 2.038$, $P = 0.176$, $\eta^2 = 0.176$). Significant differences appeared in the comparison of Trial 1 and Trial 3 ($t_{13} = -2.379$, $P = 0.033$) for words. No significant difference was noted when Trial 1 was compared with Trial 2 ($t_{13} = -1.471$, $P = 0.165$). The comparison of Trial 2 and Trial 3 trended toward significance ($t_{13} = -2.007$, $P = 0.066$).

In the SA group, a one-way repeated measures ANOVA for consequent study trials in the Acquisition subtest was significant for learning shapes ($F_{1,7} = 5.645$, $P = 0.049$, $\eta^2 = 0.446$) but not words ($F_{2,14} = 1.527$, $P = 0.251$, $\eta^2 = 0.179$). The SA group reached the highest score on average for shapes in Trial 2, which was preserved in Trial 3. The difference between average scores in Trial 1 and Trial 2 was significant ($t_7 = -2.376$, $P = 0.049$) for shapes.

The majority of the HC (12 out of 14) reached the maximum score of 15 for both shapes and words in the first study trial; the remaining two HC required a second study trial, where they also reached the maximum score.

Relationship Between Language Functions and Verbal Memory

Finally, we wanted to know whether performance on the language tests was correlated with the test scores on the words part of the 3W3S–Turkish Test in the PPA and SA groups. Correlation coefficients were calculated to reveal the strength of the relationship between each language test score and scores obtained from each subtest on the words part of the 3W3S–Turkish Test. In the PPA group, the Boston Naming Test scores significantly correlated with both the Incidental Recall (words) ($r = 0.71$, $P = 0.003$) (Figure 7A) and the Delayed Recall (words) ($r = 0.61$, $P = 0.028$) (Figure 7B) subtests. A significant correlation was also evident between the Boston Naming Test scores and the Study 1 scores ($r = 0.67$, $P = 0.012$) in the PPA group (Figure 7C).

On the other hand, a significant correlation was found between the reading scores on the Turkish Language Assessment Test for Aphasia and the scores obtained from the first study trial (Study 1) ($r = 0.73$, $P = 0.04$) in the SA group (Figure 7D). Details of the correlation analyses are presented in the SDC as Table 3 (http://links.lww.com/CBN/A111).

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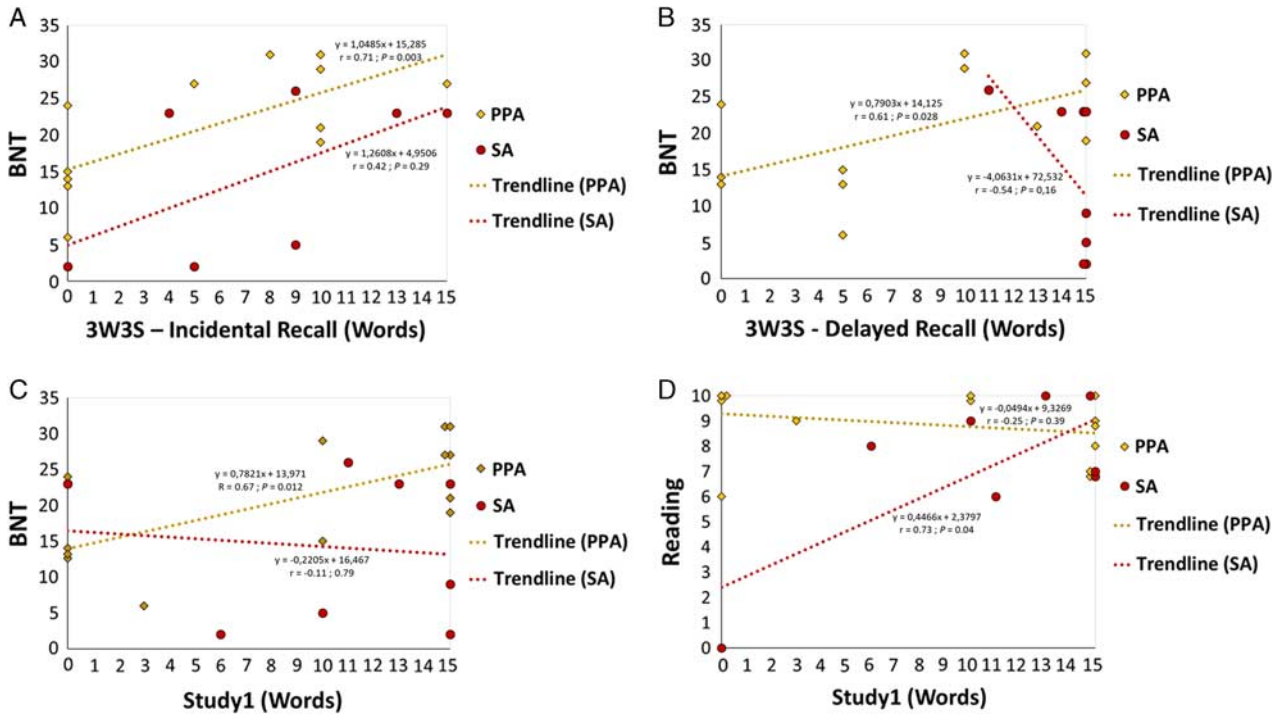


FIGURE 7. Relationship between the language test scores and the scores obtained from the words part of the 3W3S–Turkish Test. **A.** Correlation between the BNT and the Incidental Recall (words) subtest scores. **B.** Correlation between the BNT and the Delayed Recall (words) subtest scores. Please note that six of the eight SA causing a moderate negative correlation between the BNT and the Delayed Recall patients received a full score of 15 on the Delayed Recall subtest, causing a moderate negative correlation between the BNT and the Delayed Recall subtest scores that was not significant. **C.** Correlation between the BNT and the first study trial (Study1). **D.** Correlation between Reading scores from the Turkish Language Assessment Test for Aphasia and the first study trial (Study 1). **3W3S–Turkish** = Three Words Three Shapes Test—Turkish version. **BNT** = Boston Naming Test. **PPA** = primary progressive aphasia. **SA** = stroke aphasia.

DISCUSSION

We investigated how memory processing is affected in individuals with PPA and those with SA using the 3W3S–Turkish Test, which provides both verbal (words) and nonverbal (shapes) stimuli within the same modality. Both aphasia groups showed impairment in effortless learning, and the PPA group showed additional impairment in retrieval. Memory impairment for words was more prominent in the PPA group, particularly for effortless learning and retrieval. The PPA group showed a significant positive trend for effortful learning of words during the study trials. The PPA group showed retrieval impairment for words but not shapes, whereas the SA group showed no impairment for retrieval. Finally, both aphasia groups retained the acquired information regardless of the type of stimuli (words versus shapes) that was being presented.

Despite the relatively smaller sample size, our findings are compatible with previous studies investigating memory functions in individuals with PPA. Both Weintraub et al (2013) and Kielb et al (2016) showed that individuals with PPA may be impaired in both effortless learning and word retrieval.

The inclusion of the SA group in our study provided a head-to-head comparison of memory functions in two aphasia groups related to distinct etiologies with different time courses—slowly progressive incessant language dissolution due to neurodegeneration (PPA) and an acute insult to the language network and consequent partial recovery due to cerebrovascular disease (SA).

The SA group in our study also showed impairment in the effortless learning of words, as well as of shapes. Short-term memory impairment has been observed frequently in individuals with SA (Fonseca et al, 2019). The majority of the studies of individuals with SA are based on the assessment of short-term memory in the auditory modality, and memory impairment in this patient population has been associated with working memory/attention-related deficits (Minkina et al, 2017; Salis et al, 2018).

In our study, memory impairment in the SA group was also limited to the working memory/attention-related processes, including effortless learning. However, the stimuli in our study were presented in the visual rather than auditory modality, suggesting that memory impairment related to SA may not be related solely to an auditory working memory deficit. Future studies focusing on verbal short-term memory deficits in the visual modality may improve our understanding of the role of the left inferior frontal gyrus in memory processing in individuals with SA. Unlike the SA group, the PPA group showed

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additional impairment in the retrieval of words. Retrieval deficits can be detected in individuals with PPA due to the neurodegenerative nature of the disease, particularly in individuals with AD neuropathology (Kielb et al, 2016).

As expected, the cerebrovascular lesions observed in the SA group were limited to the vascular territories of the superior branch of the middle cerebral artery. These lesions were within the cortical territories of the dorsal language areas encompassing the portions of the inferior frontal gyrus, inferior parietal lobe, and posterior temporal gyrus.

However, regional distribution of the cortical atrophy in the PPA group went beyond the regions described in classic aphasia syndromes that are based on stroke models (Grossman and Irwin, 2018). The map of the PPA group showed peak atrophy of language sites such as the inferior frontal gyrus and adjacent prefrontal areas; temporoparietal junction; and anterior temporal lobe, including the temporal pole in the left hemisphere. Additional atrophy was noted at the medial part of the anterior temporal lobe; parahippocampal gyrus; and midline cortical structures, including the precuneus, posterior cingulate cortex, and middle cingulate cortex.

Material-specific Memory Impairment

Although both aphasia groups had prominent language impairment, the PPA group displayed greater difficulties for words versus shapes on the 3W3S–Turkish Test, suggesting the existence of material-specific memory impairment. A comparison of the regional distribution of atrophy sites in the PPA group and of lesions in a subset of the SA group suggested that the left anterior temporal lobe and some portions of the left medial temporal lobe (including the parahippocampal gyrus), as well as the precuneus and posterior/medial cingulate gyrus, may be distinctive regions for difficulty with verbal memory processing. These cortical areas are vulnerable to neurodegeneration but are not involved in the vascular territories that are associated with classic aphasia syndromes (Grossman and Irwin, 2018). Furthermore, as a border zone area, the left anterior temporal lobe receives blood supply from both the middle and the posterior cerebral arteries. Therefore, circumscribed ischemic damage to this cortical region is very rare (Lambon Ralph, 2014; Rogalski et al, 2011a). On the other hand, the precuneus and the middle/posterior parts of the cingulate cortex are not involved in the language network, but these structures constitute major portions of the default mode network, which is compromised early in the course of AD (Seeley et al, 2009), even in the nonamnestic presentations of the disease (Lehmann et al, 2010). However, due to the relatively small sample size, additional analyses for more precise symptom–lesion correlations could not be performed. Previous studies suggest that neurodegeneration may spread to the limbic and paralimbic areas as the disease progresses—even in the nonsemantic variants of PPA—although the medial temporal lobe is not the initial site of peak atrophy (Nilakantan et al, 2017; Rogalski et al, 2011a).

The PPA group in our study showed greater impairment in both effortless learning and retrieval of words compared with shapes, also suggesting the presence of material-specific memory impairment. Nevertheless, there is no consensus on the neural correlates of material-specific memory disorder in individuals with PPA. In individuals with nonsemantic PPA, verbal retention memory deficit is associated with the left inferior frontal gyrus and left temporal pole (Nilakantan et al, 2017). Lindberg et al (2012) reported the occurrence of hippocampal atrophy in individuals with progressive nonfluent aphasia, which is a clinical phenotype that was previously used to refer to nonsemantic/nonfluent PPA (Neary et al, 1998). On the other hand, atrophy in the left anterior hippocampus was found in individuals with lvPPA (Gorno-Tempini et al, 2004), which is often associated with AD pathology (Bergeron et al, 2018; Gefen et al, 2012; Mesulam et al, 2014b).

Surface deformities can also be seen in the left hippocampus of individuals with the nonsemantic variants of PPA (Christensen et al, 2015). A recent study published by Ramanan et al (2021) revealed that episodic memory in individuals with lvPPA was associated with atrophy of the left angular gyrus, precuneus, and posterior cingulate cortex, with additional but milder atrophy of similar regions in the right hemisphere (Ramanan et al, 2021). A similar pattern of posterior parietal involvement was also noted in the PPA group in our study.

In a recent meta-analysis, both episodic and working memory deficits were observed in all PPA variants, lvPPA being the most vulnerable (Eikelboom et al, 2018). In cases where biomarkers are not available, systematic subtyping can be extremely effective for clinicopathological predictions because up to 86% of lvPPA cases may have AD as an underlying pathology (Bergeron et al, 2018; Mesulam et al, 2014b). In our PPA group, three cases had both logopenic/agrammatic language features. However, none of the cases in our group could be subtyped solely as lvPPA according to the current criteria (Gorno-Tempini et al, 2011).

Difficulty in subtyping PPA in Turkish-speaking individuals may be due to the linguistic characteristics of the Turkish language. Similar to Japanese, Korean, Finnish, and Hungarian, Turkish is an agglutinating inflectional language (Slobin, 1991). Although subject-object-verb is the most common use of word order, Turkish is a "free" word order language, and grammar in Turkish is represented in the inflectional morphology to a great extent (Arslan et al, 2016; İşsever, 2003). Nevertheless, current PPA classification criteria are largely based on studies of English-speaking individuals with PPA, and the characteristics of aphasia in agglutinative languages may not conform to one of the subtypes, particularly in the nonsemantic variants of PPA. It has been reported that up to 31% of English-speaking individuals with PPA remain unclassified according to the 2011 guidelines (Mesulam and Weintraub, 2014; Wicklund et al, 2014).

Deficits in inflectional morphology have been reported in all three variants of PPA in English-speaking individuals with a diverse range of severity and characteristics (Wilson et al, 2014). However, differentiating

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lvPPA from nfvPPA appears to be more troublesome in Turkish because both groups may have deficits in inflectional morphology, with relatively spared syntax. Future studies investigating fine-grained details in morphosyntactic impairment may help develop an algorithm for more reliable differentiation of lvPPA from nfvPPA in Turkish and other agglutinative languages.

Cognitive impairment in individuals with PPA may extend beyond aphasia as the disease progresses. Executive deficits, visuospatial dysfunction, behavioral problems, and memory impairment can be evident in the longitudinal course of PPA (Rogalski et al, 2011b; Ulugut et al, 2021). In summary, individuals with PPA may require comprehensive evaluation during follow-up visits at neurobehavior clinics, and nonlanguage domains including memory should be considered when planning cognitive interventions.

Study Limitations

Our study had several limitations. The PPA findings from the current study need to be characterized in more detail in future studies by including different subtypes because PPA represents a heterogeneous group of syndromes that display distinct cognitive profiles. The performances of the individuals with nonsemantic PPA (including nfvPPA, lvPPA, nfvPPA/lvPPA, and the unclassified individuals) could be influencing the overall results because these individuals are overrepresented in the PPA group. Small sample size and unavailability of imaging data in some individuals in the PPA and SA groups limited further investigation and definition of the fine-grained details of symptom–lesion correlations.

Moreover, neurodegeneration biomarkers were not available for all of the individuals with PPA. Therefore, a comparison of PPA with AD and PPA-nonAD was not feasible. Although relatively more homogenous clinical features of the SA group provided convenience in interpreting the test results, the lack of individuals with Wernicke aphasia in our study limited further comparison of memory functions in nonfluent and fluent SA syndromes. Furthermore, the agglutinative nature of the Turkish language increased the difficulty of subtyping, particularly in individuals with nonsemantic language impairment that did not meet the classification criteria for either nfvPPA or lvPPA. In short, the findings of our study should be interpreted with caution due to the relatively small sample size and the heterogeneous nature of the group's characteristics.

CONCLUSION

Our study revealed unique performance patterns on the 3W3S–Turkish Test by individuals with PPA versus those with SA. The use of the 3W3S–Turkish Test, which is composed of both verbal and nonverbal stimuli, helped identify the magnitude of impairment in verbal versus nonverbal memory in these two groups. To our knowledge, this is the first study to include a head-to-head comparison of memory functions in PPA versus SA. The neurodegenerative nature of PPA and the spread of atrophy to the left anterior temporal lobe and memory-related medial cortical structures in PPA may explain the emergence of material-specific memory impairment. The dorsal prefrontal working memory/attention network may be disrupted in both patient populations, whereas the delayed recall deficit is more distinctive for individuals with PPA.

Due to its comprehensive structure for memory assessment, the 3W3S–Turkish Test can be integrated into cognitive assessment batteries for individuals with both the amnestic and aphasic forms of neurodegenerative dementias. Our findings also encourage adaptation of the 3W3S Test to different languages to help provide reliable and comparable data sets from multicentered/multinational studies. Future studies with larger cohorts including PPA and SA subtypes would help characterize the differences in amnestic processing in these patient populations in more detail.

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REFERENCES

Allen EC, Beilock SL, Shevell SK. 2011. Working memory is related to perceptual processing: a case from color perception. *J Exp Psychol Learn Mem Cogn*. 37:1014–1021. doi:10.1037/a0023257

Armentano C, Quayle J. 2007. Performance of elderly on the G: a Brazilian study. *Dement Neuropsychol*. 1:396–401. doi:10.1590/S1980-57642008DN10400012

Arslan S, Bamyaci E, Bastiaanse R. 2016. A characterization of verb use in Turkish agrammatic narrative speech. *Clin Linguist Phon*. 30:449–469. doi:10.3109/02699206.2016.1144224

Barense MD, Ngo JK, Hung LH, et al. 2012. Interactions of memory and perception in amnesia: the figure-ground perspective. *Cereb Cortex*. 22:2680–2691. doi:10.1093/cercor/bhr347

Benton A, Sivan AB, Hamsher K de S, et al. 1994. Contributions to Neuropsychological. *Assessment: A Clinical Manual*, 2nd ed. New York, New York: Oxford University Press.

Bergeron D, Gorno-Tempini ML, Rabinovici GD, et al. 2018. Prevalence of amyloid-β pathology in distinct variants of primary progressive aphasia. *Ann Neurol*. 84:729–740. doi:10.1002/ana.25333

Blessed G, Tomlinson BE, Roth M. 1968. The association between quantitative measures of dementia and of senile change in the cerebral grey matter of elderly subjects. *Br J Psychiatry*. 114:797–811. doi:10.1192/bjp.114.512.797

Carota A, Neufeld H, Calabrese P. 2015. Memory profiles after unilateral paramedian thalamic stroke infarction: a comparative study. Published online October 26. *Case Rep Med*. 2015:430869. doi:10.1155/2015/430869

Christensen A, Alpert K, Rogalski E, et al. 2015. Hippocampal subfield surface deformity in non-semantic primary progressive aphasia. *Alzheimers Dement (Amst)*. 1:14–23. doi:10.1016/j.dadm.2014.11.013

Delis DC, Kramer JH, Kaplan E, et al. 1987. *The California Verbal Learning Test: Adult Version Manual*. San Antonio, Texas: Psychological.

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Duchaine B, Nakayama K. 2006. The Cambridge Face Memory Test: results for neurologically intact individuals and an investigation of its validity using inverted face stimuli and prosopagnosic participants. *Neuropsychologia*. 44:576–585. doi:10.1016/j.neuropsychologia.2005.07.001

Eikelboom WS, Janssen N, Jiskoot LC, et al. 2018. Episodic and working memory function in primary progressive aphasia: a meta-analysis. *Neurosci Biobehav Rev*. 92:243–254. doi:10.1016/j.neubiorev.2018.06.015

Fischl B. 2012. FreeSurfer. *Neuroimage*. 62:774–781. doi:10.1016/j.neuroimage.2012.01.021

Folstein MF, Folstein SE, McHugh PR. 1975. "Mini-Mental State." A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 12:189–198. doi:10.1016/0022-3956(75)90026-6

Fonseca J, Raposo A, Martins IP. 2019. Cognitive functioning in chronic post-stroke aphasia. *Appl Neuropsychol Adult*. 26:355–364. doi:10.1080/23279095.2018.1429442

Foxe D, Irish M, Roquet D, et al. 2020. Visuospatial short-term and working memory disturbance in the primary progressive aphasias: neuroanatomical and clinical implications. *Cortex*. 132:223–237. doi:10.1016/j.cortex.2020.08.018

Gefen T, Gasho K, Rademaker A, et al. 2012. Clinically concordant variations of Alzheimer pathology in aphasic versus amnestic dementia. *Brain*. 135:1554–1565. doi:10.1093/brain/aws076

Genovese CR, Lazar NA, Nichols T. 2002. Thresholding of statistical maps in functional neuroimaging using the false discovery rate. *Neuroimage*. 15:870–878. doi:10.1006/nimg.2001.1037

Godefroy O, Dubois C, Debachy B, et al. 2002. Vascular aphasias: main characteristics of patients hospitalized in acute stroke units. *Stroke*. 33:702–705. doi:10.1161/hs0302.103653

Gorno-Tempini ML, Dronkers NF, Rankin KP, et al. 2004. Cognition and anatomy in three variants of primary progressive aphasia. *Ann Neurol*. 55:335–346. doi:10.1002/ana.10825

Gorno-Tempini ML, Hillis AE, Weintraub S, et al. 2011. Classification of primary progressive aphasia and its variants. *Neurology*. 76:1006–1014. doi:10.1212/WNL.0b013e31821103e6

Grossman M, Irwin DJ. 2018. Primary progressive aphasia and stroke aphasia. *Continuum (Minneap Minn)*. 24:745–767. doi:10.1212/CON.0000000000000618

Hsu CJ, Thompson CK. 2018. Manual versus automated narrative analysis of agrammatic production patterns: The Northwestern Narrative Language Analysis and Computerized Language Analysis. *J Speech Lang Hear Res*. 61:373–385. doi:10.1044/2017_JSLHR-L-17-0185

İşsever S. 2003. Information structure in Turkish: the word order–prosody interface. *Lingua*. 113:1025–1053. doi:10.1016/S0024-3841(03)00012-3

Jack CR Jr, Bennett DA, Blennow K, et al. 2018. NIA–AA Research Framework: toward a biological definition of Alzheimer's disease. *Alzheimers Dement*. 14:535–562. doi:10.1016/j.jalz.2018.02.018

Karakaş S, Erdoğan Bakar E, Doğutepe Dinçer E. 2013. *Nöropsikolojik Testlerin Yetişkinler için Araştırma ve Geliştirme Çalışmaları: BİLNOT- Yetişkin Vol 3*. baskı. Konya, Turkey: Eğitim Yayınevi.

Keskinkılıç C. 2008. Standardization of Benton Face Recognition Test in a Turkish normal adult population. *Turk J Neurol*. 14:179–190.

Kielb S, Cook A, Wieneke C, et al. 2016. Neuropathologic associations of learning and memory in primary progressive aphasia. *JAMA Neurol*. 73:846–852. doi:10.1001/jamaneurol.2016.0880

Kudiaki C, Aslan A. 2007. The Three Words–Three Shapes Test: normative data for the Turkish elderly. *Arch Clin Neuropsychol*. 22:637–645. doi:10.1016/j.acn.2007.04.006

Kudiaki C, Aslan A, Dinç D. 2018. Comparison of the original and parallel forms of the Three Words–Three Shapes Test. *Turk J Neurol*. 24:252–258. doi:10.4274/tnd.74508

Lam B, Masellis M, Freedman M, et al. 2013. Clinical, imaging, and pathological heterogeneity of the Alzheimer's disease syndrome. Published online January 9. *Alzheimers Res Ther*. 5:1. doi:10.1186/alzrt155

Lambon Ralph MA. 2014. Neurocognitive insights on conceptual knowledge and its breakdown. Published online December 9, 2013. *Philos Trans R Soc Lond B Biol Sci*. 369:20120392. doi:10.1098/rstb.2012.0392

Lehmann M, Rohrer JD, Clarkson MJ, et al. 2010. Reduced cortical thickness in the posterior cingulate gyrus is characteristic of both typical and atypical Alzheimer's disease. *J Alzheimers Dis*. 20:587–598. doi:10.3233/JAD-2010-1401

Lindberg O, Walterfang M, Looi JC, et al. 2012. Hippocampal shape analysis in Alzheimer's disease and frontotemporal lobar degeneration subtypes. *J Alzheimers Dis*. 30:355–365. doi:10.3233/JAD-2012-112210

McKhann GM, Knopman DS, Chertkow H, et al. 2011. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging–Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 7:263–269. doi:10.1016/j.jalz.2011.03.005

Mesulam MM. 2000. *Principles of Behavioral and Cognitive Neurology*, 2nd ed. Oxford, New York: Oxford University Press.

Mesulam MM, Weintraub S. 2014. Is it time to revisit the classification guidelines for primary progressive aphasia? *Neurology*. 82:1108–1109. doi:10.1212/WNL.0000000000000272

Mesulam MM, Rogalski EJ, Wieneke C, et al. 2014a. Primary progressive aphasia and the evolving neurology of the language network. *Nat Rev Neurol*. 10:554–569. doi:10.1038/nrneurol.2014.159

Mesulam MM, Thompson CK, Weintraub S, et al. 2015. The Wernicke conundrum and the anatomy of language comprehension in primary progressive aphasia. *Brain*. 138:2423–2437. doi:10.1093/brain/awv154

Mesulam MM, Weintraub S, Rogalski EJ, et al. 2014b. Asymmetry and heterogeneity of Alzheimer's and frontotemporal pathology in primary progressive aphasia. *Brain*. 137:1176–1192. doi:10.1093/brain/awu024

Mesulam M, Wieneke C, Rogalski E, et al. 2009. Quantitative template for subtyping primary progressive aphasia. *Arch Neurol*. 66:1545–1551. doi:10.1001/archneurol.2009.288

Minkina I, Rosenberg S, Kalinyak-Fliszar M, et al. 2017. Short-term memory and aphasia: from theory to treatment. *Semin Speech Lang*. 38:17–28. doi:10.1055/s-0036-1597261

Neary D, Snowden JS, Gustafson L, et al. 1998. Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. *Neurology*. 51:1546–1554. doi:10.1212/wnl.51.6.1546

Nilakantan AS, Voss JL, Weintraub S, et al. 2017. Selective verbal recognition memory impairments are associated with atrophy of the language network in non-semantic variants of primary progressive aphasia. *Neuropsychologia*. 100:10–17. doi:10.1016/j.neuropsychologia.2017.04.006

Ott BR, Saver JL. 1993. Unilateral amnesic stroke. six new cases and a review of the literature. *Stroke*. 24:1033–1042. doi:10.1161/01.str.24.7.1033

Petersen RC, Caracciolo B, Brayne C, et al. 2014. Mild cognitive impairment: a concept in evolution. *J Intern Med*. 275:214–228. doi:10.1111/joim.12190

Quiñones M, Gómez D, Montefusco-Siegmun R, et al. 2021. Early visual processing and perception processes in object discrimination learning. Published online January 28. *Front Neurosci*. 15:617824. doi:10.3389/fnins.2021.617824

Ramanan S, Foxe D, El-Omar H, et al. 2021. Evidence for a pervasive autobiographical memory impairment in logopenic progressive aphasia. *Neurobiol Aging*. 108:168–178. doi:10.1016/j.neurobiolaging.2021.09.004

Randolph C. 1998. *Repeatable Battery for the Assessment of Neuropsychological Status*. San Antonio, Texas: Psychological.

Reitan RM, Wolfson D. 1993. *The Halstead-Reitan Neuropsychological Test Battery: Theory and Clinical Interpretation*. Tucson, Arizona: Neuropsychology.

Rey A. 1970. *L'examen Clinique en Psychologie*. Paris, France: Presses Universitaires de France.

Rogalski E, Cobia D, Harrison TM, et al. 2011a. Anatomy of language impairments in primary progressive aphasia. *J Neurosci*. 31:3344–3350. doi:10.1523/JNEUROSCI.5544-10.2011

Rogalski E, Cobia D, Harrison TM, et al. 2011b. Progression of language decline and cortical atrophy in subtypes of primary progressive aphasia. *Neurology*. 76:1804–1810. doi:10.1212/WNL.0b013e31821ccd3c

Rogalski E, Sridhar J, Rader B, et al. 2016. Aphasic variant of Alzheimer disease: clinical, anatomic, and genetic features. *Neurology*. 87:1337–1343. doi:10.1212/WNL.0000000000003165

Rohrer JD, Rossor MN, Warren JD. 2010. Apraxia in progressive nonfluent aphasia. *J Neurol*. 257:569–574. doi:10.1007/s00415-009-5371-4

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Salis C, Martin N, Meehan SV, et al. 2018. Short-term memory span in aphasia: insights from speech-timing measures. *J Neurolinguistics*. 48:176–189. doi:10.1016/j.jneuroling.2018.04.014

Seeley WW, Crawford RK, Zhou J, et al. 2009. Neurodegenerative diseases target large-scale human brain networks. *Neuron*. 62:42–52. doi:10.1016/j.neuron.2009.03.024

Slobin DI. 1991. Aphasia in Turkish: speech production in Broca's and Wernicke's patients. *Brain Lang*. 41:149–164. doi:10.1016/0093-934x(91)90150-y

Soylu AE, Cangöz B. 2018. Adaptation and norm determination study of the Boston Naming Test for healthy Turkish elderly. *Noro Psikiyatr Ars*. 55:341–348. doi:10.5152/npa.2017.19331

Toğram B, Maviş İ. 2012. Validity, reliability and standardization study of the Language Assessment Test Aphasia. *Turk J Neurol*. 18:96–103. doi:10.4274/Tnd.16779

Ulugut H, Stek S, Wagemans LE, et al. 2021. The natural history of primary progressive aphasia: beyond aphasia. Published online July 3. *J Neurol*. doi:10.1007/s00415-021-10689-1

Weintraub S, Mesulam MM. 1985. Mental state assessment of young and elderly adults in behavioral neurology. In: Mesulam MM, ed. *Principles of Behavioral and Cognitive Neurology*. Philadelphia, Pennsylvania: F.A. Davis; 71–123.

Weintraub S, Mesulam MM. 1987. Right cerebral dominance in spatial attention. further evidence based on ipsilateral neglect. *Arch Neurol*. 44:621–625. doi:10.1001/archneur.1987.00520180043014

Weintraub S, Peavy GM, O'Connor M, et al. 2000. Three Words Three Shapes: a clinical test of memory. *J Clin Exp Neuropsychol*. 22:267–278. doi:10.1076/1380-3395(200004)22:2;1-1;FT267

Weintraub S, Rogalski E, Shaw E, et al. 2013. Verbal and nonverbal memory in primary progressive aphasia: the Three Words–Three Shapes Test. *Behav Neurol*. 26:67–76. doi:10.3233/BEN-2012-110239

Wicklund MR, Duffy JR, Strand EA, et al. 2014. Quantitative application of the primary progressive aphasia consensus criteria. *Neurology*. 82:1119–1126. doi:10.1212/WNL.0000000000000261

Wilson SM, Brandt TH, Henry ML, et al. 2014. Inflectional morphology in primary progressive aphasia: an elicited production study. *Brain Lang*. 136:58–68. doi:10.1016/j.bandl.2014.07.001

Wolf-Klein GP, Silverstone FA, Levy AP, et al. 1989. Screening for Alzheimer's disease by clock drawing. *J Am Geriatr Soc*. 37:730–734. doi:10.1111/j.1532-5415.1989.tb02234.x

Zhang X, Lv L, Min G, et al. 2021. Overview of the Complex Figure Test and its clinical application in neuropsychiatric disorders, including copying and recall. Published online August 31. *Front Neurol*. 12:680474. doi:10.3389/fneur.2021.680474

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