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PREFERENTIAL DISRUPTION OF AUDITORY WORD REPRESENTATIONS IN PRIMARY PROGRESSIVE APHASIA WITH THE NEUROPATHOLOGY OF FTLD-TDP TYPE A

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Abstract

Four patients with primary progressive aphasia (PPA) displayed greater deficits for understanding words they heard compared to words they read, and in naming objects orally rather than in writing. All 4 had FTLD-TDP Type A neuropathology, three determined at *post-mortem* and one surmised on the basis of granulin gene (*GRN*) mutation. These features of language impairment are not characteristic of any currently recognized PPA variant. They can be operationalized as manifestations of dysfunction centered on a putative auditory word form area (AWFA) located in the superior temporal gyrus of the left hemisphere. The small size of the sample makes the conclusions related to underlying pathology and AWFA dysfunction tentative. Nonetheless, a deeper assessment of such patients may clarify the nature of pathways that link modality-specific word form information to the associations that mediate their recognition as concepts. From a practical point of view, the identification of these features in PPA patients should help to design therapeutic interventions where written communication modalities are promoted to circumvent some of the oral communication deficits.

INTRODUCTION

Primary Progressive Aphasia (PPA) is a neurodegenerative syndrome of progressive and initially isolated language impairment. PPA can be classified into agrammatic (PPA-G), logopenic (PPA-L), semantic (PPA-S), and mixed (PPA-M) variants based on the status of fluency, grammar, naming, repetition and comprehension (Gorno-Tempini et al., 2011; Mesulam, Rogalski, et al., 2014). None of these variants is known to display selective impairments related to the route of stimulus input (auditory versus visual) or mode of response output (oral versus written). The current report was prompted by a PPA patient, (C1), who showed relatively selective auditory and oral impairments of word comprehension and object naming. The selectivity of her impairment lent itself to a connectivistic account centered on the disruption of a putative auditory word-form area located within the superior temporal gyrus of the left hemisphere.

Selectivity of language impairment is common in aphasia syndromes, including PPA. For example, PPA-G patients have greater difficulty naming verbs than nouns (Hillis, Oh, & Ken, 2004); PPA-L patients have longer word retrieval pauses for nouns than other parts of speech (Mack et al., 2015); and PPA-S patients have greater comprehension difficulties for words denoting living than non-living objects (Bright, Moss, Stamatakis, & Tyler, 2005). Selectivity for sensory modality, however, has an uncertain status. The first six patients that led to the delineation of the PPA syndrome included one with characteristics of pure word deafness (Mesulam, 1982). In retrospect, stability of her clinical course suggested that she should not have received a PPA diagnosis (Pinard, Chertkow, Black, & Peretz, 2002). A literature search identified only three PPA cases with features of pure word deafness, where word comprehension (but not object recognition) is selectively impaired in the auditory but not visual modality (Iizuka, Suzuki, Endo, Fujii, & Mori, 2007; S. H. Kim et al., 2011; Otsuki, Soma, Sato, Homma, & Tsuji, 1998). An auditory form of PPA is therefore exceedingly rare.

The selective impairment of oral naming and auditory comprehension in C1 was unusual and did not fit into any known subtype of PPA. In the course of clinical investigations, she was also found to carry a genetic mutation indicative of FTLTDP Type A pathology. This finding triggered a retrospective review of our PPA autopsy series and led to the identification of 3 additional cases with similar clinical features. All three turned out to have FTLTDP Type A as the primary neuropathologic diagnosis. Type A accounts for only 10% of cases in our series of 110 consecutive PPA autopsies. We therefore felt that the conjunction of such a rare clinical pattern with a rare neuropathologic correlate of PPA deserved to be reported.

METHODS

All cases had comprehensive language evaluations during the diagnostic workup for PPA. C1 had additional neurocognitive investigations validated in prior studies of PPA. In order to normalize performance, scores were expressed as percentages of correct responses. Imaging was done by standard MRI and metabolic PET.

CASE DESCRIPTIONS

CASE 1-C1

C1 was a 60 year-old right-handed woman at initial evaluation. She described progressive difficulties in word finding, grasping instructions and expressing her thoughts coherently for 3 years. Because of these difficulties, she was demoted from her managerial position. She nonetheless continued to perform household chores, maintained her checkbook, drove her car and took care of shopping. Her partner had not noticed changes in personality. She displayed adequate insight into her predicament. History provided by her partner and the cognitive neurology evaluation showed that memory of recent events, the recognition of familiar faces, visuospatial skills, and the ability to use tools and objects were all preserved.

These features led to a diagnosis of PPA. More detailed language assessment showed that speech and writing were agrammatic and that she had impaired word comprehension, a

combination characteristic of PPA-M. Her speech was not labored or dysarthric but mildly apraxic in multisyllabic words. Naming was severely impaired, as shown by a score of 15% on the Boston Naming Test (BNT (Goodglass, Kaplan, & Barresi, 2001)). Performance in the Repetition subtest of the Western Aphasia Battery-Revised (WAB-R (Kertesz, 2006)) was very low at 13%. Fluency was low because of numerous word-finding hesitations.

Surprisingly, she could circumvent some of the word retrieval failures in speech by spelling aloud or writing at least the initial few letters of the word she could not produce. Equally unusual was her ability to write the name of objects she could not name orally. Furthermore, when figurines of animals, edibles, and tools were placed in front of her, she was less successful pointing to the object that corresponded to the noun she heard than to the noun she read (e.g., cow, elephant). Although some of these findings were reminiscent of pure word deafness, the severe anomia and agrammatism were not consistent with that diagnosis.

She passed a pure tone audiometry screen from 250 to 1000 Hz at 30 decibels (dB) and from 100 to 8000 Hz at 35 dB in the right ear; and from 250 to 8000 Hz at 30 dB (with the exception of 6000 dB at 35 dB) in the left ear. In the Minimal Pair Test, which assesses phoneme discrimination (e.g., 'bin vs pin' or 'dime vs dine'), she gave accurate answers for 82% of the items. Although we did not have normative values for this test, her performance was interpreted as indicative of at most a mild impairment. Her profound deficits in auditory language tasks could therefore not be attributed to underlying deficits of elementary auditory function or phoneme identification. Additional tests were administered to quantitate the selectivity of her aphasia for the auditory modality (Table 1). On the Peabody Picture Vocabulary Test (PPVT (Dunn & Dunn, 2006)), used to assess the ability to recognize words presented in the auditory modality, performance was very poor (47%). However, on the picture form of the Pyramids and Palm Trees Test (PPT (Howard & Patterson, 1992)), used to assess non-verbal visual recognition of objects, performance was at 90%. She received a perfect score in matching 32 prerecorded environmental sounds delivered through headphones (e.g., rooster, trumpet, helicopter) to pictures that depicted the source of the sound. During a further videotaped testing session, she was shown 17 objects. She orally named only 41% and was able to write (accurately or in easily recognizable form) the names of 77% of the objects she failed to name orally (Table 2). She showed difficulty in reading words aloud in the Psycholinguistic Assessments of Language Processing in Aphasia (PALPA), scoring 0/10 for pseudo-words, 3/10 for regular words, and 0/10 for exceptional words.

She was also administered a task that required her to match a word she read or heard to one of 16 object pictures (Seckin et al., 2016). The object set comprised 48 drawings, evenly divided into four categories (animals, clothing, tools and fruits/vegetables). On each trial, a noun cue from this set was presented in either auditory or written form followed by an array of 16 objects that included the target object and 15 foils. The interval between stimulus onset and the appearance of the array was 3 seconds. The task was to touch the object corresponding to the cue (object name) and reaction times were recorded. The 48 items were split into 2 lists where the items in one list were given with an auditory cue first and the items from the other list with a written cue first. Pictures were placed equidistantly along a 31.4° by 24.2° ellipse with each picture subtending 3.4° of visual angle, allowing foveal

resolution with corrected visual acuity of at least 20/25. The corresponding nouns were balanced for lexical frequency, number of phonemes, and phonological neighborhood density (Balota & Yap, 2007). Her accuracy in this task was 92% for the visual presentation of the word and 50% for the auditory presentation. When only correct responses were considered, her reaction times were 4130 ± 394 msec for the visual presentation and 6291 ± 771 msec for the auditory presentation ($\pm$ indicates the standard error of the mean). The 95% confidence intervals for the two types of presentation were 4130 ± 772 msec for the visual and 6291 ± 1511 for the auditory modality, indicating that her level of certainty even for correct choices was less robust when linking an auditory rather than visual word to its referent.

C1's MRI showed extensive but asymmetric atrophy in the left hemisphere encompassing the inferior frontal gyrus, inferior parietal lobule as well as all parts of the left temporal cortex including the superior temporal gyrus (STG) and anterior temporal lobe (ATL). In the STG, Heschl's gyrus (primary auditory cortex, A1) appeared relatively preserved whereas the immediately adjacent lateral STG (auditory association cortex, AA) was severely atrophied (Figure 1, TOP). The patient reported that her sister had a somewhat similar condition of progressive impairment of word finding. The sister was not available for testing. Genotyping was done and C1 was found to have a disease-causing mutation in the *GRN* gene, which results in premature protein termination (p.Gln130Serfs*125). Such mutations are associated with the neuropathology of FTLTDP Type A (Mackenzie et al., 2010).

CASE 2 – C2

C2 was a 55 year-old right-handed man when he first noticed word-finding difficulties. Although he had to quit work because of his communication problems, he maintained customary activities, including highly complex hobbies such as flying his own airplane. At the initial examination 3 years later, language was the only area of cognitive impairment. Speech had many word-finding pauses and circumlocution. The circumlocution made it difficult to assess the grammatical structure of speech. There were no motor speech impairments. Comprehension of sentences based on familiar words he could understand was preserved in the auditory and visual modalities except for statements that were syntactically complex (e.g., passive voice). Single word comprehension was generally but not completely preserved (see below). Confrontation naming and sentence repetition were severely impaired. His examination most closely fit the pattern of logopenic PPA.

When asked to name an object, he would frequently take his pen out, grab a piece of paper and write the name of the object while saying 'that's just like it, just like it.' In the vast majority of cases, the noun he wrote was accurate (e.g., goose, turtle, button). Performance in the BNT was 23% for oral responses and 43% for written responses (Table 2). The rare single word comprehension failures were also more pronounced in the auditory modality. In a test of synonym judgment for example, performance was 90% for written words and 60% for auditory words. When presented with geometric shapes, he failed to orally name the cube, triangle and rectangle and also failed to point to the correct shape when he heard the corresponding word, indicating an auditory recognition failure for the noun. Nonetheless, he could correctly write the names of the shapes, showing that the word retrieval and

recognition problems were selective for the auditory modality. He passed a bilateral pure tone screen at 35dB except at 4000 Hz in the right ear where a threshold of 55 dB was recorded.

The MRI showed asymmetric atrophy of the left inferior parietal lobule and left temporal lobe, mostly the STG. Metabolic PET showed relatively preserved metabolism in Heschl's gyrus (A1) but severe hypometabolism in the adjacent auditory association cortex of the left STG (Fig. 1 MIDDLE). Family history indicated that his mother had been diagnosed with 'dementia' at the age of 50. Post-mortem examination revealed FTLD-TDP of type A. Genetic testing showed a *GRN* mutation (p.Ala237Thrfs*6).

CASE 3- C3

At the age of 55, this right-handed woman noted progressive word-finding difficulties in speech and writing. Daily living activities and other cognitive and behavioral domains were relatively preserved. Verbal output was sparse (9 words per minute), halting, labored and agrammatic. Repetition of phrases and sentences was impaired. She could recite the months of the year in 20 seconds, which is slow but not as slow as her spontaneous speech. The difference between spontaneous versus ordered word output suggested that the low fluency in her narrative was driven to a large extent by word finding difficulties rather than speech impairment. She had no auditory or visual word comprehension deficit, as determined by a PPVT score of 89% and a score of 100% in a test where she was asked to match each of 20 written words to one of 20 corresponding object pictures (Mesulam et al., 2013). She received a diagnosis of agrammatic PPA (PPA-G). In the traditional administration of the BNT, where she was allowed up to 20 seconds to respond verbally, she had very low score of 27%. However, when allowed to write the names (and also had up to 20 seconds to respond), her score increased to 82%.

The MRI showed asymmetric atrophy. Heschl's gyrus was relatively preserved compared to the asymmetrical atrophy of the left STG, superior temporal sulcus and middle temporal gyrus (Figs. 1 BOTTOM). Posterior parietal cortex and the inferior frontal gyrus also showed atrophy. She had a brother with early onset dementia also displaying unspecified language problems. The brother had never been tested cognitively. Both C3 and her brother came to autopsy and were both found to have FTLD-TDP Type A pathology. The *GRN*, *TDP-43* and *C9orf72* genes, each of which can be associated with genetic forms of FTLD-TDP had no disease-causing mutations. Investigations are continuing to identify a potential genetic cause.

CASE 4- C4

At the age of 68, this right-handed woman noticed difficulty finding and producing words. She was tested 2 years later and found to have effortful and hesitant speech with paraphasias and difficulty pronouncing multisyllabic words. Repetition was severely impaired. Written language was more fluent but agrammatic. Auditory and reading comprehension did not show significant impairment. Neuropsychological evaluation found other cognitive domains to be relatively spared. Daily living activities that did not depend on language were also mostly spared. Based on this profile a diagnosis of PPA-G was made.

Her speech was deemed intelligible for phrase length responses. Nonetheless, she was unable to name any of the BNT pictures orally but she successfully wrote the names of 88% of the items. A clinical MRI was reported unremarkable while metabolic PET reported areas of hypometabolism in the left parietal and superior temporal lobes. The scans were not available for further examination. There was no family history of similar condition. The post-mortem examination revealed FTLD-TDP Type A as the principal diagnosis.

DISCUSSION

C1 had the most systematic assessment. She displayed two dissociations, one at the input stage (auditory vs visual) and the second at the output stage (spoken vs written). With respect to input, her comprehension was better for words she read than words she heard. With respect to the response stage, naming was less impaired when she was allowed to spell or write the word than when she had to speak it. These dissociations could not be attributed to hearing loss, phoneme discrimination problems, or motor speech impediments.

Her performance in the 16-item word-picture matching experiment was particularly informative. As expected, accuracy was much higher when the word was presented in the visual modality. An even more interesting difference emerged in reaction times for targets where she correctly matched the word to the picture. These reaction times were slower when she heard than when she read the word. Thus, even when the word ended up being recognized accurately, the process was less robust if the word had been accessed through the auditory modality. This dissociation was specific to the language domain since recognition of auditory and visual objects was preserved.

These modality-based dissociations can be depicted diagrammatically as consequences of information processing bottlenecks along routes that link unimodal sensory areas to transmodal cortices of the language network (Fig. 2). The 'areas' and 'connections' in Figure 2 reflect idealized information flow blueprints (or circuit boards) rather than discrete anatomical entities. The anatomical terms in the figure correspond to some of the locations where areas with analogous functionalities have been reported. The literature on each of the functional areas depicted in Figure 2 is vast (Mesulam, 1998). In this paper, only representative works will be cited to support the plausibility of this circuitry but without discussing the range of opinion related to the nature of these areas and their interactions.

According to the diagram in figure 2, C1's pattern of impairment can be hypothetically accounted for by the dysfunction of an 'auditory word-form area' (AWFA) situated at the confluence of pathways mediating naming, word recognition (comprehension), and repetition. The AWFA is synaptically downstream from neurons sensitive to word-like but meaningless auditory patterns (e.g., distorted backward speech) and responds selectively to word-like patterns that are also recognized as plausible words in the speaker's language (Creutzfeldt, Ojemann, & Lettich, 1989). Evidence from lesion and recording studies support the presence of such a word-form area within the mid regions of the left STG (DeWitt & Rauschecker, 2016). This area receives input from more posterior areas selectively responsive to phonemes (path 1), is selectively tuned to auditory patterns with familiar word-like properties, and projects to transmodal areas of the anterior temporal lobe

(path 2). Through these transmodal nodes, auditory word-forms can become linked to the distributed associations that collectively encode their meaning (Mesulam, 1998).

The transmodal associations include the linkage of the auditory word-form to the visual representation of the object it denotes (path 3). Areas specialized for encoding objects in the form of visual percepts, have been located in posterior fusiform and lateral occipitotemporal cortex (Haxby et al., 2001). Paths 1, 2, 3 would collectively mediate the recognition of an auditory word as assessed by word-object matching tasks that C1 could not perform with any degree of efficiency. Her deficit in these tasks cannot be attributed to impairment of the visual object area because C1's non-verbal object recognition skills were intact. Nor could the deficit be attributed to a primary impairment of transmodal cortices because such a lesion would have caused equally severe impairments in recognizing auditory and written words, a pattern characteristic of PPA-S. A primary defect along path 1 can be excluded because of her relatively successful performance in basic auditory tasks. In fact, a defect confined to path 1 and its origins would have caused the different syndrome of pure word deafness where phoneme identification is impaired whereas confrontation naming is intact (Coslett, Brashear, & Heilman, 1984). Within the context of the information flow diagram depicted in Figure 2, C1's auditory word recognition impairment implies a dysfunction centered within the AWFA and its output through path 2.

In comparison to impaired auditory word recognition, C1's visual word recognition was better preserved. Preservation of this function can be attributed to the integrity of a visual word form area known to exist in the fusiform gyrus (Nobre, Allison, & McCarthy, 1994), which communicates with visual object form areas via transmodal cortex of the temporal lobe (paths 4 and 3). Although direct connectivity between the visual object form and word form areas almost certainly exists, it would not be expected to sustain the associative elaboration required for word recognition without the obligatory mediation of transmodal areas (Mesulam, 1998).

In the course of object naming, a visual object form is presumably conveyed to transmodal nodes (via path 5), which activate the corresponding multimodal associations of the object, including its lexical label (lemma) in oral (via path 6) and orthographic (via path 7) form. Oral naming was selectively impaired in C1 presumably because the process depends on AWFA as an obligatory gate along pathways that link the visual object percept to its orally articulated name (paths 5, 6, 8). In contrast, writing the name requires paths 5, 7, 9 that do not include or cross the AWFA. The impairment of oral naming cannot be attributed to a failure of phonological or articulatory encoding (path 8) because C1 had no motor speech impairment. The proposed AWFA dysfunction would also account for the severe repetition impairment by interrupting the linkage between path 1 (hearing words) and path 8 (articulating the words) and perhaps also by undermining the auditory working memory span. The AWFA depicted in Figure 2 could conceivably encompass more than one component, each preferentially related to repetition, naming (output) and comprehension (input).

The dissociation at the input stage (auditory versus visual word comprehension) was seen in only one other patient (C2), and even then to a lesser extent than in C1 (Table 2). This

probably reflects the method of testing where comprehension was assessed by word-picture verification, a process that may be computationally easier and therefore less sensitive to AWFA dysfunction than the naming task, which requires retrieval and production of the relevant word. All four patients shared the feature of being more impaired in oral than written naming. All four also had poor language repetition. All patients, therefore, had a central deficit in at least part of the putative functionality of the AWFA. The common site of atrophy in auditory association cortex of the STG is in keeping with this conclusion. However, STG atrophy is very common in PPA, including the other cases we have seen with TDP Type A, but does not generally cause the selective impairments of the 4 patients described above. The precise anatomical bases of the auditory and oral features in the aphasia of our patients therefore remains unexplained and will require more sophisticated imaging studies based on functional connectivity and diffusion tensor imaging. In the 3 cases where scans were available for inspection (C1, C2, C3), atrophy could also be identified in additional temporal, frontal and parietal cortices. Two of these cases with agrammatism (C1 and C3) had atrophy in the inferior frontal gyrus (IFG) where Broca's area is located whereas C2 did not. C1, who had the most pronounced comprehension impairment, had the most severe atrophy of the anterior temporal lobe, a region known to be critical for word comprehension.

An unexpected finding was the presence of FTLT-DTP as the primary neuropathologic diagnosis in all 4 cases. The neuropathologic associations of PPA are heterogeneous. The most common include Alzheimer's disease (AD), frontotemporal lobar degeneration (FTLD) with tauopathy and FTLD with TDP-43 proteinopathy (FTLD-TDP) (Mesulam, Weintraub, et al., 2014). FTLD-TDP is classified into types A-D based on the morphology and distribution of abnormal TDP-43 inclusions (Mackenzie et al., 2010; Mackenzie et al., 2011). Types A and C are the most relevant to PPA. Type C is almost never caused by a genetic mutation and frequently gives rise to anterior temporal lobe atrophy and semantic PPA (PPA-S)(Mackenzie et al., 2006; Mesulam et al., 2017). Type A can be genetic (associated with GRN mutations) or sporadic and can give rise to FTD, PPA or even amnesic dementia (Baker et al., 2006; van Swieten & Heutink, 2008). The clinical phenotype (FTD vs PPA) is determined by the anatomical distribution of cortical atrophy and cellular pathology (Rohrer et al., 2010) (Kim et al., 2016).

Of 110 consecutive PPA autopsies in our brain bank, only 11 (10%) have the pathology of FTLD-TDP Type A, with clinical pictures of PPA-L, G and M without a clear pattern of selectivity (Mesulam, Weintraub, et al., 2014). Based on her GRN mutation, C1 is the 12th such case. The presence of agrammatism in three of the patients in this report may reflect the known association of Type A pathology with atrophy in dorsolateral frontal cortex, including the IFG (Rohrer et al., 2010). Although FTLD-TDP Type A is a relatively uncommon correlate of our PPA cases, this report shows that a third of such cases in our brain bank display the rare auditory/oral language impairments described above. This association of a rare clinical syndrome with an infrequent pathology raises the possibility of a preferential (but not obligatory) relationship between FTLD-TDP Type A and auditory/oral language impairments in PPA. One purpose of this report is to promote the identification of additional cases with these features so that the generality of this clinicopathologic correlation can be tested. Even if additional cases fail to support this association, the investigation of patients

with these features should advance our understanding of the language network and also help to personalize treatment approaches aimed at circumventing the preferential auditory and oral impairments.

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Figure 1:

TOP: MRI of C1; MIDDLE: Metabolic PET of C2. BOTTOM: MRI of C3.

Abbreviations: A1- Primary auditory cortex (Heschl's gyrus); AA- Auditory association cortex; L- left hemisphere; R- right hemisphere; STG- superior temporal gyrus.

Figure 2:

Information flow diagram depicting the circuitry that could underlie the selective language impairments in the patients. The anatomical sites are conceptual and refer to the locations where such functionalities have been reported in the literature. The identity of the pathways indicated by arrows remains to be identified. Additional functional nodes (e.g., the auditory equivalent of the visual object form area) could have been added to this diagram but have been left out to emphasize the circuitry underlying the major clinical deficits.

Abbreviations: ATL- anterior temporal lobe; FG- fusiform gyrus; IFG- inferior frontal gyrus; MTG- middle temporal gyrus; STG- superior temporal gyrus; TPJ- temporoparietal junction.

TABLE 1

TEST PERFORMANCE FOR CASE 1- C1	
PPVT (test of auditory word recognition)	47%
PPT (pictorial test of object recognition)	90%
BNT (object naming)	15%
WAB-R (repetition)	13%
Match 32 sounds to corresponding object picture	100%
Hear a noun and touch one of 16 object pictures	50%
• Reaction time for correct responses	6291 ± 771 msec
Read a noun and touch one of 16 object pictures	92%
• Reaction time for correct responses	4130 ± 394 msec

TABLE 2

	Word Recognition Worse in Auditory vs Visual Modality	Written vs Oral Object Naming
C1	Yes- pronounced	77% vs 41%
C2	Yes- mild	43% vs 23%
C3	No	82% vs 27%
C4	No	88% vs 0%