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Tonal and orthographic analysis in a Cantonese-speaking individual with nonfluent/agrammatic variant primary progressive aphasia

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Abstract

Clinical understanding of primary progressive aphasia (PPA) has been established based on English-speaking population. The lack of linguistic diversity in research hinders the diagnosis of PPA in non-English speaking patients. This case report describes the tonal and orthographic deficits of a multilingual native Cantonese-speaking woman with nonfluent/agrammatic variant PPA (nfvPPA) and progressive supranuclear palsy. Our findings suggest that Cantonese-speaking nfvPPA patients exhibit tone production impairments, tone perception deficits at the lexical selection processing, and linguistic dysgraphia errors unique to logographic script writer. These findings suggest that linguistic tailored approaches offer novel and effective tools in identifying non-English speaking PPA individuals.

Keywords

Primary progressive aphasia; tone; logographic script; orthography

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Introduction

Primary progressive aphasia(PPA) is a neurodegenerative disorder that manifests predominantly with speech and language impairment(Gorno-Tempini et al., 2011). PPA is classified into three variants based on clinical and neuroanatomical features (Gorno-Tempini et al., 2011). Semantic variant PPA (svPPA) typically presents with loss of semantic knowledge and is associated with anterior temporal lobe atrophy on brain magnetic resonance imaging (MRI) or hypometabolism on 18 F-fluorodeoxyglucose-positron emission tomography (FDG-PET); nonfluent/agrammatic variant PPA (nfvPPA) is associated with motor speech impairment and/or agrammatism with atrophy or hypometabolism in the left frontoinsula region; and logopenic variant PPA (lvPPA) presents with phonological and auditory-verbal short-term memory deficits and is associated with atrophy or hypometabolism in the left temporoparietal junction(Gorno-Tempini et al., 2011). PPA literature to-date has predominantly described the syndrome in speakers of Indo-European languages. As a result, certain linguistic features that are nonexistent in Indo-European language, such as linguistic tone or logographic orthography, have been largely ignored in PPA populations.

In general, all living languages utilize pitch at varying degrees to convey information. When pitch is used to express semantic or grammatical meaning at the word level, it is referred to as tone. Conversely, when pitch is inflected throughout an utterance or sentence to signify prosody or pragmatics, it is called intonation. It is estimated that 50% of the world's languages have a tonal component, and are termed "tonal languages".(Zhiming & Moira Yip (2002, 2003)) Evidence from neuropsychological and functional imaging studies suggest that tone and intonation are supported by different neuronal networks.(Hughes et al., 1983; Liang & Du, 2018) The world's most spoken native language, Chinese, is an example of a language that uses tone to convey lexical-semantic meaning, i.e., a change of tone in the same syllable signify different lexical meanings. Chinese tones are acoustically distinguishable based on the height and/or contour of the fundamental frequencies produced, all of which is a product of vocal cord vibration (Ohala, 1978). Cantonese consists of six lexical contrastive tones. When a Cantonese syllable ends with phonemic consonant of "p", "t", or "k", the syllable is shorter and referred as "checked syllable". When accounting the checked syllables, Cantonese have nine sound patterns, with the three checked syllables (Tone 7, 8, 9) harboring similar tone frequencies and contours as Tone 1, 3 and 6 (Supplementary Figure 1). Tone perception and tone production errors have been reported in Chinese and Thai-speaking patients with aphasia due to stroke and tumors.(Eng et al., 1996; Gandour et al., 1992; Packard, 1986) Functional imaging studies in tonal language speakers have shown additional or stronger activation over the bilateral superior temporal, and left precentral gyrus during lexical tone processing.(Ge et al., 2015; Liang & Du, 2018) Given that these neuroanatomical locations overlap with PPA atrophy regions, we hypothesize that tonal language speakers with PPA will exhibit tonal perception and production errors.

Another linguistic feature that contrast between Indo-European and Chinese languages is the orthographic system. While alphabetic languages rely on letters to construct sounds and words, Chinese language adopts a logosyllabic script, in which the characters are logograms that are comprised of strokes (e.g., "一" and "丿") and radicals (i.e., graphical

units that carry semantic and/or phonetic meanings, e.g.: “彳” and “亠”). More than 80% of modern Chinese characters contain two or more radicals and are termed semantic-phonetic compound (SP) characters. (Li & Kang, 1993) Despite having phonetic radicals, only about 19–39% of the SP characters are regular characters (i.e., characters carrying the same pronunciation as the phonetic components). (Liu et al., 2003) In contrast, the semantic radicals in the SP characters are largely radically transparent, implying that both the semantic radicals and the SP characters carry related semantic meanings (e.g., “馬” represents horse and is a semantic radical for SP characters such as “騎” (ride) or “驢” (donkey), both characters semantically related to horse). Therefore, Chinese language has a highly opaque phonologic-orthographic correspondence and a highly transparent semantic-orthographic correspondence. Moreover, orthographic processing in Chinese is highly dependent on awareness of radical position and function. (Taft & Zhu, 1997) There are more than 200 semantic radicals and 800 phonetic radicals with roughly 16 different radical spatial configurations to form the 106,230 characters existing in the traditional Chinese dictionary (Hoosain, 1991). As Chinese characters are monosyllabic, modern Chinese languages adopted two-character words to narrow lexicosemantic selection when retrieving a target character. This case report provides a detailed description of the orthography presentations in a Cantonese-speaking woman with nvfPPA.

Case description

JA was born in Hong Kong with no known history of developmental delay or learning disabilities. Her first language was Cantonese and she later learned Taiwanese, Mandarin, English, and Toishanese (Supplementary Table 1). Her career began as a fifth-grade English teacher in Hong Kong. She then immigrated to the United States for college at age 23 and received a bachelor’s degree in psychology. After college, JA worked in real estate as a broker, investor, and property manager for more than 40 years. Her medical history included dyslipidemia, hypertension, and renal cell carcinoma status-post nephrectomy. She denied previous brain trauma or substance use. There was no family history of dementia or psychiatric illnesses, apart from her biological father who suffered from cognitive impairment after multiple strokes in his 70s.

JA started to develop speech and language difficulties at 72 years of age. She described her initial symptoms as “*words won’t come out*”, hindering her from verbally expressing opinions. Additional reported speech and language symptoms included speech sound errors, incorrect word order, and binary word reversal errors (e.g., mixing up yes/no). We first evaluated her at age 74. At that time, her speech production was slow, effortful and monotonous, especially with long and complex sentences. She also showed morphological errors in verb and pronoun usage. These symptoms were most evident in Mandarin, Taiwanese and Toishanese, the languages that she acquired later in life or rarely spoke around symptoms onset. She developed similar traits in English or Cantonese, albeit to a milder degree, about 6 months after her first symptoms.

One year later, she developed motor symptoms, including right hand postural and action tremor, especially when signing her name or buttoning clothes, and frequent falls. This was accompanied by depression, increased irritability and insomnia. Insomnia was mainly

characterized by prolonged sleep latency and poor sleep maintenance without evidence of REM sleep behavior disorder. Due to communication challenges, JA became increasingly socially isolated. At age 75, she developed an increased appetite for sweets, leading to a 7–8% weight gain.

Neurological examination

At age 74, JA was noted to have evidence of mild parkinsonism, including facial hypomimia, limb bradykinesia and cogwheel rigidity in the upper limbs, right worse than left. There was slowed saccade initiation both vertically and horizontally without limitation in amplitude. She had a stooped gait with decreased stride length and arm swing.

When JA was reevaluated at age 77, she developed additional findings of orobuccal apraxia and square wave jerks. Speech was increasingly monotonous with mild spastic dysarthria, and she was noted to cough with liquids. There was a bilateral, pill-rolling resting tremor as well as a kinetic upper limb tremor. Right hyperreflexia with positive Trömner reflex was found. Posture was stooped and gait showed decreased stride length, turn-en-bloc, and bilateral decreased arm swing. On pull test, retropulsion with suboptimal postural reflexes was noted.

Neuropsychological evaluation

Cognitive assessment

At the ages of 75 and 77, JA received an English cognitive assessment battery consisting of memory, language, executive, and visuospatial tests as previously described in Kramer et al. (Delis et al., 2001; Deliset al., 2000; Folstein et al., 1975; Kramer et al., 2003; Nasreddine et al., 2005; Stuss et al., 2002) (scores listed in Table 1). JA cognitive assessment at age 75 indicated verbal and visual memory impairments that were more consistent with retrieval deficits. Verbal category fluency and design fluency were markedly reduced, and her cognitive processing speed was evidently decreased in timed executive tasks. Although most executive tasks are dependent on language and motor functions, her executive task performance is disproportionate to her language and motor deficits, thus suggestive of executive dysfunction with slowing of cognitive processing. Additionally, JA scored high on the Geriatric Depression Scale, which indicates a depressive mood disorder. At age 77, JA's performance in memory tasks remained stationary but her performance in language and executive tasks deteriorated further. In addition, JA scored low on the Visual Object and Spatial Perception test, which support additional visuospatial impairment. In summary, JA's neuropsychological assessments revealed prominent speech and language impairment, executive dysfunction and significant mood symptoms, which worsened over time, and additional visuospatial impairment was noted at age 77.

English speech and language assessment

JA spoke in Cantonese-accented English language with slow, nonfluent, effortful and monotonous speech. She primarily produced short phrases and sentences with inconsistent speech sound distortions, sound omissions, simplification of speech sounds, and equal stress on syllables (e.g., “krihs-em” for “christian”, “dee-teer-ay-shun” for “deteriorated”). JA

also omitted function words and made errors in inflectional morphology and verb tense agreement, though these features may be partially confounded by her being a non-native English speaker.

Further assessment of alternating and sequential motor rates and multiple repetitions of polysyllabic words revealed slow verbal initiation, groping and voicing errors, consonant and vowel distortions and substitutions, and infrequent sound sequencing errors. Her voice was strained, harsh, and lacked variation in pitch and loudness. Vocal breaks were noted during sustained phonation. When asked to count from 1 to 5 with increasing loudness, she was unable to substantially modulate the loudness of her voice. Results from the motor speech were consistent with moderate apraxia of speech (AOS rating of 4 out of 7) and mild spastic dysarthria (Dysarthria rating scale of 2). (Ogar et al., 2006) On tests of syntax, JA was observed to be agrammatic. She struggled with constructing noncanonical sentences on a shortened version of the Northwestern Anagram test (7 out of 12). (Weintraub et al., 2009) Her syntax comprehension was relatively better in comparison, but struggled with grammatically complex sentences (Table 1). In contrast, repetition of words and sentences, auditory word comprehension of objects was intact. (Shewan & Kertesz, 1980) In terms of semantic processing, she performed well on a test of semantic associations of objects, but showed some difficulty with naming. (Goodglass et al., 1983; Howard & Patterson, 1992) Reading and spelling of irregular words and pseudowords were more difficult compared to that of regular words. In summary, JA's English speech and language was characterized by moderate AOS with mild spastic dysarthria and linguistic deficits in syntactic processing with relative sparing of object knowledge, auditory word comprehension, repetition, and reading and spelling of regular words.

Cantonese speech and language assessment

For the Cantonese speech, tone, and language assessment, JA was evaluated three times at the ages of 76 and 77-years and compared with nine cognitive normal Cantonese native speakers [mean age (s.d.): 63.44 (4.8); mean education years (s.d.): 15.44 (5.34); MMSE (s.d.): 29.22 (1.72); 3 males and 6 females] (Table 2). On all exam time-points, JA could understand multi-step commands and spoke in slow, effortful and monotonous Cantonese speech. To assess speech motor functions, participants are asked to repeat for five times four-character phrases that transited between different places of articulation (e.g.: 答 daap3 架 ga3 八 baat3 駕 ga3), manners of articulation (e.g.: 逼 bik1 的 dik1 即 jik1 吉 gat1), and tones (e.g.: 意 yi3 兒 yi4 宜 yi4 衣 yi1) while controlling for the other two factors. JA often exhibited tonal errors (most commonly tonal substitution errors, Figure 2(a)) and demonstrated signs of AOS when repeating phrases that transit in manners of articulation and tones. JA's prosody was flat when repeating neutral sentences with varying emotional contexts. She scored lower on Cantonese syntax production and comprehension tasks when compared to control participants. When comparing her performances between age 76 and age 77, sentence repetition in Cantonese became more challenging due to increased effortful and halting speech, but performance in confrontation naming was relatively preserved across time.

JA also described the cookie theft picture in Cantonese, English and Mandarin. She demonstrated a slow speech rate and frequent pauses in all languages with 61.4, 73.0 and 54.3 words per minute in Cantonese, English, and Mandarin, respectively. Her performance also indicated difficulty in language code-switching. When asked to describe the cookie theft picture in Taiwanese, JA was unable to produce any phrases or sentences.

In summary, JA's speech and language assessments identified apraxia of speech, spastic dysarthria, syntax comprehension and production difficulties in both English and Cantonese.

Cantonese tone assessment

Tone perception abilities were assessed via two different tasks: tone detection and tone discrimination tasks. In the tone detection task, participants are presented with 12 auditory syllables that exist in Cantonese but paired with tones of Mandarin, Vietnamese and Thai languages. Participants are required to decide whether each auditory stimulus has a Cantonese tone. In the tone discrimination test, participants are presented with 10 pairs of Cantonese words and asked whether each pair of Cantonese words sounds similar or different in tone. Tone comprehension is evaluated using tone-to-tone picture and tone-to-tone word matching tests that consist of 10 auditory stimuli with different Cantonese monosyllabic tones. For each auditory stimuli, participants are presented with sets of four pictures or four words that represent Cantonese words that are phonemically alike but differ in tone (e.g.: 史 si 2 詩 si 1 時 si 4 市 si 5). Participants are asked to select the picture or word that matches the given auditory stimulus.

Tone production was evaluated with three tasks: serial tone-reading, tone-word reading and consecutive tone repetition. The serial tone reading task requires participants to read out loud six sets of Cantonese words that are syllabically alike, but differ in tones (e.g.: 因 jan1 忍 jan2 印 jan3 人 jan4 引 jan5 刀 jan6 壹 jat1 日 jat6). The tone-word reading task asks participants to read out loud 12 sets of uni-character and bi-character Cantonese words that carry the same tones but differ in syllables (e.g.: 粉 fan2 寫 se2 左手 zo2 sau2). In the consecutive tone repetition task, participants are tasked to repeat tongue twisters that are mainly composed of characters with the same syllables but differ in tones (e.g.: 圓圓遠遠 叫圓月 jyun4 jyun4 jyun5 jyun5 giu3 jyun4 jyut6).

To investigate motor control of tone production in the serial tone reading task, spectrogram analysis (calculation of jitter and shimmer) was performed using PRAAT (<http://www.fon.hum.uva.nl/praat/>) (Coupe, 2014). Jitter is a measure of the stability of acoustic frequency while shimmer measures amplitude stability (Teixeira et al., 2013). Taken together, the jitter and shimmer ratio are inversely correlated with the stability of phonation.

On the tone detection and tone discrimination tasks, JA scored within two standard deviations of the nine control participants. On the tone-to-tone picture and tone-to-tone word matching tests, she struggled with correctly matching the tones to specific pictures and words after the first visit. On the serial tone reading task, she accurately pronounced 13/38 words. She accurately pronounced 37/40 words on the tone-word reading task. On the consecutive tone repetition task, she correctly repeated the tones of 10 of the 15 words.

We further analyzed JA's error responses on the serial tone reading task and compared with six age-matched native Cantonese-speaking females [mean age (s.d.): 73.67 (1.51); mean education years (s.d.): 7.5 (1.17)] using spectrogram analysis. JA's tone reading accuracy was markedly lower than controls (34.21% versus 81.58%, Z-score: -7.15), with the contrast being most evident in the unchecked syllables (Figure 2(a, b)). Among the inaccurate responses, JA produced substantially more tone than syllabic errors (i.e., consonant and vowel errors) (tone versus syllabic: 63.16% versus 2.63%). This pattern differed from the controls, who showed less discrepancy in the relative occurrence of tone and syllabic errors (tone versus syllabic: 13.15% vs 5.26%) (Figure 2(b)). Additionally, JA had higher jitter and shimmer when compared with controls (Jitter: 2.21–8.81% versus 1.21–2.70%, Z-score: 1.62–8.16; Shimmer: 12.97–20.27% versus 6.32–15.04%, Z-score: 1.78–9.62; Figure 2 (c)), suggesting instability in phonation.

Cantonese orthographic assessments

To evaluate JA's orthographic abilities, we developed a writing dictation list consisting of 60 characters, divided between pictographic, ideographic and SP words. Within these groups, word characters were further subcategorized into low- and high-word frequencies and low- and high-stroke numbers (Supplementary Figure 3). Since Chinese characters generally have a high homophone density (e.g., a high number of same-sounding words), two-character auditory stimuli were provided to specify the word for dictation (e.g.: 恐龍的龍, the word “lung4” in “hung2 lung4”). Writing dictation errors were evaluated and categorized by a board-certified speech-language pathologist (L.K.C.L.Y.) and a neurologist (B.L.T.) who had received more than 16 years of formal education in Chinese language. Definitions and examples of the errors produced by JA are provided in Figure 3b.

JA writing dictation ability was evaluated at the age of 76 years 8 months, 77 years 1 month and 77 years 7 months. She wrote characters accurately for 32%, 20% and 12% of the 60 stimuli and failed to produce responses for 17%, 13% and 18% of the target characters across the three-time points, respectively. Her writing accuracy was far below that of the control participants, whose accuracy averaged 81% (range: 75% to 90%). JA was most accurate on high-frequency characters with fewer numbers of strokes (Figure 3a).

Examples of JA's writing errors are shown in Figure 3a. She produced three main types of errors: dyskinetic, radical, and phonologically plausible errors (PPE). Motor-dyskinetic errors are defined as those in which the formation of characters overall remains intact but contain interrupted, incomplete or disproportionate strokes (e.g.: “明” as 𠄎, Figure 3a). These were the most common type of error for JA, and they became increasingly frequent over the three time points of testing (Time-point 1: 23%, Time-point 2: 35%, Time-point 3: 45%), which corresponded with her progressive parkinsonian features.

Radical errors and phonologically plausible errors appeared in comparable proportions across the three testing time points. The majority of radical errors (73%) were radical substitution errors, in which one of the radicals in the characters was substituted with another existing but inappropriate radical (e.g.: the character 露 is written as 𩇛 in which the radical “各” is substituted by “失”). Approximately 70% of the radical substitutions occurred in the semantic radical portion of SP characters, and these semantic radicals tended

to have low radical transparency. For example, JA wrote “趣” (interest) as 𠄎 in which the semantic radical “走” (walk) was replaced by “言” (speak). The word “趣” (interest) is considered low in semantic radical transparency since “趣” (interest) and “走” (walk) are not semantically related.

JA produced 17 phonologically plausible errors. Almost half of the errors (42%) shared identical syllabic pronunciations with the target characters. Three were homophones (i.e., identical in both syllabic and tone pronunciations; e.g., “架” (frame/rack) written as 價 (price) and both characters are pronounced as “gaa3” in Cantonese). Out of the 17 phonological plausible errors (PPE), all but one of the 17 phonologically plausible errors were replaced by characters that have a higher word frequency in comparison to targeted characters.

Less common errors produced by JA included visual errors, spatial errors, stroke errors and compound word errors. Visual errors refer to errors in which components of the Chinese characters are replaced by non-existing radicals that generally bear visual resemblance (e.g.: “蟹” (crab) was written as 𧈧 with 趣 being non-existent in Chinese and visually resembling “解”). JA also produced spatial errors (e.g., “鸞” written as 𧈧 in which the radical 鳥 was inaccurately placed underneath radical 央), stroke errors (e.g., “晨” written as 𧈧 in which a stroke “一” is missing in the radical “辰” and compound word errors (e.g., the character “整” of the word “整齊” was written as 齊 instead of “整”) (Figure 3b).

Neuroimaging studies

At age 75, an MRI brain without contrast showed a mild degree of bilateral fronto-insular and left superior temporal gyrus atrophy with a mild burden of white matter hyperintensities in the periventricular and subcortical regions. At age 77, a repeat MRI brain without contrast revealed increased atrophy over bilateral fronto-insular regions and bilateral superior temporal gyri with additional involvement of the bilateral frontal and parietal, medial frontal and dorsolateral prefrontal cortices and dorsal midbrain. Thinning of the genu and body of the corpus callosum was also noted (Figure 1(a, b)). Further brain volumetric analysis revealed volume loss most prominent over fronto-insular, medial frontal, superior temporal gyri and occipital cortices bilaterally (Figure 1(c)). A (11)C-labeled Pittsburgh Compound-B ((11)C- PIB) Positron Emission Tomography (PET) scan indicated no evidence of increased radiotracer uptake.

Clinical diagnosis

Given JA’s prominent motor speech impairments with agrammatism, her clinical syndrome was thought to be most consistent with nonfluent/agrammatic variant primary progressive aphasia (nfvPPA). The extrapyramidal features on exam were also consistent with probable progressive supranuclear palsy (PSP) (Richardson’s syndrome) (O1P1C1A3). Since her speech and language symptoms preceded her motoric symptoms, the former diagnosis took precedence. Her clinical diagnosis was best depicted as nfvPPA with probable PSP.

Discussion

We believe that this is the first case report to examine in detailed the tonal speech and orthographic writing deficits in a Cantonese-speaking individual with PPA. Characterizing

the tonal and orthographic presentations produced by PPA individuals can better inform clinical diagnoses in populations that speak tonal languages or adopt logographic scripts.

In this case study, JA primarily presented with prominent articulation deficits compatible with apraxia of speech (AOS) traits in both English and Cantonese languages, supporting the diagnosis of nfvPPA. In addition to reduced accuracy in the tone production tasks, JA showed higher preponderance for tone errors than syllabic errors in comparison to controls. On the multi-character multi-repetition task, JA scored lowest when repeating multi-characters that differed in tones but were similar in syllables. These findings suggest that tone articulation is a more sensitive marker than syllabic production in detecting motor speech impairments among tonal languages speakers. JA also exhibited more accurate performance on tone production of checked syllables compared to unchecked syllables. Since unchecked syllables are relatively longer in pronunciation duration, they require higher demands to the motor speech control system and are more sensitive tonemes to illicit AOS. Additionally, acoustic analysis revealed that JA's jitter and shimmer were markedly higher than controls, indicating poor motor control of the musculature in and around the vocal folds, and previously described in English-speaking PPA and PSP individuals. (Fraser et al., 2013; Rusz et al., 2015) Due to the linguistic variations, AOS features reported in English speakers such as voicing and lexical stress errors are typically absent in Cantonese speakers. (Wong et al., 2020) The strategy of using polysyllabic words with consonant cluster to illicit AOS in English speakers is inapplicable for Cantonese speakers as Chinese characters are generally monosyllable and lack consonant clusters. Thus, establishing additional motor speech features such as tone production deficit is valuable for the identification of AOS traits in Cantonese speakers. Neuroanatomical changes over the left inferior fronto-insular region are shown to correlate with motor speech planning skill in English speakers. (Ogar et al., 2006) Analogous to English speakers, we speculate that atrophy over the left fronto-insular region typically noted in nfvPPA cases affects the motor speech planning ability around the vocal cord area and manifests as tone production impairments in tonal language speakers.

In terms of tone comprehension, JA showed selective errors on the tone-to-tone picture and tone-to-tone word matching tasks with intact performance on the tone perception tasks. Additionally, JA showed relatively preserved performance on a confrontational naming task. This pattern of deficits implies that JA had intact primary auditory processing and semantic knowledge functions, but deficits in lexical selection ability based on tones. Similar findings were reported in a study of six Toishanese and Mandarin-speaking stroke aphasia patients with left hemispheric lesions, who also demonstrated lower accuracy in a tone-to-tone picture matching task when compared to controls, although tone perception function was not examined. (Eng et al., 1996; Naeser & Chan, 1980) Indeed, functional imaging and electrophysiological studies offer corroborative evidence that tone perception is left-lateralized, with the bilateral superior temporal gyri and left inferior fronto-insular region playing a role in the lexical tone perception and lexical tone selection processes (Bidelman & Chung, 2015; Chien et al., 2021; Klein et al., 2001; Kwok et al., 2017; Liang & Du, 2018). Hence, it is not surprising that individuals with nfvPPA that exhibit hypometabolism or atrophy over left inferior fronto-insular regions have tone-lexical selection impairments.

JA consistently showed higher accuracy on dictation of Chinese orthographic characters with lower number of strokes and higher word frequency. This is consistent with previous literature highlighting that writing accuracy in Chinese speakers correlates with word frequency and number of strokes that compose the character. (Law, 2004; Law et al., 2005) Writing Chinese characters also requires fine motor skills of hand and fingers that are often impaired in nfvPPA and PSP. JA's most common writing errors were consistent with dyskinetic agraphia. This result suggests that orthographic tasks may serve as a sensitive marker for dyskinetic movement disorders in Chinese-speaking individuals. In view of the graphical formation of these characters remained intact, JA's dyskinetic agraphia should be considered as a form of mechanical dysgraphia (i.e., writing problems secondary to motor deficits)(Benson et al., 1996). Dyskinetic agraphia was the only orthographic error type that increased over time on testing, which aligned with JA's progressive parkinsonism features. The presence of radical errors in writing is more unique in logographic languages. The presence of these errors in JA supports the concomitant presence of a linguistic/aphasic agraphia (i.e., agraphia due to linguistic impairment) (Benson et al., 1996; Ardila, 2012). Radical writing errors have been reported in Cantonese speakers with right middle cerebral artery infarcts, right temporoparietal occipital hematomas, left cerebral thromboses, and in Mandarin speakers with left posterior temporal–occipital tumors, left temporal hemorrhages and Alzheimer's disease, albeit in varying degrees(Han & Bi, 2009; Law, 2004; Law et al., 2005; Reich et al., 2003; Zhou et al., 2016). Han et al. have proposed that radical errors are the product of deficits in the orthographic retrieval process(Han et al., 2007). Law et al. and Taft et al. have hypothesized that radical substitutions appear when information on the radical identity of a character is compromised, but the configuration template or positional information of the character remains intact. Radicals are therefore substituted to maintain the structural integrity of the character.(Law, 2004; Taft & Zhu, 1997) The tendency to substitute and make errors on low transparency semantic radicals may relate to the increasing challenges in orthographic retrieval when the semantic radicals have weaker semantic correlations with the characters.

In JA's case, phonologically plausible errors (PPEs) were noted in writing dictation task at all three time points. PPEs were previously reported in two Cantonese native speakers with brain contusions who underwent left frontotemporal lobectomy and right temporoparietal occipital hemorrhage. (Law, 2004; Law & Or, 2001) It was speculated that the patients replaced target characters with phonologically similar characters due to difficulty in identifying specific orthographic lexicons.(Law et al., 2005) Given that most PPEs were replaced by characters with higher frequency, there may exist a word frequency effect in the lexical selection process. Chinese is a language with high homophone density and the identification of the accurate characters relies on the semantic context(Law, 2004). Functional MRI study of 10 healthy adults during the homophone judgment task revealed the strongest activation over the left temporoparietal cortex and left inferior frontal gyrus (Kuo et al., 2004). Left inferior frontal gyrus has also been shown to be associated with lexical selective processing of Chinese characters.(Kwok et al., 2017) Thus, we speculate that auditory stimuli may activate the phonological input lexicon that resides in the left temporoparietal region, which then travels via the dorsal pathway to the frontal area that selects the specific orthographic lexicon with guidance of semantic input from the left

temporal region. Given that lexical selection process and radical knowledge are believed to involve the left inferior frontal and bilateral superior temporal gyri (Chien et al., 2021; Deng et al., 2011; Kwok et al., 2017), orthographic patterns such as radical and phonological plausible errors can potentially serve as neurolinguistic indicators for PPA that adopts logographic scripts.

This case provides novel neurolinguistic hypotheses for the field of PPA in Chinese-speaking individuals. The description of a single case report cannot fairly represent all Cantonese-speaking nfvPPA individuals and further data collection is necessary to establish concrete conclusions. To date, there are no validated and standardized tests to evaluate the speech, language, tonal and orthographic functions in Cantonese-speaking PPA individuals, and the tasks employed in this study have yet to be validated. To compensate for this limitation, tonal tasks were quantitatively assessed, orthographic tasks were tested at multiple time points to establish reproducibility, and results were compared against age and gender matched controls. Given that the case presented resides mainly in a country with English-speaking environment, the generalizability of these findings in Cantonese-speaking nfvPPA patients with Cantonese-speaking environment is yet to be confirmed.

Conclusion

This case report provides an in-depth description of the tone and orthographic deficits in a multilingual woman with nfvPPA. Using novel tonal and orthographic tasks, we highlighted the potential of tone production ability as a potential sensitive indicator of speech motor impairments for nfvPPA individuals that speak tonal languages. Tasks that stress radical/lexical selection processing are also promising clinical markers to identify nfvPPA that adopts logographic scripts. These findings should motivate further neurolinguistic studies into deficits in PPA patients who speak/write tonal and logographic languages and add to our understanding of the neural bases of linguistic tone and orthographic processing.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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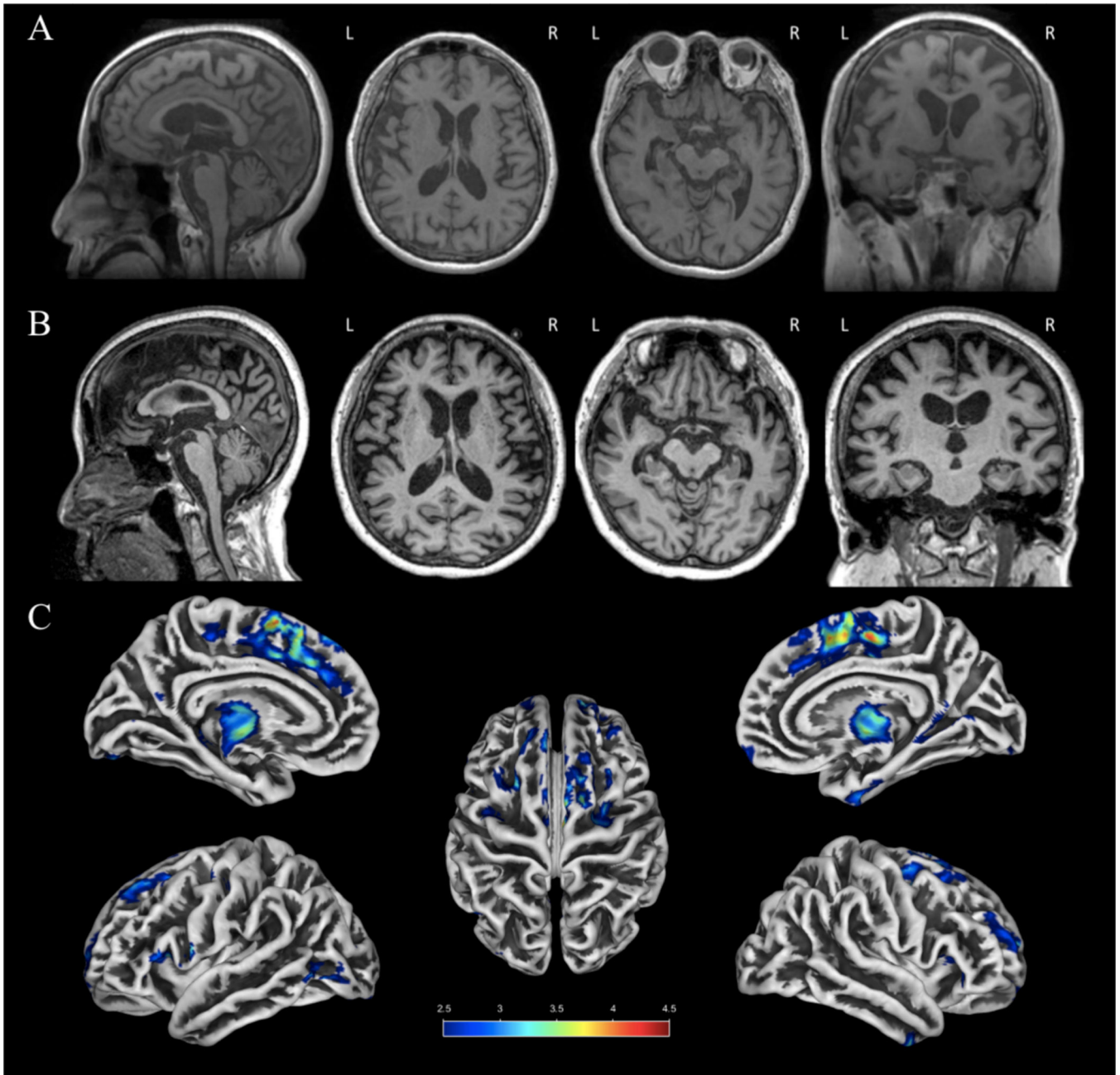


Figure 1.

Brain MRI at age 75 (A) and 77 (B) and MRI brain volumetric analysis (C). Brain MRI at age 75 (A) and 77 (B) and MRI brain volumetric analysis (C). (A) MRI T1 images at age 75 (sagittal, axial, and coronal) showed mild atrophy over bilateral fronto-insular regions and left superior temporal gyrus. (B) MRI T1 images (sagittal, axial, and coronal) revealed increased atrophy over bilateral fronto-insular regions, bilateral superior temporal gyri, dorsal midbrain, and bilateral parietal, medial frontal and dorsolateral prefrontal cortices with thinning of genu and body of the corpus callosum. (C) MRI volumetric brain analysis of JA's at age 77. Highlighted areas represent regions with volumes that are 2.5 standard

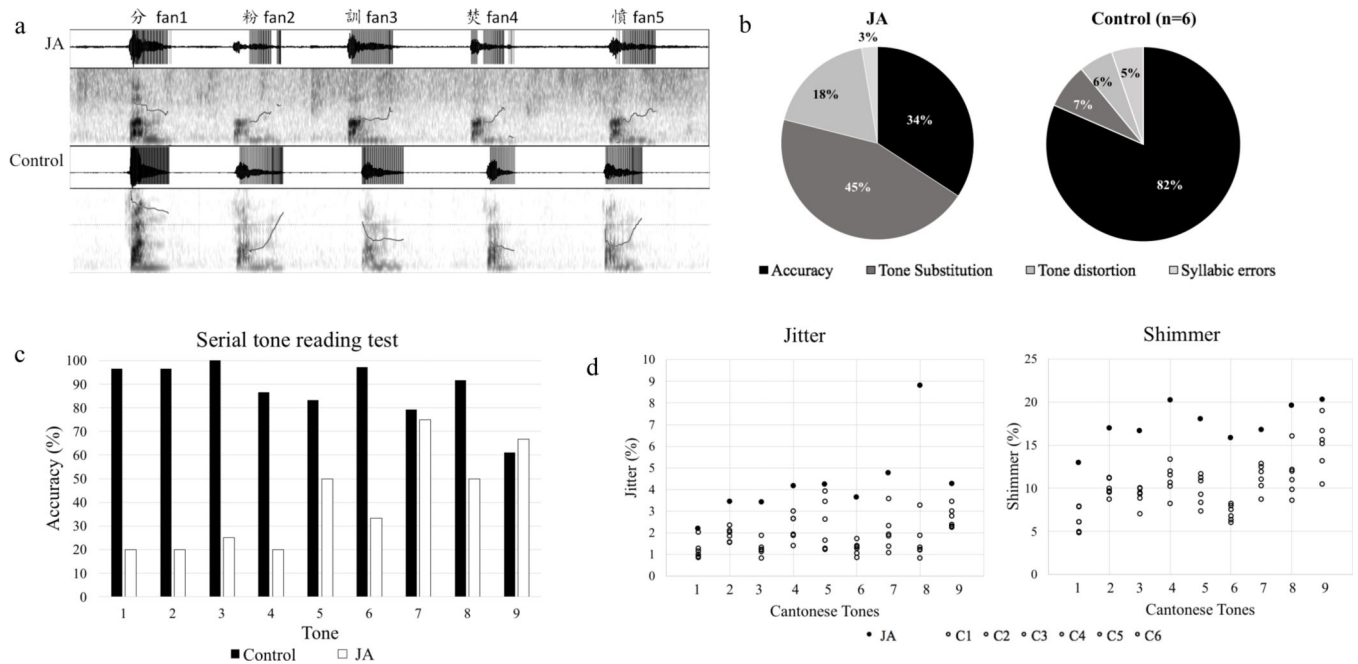
deviations below-average volume when compared to 135 female controls (mean age 73.5 years, SD = 2.6) from the UCSF Memory and Aging Center Hilblom Cohort, adjusted for age, gender and total intracranial volume.

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**Figure 2.**

Error and acoustic analysis for serial tone reading tasks. Figure 2 depicts the error and acoustic analysis (using PRAAT software) of the tones produced in serial tone reading tasks by JA and 6 age-gender-matched controls. (a) Spectrogram of JA and control participant when pronouncing “分 fan1 粉 fan2 訓 fan3 焚 fan4 憤 fan5”; tone substitution noted when JA pronounced “焚” fan4 → fan2. (b) In comparison to controls, JA produced more tone substitution and distortion errors with relative comparable proportion of syllabic errors. (JA versus Controls: Tone errors: 63.16% versus 13.16, syllabic errors: 2.63% versus 5.26%). (c) Accuracy in tone production was higher among checked syllables than unchecked syllables, (d) Jitter and shimmer analyses indicated that JA had much higher jitter and shimmer when compared with controls (Jitter: 2.21–8.81% versus 1.21–2.70%, Z-score: 1.62–8.16; Shimmer: 12.97–20.27% versus 6.32–15.04%, Z-score: 1.78–9.62).

a

| Orthographic-dictation stimuli | Accurate response (%) | | |
|---------------------------------------|-----------------------|--------------|--------------|
| | Time point 1 | Time point 2 | Time point 3 |
| <u>Lexicography</u> | | | |
| Pictography (n=12) | 3 (25) | 2 (20) | 1 (8.33) |
| Ideography (n=12) | 7 (58.33) | 3 (25) | 3 (25) |
| SP compound words (n=36) | 9 (25) | 7 (28) | 3 (8.33) |
| <u>Word frequency</u> | | | |
| High (n=30) | 15 (50) | 9 (30) | 6 (20) |
| Low (n=30) | 4 (13.33) | 3 (10) | 1 (3.33) |
| <u>Number of strokes in character</u> | | | |
| High (n=30) | 4 (13.33) | 1 (3.33) | 3 (10) |
| Low (n=30) | 15 (50) | 11 (36.67) | 4 (13.33) |

b Definition of writing errors for single character dictation task

| Errors | Descriptions | Examples |
|--------------------------------|---|--|
| Dyskinetic error | Dyskinetic movement disorders leading to dysgraphia. | 趣 趣 電 電 龍 龍 人 人 |
| Radical error | Radical substitution, adding or omission by existing radicals. | 露 露 趣 趣 影 影 琶 琶 |
| Stroke error | Stroke adding, omission, reforming, and moving. | 晨 晨 鹿 鹿 |
| Phonologically plausible error | Substituting with another characters that carries similar pronunciations. | 晃 (fong 2) 方 (fong 1) 卉 (wai 2) 圍 (wai 4) |
| Visual error | Substituting with visually alike unintelligible characters. | 壺 壺 蟹 蟹 矚 矚 解 解 |
| Spatial error | Radicals improperly positioned | 鴛 鴛 校 校 |
| Morphological error | Substituting target character with the other character of a compound word | 整 (整齊) 嶺 霓 (霓虹) 虹 |
| Semantic error | Substituting target characters with semantically related characters | 胸 舌 |

Figure 3a.

The orthographic dictation performance of JA. Figure 3a, Figure 3b shows JA's performance in the orthographic dictation task over three different time points. (a) JA achieved higher accuracy on writing high-frequency words with fewer strokes. (b) Definitions of writing errors for a single character dictation task and examples of errors produced by JA.

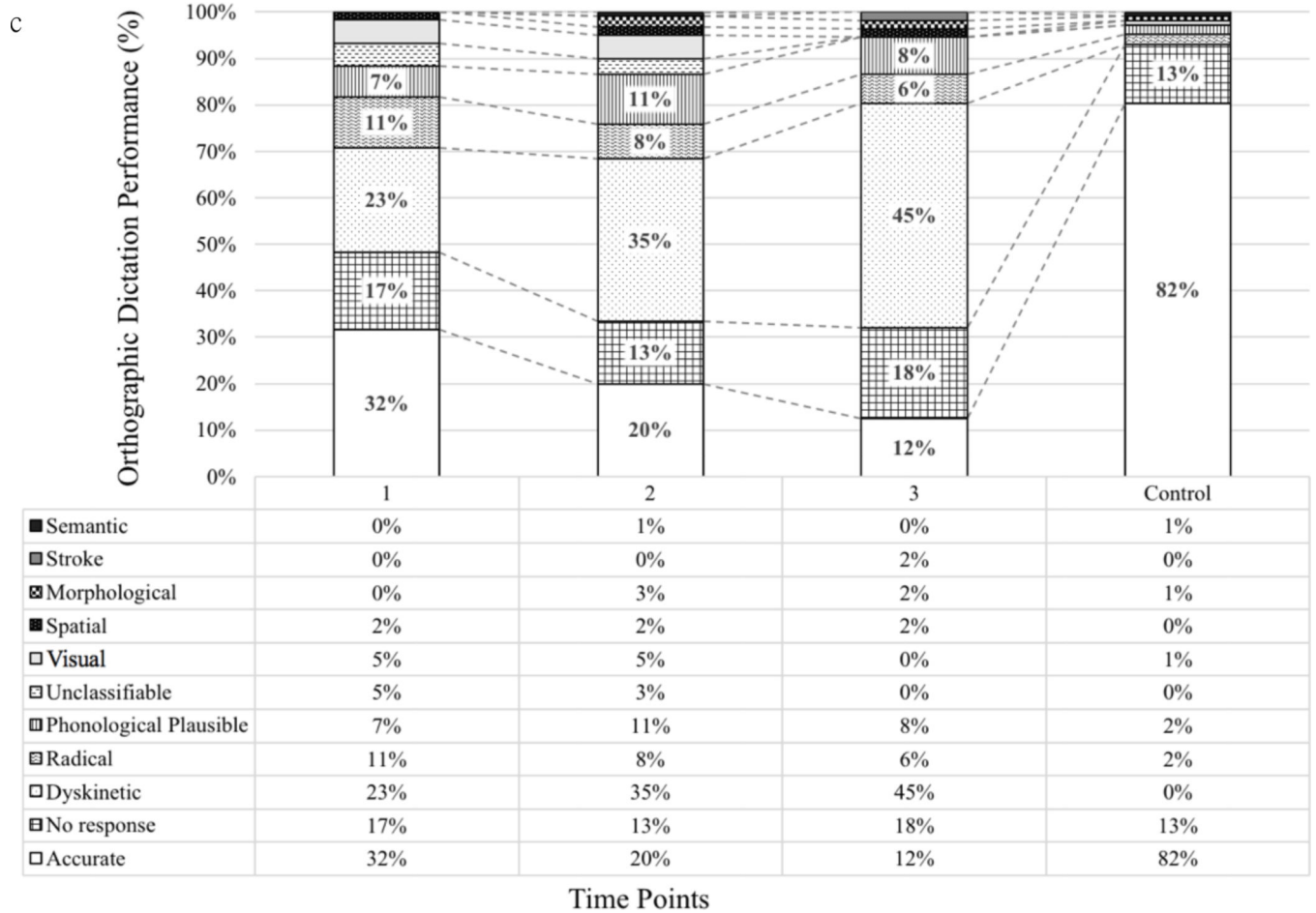


Figure 3b.

(c) Percentage of orthographic responses noted over all three different time points. Note that the error patterns are largely consistent across time points, with the exception of dyskinetic errors that increase over time.

Table 1.

Neuropsychological and language assessment results for JA at age 75 and 77.

| Neuropsychological assessments (full score) | Age 75 | Age 77 |
|---|--|--|
| Global | | |
| MMSE (30) | 28 | 27 |
| MOCA (30) | 26 | - |
| Memory | | |
| CVLT (9) | Learning curve: 4-6-6-5 10 mins recall: 6 Recognition: 9 | Learning curve: 5-6-7-8 10 mins recall: 6 Recognition: 9 |
| Benson delayed recall (17) | 6 | 10 |
| English speech and Language | | |
| Boston naming | 20/30 | 40/60 |
| Irregular words (6) | 5 | |
| Sentence comprehension (5) | 4 | 4 |
| Verbal agility (5) | 3 | 0 |
| Repetition (5) | 3 | 1 |
| Western Aphasia Battery-Aphasia Quotient | - | 92% |
| Pyramid and Palm Tree (14) | - | 14 |
| Motor Speech-Apraxia rating (7) | - | 3 |
| Motor Speech- Dysarthria rating (7) | - | 1 |
| Northwestern Anagram Test (12) | - | 7 |
| Visuospatial | | |
| Benson copy (17) | 16 | 14 |
| Visual Object and Spatial Perception (10) | - | 3 |
| Executive functions | | |
| Digit Forward/ Backward | 5/3 | 4/3 |
| Stroop naming/ inhibition | 46/26 | 19/14 |
| Category /Lexical | 7/ 15 | 3/8 |
| Mood assessment | | |
| Geriatric Depression Scale (30) | 17 | 13 |

* MMSE: Mini-Mental State Exam; MOCA: Montreal Cognitive Assessment; CVLT: California Verbal Learning Test.

Table 1 is reported in raw scores.

Table 2.

Cantonese speech and language assessment results for JA at age of 76 and 77 years.

| Cantonese speech and language | Age 76 | Age 77 | Controls (n=10) |
|--------------------------------------|---------------|---------------|------------------------|
| <u>Tone Perception</u> | | | |
| Tone detection | 100% | 85% | 89% (6.9) |
| Tone discrimination | 100% | 80% | 89% (7.2) |
| <u>Tone Comprehension</u> | | | |
| Tone-to-tone word matching | 60% | 50% * | 81% (13.5) |
| Tone-to-tone picture matching | 60% | 30% * | 77% (9.5) |
| <u>Tone Production</u> | | | |
| Serial tone reading | 34% * | - | 83% (6.8) |
| Tone-picture reading | 94% | - | - |
| Tone-word reading | 93% | - | - |
| Consecutive tone repetition | - | 67% * | 96% (4.6) |
| <u>Motor speech</u> | | | |
| Multi-character multi-repetition | | | |
| • Travel | 72% * | 88% | 94% (10.0) |
| • Manner | 88% * | 40% * | 93% (3.0) |
| • Tone | 56% * | 0% * | 94% (9.8) |
| Prosody ^a | 20% * | 20% * | 80% (4.0) |
| <u>Confrontational Naming</u> | | | |
| High frequency | 93% * | 96% * | 100% (1.3) |
| Middle frequency | 100% | 88% * | 98% (4.4) |
| Low frequency | 95% | 92% * | 99% (2.7) |
| <u>Syntax^b</u> | | | |
| Comprehension | 85% * | 76% * | 98% (2.5) |
| Production | - | 28% * | 93% (5.9) |
| Repetition ^c | - | 50% * | 85% (9.2) |
| Writing Dictation | 32% * | 10% * | 81% (5.0) |

Table 2 list the mean and standard deviation scores of JA and controls (9 Cantonese native speakers [mean age (s.d.): 63.44 (4.8); mean education years (s.d.): 15.44 (5.34), 3 male and 6 females]) when assessed via a Cantonese speech and language assessment battery developed by researchers and clinicians from University of California, San Francisco, Buddhist Tzu Chi hospital, The Education University of Hong Kong and National Tsing Hua University under Chinese language Assessment for PPA (CLAP) project.

^aProsody task: Illustrating different verbal expressions (e.g.: angry, happy, statement, sad and question) using the same neutral sentences.

^bSyntax comprehension and production tasks: Matching and constructing canonical and noncanonical Cantonese sentences with the picture given.

^cRepetition task: Repeating sensical and nonsensical phrases and sentences ranging from 3 to 11-character length.

* Scored lower than 2 standard deviation when compared to the control participants.

- Missing data; likely due to fatigability or reluctance to complete assessment.