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Anatomic, clinical, and neuropsychological correlates of spelling errors in primary progressive aphasia

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ABSTRACT

This study evaluates spelling errors in the three subtypes of primary progressive aphasia (PPA): agrammatic (PPA-G), logopenic (PPA-L), and semantic (PPA-S). Forty-one PPA patients and 36 age-matched healthy controls were administered a test of spelling. The total number of errors and types of errors in spelling to dictation of regular words, exception words and nonwords, were recorded. Error types were classified based on phonetic plausibility. In the first analysis, scores were evaluated by clinical diagnosis. Errors in spelling exception words and phonetically plausible errors were seen in PPA-S. Conversely, PPA-G was associated with errors in nonword spelling and phonetically implausible errors. In the next analysis, spelling scores were correlated to other neuropsychological language test scores. Significant correlations were found between exception word spelling and measures of naming and single word comprehension. Nonword spelling correlated with tests of grammar and repetition. Global language measures did not correlate significantly with spelling scores, however. Cortical thickness analysis based on MRI showed that atrophy in several language regions of interest were correlated with spelling errors. Atrophy in the left supramarginal gyrus and inferior frontal gyrus (IFG) pars orbitalis correlated with errors in nonword spelling, while thinning in the left temporal pole and fusiform gyrus correlated with errors in exception word spelling. Additionally, phonetically implausible errors in regular word spelling correlated with thinning in the left IFG pars triangularis and pars opercularis. Together, these findings suggest two independent systems for spelling to dictation, one phonetic (phoneme to grapheme conversion), and one lexical (whole word retrieval).

1. Introduction

1.1. Agraphia

Damage or atrophy in the left hemisphere causes a variety of language deficits. While often not the main complaint of patients with language impairment, these individuals often complain about or demonstrate difficulty in spelling, known as agraphia.

According to cognitive models, linguistic information can take multiple routes to get from input to output (Ellis & Young, 1988). In the case of spelling by dictation, a heard word may either be recognized, and the spelling retrieved from long term memory, or sounded out, mapping each sound onto a written symbol (a process referred to as *phoneme-to-grapheme conversion*). We will refer to the former as the lexical or whole-word route to spelling, and the latter as the phonologic route.

Lexical agraphia is based on failure to access orthographic whole-word forms (Beauvois & Derouesne, 1981), while the phonetic route remains relatively intact. Regular words (e.g. "cat") contain predictable mappings of phoneme to grapheme, and may thus be spelled by either the lexical or phonologic route, while exception words (e.g. "freight") violate these standard mappings and therefore can only be correctly spelled via the lexical route. Hence, the spelling of regular words would be spared, while spelling of exception words would be impaired. Additionally, misspelled words would likely be spelled in a phonetically plausible manner, leading to regularization of irregular words (e.g., misspelling "was" as "wuzz"), known as surface agraphia.

In *phonologic* (*or phoneme-to-grapheme*) *agraphia*, the primary deficit is in the ability to convert phonemes into corresponding orthographic symbols (Roeltgen, Sevush, & Heilman, 1983; Shallice, 1981). If the phonologic route is selectively affected, the spelling of familiar and regular words should be relatively spared, as patients still have access to whole word representations. However, the patient will be unable to spell unfamiliar words or

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stimuli that are not real words (nonwords), which rely on phoneme-to-grapheme conversion. Additionally, when these patients make errors they tend to be phonologically implausible, such as "quand" for "queen" (Rapcsak et al., 2009).While these patterns were initially described in patients with focal brain damage such as vascular lesions, both phonologic and lexical agraphia have also been described in patients whose cognitive deficits are caused by neurodegeneration (Neils-Strunjas, Groves-Wright, Mashima, & Harnish, 2006; Rapcsak, Arthur, Bliklen, & Rubens, 1989).

1.2. Localization of agraphia

Gerstmann (1957) described agraphia related to damage to the left angular gyrus, as part of the syndrome now known by his name. However, further investigation has shown that written language impairments do not localize specifically to the angular gyrus, but instead appear to be related to left parietal damage in general (Benton, 1961; Critchley, 1953). In fact, study of spelling deficits in general has shown that a widespread network of brain regions are involved in spelling including areas in all lobes of the left hemisphere and numerous subcortical areas (Cloutman et al., 2009).

While these findings show that many areas of the brain are involved in written language, they do not address critical areas specifically involved in spelling. For this, analysis by type of agraphia has been more telling. In patients with damage in the left perisylvian cortex, including the inferior frontal gyrus and surrounding cortex, and the temporoparietal junction, spelling was more affected than reading, and the agraphia followed the phonologic pattern (Alexander, Friedman, Loverso, & Fischer, 1992; Marien, Pickut, Engelborghs, Martin, & De Deyn, 2001; Rapcsak et al., 2009). In patients with lexical agraphia, structural lesions were located in the left temporo-occipital cortex (Rapcsak & Beeson, 2004).

These findings demonstrate two routes for processing of spelling with different neural substrates: a phoneme to grapheme route, and a whole word route. As described by Saur et al. (2008), this model places lexical and "higher level" language processes in a ventral pathway, involving extrasylvian areas of the temporal lobe (anterior and inferolateral temporal cortices) and ventrolateral prefrontal regions. Phonologic and articulatory information is subserved by a separate pathway, the dorsal pathway, involving the superior temporal lobe and the premotor cortex (perisylvian regions). In the context of spelling, phonologic agraphia is thus caused by dysfunction of the dorsal pathway while lexical agraphia is caused by dysfunction of the ventral pathway.

1.3. Primary progressive aphasia

Mesulam presented six cases of isolated language decline in 1982 and named the syndrome primary progressive aphasia in 1987, as a dementia syndrome marked by prominent and isolated language deficits (Mesulam, 1982, 1987). While other cognitive domains such as memory, visuospatial skills, and executive abilities may be affected, especially later in the disease process, language remains the most salient feature of the disease process. This specificity for language is echoed by a predominance of atrophy in the left hemisphere in areas implicated in language (Gorno-Tempini et al., 2004; Mesulam et al., 2009; Rogalski et al., 2011). The neurodegeneration of these regions provides a unique opportunity to study the language network because atrophy occurs in patterns that are different from those commonly found in patients with vascular or surgical lesions (Rogalski et al., 2011). In contrast to stroke-induced lesions where the damaged area is completely destroyed, neurodegenerative diseases kill only a fraction of neurons even within areas of significant atrophy. Since the residual neurons maintain some functionality (Sonty et al., 2003), clinicoanatomical correlations can reveal more subtle relationships than in patients with stroke. Based on the pattern of language impairments, three variants have been identified: agrammatic (PPA-G), logopenic (PPA-L), and semantic (PPA-S) (Mesulam et al., 2009, Gorno-Tempini et al., 2011). Each has a different pattern of language deficits, outlined in Table 1.

1.4. Agraphia in primary progressive aphasia

In contrast to lesion patients and dementia of the Alzheimer type, there are very few published studies focusing on agraphia in PPA. Noble, Glosser, and Grossman (2000) described a pattern of regularization errors in spelling (surface agraphia) in patients with a diagnosis of semantic dementia (a syndrome that partially overlaps with the PPA-S variant), which was not found in those with other forms of PPA, nor in those with dementia of the Alzheimer type. Sepelyak et al. (2011) analyzed patterns of spelling errors in PPA, and found several discrete patterns of deficits variably involving phoneme to grapheme conversion, lexical access, and working memory. While this study successfully links identified patterns of spelling errors to a model of spelling, it does not directly compare types of words misspelled or types of errors to neuropsychological measures, clinical diagnoses, or atrophy patterns.

In a recent study, Henry, Beeson, Alexander, and Rapcsak (2011) evaluated various written language measures in 15 PPA patients and 15 controls. Each was given a battery of words to spell and to read, including nonwords, exception, and regular words. Complex composite scores were calculated for semantic and phonetic components of reading and writing. Comparison with gray matter volume using voxel based morphometric MRI analyses (VBM) revealed correlations with semantic scores in the extrasylvian left temporal lobe and angular gyrus, whereas phonetic scores correlated with the perisylvian system, specifically in the inferior frontal lobe and supramarginal gyrus.

The present study compares spelling deficits in each of the clinical PPA subtypes, and correlates spelling scores and error types to cortical thinning (atrophy) and neuropsychological language measures of confrontation naming, repetition, syntax, lexical-semantic processing, and overall language processing using a larger group of PPA patients ($n=41$) than used in previous studies. One goal of this study was to see if these patterns of agraphia in our sample of PPA patients confirm our current understanding of the neural substrates of spelling and other language processes. Our anatomical findings using cortical thickness correlations should complement previous VBM finding. Additionally, we set out to show that specific measures of spelling may be useful in probing the variable language deficits in patients with PPA.

Table 1
Key neuropsychological features of PPA subtypes (adapted from Rogalski et al., 2011 to reflect recent subtyping consensus paper Gorno-Tempini et al., 2011).

PPA-G	Abnormality of syntax or motor speech impairments with relatively preserved single word comprehension. Fluency is impaired
PPA-L	Intermittent word finding hesitations. Repetition is impaired
PPA-S	Abnormality of single word comprehension with relatively preserved grammar and fluency. Naming is severely impaired