Abnormal language-related oscillatory responses in primary progressive aphasia

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A B S T R A C T

Patients with Primary Progressive Aphasia (PPA) may react to linguistic stimuli differently than healthy controls, reflecting degeneration of language networks and engagement of compensatory mechanisms. We used magnetoencephalography (MEG) to evaluate oscillatory neural responses in sentence comprehension, in patients with PPA and age-matched controls. Participants viewed sentences containing semantically and syntactically anomalous words that evoke distinct oscillatory responses. For age-matched controls, semantic anomalies elicited left-lateralized 8–30 Hz power decreases distributed along ventral brain regions, whereas syntactic anomalies elicited bilateral power decreases in both ventral and dorsal regions. In comparison to controls, patients with PPA showed altered patterns of induced oscillations, characterized by delayed latencies and attenuated amplitude, which were correlated with linguistic impairment measured offline. The recruitment of right hemisphere temporo-parietal areas (also found in controls) was correlated with preserved semantic processing abilities, indicating that preserved neural activity in these regions was able to support successful semantic processing. In contrast, syntactic processing was more consistently impaired in PPA, regardless of neural activity patterns, suggesting that this domain of language is particularly vulnerable to the neuronal loss. In addition, we found that delayed peak latencies of oscillatory responses were associated with lower accuracy for detecting semantic anomalies, suggesting that language deficits observed in PPA may be linked to delayed or slowed information processing.

1. Introduction

Primary progressive aphasia (PPA) is a neurodegenerative syndrome in which selective degeneration of cortical areas supporting language processing leads to a progressive impairment of language functions, with initial preservation of other cognitive domains (Mesulam, 2003; Mesulam et al., 2009). Recent diagnostic guidelines recognize three main variants of PPA (Gorno-Tempini et al., 2004, 2011; Mesulam et al., 2009, 2014): nonfluent/agrammatic, logopenic, and semantic, although considerable overlap exists between these groups, and many patients remain unclassifiable within the present guidelines (Mesulam et al., 2014; Mesulam and Weintraub, 2014; Wicklund et al., 2014). The language symptoms evinced by the three variants depend largely on the distribution and location of cortical atrophy, and there is a significant but variable link between the most strongly affected brain networks and distinct forms of molecular pathology, each variant being characterized by abnormal deposits of a different protein (Davies et al., 2005; Grossman, 2010; Gorno-Tempini et al., 2004; Mesulam et al., 2009, 2014; Snowden et al., 2007; Wilson et al., 2012). The semantic variant, with TDP-43-based neurodegeneration centered in the left temporal lobe, differs strongly from the other two, with marked impairment of single word comprehension and object naming, with relatively preserved grammatical structure and fluency (Mesulam et al., 2014). Agrammatic and logopenic PPA are more difficult to distinguish, with the former characterized by breakdown of grammatical production linked to tau protein-based degeneration of the inferior frontal gyrus, and the latter by reduced and slowed speech production, preserved grammar, and repetition deficits, linked to Alzheimer's (beta-amyloid and tau protein) pathology centered in the parietal lobe.

Although the location of neurodegeneration is thus far the best predictor of individual variation in linguistic performance across
patients, alterations in network function beyond the regions of frank atrophy may provide valuable information on how the brain copes with ongoing neurodegeneration, and can help explain why some patients can maintain a high degree of function late into the disease course. Characterization of functional alterations in PPA will also inform efforts to develop effective interventions that harness the brain's capacity for adaptive plasticity, including the compensatory engagement of structurally intact networks to support language processing. Functional neuroimaging studies have the potential to reveal these characteristics of the disease and their link to cognitive preservation in PPA. Although the variants of PPA have largely been characterized by differences in language production, it is far easier to experimentally probe linguistic processing through comprehension paradigms, rather than production paradigms. Language comprehension is also strongly affected in PPA, although these deficits have received less attention than the production deficits.

In the semantic variant, comprehension can be severely compromised on the single word level, while this is usually preserved in the other variants. Most PPA patients exhibit some degree of comprehension impairment on the sentence level (Grossman et al., 1996; Grossman and Moore, 2005). A recent study investigating quantitative relationships of comprehension with patterns of cortical atrophy across PPA patients found that single-word comprehension deficits were strongly related to atrophy in the left anterior temporal lobe, characteristic of the semantic variant, whereas impaired comprehension of syntactically complex, semantically reversible sentences was associated with atrophy in both frontal and tempo-parietal regions, associated with the agrammatic and logopenic variants, respectively (Peelle et al., 2008; Mesulam et al., 2015). Interestingly, these are the same areas in which increased fMRI activation has been observed during comprehension of syntactically complex sentences relative to simpler sentences (Chen et al., 2006; Meltzer et al., 2010; Peelle et al., 2010).

Difficulties with sentence comprehension may arise at both semantic and syntactic levels, as listeners (or readers) must combine both the meaning of words and their grammatical relationships to arrive at the correct interpretation of the sentence. Results of word monitoring studies have provided evidence that sentence comprehension problems in PPA may be caused by deficits in various aspects of on-line grammatical processing (Grossman et al., 2005; Grossman et al., 2005; Peelle et al., 2007). It has been suggested that PPA patients’ sentence comprehension difficulty may be due to slowed information processing speed (Grossman et al., 2005). Delayed processing of phonological information during naming has also been observed in logopenic and agrammatic PPA (Mack et al., 2015). With their high temporal resolution, electrophysiological techniques such as electroencephalography (EEG) or magnetoencephalography (MEG) can directly probe altered neural dynamics in PPA, particularly with respect to the brain's response to specific words within a sentence.

To date, only a few studies have examined electrophysiological activity related to the linguistic impairments in PPA patients, and most of them have investigated language processing at the single word level. These studies indicate that event-related potential (ERP) responses elicited by linguistic stimuli are altered in patients with PPA. For example, Giaquinto and Ranghi (2009) recorded event related potentials while participants with PPA performed a word recognition task. They found that the N400 potential, associated with word recognition, was delayed and reduced in amplitude in these patients, and progressively deteriorated until it was no longer present. Similarly, PPA patients showed abnormal N400 effects to unrelated mismatch words in an object-word matching task (Hurley et al., 2009).

### 1.1. MEG oscillatory measures of task-related activation

Pathological alterations of neural activity can be identified with high spatial and temporal resolution using MEG. This non-invasive technique detects magnetic fields at the surface of the head and can spatially localize post-synaptic currents generated in synchronously firing neuronal assemblies. Compared to EEG, MEG allows for more accurate reconstruction of source activity because magnetic fields are only minimally affected by passing through the skull, (Hamalainen, 1993). Furthermore, MEG is ideally suited for characterization and localization of oscillatory signals generated by neural activity. These signals may carry unique information useful for understanding the pathophysiology of PPA and how it affects language function.

Induced oscillations in MEG have been studied using beamforming techniques for source analysis (Vrba, 2002; Vrba and Robinson, 2001). This method estimates a virtual signal at a particular location in the brain while attenuating activity arising from other brain areas and extracranial sources, such as ocular artifacts (Cheyne et al., 2006; Robinson, 2004). Several studies with neurologically unimpaired participants identified power decreases in the alpha (8–12 Hz) and beta (15–30 Hz) ranges as a reliable indicator of increased neural activity, with close correspondence to the blood-oxygen-level-dependent (BOLD) responses in diverse parts of the cortex (Brookes et al., 2005; Hillebrand et al., 2005; Hanslmayr et al., 2012; Meltzer and Braun, 2011).

In a recent set of studies, we used MEG with beamforming to map the brain regions involved in the processing of semantic and syntactic aspects of language in healthy controls and patients with stroke-induced aphasia (Kieler et al., 2015; Kieler et al., 2016). We found that activation of specific language regions was detectable as an event-related desynchronization (ERD), or power decrease, in a broad frequency range covering both the alpha and beta bands (8–30 Hz). Processing of semantic anomalies was associated with 8–30 Hz ERD in a left-lateralized set of ventral frontotemporal regions, whereas syntactic anomalies activated both dorsal and ventral regions bilaterally. Power modulations in this frequency range have also been reported in other MEG studies examining induced oscillations to semantically or syntactically anomalous words (Bastiaansen et al., 2009; Wang et al., 2012).

Changes in language-related oscillatory responses associated with PPA have not yet been extensively investigated with MEG. In a recent study, Miller et al. (2013) studied changes in oscillatory responses during a verb generation task in one patient with semantic variant of PPA. In contrast to the left lateralized activation observed in the healthy controls, the patient with PPA showed beta band ERD localized to the right hemisphere. The possibility of compensatory linguistic processing occurring in preserved brain networks is highly relevant for intervention, as future treatments may focus on maximizing the compensatory potential of such areas through behavioral therapy, noninvasive brain stimulation, and pharmacological approaches. The engagement of right-hemisphere homologous networks in PPA is especially intriguing, given that this has been seen often in post-stroke aphasia, and has been interpreted as both adaptive (Crinion and Price, 2005; Thulborn et al., 1999) and maladaptive (Perani et al., 2003; Naeser et al., 2004) in different contexts.

### 1.2. Present study

The goal of the present study is to identify patterns of MEG induced oscillatory responses during sentence comprehension related to impairment and preservation of linguistic function in PPA. We studied both semantic and syntactic processing to identify changes in oscillatory patterns and neural recruitment associated with these different types of linguistic information. We asked whether impaired language processing in PPA is associated with altered patterns of oscillatory responses, and whether spared language functions can be associated with recruitment of preserved brain regions in the left and right hemispheres. Finally, we wanted to determine whether the magnitude and type of neural recruitment differs for semantic and syntactic processing. The design of the present study allowed us to identify relationships between neural responses to semantic and syntactic anomalies, online and offline language performance, and patterns of cortical atrophy within the PPA group. Because both agrammatic and logopenic variants...
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