



## Disrupted functional connectivity in primary progressive apraxia of speech

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### ABSTRACT

Apraxia of speech is a motor speech disorder thought to result from impaired planning or programming of articulatory movements. It can be the initial or only manifestation of a degenerative disease, termed primary progressive apraxia of speech (PPAOS). The aim of this study was to use task-free functional magnetic resonance imaging (fMRI) to assess large-scale brain network pathophysiology in PPAOS. Twenty-two PPAOS participants were identified from a prospective cohort of degenerative speech and language disorders patients. All participants had a comprehensive, standardized evaluation including an evaluation by a speech-language pathologist, examination by a behavioral neurologist and a multimodal imaging protocol which included a task-free fMRI sequence. PPAOS participants were age and sex matched to amyloid-negative, cognitively normal participants with a 1:2 ratio. We chose a set of hypothesis driven, predefined intrinsic connectivity networks (ICNs) from a large, out of sample independent component analysis and then used them to initialize a spatiotemporal dual regression to estimate participant level connectivity within these ICNs. Specifically, we evaluated connectivity within the speech and language, face and hand sensorimotor, left working memory, salience, superior parietal, supramarginal, insular and deep gray ICNs in a multivariate manner. The spatial maps for each ICN were then compared between PPAOS and control participants. We used clinical measures of apraxia of speech severity to assess for clinical-connectivity correlations for regions found to differ between PPAOS and control participants. Compared to controls, PPAOS participants had reduced connectivity of the right supplementary motor area and left posterior temporal gyrus to the rest of the speech and language ICN. The connectivity of the right supplementary motor area correlated negatively with an articulatory error score. PPAOS participants also had reduced connectivity of the left supplementary motor area to the face sensorimotor ICN, between the left lateral prefrontal cortex and the salience ICN and between the left temporal-occipital junction and the left working memory ICN. The latter connectivity correlated with the apraxia of speech severity rating scale, although the finding did not survive correction for multiple comparisons. Increased connectivity was noted in PPAOS participants between the dorsal posterior cingulate and the left working memory ICN. Our results support the importance of the supplementary motor area in the pathophysiology of PPAOS, which appears to be disconnected from speech and language regions. Supplementary motor area connectivity may serve as a biomarker of degenerative apraxia of speech severity.

**Abbreviations:** AES, Articulatory Error Score; AOS, Apraxia Of Speech; agPPA, Agrammatic/Nonfluent PPA; AQ, Aphasia Quotient; ASRS, Apraxia of Speech Severity Rating Scale; BNT, Boston Naming Test; FAB, Frontal Assessment Battery; FBI, Frontal Behavioral Inventory; ICN, Intrinsic Connectivity Network; MMSE, Mini-Mental State Examination; NPI-S, Neuropsychiatric Inventory – Severity; NVOA, Nonverbal Oral Apraxia; PCC, Posterior Cingulate Cortex; PFC, Prefrontal Cortex; PPA, Primary Progressive Aphasia; SMA, Supplementary Motor Area; TOJ, Temporal-Occipital Junction; TT, Token Test; UPDRS, Unified Parkinson Disease Rating Scale; WAB, Western Aphasia Battery

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## 1. Introduction

Apraxia of speech (AOS) is a motor speech disorder resulting from impaired planning or programming of articulatory movements (Darley et al., 1969; McNeil et al., 2009; Wambaugh et al., 2006). In adults, AOS is usually seen as a result of focal injury, with stroke accounting for the majority of AOS cases (Duffy, 2013b; Schiff et al., 1983), or as a manifestation of a degenerative disease (Duffy, 2006; Duffy and Josephs, 2012). In neurodegenerative cases AOS is often embedded within a broader dysfunction of cognition, language or motor systems (Duffy, 2006). For example, it is one of the core criteria for the non-fluent/agrammatic variant of primary progressive aphasia (PPA), along with agrammatism (Gorno-Tempini et al., 2011), and is considered part of the new criteria for progressive supranuclear palsy (PSP) (Hoglinger et al., 2017) and corticobasal syndrome (CBS) (Armstrong et al., 2013), with ~50% of CBS participants experiencing speech changes over the course of their illness (Alexander et al., 2014).

However, AOS can also be the initial or only manifestation of a degenerative disease. Over the last decade this phenomenon, termed primary progressive apraxia of speech (PPAOS), has been characterized in great detail. These patients have a distinct clinical presentation and temporal evolution (Duffy and Josephs, 2012; Duffy et al., 2015; Josephs et al., 2014), with approximately half developing a CBS-PSP hybrid syndrome ~5 years into the illness (Josephs et al., 2014). They have also been found to differ from PPA patients using temporal acoustic measures (Duffy et al., 2017). While aphasia can develop, this usually happens after several years and AOS typically continues to dominate the clinical presentation (Josephs et al., 2014; Josephs et al., 2013). It is associated with bilateral supplementary motor area (SMA), dorsolateral premotor and primary motor cortex abnormalities on imaging, including atrophy (Josephs et al., 2012), hypometabolism (Josephs et al., 2012; Josephs et al., 2006) and flortaucipir (tau-PET) uptake (Utianski et al., 2018). Bilateral involvement of frontal white matter tracts has also been documented (Botha et al., 2015). PPAOS patients appear to almost always harbor an underlying 4-repeat tauopathy (Deramecourt et al., 2010; Josephs and Duffy, 2008; Josephs et al., 2006).

There is a growing body of evidence supporting the idea that degenerative diseases target large scale systems or networks in the brain (Seeley et al., 2009). Task-free functional MRI (TF-fMRI) has been used to assess functional connectivity in stroke-related AOS, where reduced connectivity between bilateral premotor cortex regions was found to correlate with AOS severity (New et al., 2015). It has also been applied to the nonfluent/agrammatic variant of PPA (agPPA), a disorder that is often associated with AOS, where functional connectivity predicted gray matter atrophy within a “speech production network” (Mandelli et al., 2016). Despite the aforementioned advances in our understanding of PPAOS, network or functional connectivity changes have not been explored in the disorder, a knowledge gap we aimed to address in the current study.

There are numerous methodological frameworks within which functional connectivity can be assessed, including seed-based analyses, which are typically model based, and data driven methods such as independent component analysis (ICA), which doesn't require the a priori selection of regions or seeds (Friston, 2009). When the goal is to assess connectivity between a limited set of predefined regions of interest (ROIs), seed-based analyses may be preferable. However, ICA has a distinct advantage when the objects to be studied are the intrinsic connectivity networks (ICNs) of the brain. This is due to the fact that the connectivity within an entire ICN can be quantified, as opposed to connectivity to a node thought to represent the ICN, as is the case in a seed based analysis (Leech et al., 2011). Prior work has shown the ICA may be more sensitive to group differences than seed based methods (Smith et al., 2014). In the current study we used a hybrid approach: we chose a set of hypothesis driven, predefined ICNs from a large, out-of-sample ICA and then used them to initialize a spatiotemporal dual

regression (STR) to estimate participant level connectivity within these ICNs. Given that PPAOS is a relatively rare disorder that has never been subjected to functional connectivity analyses we felt this was the best compromise between hypothesis driven and data driven methods.

## 2. Materials and methods

### 2.1. Participants

Participants were members of a prospective cohort of degenerative speech and language patients evaluated at the Mayo Clinic Department of Neurology between 2010 and 2016. Details of the evaluation and diagnostic procedures are described elsewhere (Botha et al., 2015; Josephs et al., 2012). Briefly, participants with suspected degenerative speech or language disorders were prospectively recruited into the study. Each participant was interviewed and examined by a behavioral neurologist (KAJ), underwent detailed speech and language examination by a speech-language pathologist (EAS, JRD or HMC) and had MR imaging performed as part of a standardized protocol described below. As part of the neurologic evaluation the Mini-Mental State Examination (MMSE) (Folstein et al., 1975), Frontal Assessment Battery (FAB) (Dubois et al., 2000), Frontal Behavioral Inventory (Kertesz et al., 1997), Ideomotor Apraxia (IMA) part of the Western Aphasia Battery (WAB) (Kertesz, 2007), Movement Disorder Sponsored Revision of the Unified Parkinson's Disease Rating Scale (UPDRS) Part 3 (Goetz et al., 2008) and the brief questionnaire form of the Neuropsychiatric Inventory (NPI-Q) (Cummings et al., 1994) were administered. The speech and language evaluation was recorded and reviewed by two speech-language pathologists who reached consensus on the presence and severity of dysarthria, the presence and severity of AOS, and the presence of nonverbal oral apraxia (NVOA) (Duffy, 2013b). The evaluation also included the WAB, with the aphasia quotient (WAB-AQ) serving as a measure of aphasia severity (Kertesz, 2007), the 22-item Token Test (TT) (De Renzi and Vignolo, 1962), the Boston Naming Test Short Form (BNT) (Lansing et al., 1999), the Apraxia of Speech Rating Scale (ASRS) (Strand et al., 2014), and a NVOA scale (Botha et al., 2014; Duffy, 2013a). Supplementary speech tasks, described previously (Duffy et al., 2015), were also administered, which included the repetition of mostly multisyllabic words (thirteen words, three repetitions each). This supplemental task was used to derive a quantitative measure of articulatory errors by taking the percentage of words with articulatory errors (articulatory error score or AES).

Based on the clinical examination alone, blinded to the results of imaging, a diagnosis of PPAOS was given if AOS was the predominant speech disturbance; mild dysarthria could be present but aphasia was absent (Botha et al., 2015; Josephs et al., 2012). In other words, the root criteria for PPA were not met (Gorno-Tempini et al., 2011). In addition, participants could not meet criteria for an alternative neurodegenerative disease, such as CBS (Armstrong et al., 2013), behavioral variant frontotemporal dementia (bvFTD) (Rascovsky et al., 2011), or possible/probable PSP (Hoglinger et al., 2017), to name but a few. Participants were also excluded if their imaging studies did not pass quality control (detailed below), if they were amyloid positive (SUVR  $\geq 1.5$ ) on Pittsburgh Compound B PET imaging, or if there was a structural MR abnormality that could confound connectivity analyses. A total of 30 participants with PPAOS were eligible for inclusion in the current study. Three were excluded because no TF-fMRI sequence was available or because the available sequence failed quality control. Four were excluded on account of being amyloid positive. One participant had a prior meningioma resected with left frontal gliosis and was excluded because this might potentially confound connectivity analyses.

For the imaging analysis, PPAOS participants were age and sex matched 1:2 to cognitively and neurologically normal amyloid PET negative participants from the Mayo Clinic Study of Aging (Roberts et al., 2008), who completed the same imaging protocol.

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