



Emotion detection deficits and changes in personality traits linked to loss of white matter integrity in primary progressive aphasia



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ABSTRACT

Non-cognitive features including personality changes are increasingly recognized in the three PPA variants (semantic-svPPA, non fluent-nfvPPA, and logopenic-lvPPA). However, differences in emotion processing among the PPA variants and its association with white matter tracts are unknown. We compared emotion detection across the three PPA variants and healthy controls (HC), and related them to white matter tract integrity and cortical degeneration. Personality traits in the PPA group were also examined in relation to white matter tracts. Thirty-three patients with svPPA, nfvPPA, lvPPA, and 32 HC underwent neuropsychological assessment, emotion evaluation task (EET), and MRI scan. Patients' study partners were interviewed on the Clinical Dementia Rating Scale (CDR) and completed an interpersonal traits assessment, the Interpersonal Adjective Scale (IAS). Diffusion tensor imaging of uncinate fasciculus (UF), superior longitudinal fasciculus (SLF) and inferior longitudinal fasciculus (ILF), and voxel-based morphometry to derive gray matter volumes for orbitofrontal cortex (OFC), anterior temporal lobe (ATL) regions were performed. In addition, gray matter volumes of white matter tract-associated regions were also calculated: inferior frontal gyrus (IFG), posterior temporal lobe (PTL), inferior parietal lobe (IPL) and occipital lobe (OL). ANCOVA was used to compare EET performance. Partial correlation and multivariate linear regression were conducted to examine association between EET and neuroanatomical regions affected in PPA. All three variants of PPA performed significantly worse than HC on EET, and the svPPA group was least accurate at recognizing emotions. Performance on EET was related to the right UF, SLF, and ILF integrity. Regression analysis revealed EET performance primarily relates to the right UF integrity. The IAS subdomain, cold-hearted, was also associated with right UF integrity. Disease-specific emotion recognition and personality changes occur in the three PPA variants and are likely associated with disease-specific neuroanatomical changes. Loss of white matter integrity contributes as significantly as focal atrophy in behavioral changes in PPA.

1. Introduction

Primary progressive aphasia (PPA) refers to a group of neurodegenerative disorders presenting initially with isolated language impairment. Currently three clinical variants are recognized: semantic variant PPA (svPPA), non-fluent variant PPA (nfvPPA) and logopenic variant PPA (lvPPA) (Gorno-Tempini et al., 2011). Each PPA variant is

associated with deterioration of distinct language features: (i) progressive single-word comprehension deficits and anomia in svPPA; (ii) agrammatism and effortful speech in nfvPPA; (iii) profound word-finding difficulty and sentence/phrase repetition deficits in lvPPA (Gorno-Tempini et al., 2011). Moreover, emotional and personality changes can also occur in some patients. Decreased extroversion, warmth and dominance have been described in patients with svPPA,

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and agitation, depression and apathy in patients with nvfPPA (Rohrer and Warren, 2010; Sollberger et al., 2011).

The diverse linguistic profile of each PPA variant is associated with different patterns of neuroanatomical degeneration that includes both gray and white matter abnormalities. In recent years, Diffusion Tensor Imaging (DTI) studies have revealed significant white matter tract abnormalities in addition to the previously known gray matter atrophy (Galantucci et al., 2011). DTI allows in vivo evaluation of white matter integrity by examining distribution of water molecules within fiber tracts (Ciccarelli et al., 2008) and so facilitates investigation of the contribution of white matter tract deterioration to the deficits observed in PPA. SvPPA is characterized by left anterior temporal lobe (ATL) atrophy, as well as damage to the uncinate fasciculus (UF), the inferior longitudinal fasciculus (ILF), left arcuate fasciculus (AF) and left temporoparietal superior longitudinal fasciculus (SLF-tp) (Galantucci et al., 2011; Gorno-Tempini et al., 2011). Patients diagnosed with nvfPPA display left inferior frontal gyrus (IFG) atrophy and alteration of the left SLF, aslant and fronto-striatal tracts (Catani et al., 2013; Galantucci et al., 2011; Gorno-Tempini et al., 2011; Mandelli et al., 2014). These two variants of PPA are usually associated with frontotemporal lobar degeneration (FTLD) pathology, whereas, lvPPA is caused by Alzheimer disease (AD) pathology and is associated with degeneration of the left temporo-parietal region and significant involvement of left SLF-tp, AF, SLF-II, SLF-III and anterior ILF tracts (Galantucci et al., 2011; Gorno-Tempini et al., 2011). Therefore, white matter tract abnormality in conjunction with gray matter atrophy provides a distinct neuroanatomical profile that is associated with specific features in each PPA variant.

Focal frontal and temporal degeneration in the three PPA variants is associated with behavioral changes in conjunction with the language deficits (Couto et al., 2013; Kumfor et al., 2011; Mahoney et al., 2011; Piguet et al., 2015; Rohrer et al., 2012; Rohrer and Warren, 2010; Rosen et al., 2006). The temporal and frontal lobes are associated with social cognitive functions, including empathy (Kumfor and Piguet, 2012). This allows individuals to infer others' internal emotions, intentions and beliefs, and behavioral response selection (Adolphs, 2009). In svPPA, where there is usually significant change in personality and loss of social cognition, the loss of empathy is usually attributed to right temporal pole atrophy (Rankin et al., 2006) while the orbitofrontal cortex (OFC) and insular atrophy is often associated with apathy, anxiety, abnormal feeding behavior, disinhibition and irritability (Rohrer and Warren, 2010).

Emotion processing is an essential component of social cognition (Ibanez et al., 2014). Accurate recognition of expressive emotions allows effective response to social cues, prevents conflicts and strengthens interpersonal relationships. The following cortical regions are implicated in emotion perception: ventromedial prefrontal cortex, insula, ATL, OFC, right inferior temporal gyrus and right amygdala (Kumfor and Piguet, 2012; Olson et al., 2007). Certain white matter tracts, such as the UF and ILF, are also involved in emotion processing (Philippi et al., 2009; Von Der Heide et al., 2013).

Given that some of the neuroanatomical areas that sub-serve social cognition are atrophied in PPA and there is significant alteration in certain white matter tracts such as the UF and ILF that are also important during emotion processing, we hypothesized that the UF and ILF abnormality will significantly correlate with inaccurate emotion detection. Moreover, we expected the svPPA patients to perform significantly worse than the other PPA variants due to the UF and ILF tract deterioration observed in this group. The purpose of the current study was to compare emotion recognition performance in the three PPA variants and healthy controls and ascertain the relative contribution of white matter tract alterations to their performance in emotion perception. We were also interested in examining the relative contribution of gray matter and white matter abnormalities to personality traits in PPA.

2. Material and methods

2.1. Subjects

Patients diagnosed with PPA ($N = 33$) and age-matched healthy controls ($N = 32$) were recruited at the University of California, San Francisco Memory and Ageing Centre ($N = 65$) from November 2007 to October 2009. Each patient was diagnosed with one of the three PPA variants, svPPA ($N = 13$), nvfPPA ($N = 11$) and lvPPA ($N = 9$), according to the latest criteria (Gorno-Tempini et al., 2011). The UCSF Institutional Review Board approved the study. Patients with prior or current diagnosis of other neurological, psychiatric, major medical condition and substance abuse were excluded from the study. Only subjects who underwent DTI were included in the study. Each study participant underwent neuroimaging, neuropsychological and neurological examination. In addition, study partners completed several questionnaires pertaining to patients' current behavior and personality.

2.2. Neuropsychological assessment

For the purpose of this paper, only a subset of neuropsychological tests were examined. All subjects underwent the Mini Mental State Examination (MMSE) and the PPA group also completed the Western Aphasia Battery (WAB) auditory word recognition subtest. The auditory word recognition assesses individuals' ability to comprehend words. In addition, a subset of participants ($N = 42$; svPPA = 12, nvfPPA = 10, lvPPA = 9, HC = 11) completed an Emotion Evaluation Task (EET), a sub-test of The Awareness of Social Inference Test, TASIT (McDonald et al., 2003). The EET consists of short video vignettes to evaluate recognition of basic emotional expressions (McDonald et al., 2003). At the end of each video clip, the subject is required to select an emotion (from a list) which most accurately represents the emotion the actor is portraying. Study partners were interviewed to complete a Clinical Dementia Rating (CDR). The CDR is a staging scale, which is used to assess severity of dementia. It assesses impairment in six different domains (memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care) and provides an overall global score (Morris, 1993). Lastly, a subset of study partners ($N = 21$; HC = 11 PPA = 10; svPPA = 5, nvfPPA = 4, lvPPA = 1) completed the Interpersonal Adjectives Scale (IAS), which provides a measure of the following personality traits: assured-dominant, gregarious-extraverted, warm-agreeable, unassuming-ingenuous, unassertive-submissive, aloof-introverted, aloof-introverted, cold-hearted, arrogant-calculating (Wiggins et al., 1988).

2.3. MRI acquisition

A 3T Siemens TrioTim syngo with a standard 8-channel head-coil was used to acquire T1-weighted and diffusion-weighted images. The parameters of each scan are outlined in our previous paper (Galantucci et al., 2011).

2.4. Diffusion tensor imaging analysis

The FMRIB Software Library (FSL) was used to conduct DTI analysis (<http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/>). Region of interest (ROI)-based DTI analysis was performed for the following tracts: ILF, UF and SLF (Fig. 1). Various DTI metrics were generated to represent different aspects of fiber tract integrity: (i) fractional anisotropy (FA) represents movement of water diffusion along the axon; (ii) axial diffusivity (AD), which measures diffusivity of water molecules along the axon, is interpreted as a measure of axonal damage; (iii) diffusivity of water molecules perpendicular to the axon or myelin damage is represented by radial diffusivity (RD); (iv) mean diffusivity (MD) reflects average motion of water molecules in every direction (Ciccarelli et al., 2008). The preprocessing and tractography analysis are reported in our

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