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Research report

Atrophy and structural covariance of the cholinergic basal forebrain in primary progressive aphasia

Stefan Teipel [a,b,*], Theresa Raiser [c], Lina Riedl [d], Isabelle Riederer [e], Matthias L. Schroeter [f,g], Sandrine Bisenius [f,g], Anja Schneider [h], Johannes Kornhuber [i], Klaus Fliessbach [j,m], Annika Spottke [j], Michel J. Grothe [a,b], Johannes Prudlo [k], Jan Kassubek [l], Albert Ludolph [l], Bernhard Landwehrmeyer [l], Sarah Straub [l], Markus Otto [l,2], Adrian Danek [c,2] and the FTLDc study group[1]

[a] German Center for Neurodegenerative Diseases (DZNE) – Rostock/Greifswald, Rostock, Germany
[b] Department of Psychosomatic Medicine, University of Rostock, Rostock, Germany
[c] Department of Neurology, University of Munich, Munich, Germany
[d] Department of Psychiatry, Technical University of Munich, Munich, Germany
[e] Department of Neuroradiology, Technical University of Munich, Munich, Germany
[f] Clinic of Cognitive Neurology, University of Leipzig, Leipzig, Germany
[g] Max Planck Institute for Human Cognitive & Brain Sciences, Leipzig, Germany
[h] Department of Psychiatry, University of Göttingen, Göttingen, Germany
[i] Department of Psychiatry, University of Erlangen, Erlangen, Germany
[j] German Center for Neurodegenerative Diseases (DZNE) – Bonn, Bonn, Germany
[k] Department of Neurology, University of Rostock, Rostock, Germany
[l] Department of Neurology, University of Ulm, Ulm, Germany
[m] Department of Psychiatry, University of Bonn, Bonn, Germany

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ABSTRACT

Primary progressive aphasia (PPA) is characterized by profound destruction of cortical language areas. Anatomical studies suggest an involvement of cholinergic basal forebrain (BF) in PPA syndromes, particularly in the area of the nucleus subputaminalis (NSP). Here we aimed to determine the pattern of atrophy and structural covariance as a proxy of structural connectivity of BF nuclei in PPA variants. We studied 62 prospectively recruited cases with the clinical diagnosis of PPA and 31 healthy older control participants from the

* *Corresponding author*. University Medicine Rostock, and DZNE Rostock/Greifswald, Gehlsheimer Straße 20, 18147 Rostock, Germany. E-mail address: stefan.teipel@med.uni-rostock.de (S. Teipel).

[1] FTLDc: Nibal Ackl (München), Sönke Arlt (Hamburg), Ambros Beer (Ulm), Kai Boelmans (Hamburg), Janine Diehl-Schmid (TU München), Marie Fischer (Erlangen), Stefan Förster (TU München), Hans Förstl (TU München), Anke Hammer (Erlangen), Sonja Henz (München), Walter Just (Ulm), Karsten Mueller (Leipzig), Maxine Luley (Homburg/Saar), Nicolai Marroquin (Ulm), Hans Peter Müller (Ulm), Magdalena Nagl (Ulm), Timo Oberstein (Erlangen), Hannah Pellkofer (Göttingen), Catharina Prix (München), Tanja Richter-Schmidinger (Erlangen), Katharina Schümberg (Leipzig), Elisa Semler (Ulm), Philipp Spitzer (Erlangen), Petra Steinacker (Ulm), Katharina Stuke (Leipzig), Amir Yassari (Hamburg), Heike Zech (Göttingen).

[2] Both authors contributed equally.

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cohort study of the German consortium for frontotemporal lobar degeneration (FTLD). We determined cortical and BF atrophy based on high-resolution magnetic resonance imaging (MRI) scans. Patterns of structural covariance of BF with cortical regions were determined using voxel-based partial least square analysis. We found significant atrophy of total BF and BF subregions in PPA patients compared with controls [$F(1, 82) = 20.2$, $p < .001$]. Atrophy was most pronounced in the NSP and the posterior BF, and most severe in the semantic variant and the nonfluent variant of PPA. Structural covariance analysis in healthy controls revealed associations of the BF nuclei, particularly the NSP, with left hemispheric predominant prefrontal, lateral temporal, and parietal cortical areas, including Broca's speech area ($p < .001$, permutation test). In contrast, the PPA patients showed preserved structural covariance of the BF nuclei mostly with right but not with left hemispheric cortical areas ($p < .001$, permutation test). Our findings agree with the neuroanatomically proposed involvement of the cholinergic BF, particularly the NSP, in PPA syndromes. We found a shift from a structural covariance of the BF with left hemispheric cortical areas in healthy aging towards right hemispheric cortical areas in PPA, possibly reflecting a consequence of the profound and early destruction of cortical language areas in PPA.

1. Introduction

In 1892 Arnold Pick first described the syndrome of progressive aphasia in a patient with frontal and temporal lobe atrophy at autopsy (Pick, 1892). Almost 100 years later Marsel Mesulam defined the clinical entity of primary progressive aphasia (PPA) (Mesulam, 1982) which only recently has been stratified according to clinical phenomenology into the subtypes of semantic variant, logopenic variant and nonfluent/agrammatic aphasia (Gorno-Tempini et al., 2011). The relationship between the clinical syndromes of PPA and underlying neuropathology is not consistent. Tau pathology is most often found in nonfluent PPA, whereas the semantic variant frequently presents with Transactive response DNA binding protein 43 kDa (TDP-43) pathology (Bigio et al., 2010; M. Mesulam, 2013; Mesulam et al., 2008); Alzheimer's disease is the underlying pathology in more than 50% of cases with logopenic variant PPA, but is also found in 15–30% of cases with other PPA variants (Chare et al., 2014; Harris et al., 2013).

The clinical variants of PPA show distinct patterns of cortical atrophy (Bisenius, Neumann, & Schroeter, 2016; Gorno-Tempini et al., 2011; Rogalski et al., 2011; Schroeter, Raczka, Neumann, & Yves von Cramon, 2007). In addition to cortical atrophy, subcortical atrophy involving striatal and thalamic grey matter (GM) has been described in frontotemporal lobar degeneration (FTLD), including cases with PPA (Chow et al., 2008). In Alzheimer's disease (AD), a large body of evidence suggests early and selective involvement of the cholinergic system including decline of presynaptic markers of cholinergic activity in the cortex (Geula, Nagykery, Nicholas, & Wu, 2008; Henke & Lang, 1983) as well as degeneration and loss of cholinergic neurons in the basal forebrain (BF) nuclei (Baker-Nigh et al., 2015; Boissiere, Faucheux, Ruberg, Agid, & Hirsch, 1997; Strada et al., 1992; Vana et al., 2011). The involvement of the cholinergic system in PPA is still a matter of debate. The notion that a relevant proportion of PPA cases is associated with AD pathology would suggest involvement of the BF at least in subtypes of PPA. In addition, neurobiological evidence suggests that a dysbalance of the temporal lobe cholinergic and the dopaminergic innervation may play a significant role in language integrity (Tanaka & Bachman, 2000). Furthermore, Broca's region, the anterior language area, is characterized by a strong cholinergic innervation (Amunts et al., 2010). The nucleus subputaminalis (NSP), a cholinergic neuron cluster in the lateral extension of the Nucleus basalis Meynert, has first been described by Ayala in 1915 (Ayala, 1915). The nucleus of Ayala has only been described in humans and anthropoid monkeys, but not in other species including non-anthropoid primates. The NSP exhibits a strong left laterality; it is located in close proximity to the external capsule, suggesting a strong connectivity to the cortical language areas (Simic et al., 1999). These findings have raised the question whether the NSP is related to language function in the human brain.

Together, these findings point to a potential role of the cholinergic BF in the development of PPA syndromes. However, this question has only little been studied so far. While cholinergic markers have been studied post mortem in the behavioural variant of FTLD without evidence of major alterations (Procter, Qurne, & Francis, 1999), we are not aware of a post-mortem study on cholinergic markers in PPA. In a previous magnetic resonance imaging (MRI) study in a small sample of 10 patients with PPA, we showed a significant atrophy of the cholinergic BF nuclei, including Ayala's nucleus, compared to 18 age-matched healthy control individuals (Teipel, Flatz, et al., 2014). The number of participants in this previous study, however, was too small to allow for a comparison of the pattern of BF atrophy between subtypes of PPA.

In the present study, we determined the pattern of atrophy of the cholinergic BF in 62 patients with the diagnosis of PPA stratified into the clinical variants according to Gorno-Tempini et al. (2011) in comparison with 31 cognitively healthy controls. Data were retrieved from a prospective