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Cholinergic depletion and basal forebrain volume in primary progressive aphasia

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ABSTRACT

Primary progressive aphasia (PPA) is a heterogeneous syndrome with various neuropathological causes for which no medical treatment with proven efficacy exists. Basal forebrain (BF) volume loss has been reported in PPA but its relation to cholinergic depletion is still unclear. The primary objective of this study was to investigate whether cholinergic alterations occur in PPA variants and how this relates to BF volume loss. An academic memory clinic based consecutive series of 11 PPA patients (five with the semantic variant (SV), four with the logopenic variant (LV) and two with the nonfluent variant (NFV)) participated in this cross-sectional *in vivo* PET imaging study together with 10 healthy control subjects. Acetylcholinesterase (AChE) activity was quantitatively measured in the neo- and allocortex using N-[^{11}C]-Methylpiperidin-4-yl propionate (PMP)-PET with arterial sampling and metabolite correction. Whole brain and BF volumes were quantified using voxel-based morphometry on high-resolution magnetic resonance imaging (MRI) scans.

In the PPA group, only LV cases showed decreases in AChE activity levels compared to controls. Surprisingly, a substantial number of SV cases showed significant AChE activity increases compared to controls. BF volume did not correlate with AChE activity levels in PPA. To conclude, in our sample of PPA patients, LV but not SV was associated with cholinergic depletion. BF atrophy in PPA does not imply cholinergic depletion.

1. Introduction

Primary progressive aphasia (PPA) is characterized by an isolated language impairment and is divided clinically into the subtypes of logopenic (LV), nonfluent (NFV) and semantic variant (SV) aphasia (Gorno-Tempini et al., 2011; Vandenberghe, 2016). Of the LV cases, 50–60% have underlying Alzheimer's disease (AD) pathology. In 50–70% of NFV cases the underlying cause is frontotemporal lobar degeneration (FTLD)-tauopathy (*i.e.* corticobasal degeneration (CBD), progressive supranuclear palsy (PSP) or Pick's disease pathology) and 69–83% of SV cases have FTLD-Transactive response DNA binding Protein 43 kDa (TDP-43) type C pathology (Grossman, 2010; Vandenberghe, 2016). Cholinergic depletion has been documented in typical AD (Bohnen et al., 2005, 2003; Kuhl et al., 1999), but it is currently unknown whether a cholinergic deficit also occurs in atypical AD presenting as PPA or in PPA due to a tauopathy or TPD-43 proteinopathy.

According to MRI volumetric studies, the basal forebrain (BF) is atrophic in PPA SV and NFV (Teipel et al., 2016, 2014), and mainly so the posterior part of the nucleus basalis (Ch4) and nucleus subputaminalis (NSP). The BF is the primary source of cholinergic transmission to the neo- and allocortex (Zaborszky et al., 2015), hence the hypothesis that a cholinergic deficit may also exist in non-AD cases of PPA.

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Post mortem morphometric studies of the BF have mainly focused on AD or on FTLD-tau. In AD, severe degeneration of the BF, mainly the posterior part of Ch4, has been reported (Baker-Nigh et al., 2015; Grothe et al., 2014; Kerbler et al., 2015; Teipel et al., 2005). In FTLD-tau, Ch4 degeneration has been shown in PSP (Kasashima and Oda, 2003; Tagliavini et al., 1984), whereas both degeneration (Kasashima and Oda, 2003) and preservation (Dickson, 1999) of Ch4 have been reported in CBD.

Cholinergic denervation resulting from BF volume loss may be reflected in altered AChE activity levels. AChE activity levels can be mapped *in vivo* using N-[^{11}C]-Methyl-4-piperidyl acetate ([^{11}C]MP4A)- or N-[^{11}C]-Methylpiperidin-4-yl propionate ([^{11}C]PMP)-PET (Irie et al., 1996). The rate-dependent enzyme for acetylcholine (ACh) degradation *i.e.* acetylcholinesterase (AChE) is present at pre- and postsynaptic neurons (Wevers, 2011) and in a soluble form at the synaptic cleft (Schegg et al., 1992).

Studies using [^{11}C]MP4A and [^{11}C]PMP-PET have shown thalamic cholinergic depletion in PSP (Hirano et al., 2010; Shinotoh et al., 1999) and cortical cholinergic depletion in CBD (Shinotoh, 2007) and typical AD. Reduced AChE levels, as measured with [^{11}C]PMP-PET, have also been found in the neocortex and thalamus in two patients with FTDP-17 mutations (Hirano et al., 2006).

To date, no PET study investigated the cholinergic system in PPA exclusively.

The primary objective of this study was to investigate whether cholinergic alterations occur in PPA and how this depends on the variant. Cholinergic activity is crucial for several cognitive processes (Wevers, 2011) and plays a hypothetical role in language (Boban et al., 2006; Simić et al., 1999). As a consequence, a cholinergic deficit in PPA may have implications for therapeutic interventions.

2. Materials and methods

2.1. Subjects

Patients were recruited between 2004–2006 and between 2009 and 2015 at the memory clinic University Hospitals Leuven. Each PPA case was diagnosed according to Gorno-Tempini et al., 2011 recommendations (Gorno-Tempini et al., 2011). Healthy control subjects were recruited through advertisement in local newspapers or internet. Eleven patients with PPA (five SV, four LV and two NFV) (Table 1) participated as well as 10 control subjects. Three patients received a neuropathological examination (interval from [^{11}C]PMP-PET till death: 6.00 ± 3.61 years). LV case 8 received a diagnosis of pathologically definite AD 3 years *post* [^{11}C]PMP-PET, NFV case 1 a diagnosis of pathologically definite CBD 5 years *post* [^{11}C]PMP-PET and SV case 9 a diagnosis of pathologically definite FTLD with TDP-43 inclusions subtype I pathology 10 years *post* [^{11}C]PMP-PET. There was no significant history of stroke, psychiatric illness or vascular disease in study participants. Patients were naive for cholinesterase inhibitors and none of the study participants took anticholinergic medication. All subjects received a [^{11}C]PMP-PET scan along with a volumetric MRI scan. For MRI volumetric comparisons, we included an additional set of 24 healthy controls (67.3 ± 8.83 years), scanned on the same scanner, as well as 17 additional PPA patients (4 LV, 6 NFV and 7 SV) (Table 1) (Grube et al., 2016) and 77 additional controls (64.6 ± 5.86 years) who were scanned on a different scanner (see MRI acquisition and analysis).

The study was approved by the Ethics Committee, University Hospitals Leuven. All participants provided written informed consent in accordance with the Declaration of Helsinki.

Table 1
Demographics and neuropsychological characteristics.

Case	PPA	*Post mortem*	Age (y)	Symptom duration (y)	Gender	CDR	BNT	PALPA	AAT-compr	BORB-hard	BORB-easy	CPM
5[b]	LV	/	59	2.5	m	2	/	15[a]	83[a]	21[a]	27[a]	20[a]
6[b]	LV	/	77	2	m	1	39[a]	25	102[a]	22[a]	30	29
7[b]	LV	/	66	3	m	1	35[a]	27	94[a]	23a	32	23[a]
8[b]	LV	AD	72	2.5	f	1	24[a]	26	83[a]	25	29	17
13	LV	/	57	0.5	f	0.5	56	28	120	25	29	35
17	LV	/	64	3	m	0.5	41[a]	23[a]	114	25	31	33
23	LV	/	71	1	m	0	53	28	118	26	31	33
18	LV	/	62	1.5	f	1	53	27	106	24	31	31
1[b]	NFV	CBD	77	3	m	1	43[a]	25	105	21[a]	30	24[a]
11[b]	NFV	/	71	2.5	m	1	45[a]	29	112	27	30	21[a]
15	NFV	/	52	2	f	2	58	28	120	26	31	31
20	NFV	/	79	5	f	1	48	22[a]	105	25	30	24[a]
22	NFV	/	71	1.5	m	0.5	55	28	102[a]	26	31	24[a]
26	NFV	/	78	2.5	m	1	48	23[a]	77[a]	26	29	30
27	NFV	/	72	2.5	f	1	30[a]	19[a]	85[a]	21[a]	18[a]	12[a]
28	NFV	/	63	5	f	0	41[a]	24[a]	104[a]	22[a]	28	32
2[b]	SV	/	59	4	m	1	36[a]	22[a]	78[a]	17[a]	23[a]	21[a]
3[b]	SV	/	63	3	f	1	14[a]	24[a]	95[a]	22[a]	25[a]	23[a]
4[b]	SV	/	71	6	m	1	13[a]	22[a]	95[a]	24	28	17[a]
9[b]	SV	TDP-43 I	52	1.5	f	1	/	17[a]	62[a]	21[a]	23[a]	36
10[b]	SV	/	57	2	m	1	14[a]	22[a]	87[a]	19[a]	26[a]	34
12	SV	/	76	6	m	1	34[a]	27	90[a]	20[a]	23[a]	29
14	SV	/	70	1.5	f	1	22[a]	17[a]	74[a]	20[a]	18[a]	24[a]
16	SV	/	61	3	m	2	7[a]	18[a]	73[a]	18[a]	20[a]	36
19	SV	/	64	3	m	1	20[a]	14[a]	74[a]	18[a]	26[a]	29
21	SV	/	48	6	f	1	12[a]	24[a]	82[a]	17[a]	26[a]	35
24	SV	/	58	2	f	1	35[a]	27	93[a]	27	31	36
25	SV	/	68	5	f	1	16[a]	23[a]	114	25	31	34
Groupdata	PPA	Mean (SD)	65.8(8.5)	2.96(1.5)	13f/15m	0.89	34.3(15.7)	23.4(4.2)	94.5(16.1)	22.6(3.1)	27.4(4.1)	27.6(6.7)
	Controls	Mean (SD)	65.4(6.7)	/	48f/63m	0	53.7 (4.7)	27.6(1.8)	114.8(4.8)	27.2(1.97)	29.8(1.5)	32.2(3.2)
		p	0.7	/	0.92	<0.001	<0.001	<0.001	<0.001	<0.001	0.01	0.005

Abbreviations: AAT = Aachen aphasia test, comprehension (/120), BORB-hard/-easy = Birmingham object recognition battery (/32), BNT = Boston Naming test (/60), CBD = corticobasal degeneration, CDR = Clinical dementia rating scale, CPM = colored progressive matrices (/36), PALPA = Psycholinguistic assessment of language in aphasia, subtest 49: associative-semantic task for words (/30). PPA variants: LV = logopenic variant, NFV = nonfluent variant, SV = semantic variant PPA patients.

[a] Scores which are significantly different compared to controls based on a modified *t*-test.

[b] Patients who received [^{11}C]PMP-PET.