Validation of Diagnostic Imaging Criteria for Primary Progressive Aphasia

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Table of Contents

List of Abbreviations

AD	Alzheimer's disease
ALE	anatomical likelihood estimation
BAs	Brodmann areas
CDR	Clinical Dementia Rating Scale
FDR	false discovery rate
FWE	family-wise error
FDG-PET	fluorodeoxyglucose positron emission tomography
FTD	frontotemporal dementia
FTLD	frontotemporal lobar degeneration
FTLD-CDR	FTLD-modified Clinical Dementia Rating Scale
HC	healthy controls
lvPPA	logopenic variant PPA
MMSE	Mini-Mental State Examination
MNI	Montreal Neurological Institute
MRI	magnetic resonance imaging
PET	positron emission tomography
PPA	primary progressive aphasia
nfvPPA	nonfluent/agrammatic variant PPA
ROI	regions-of-interest
SPECT	single photon emission computed tomography
TDP	TAR DNA-binding protein 43
svPPA	semantic variant PPA
SVM	support vector machine
VBM	voxel-based morphometry

List of Figures

List of Tables

1 General Introduction

1.1 Development of the terminology and diagnostic criteria for primary progressive aphasia

Progressive fluent and nonfluent language disorders associated with atrophy in left frontal, perisylvian, and temporal regions were first described by Pick, Sérieux, and Rosenfeld (Pick, 1892; 1904 available in translation by Girling and Berrios, 1994, 1997; Rosenfeld, 1909; Sérieux, 1893). Pick (1892) described a woman who suffered from a social disorder characterized by disinhibition and poor insight and whose language abilities progressively deteriorated until she finally became mute. Sérieux (1893) provided the first case report of an isolated progressive language disorder by describing a patient with halting speech, but intact memory, visuospatial abilities, and social functioning. Rosenfeld provided an early description of a patient with word-finding difficulties, including a striking loss of the names of objects, circumlocutions, and semantic paraphasic errors in spontaneous speech (Rosenfeld, 1909). A few decades later, more single cases with fluent and nonfluent aphasia were described (Holland, McBurney, Moossy, & Reinmuth, 1985; Tyrrell, Kartsounis, Frackowiak, Findley, & Rossor, 1991; Warrington, 1975). Selective impairment of semantic memory (component of long-term memory containing knowledge of objects, facts, and concepts as well as words and their meaning; Tulving, 1972, 1983) was first introduced by Warrington (1975) to describe three patients with cerebral atrophy presenting with progressive anomia (i.e., problems recalling words or names) and impaired word comprehension.

Mesulam (1982) introduced slowly progressive aphasia without dementia as a syndrome that maintains relatively isolated aphasia until the terminal stages of the disease and is mainly associated with neurodegeneration in left perisylvian regions. Five years later, he renamed this syndrome into primary progressive aphasia (PPA; Mesulam, 1987). Snowden, Goulding, and Neary (1989) proposed to distinguish between three subtypes of PPA: fluent progressive aphasia, non-fluent progressive aphasia, and a mixed subtype. These authors furthermore introduced the term semantic dementia to designate fluent progressive aphasia characterized by a

progressive breakdown in language and visual perception due to loss of semantic information and circumscribed cerebral atrophy in the temporal lobes (Snowden et al., 1989). Hodges, Patterson, Oxbury, and Funnell (1992) provided a comprehensive characterization of five case reports suffering from semantic dementia, and Grossman et al. (1996) described extensively four case reports of progressive nonfluent aphasia.

The Lund and Manchester Groups proposed the first general guidelines for the clinical diagnosis of frontotemporal dementia (FTD), mentioning PPA by referring the reader to single case studies for a more detailed description of PPA (Brun et al., 1994; Neary, Snowden, & Mann, 1993a, 1993b; Snowden, Neary, Mann, Goulding, & Testa, 1992). A consensus on more specific clinical and research diagnostic criteria for PPA was reached in 1998 (Neary et al., 1998). Here, the core diagnostic features for progressive nonfluent aphasia encompassed the insidious onset and gradual progression of the disease as well as nonfluent spontaneous speech with agrammatism, phonemic paraphasias, and/or anomia. The core diagnostic criteria for semantic dementia, on the other hand, included the insidious onset and gradual progression of the disease, progressive fluent empty spontaneous speech, loss of word meaning which becomes manifest by impaired naming and comprehension, semantic paraphasias and/or a perceptual disorder characterized by prosopagnosia (i.e., impaired recognition of identity of familiar faces) and/or associative agnosia (i.e., impaired recognition of object identity). Perceptual matching and drawing reproduction, preserved single-word repetition, and ability to read aloud and write to dictation orthographically regular words were assumed to be preserved in patients suffering from semantic dementia (Neary et al., 1998). In 2001, an international group of clinical and basic scientists reassessed the clinical criteria for FTD and proposed that a part of the patients suffering from FTD could be characterized by an early progressive change in language, characterized by problems with expression of language or severe naming difficulties and problems with word meaning (McKhann et al., 2001).

At the same time, Mesulam (2001) proposed to define PPA as a disease starting with anomia that progresses either into a) nonfluent language with phonemic paraphasia associated with atrophy and hypometabolism within left frontal and perisylvian atrophy or b) semantic memory loss associated with atrophy and hypometabolism within the left temporal lobe (Abe, Ukita, & Yanagihara, 1997; Mesulam, 2001). Mesulam (2001) furthermore proposed that language impairments should be the most important symptoms for at least two years and to refine the use of semantic dementia that had originally been adopted for patients showing a combination of verbal and visual processing deficits (e.g., Neary et al., 1998) to patients without visual processing deficits.

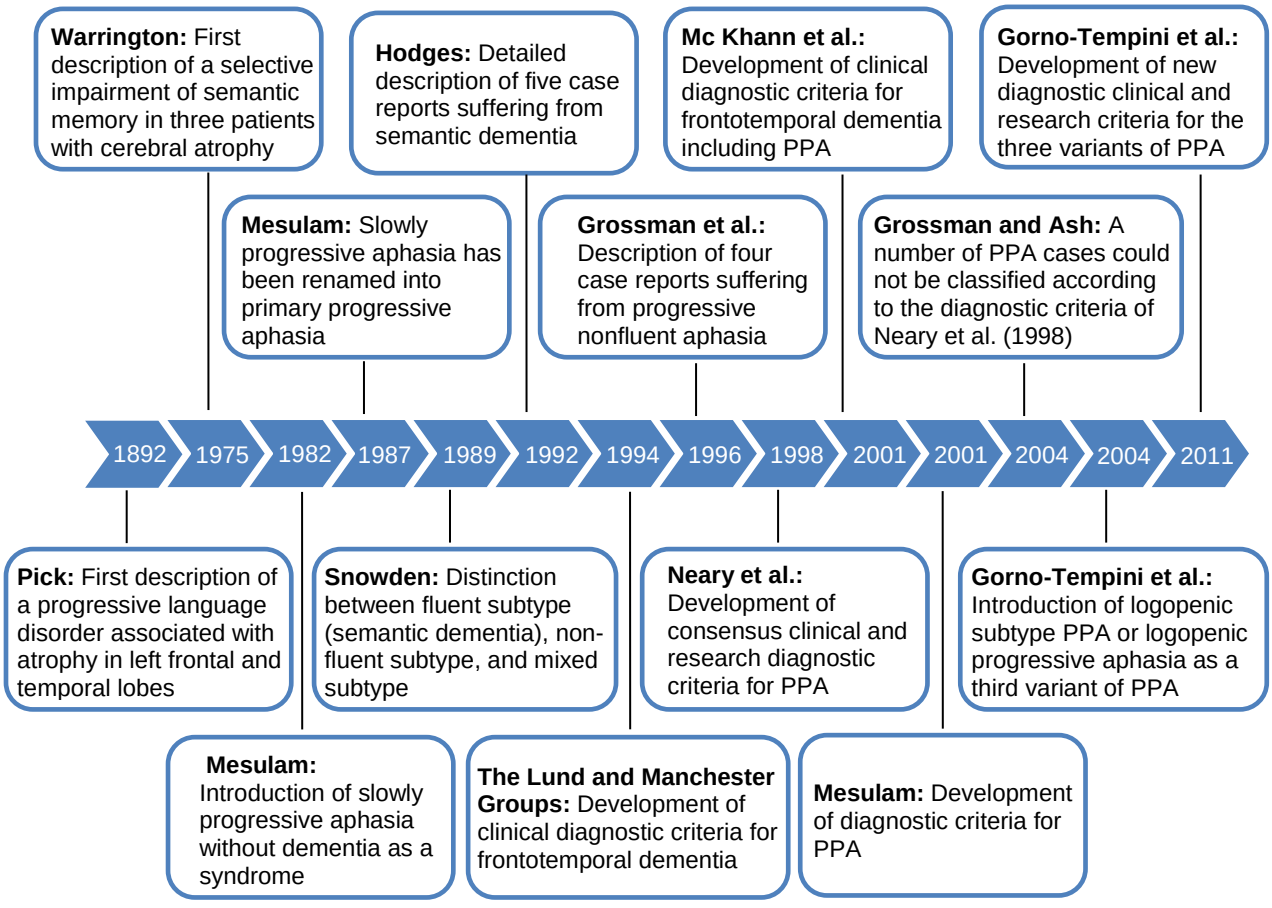

Figure 1: Timeline of the development of the terminology and diagnostic criteria for primary progressive aphasia.

For two decades, researchers and clinicians have been using the diagnostic criteria for FTD (Brun et al., 1994; McKhann et al., 2001) to generally diagnose a patient as

suffering from PPA and the criteria of Neary et al. (1998) to further specify the diagnosis as progressive nonfluent aphasia or semantic dementia. However, there were a number of PPA cases that could not be classified according to the criteria of Neary and colleagues (Gorno-Tempini et al., 2004; Grossman & Ash, 2004; Neary et al., 1998). Given that many of these unclassifiable cases of PPA showed a similar pattern of symptoms, Gorno-Tempini et al. (2004) proposed to introduce a third subtype for PPA named logopenic progressive aphasia or logopenic variant PPA. Logopenic variant PPA is mainly characterized by impaired single-word retrieval in spontaneous speech and naming, impaired repetition of sentences and phrases, phonologic errors in spontaneous speech and naming, spared single-word comprehension and object knowledge, spared motor speech, and absence of frank agrammatism (Gorno-Tempini et al., 2008; Gorno-Tempini et al., 2004). In response to these new insights into PPA, an international consortium proposed new diagnostic clinical and research criteria in 2011 (Gorno-Tempini et al., 2011). The chronological development of the terminology and diagnostic criteria for PPA are shown in Figure 1.

According to the revised diagnostic clinical and research criteria (Gorno-Tempini et al., 2011), a patient first needs to meet the basic criteria for PPA in general (i.e., prominent, isolated language disorder during the initial phase of the disease) as proposed by Mesulam in 2001. Thereafter, the patient can be further diagnosed more specifically as suffering from one of the three subtypes of PPA. In order to standardize the terminology for PPA, it has been proposed to use the terms nonfluent/agrammatic variant PPA (nfvPPA), semantic variant PPA (svPPA), and logopenic variant PPA (lvPPA). In the following, we will apply this terminology. Note that the abbreviated form nonfluent variant PPA instead of nonfluent/agrammatic variant PPA will be used to increase the readability. The current diagnosis of the variants of PPA is threefold, designating the probability of the diagnosis: clinical diagnosis, imaging-supported diagnosis, and diagnosis with definite pathology (Gorno-Tempini et al., 2011; see Table 1).

Table 1

Current diagnostic clinical and research criteria for primary progressive aphasia (adapted from Gorno-Tempini et al., 2011)

nonfluent/agrammatic variant PPA	semantic variant PPA	logopenic variant PPA
Clinical diagnosis At least one of the following core features: - Agrammatism in language production - Effortful, halting speech with inconsistent speech sound errors and distortions (apraxia of speech) At least 2 of the following other features: - Impaired comprehension of syntactically complex sentences - Spared single-word comprehension - Spared object knowledge	*Clinical diagnosis* Both of the following core features: - Impaired confrontation naming - Impaired single-word comprehension At least 3 of the following other features: - Impaired object knowledge, particularly for low frequency or low-familiarity items - Surface dyslexia or dysgraphia - Spared repetition - Spared speech production (grammar and motor speech)	*Clinical diagnosis* Both of the following core features: - Impaired single-word retrieval in spontaneous speech and naming - Impaired repetition of sentences and phrases At least 3 of the following other features: - Speech (phonologic) errors in spontaneous speech and naming - Spared single-word comprehension and object knowledge - Spared motor speech - Absence of frank agrammatism
Imaging-supported diagnosis Both of the following criteria: - Clinical diagnosis of nonfluent/agrammatic variant PPA - Imaging must show: Predominant left posterior fronto-insular atrophy on MRI or hypoperfusion or hypometabolism on PET/SPECT	*Imaging-supported diagnosis* Both of the following criteria: - Clinical diagnosis of semantic variant PPA - Imaging must show: Predominant anterior temporal lobe atrophy on MRI or hypoperfusion or hypometabolism on PET/SPECT	*Imaging-supported diagnosis* Both criteria must be present: - Clinical diagnosis of logopenic variant PPA - Imaging must show: Predominant left posterior perisylvian or parietal atrophy on MRI or hypoperfusion or hypometabolism on PET/SPECT
Diagnosis with definite pathology Clinical diagnosis of nonfluent/ agrammatic variant PPA and histo-pathologic evidence of a specific neurodegenerative pathology (e.g., FTLD-tau, FTLD-TDP, AD, other) or presence of a known pathogenic mutation	*Diagnosis with definite pathology* Clinical diagnosis of semantic variant PPA and histopathologic evidence of a specific neurodegenerative pathology (e.g., FTLD-tau, FTLD-TDP, AD, other) or presence of a known pathogenic mutation	*Diagnosis with definite pathology* Clinical diagnosis of logopenic variant PPA and histopathologic evidence of a specific neurodegenerative pathology (e.g., AD, FTLD-tau, FTLD-TDP, other) or presence of a known pathogenic mutation

Note. AD Alzheimer's disease; FTLD frontotemporal lobar degeneration; MRI magnetic resonance imaging; PET positron emission tomography; PPA primary progressive aphasia; SPECT single photon emission computed tomography; TDP TAR DNA-binding protein 43

The current diagnostic criteria for PPA variants with definite pathology are relatively unspecific because there is no straightforward correspondence between any variant of PPA and a given pathology (Gorno-Tempini et al., 2011). In most cases, the pathology is either FTLD (predominantly FTLD-TDP or FTLD-tau) or an atypical form of Alzheimer's disease (AD; Gorno-Tempini et al., 2011; Grossman, 2014; Mesulam et al., 2014). FTLD-TDP refers to an accumulation in central nervous system neurons of transactive response DNA-binding protein of ~ 43kD, known as TDP-43 and FTLD-tau refers to an accumulation of the microtubule-associated protein tau (MAPT) in neurons and glia (Grossman, 2014). FTLD pathology can arise either sporadically (most cases) or autosomal dominantly inherited with mutations most commonly in the progranulin (GRN) gene (associated with FTLD-TDP pathology), the MAPT gene (associated with FTLD-tau pathology), or the chromosome 9 open reading frame 72 (C9orf72) gene (associated with FTLD-TDP pathology; Grossman, 2014). Regardless whether sporadic or autosomal dominantly inherited, studies on clinical-pathologic correlations in PPA suggest that nfvPPA might be rather related to tau-positive pathology, while svPPA might be rather related to TDP-43-positive pathology (Josephs et al., 2006; Mesulam et al., 2014; Mesulam et al., 2008). LvPPA has been proposed to be rather related to AD pathology (Mesulam et al., 2014; Mesulam et al., 2008; Rabinovici et al., 2008). However, there is no one-to-one correspondence between a PPA variant and a given pathology as each PPA variant has been related to several different pathologies (Gorno-Tempini et al., 2011; Mesulam et al., 2014).

1.2 Risk factors for primary progressive aphasia

Identical underlying pathology can thus lead to different syndromes (e.g., AD, PPA or bvFTD; Gorno-Tempini et al., 2011; Mesulam et al., 2014). It has been proposed that there might exist susceptibility factors that interact with the neurodegenerative disease to determine its primary anatomical location (Rogalski, Weintraub, & Mesulam, 2013). Except for a high prevalence of learning disabilities (especially dyslexia) in the personal history of PPA patients (regardless of the underlying pathology or PPA variant) or in the history of their first-degree relatives, there is however little evidence for the existence of susceptibility factors until now (Rogalski et al., 2013). One study showed that vasectomy rates were significantly higher in

PPA patients (40 %) as compared to healthy controls (16 %) (Weintraub et al., 2006). Weintraub et al. (2006) speculated that vasectomy might induce an immune response to sperm, akin to paraneoplastic encephalitis, which somehow interacts with the primary neurodegenerative disease to make the language network the most important locus of neurosynaptic loss. However, there is currently no evidence of an overt immune-mediated neuropathology in PPA. Therefore, this suggestion remains highly speculative (Rogalski et al., 2013).

1.3 Incidence and prevalence of primary progressive aphasia

During the last decade, several population studies investigated the prevalence and incidence of FTD patients in Italy, the Netherlands, Spain, Finland, the United Kingdom, Canada, the United States, Australia, Korea, China, Japan, and India (Kim et al., 2014; Luukkainen, Bloigu, Moilanen, & Remes, 2015; Riedl, Mackenzie, Förstl, Kurz, & Diehl-Schmid, 2014; Withall, Draper, Seeher, & Brodaty, 2014). LvPPA is only rarely included in population studies on FTD, because this syndrome has rather been related to AD pathology (Mesulam et al., 2014; Mesulam et al., 2008; Rabinovici et al., 2008).

The estimates for the prevalence of FTD range from 2/100,000 to 31/100,000 (Riedl et al., 2014). This wide variation is due to several reasons. Many population studies report point prevalence estimates, while some studies report (cumulative) period prevalence estimates. Another reason is that different studies considered different age ranges and partly also different diagnostic criteria (Riedl et al., 2014). Unfortunately, most population studies report prevalence and/or incidence estimates across FTD syndromes and there are only a few studies which actually included PPA patients. In studies, where PPA patients were included, the estimated point prevalence of FTD is estimated at 15-22 per 100,000 in the population between 45 and 65 years (Borroni et al., 2015; Harvey, Skelton-Robinson, & Rossor, 2003; Knopman & Roberts, 2011; Onyike & Diehl-Schmid, 2013; Ratnavalli, Brayne, Dawson, & Hodges, 2002; Riedl et al., 2014). This point prevalence corresponds approximately to the prevalence of AD in this age group (Onyike & Diehl-Schmid, 2013; Riedl et al., 2014). The incidence for FTD (including PPA patients) estimates

for this age group ranged from 2.7-4.1 per 100,000 in the population (Onyike & Diehl-Schmid, 2013).

Until now, there are however no community-based prevalence and incidence estimates for the three PPA variants available (Grossman, 2014). Based on autopsy-proven cases, however, it has been estimated that about 40 % of the patients with FTLD pathology have PPA (Grossman, 2014). BvFTD is thus almost three to four times as common as one of the three PPA variants (Hogan et al., 2016; Knopman & Roberts, 2011). This suggests a prevalence for PPA of 1.1-6.0 per 100,000 in the population with FTLD pathology and additional cases with AD pathology (Grossman, 2014). The estimated incidence for PPA is approximately 0.88-1.4 per 100,000 in the population with FTLD pathology. Men and women seem to be equally affected (Hogan et al., 2016; Riedl et al., 2014) and the mean age of onset is approximately 58 years with later peak ages at initial diagnosis for nfvPPA (70-79 years; Coyle-Gilchrist et al., 2016; Grossman, 2014; Riedl et al., 2014). The survival time after initial diagnosis varies between 3-14 years with svPPA patients surviving a little bit longer (median of 12 years) than nfvPPA (median of 9 years). For lvPPA, there are currently no data on gender distribution, age at initial diagnosis and average survival time available. Due to its rareness, PPA has been declared an orphan disease (Orpha number ORPHA282, http://www.orpha.net).

1.4 German and Italian Consortium of Frontotemporal Lobar Degeneration

In order to gain more insight into prevalence and incidence estimates of the different clinical syndromes of frontotemporal lobar degeneration (FTLD), several national and international consortia have been established during the last years. Examples include the Italian FTD Network under the aegis of the Italian Neurological Society for Dementia (SINDEM) which includes 85 study centers (Borroni et al., 2015), the longitudinal study on FTD of the Clinical Research Center for Dementia of South Korea including 16 centers (Kim et al., 2014), or the German and Italian Research Consortium of FTLD (Otto et al., 2011).

The German and Italian Research Consortium of FTLD encompasses currently 12 centers in Germany (see Figure 2) and 11 centers in Italy (www.ftld.de). All centers use a common study protocol involving medical assessment, neuropsychological and language assessment, MRI (and PET if available) scanning, as well as blood sampling. All instructions and materials are available in German and Italian language. The aims of this consortium besides collecting data on epidemiology, are to improve disease recognition along with its management, monitor disease progression, find early disease markers and to develop and evaluate possible therapeutic approaches (Otto et al., 2011)

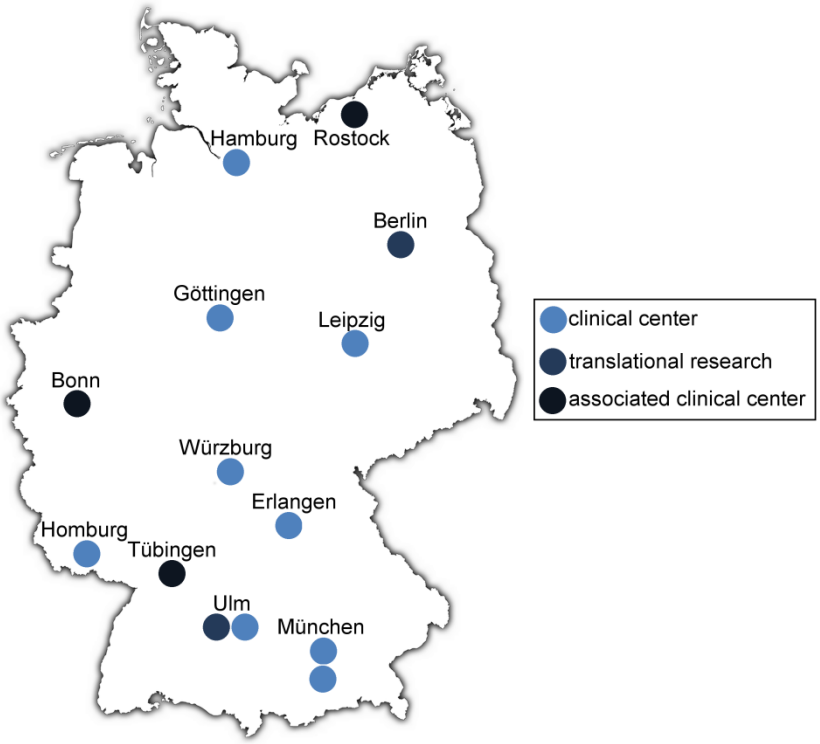

Figure 2: Sites of the German study centers involved in the German and Italian Research Consortium for Frontotemporal Lobar Degeneration (modified from http://www.ftld.de).

1.5 Therapeutic approaches for primary progressive aphasia

There are a few studies that report minor improvements of confrontation naming immediately following speech therapy on word-finding abilities in patients with PPA and two studies reported successful short-term outcomes of treatment of written language (Riedl et al., 2014; Tippett, Hillis, & Tsapkini, 2015). A few studies also

showed short-term improvement of language abilities when repetitive transcranial magnetic stimulation or transcranial direct current stimulation was applied while participants were performing a language task. Note however that most intervention studies were case reports or included only a small number of participants (Tippett et al., 2015) and that there is no evidence for the sustainability and generalizability of any of these treatments (Riedl et al., 2014; Tippett et al., 2015). Symptoms in lvPPA might be reduced with medications that have been shown to reduce or delay the progression of symptoms in AD (acetylcholinesterase inhibitors as donepezil, rivastigmine, or galantamine and/or N-Methyl-D-Aspartat glutamate receptor antagonists as memantine) as most lvPPA patients show underlying AD pathology (see section 1.1). This assumption needs however still to be empirically supported by large-scale randomized clinical trials (Otto et al., 2011; Tippett et al., 2015). Selective serotonin reuptake inhibitors such as citalopram or sertraline have been shown to reduce behavioral disturbances such as obsessive-compulsive behavior, restlessness, eating disorders or disinhibition (Manoochehri & Huey, 2012). Therefore, clinicians are currently advised to prescribe selective serotonin reuptake inhibitors to PPA patients who show additionally symptoms that are rather prototypical for bvFTD (Manoochehri & Huey, 2012; Otto et al., 2011). All in all, there are currently no recommended medications for the treatment of PPA symptoms.

1.6 Neuroimaging

1.6.1 Positron emission tomography

In positron emission tomography (PET), the patient receives an intravenous injection of a radiotracer that emits a positron (Berns, 1999; Small et al., 2008). When the positron encounters an electron, they annihilate each other and their collective energy is transformed into two gamma photons that are emitted in opposite directions and can be recorded by detectors that are 180° apart from each other. PET scanners are equipped with a ring of detectors that determine the line along which the annihilation occurs in order to reconstruct the 3D localization of the physiological process of interest with a spatial resolution of 3-5 mm. A physiological process that is often measured using PET is local glucose metabolism which changes in response to

synaptic activity and depends on cell density. PET is thus well suited to detect neurodegenerative diseases and monitor their disease progression. The most common radioactive tracer used to measure local glucose metabolism in the brain is fluoro-deoxyglucose (^{18}FDG) which leads to the general use of the term FDG-PET to designate this neuroimaging method (Berns, 1999; Small et al., 2008).

1.6.2 Structural magnetic resonance imaging

Another neuroimaging method that is well suited to detect neurodegenerative diseases and monitor their progression is structural MRI. Structural MRI has some advantages over FDG-PET: it does not require the injection of a radioactive tracer (and is thus not invasive) and it provides images with a high resolution of ~1 mm (e.g., Berns, 1999).

The magnetic resonance imaging technique is based on an intrinsic property of hydrogen protons, namely their spin (Berns, 1999; Small et al., 2008). Normally, the spin axes are oriented randomly, but when a strong external magnetic field (e.g., MRI scanner) is applied, the axes align themselves in the direction of that field. This leads to a measurable magnetization along the scanner magnet. The time to reach this magnetization is called T1. Similar to a spinning top, the single hydrogen protons do not spin exactly along a single axis, but instead, there is a slow wobble called precession. In MRI, after the hydrogen protons' spins are aligned, a radiofrequency pulse at the precession frequency of the hydrogen protons is applied to knock the precession axis out of its original orientation. If enough protons get bumped, the tissue acquires a slight magnetization perpendicular to the external field which is called transverse magnetization. After switching off the radiofrequency pulse, the transverse magnetization decays. Different processes reflect the decay of the induced transverse magnetization, called T1-, T2- and T2*-relaxation. The duration of these different relaxation processes depends on the molecular environment of the protons, which allows differentiating between grey matter, white matter, and cerebrospinal fluid. By repeating the process of excitation and relaxation several times and varying the magnetic field gradients, 3D images of the brain can be encoded and reconstructed.

Before structural 3D images of the brain (acquired using PET or MRI) can be used in group-level analyses, they need to be preprocessed which includes realignment of the single slices, coregistration and normalization to a standard brain template, and segmentation of the different tissue types (grey matter, white matter, and cerebrospinal fluid) as well as smoothing by a Gaussian kernel (e.g., Ashburner & Friston, 2000, see section 3.2.3.2).

1.7 Aim of this thesis

For two decades, researchers and clinicians have been using the diagnostic criteria for FTD (Brun et al., 1994; McKhann et al., 2001) to generally diagnose a patient as suffering from PPA and the criteria of Neary et al. (1998) to further specify the diagnosis as progressive nonfluent aphasia or semantic dementia. However, there were a number of PPA cases that could not be classified according to the criteria of Neary and colleagues (Gorno-Tempini et al., 2004; Grossman & Ash, 2004; Neary et al., 1998), which led to a revision of the diagnostic clinical and research criteria for PPA (Gorno-Tempini et al., 2011). The revised criteria encompass three PPA variants (svPPA, nfvPPA, and lvPPA) with three stages characterized by increasing evidence: clinical diagnosis, imaging-supported diagnosis, and diagnosis with definite pathology. As compared to the previous diagnostic criteria, more emphasis is placed on imaging markers as supportive features. These imaging criteria were however proposed based on a purely qualitative evaluation of the literature and have not been validated so far.

The aim of this thesis was to evaluate the validity of the new diagnostic imaging criteria for PPA variants (first study) and to investigate the usefulness of these imaging criteria for the individual diagnosis of PPA patients in clinical routine (second study).

In the first study (Bisenius et al., 2016), we raised the question whether the proposed diagnostic imaging criteria indeed represent subtype-specific prototypical atrophic networks for PPA variants (chapter 2). In order to address this question, we provided a quantitative evaluation (meta-analyses) of all currently available imaging studies on PPA. We hypothesized to find specific atrophic networks for each of the PPA variants

that are in line with the current diagnostic imaging criteria. Furthermore, we raised the question whether the proposed imaging criteria apply similarly to different imaging modalities (MRI and PET) as suggested in the current diagnostic criteria for PPA (Gorno-Tempini et al., 2011). Given that for other types of dementia (e.g., AD and bvFTD), separate diagnostic imaging criteria have been proposed for MRI and PET scans (Dubois et al., 2007; Schroeter et al., 2014), we hypothesized that separate imaging modality-specific criteria might also apply for PPA.

In the second study (Bisenius et al., 2017), we first addressed the question whether (whole brain) structural MRI scans provide indeed useful information for the correct individual diagnosis of PPA patients (chapter 3). We were also interested in finding out which brain regions would be the most indicative for the correct diagnosis of PPA patients. We hypothesized that, when considering the whole brain MRI scan, the most important brain regions for the correct individual diagnosis of PPA patients would correspond to brain regions that are largely atrophied in these patients. In a second step, we raised the question whether focusing exclusively on the prototypical atrophic networks for PPA revealed by the meta-analyses reported in the first study, would enhance the diagnostic value of MRI scans for the correct diagnosis of PPA patients. These prototypical atrophic networks constitute in a sense a quantification of the current imaging criteria for PPA. Therefore, we hypothesized that considering only these prototypical atrophic networks would further enhance the diagnostic value of MRI scans (and thus provide empirical support for the usefulness of the proposed diagnostic imaging criteria for PPA in clinical routine).

2 Validating New Diagnostic Imaging Criteria for Primary Progressive Aphasia via ALE Meta-Analyses

2.1 Introduction

Primary progressive aphasia (PPA) subsumes three gradually progressive language disorders, namely its semantic variant (svPPA) or semantic dementia, the nonfluent variant (nfvPPA) or progressive nonfluent aphasia, and the logopenic variant (lvPPA) or logopenic progressive aphasia (Gorno-Tempini et al., 2008; Gorno-Tempini et al., 2004; Gorno-Tempini et al., 2011; Mesulam, 1982; Neary et al., 1998). Recently, an international consortium has refined the diagnostic clinical and imaging criteria for PPA variants (Gorno-Tempini et al., 2011). The imaging criteria include changes of structure, metabolism or perfusion in the anterior (ventral and lateral) temporal lobe for svPPA, in left posterior fronto-insular regions (inferior frontal gyrus, insula, premotor, and supplementary motor areas) for nfvPPA, and in left posterior perisylvian or parietal areas (posterior parietal, supramarginal, and angular gyri) for lvPPA (Gorno-Tempini et al., 2011).

Here, we used anatomical likelihood estimation (ALE) meta-analyses to validate the current imaging criteria with higher statistical power than can be provided by single studies (Chein, Fissell, Jacobs, & Fiez, 2002; Turkeltaub, Eden, Jones, & Zeffiro, 2002). ALE meta-analyses have been applied to investigate neurodegenerative diseases like mild cognitive impairment, AD, or FTD (Schroeter, Raczka, Neumann, & von Cramon, 2008; Schroeter, Stein, Maslowski, & Neumann, 2009; Yang, Pan, Song, Huang, et al., 2012; Yang, Pan, Song, & Shang, 2012). We wanted to identify the neural networks affected in the three PPA variants and examine their regional specificity in subtraction and conjunction analyses identifying specific and overlapping networks, respectively. It has been proposed that different diagnostic imaging criteria should be applied for AD and bvFTD to different imaging modalities – FDG-PET visualizing hypometabolism, MRI showing atrophy, and perfusion changes

(Dubois et al., 2007; Schroeter et al., 2014). Accordingly, we hypothesized that the new diagnostic imaging criteria for PPA should be differentiated for MRI and PET.

2.2 Materials and methods

2.2.1 General study selection criteria

The present work was done following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines (Moher, Liberati, Tetzlaff, & Altman, 2010). PubMed was queried for abstracts published between January 1990/April 2012 containing following keywords: (primary progressive aphasia OR progressive nonfluent aphasia OR semantic dementia OR logopenic progressive aphasia) AND (positron emission tomography OR PET OR magnetic resonance imaging OR MRI). Following inclusion criteria were applied: peer-reviewed original studies, patients classified according to internationally recognized diagnostic criteria (Brun et al., 1994; Gorno-Tempini et al., 2011; McKhann et al., 2001; Neary et al., 1998), age-matched healthy controls, whole-brain analyses reporting 3D-coordinates of atrophy/hypometabolism maxima in standardized stereotaxic space, Talairach atlas or Montreal Neurological Institute (MNI) templates. Studies reporting only regions-of-interest (ROI) analyses were excluded to avoid a potential publication bias. When studies fulfilled the inclusion criteria, but no coordinates were reported, authors were asked to provide coordinates.

2.2.2 Anatomical likelihood estimation meta-analysis method

ALE meta-analyses were computed within BrainMap Ginger ALE 2.1.1 (online at http://www.brainmap.org/ALE; Eickhoff, Bzdok, Laird, Kurth, & Fox, 2012; Eickhoff et al., 2009; Laird et al., 2005; Turkeltaub et al., 2002). Before data analysis, coordinates in Talairach space were converted into MNI coordinate space using the tal2icbm transform (Lancaster et al., 2007) except for one study (Perneczky, Diehl-Schmid, Pohl, Drzezga, & Kurz, 2007) where we used the tal2mni transform (Brett, Johnsrude, & Owen, 2002) because these authors transformed data via mni2tal transform (Brett et al., 2002) into Talairach space.

In the ALE method, foci are modeled as 3D Gaussian probability distributions with variable full width at half maximum that takes into account between-subject and between-template variance (Eickhoff et al., 2009). We computed separate meta-analyses for each of the three PPA variants at a false discovery rate (FDR) corrected significance level of $p < 0.05$. Cluster inference thresholds were chosen to exceed the number of voxels corresponding to 5 % possible false positives.

We additionally computed subtraction analyses (Eickhoff et al., 2011) between the different meta-analyses on svPPA (MRI vs. PET) and the different variants of PPA. Here, the ALE maps ($p < 0.05$, FDR corrected) resulting from the separate meta-analyses are subtracted from each other and compared against a null-distribution of differences in ALE scores (5000 permutations). The cluster inference threshold for the subtraction analyses was set to 200 mm^3 ($p < 0.05$, uncorrected; Huang et al., 2012). Conjunctions were assessed by a minimum statistic of images containing significant results from the individual meta-analyses (Nichols, Brett, Andersson, Wager, & Poline, 2005).

2.3 Results

2.3.1 Identified studies

Out of 658 originally identified studies, 478 studies had to be excluded due to none-relevant topics and 150 studies for specific reasons (see Supplementary Figure A). The final pool consisted of 30 studies (20 MRI, seven FDG-PET, three MRI & FDG-PET) fulfilling the inclusion criteria. As some studies investigated more than one variant of PPA, the search resulted finally in 22 studies for semantic variant PPA (15 MRI, six FDG-PET, one MRI & FDG-PET), 14 for nfvPPA (11 MRI, three FDG-PET), and six for lvPPA (six MRI, zero FDG-PET) including 396 patients. The one study on svPPA that reported both MRI and FDG-PET coordinates (Desgranges et al., 2007) was counted as one MRI and one FDG-PET study. Age, duration, and severity of disease as measured with the Mini-Mental State Examination did not differ between patients of the different PPA variants (Table 2). Detailed information for all included studies is available in the supplement (Supplementary Table A.1 and Supplementary References A).

Table 2

Clinical characteristics of the patient groups

	svPPA MRI	svPPA PET	nfvPPA MRI	nfvPPA PET	lvPPA MRI	ANOVA (df, F, *p*)
Number of studies/foci	16/177	7/36	11/101	3/26	6/70	
Number of patients	169	57	93	26	51	
Age	64.66 ± 2.91	64.29 ± 1.57	66.64 ± 2.32	67.90 ± 2.57	64.55 ± 4.47	(4,41), 1.32, 0.28
Disease duration	4.87 ± 1.64	3.82 ± 0.47	4.03 ± 1.22	3.30 ± 0.14	3.73 ± 1.30	(4,31), 1.86, 0.14
MMSE	23.12 ± 2.18	23.10 ± 2.51	23.20 ± 3.44	21.34 ± 2.15	21.38 ± 1.15	(4,39), 0.89, 0.48

Note. lvPPA logopenic variant PPA, MMSE Mini-Mental State Examination, MRI magnetic resonance imaging, nfvPPA nonfluent variant PPA, PET positron emission tomography, svPPA semantic variant PPA. Age, disease duration, and MMSE are indicated as mean±standard deviation. Age and disease duration are indicated in years.

2.3.2 Separate meta-analyses for the different variants of primary progressive aphasia

2.3.2.1 Semantic variant PPA

MRI: As illustrated in dark green color in Figure 3 on the top, the meta-analysis on svPPA across the 16 MRI studies including 177 foci and 169 subjects yielded significant clusters of atrophy bilaterally in the inferior, middle, and superior temporal gyri, fusiform gyri, hippocampus, parahippocampal gyri, and right amygdala. Details on the respective MNI coordinates, cluster sizes, ALE values, and Brodmann Areas (Bas) are given in Table 3.

FDG-PET: The meta-analysis on svPPA across the seven FDG-PET studies encompassed 36 foci and 70 subjects. As illustrated in light-green in Figure 3, second row, consistent hypometabolism was found bilaterally in the anterior inferior temporal gyri, the left fusiform gyrus, posterior midcingulate gyrus, corpus callosum, and left medial thalamus (for more details, see Table 3).

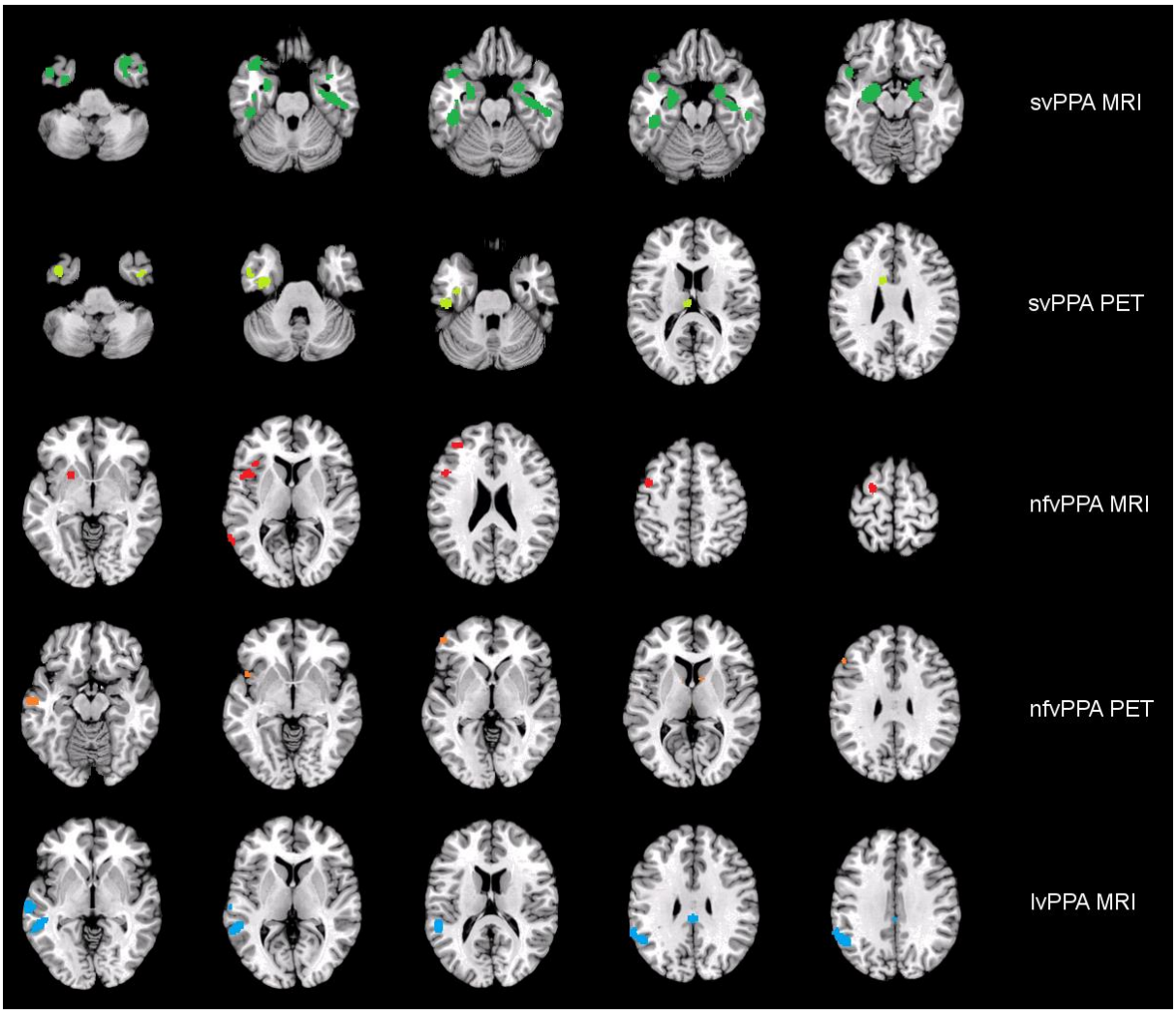

Figure 3: Results of the anatomical likelihood estimation (ALE) meta-analyses for each of the different variants of primary progressive aphasia. Atrophy was measured with magnetic resonance imaging (MRI), glucose hypometabolism with fluorodeoxyglucose positron emission tomography (PET). Logopenic variant PPA (lvPPA), nonfluent variant PPA (nfvPPA), semantic variant PPA (svPPA). False discovery rate (FDR) corrected $p < 0.05$. Left side is left.

Table 3

Results of the anatomical likelihood estimation meta-analyses on semantic variant PPA, nonfluent variant PPA, and logopenic variant PPA

Region	Lat.	Bas	MNI			Volume	ALE
			x	y	z	(mm3)	
svPPA MRI							
Inferior, middle, & superior temporal gyri/fusiform gyrus/hippocampus/ parahippocampal gyrus/amygdala	R	20/21/ 36/38	24	0	-22	11312	0.0202
Hippocampus/parahippocampal gyrus/fusiform gyrus	L	36	-26	-12	-16	6744	0.0235
Superior temporal gyrus	L	38	-38	16	-28	2568	0.0172
Inferior & middle temporal gyrus	L	21/38	-46	2	-44	1552	0.0167
Fusiform gyrus	L	20	-44	-32	-24	1536	0.0227
svPPA PET							
Inferior temporal gyrus/fusiform gyrus	L	20/21	-38	-12	-34	1976	0.0127
Inferior temporal gyrus	L	20	-48	-26	-30	520	0.0108
Inferior temporal gyrus	R	20	42	-2	-42	448	0.0076
Inferior temporal gyrus	L	38	-40	2	-46	424	0.0106
Posterior midcingulate gyrus/corpus callosum	L	24	-10	6	26	424	0.0083
Thalamus	L		-6	-20	14	376	0.0080
nfvPPA MRI							
Insula/inferior frontal gyrus	L	13	-44	12	2	1360	0.0107
Middle & superior temporal gyri	L	21	-62	-58	6	624	0.0109
Inferior & middle frontal gyrus	L	9/10	-34	46	20	552	0.0097
Inferior frontal gyrus	L		-48	16	24	544	0.0131
Superior frontal gyrus	L	6	-22	-4	64	448	0.0102
Putamen	L		-22	10	-6	424	0.0110
Middle frontal gyrus/precentral gyrus	L	6	-42	2	50	424	0.0115
nfvPPA PET							
Superior temporal gyrus	L	21	-62	-14	-16	744	0.0089
Insula/inferior frontal gyrus, pars opercularis	L	13	-46	12	-6	160	0.0067
Lateral orbital gyrus	L	46	-50	46	-2	160	0.0073
Middle temporal gyrus	L		-50	-28	-12	88	0.0068
Nucleus caudatus	R		10	6	4	88	0.0068
Thalamus	L		-2	-22	6	88	0.0068
Nucleus caudatus	L	22	-10	2	6	88	0.0068
Middle frontal gyrus	L	9	-52	28	28	88	0.0068
lvPPA MRI							
Middle & superior temporal gyri/parallel sulcus	L	22/41	-54	-38	14	3344	0.0120
Supramarginal gyrus	L	39/40	-54	-54	32	2184	0.0136
Superior temporal gyrus	L	21	-66	-22	-4	1192	0.0135
Dorsal posterior cingulate gyrus	L	23	0	-32	28	488	0.0117

Note. ALE anatomical likelihood estimation, Bas Brodmann areas, FDG-PET fluorodeoxyglucose positron emission tomography, Lat. Lateralization, L left, lvPPA logopenic variant PPA, MNI Montreal Neurological Institute, MRI magnetic resonance imaging, nfvPPA nonfluent variant PPA, R right, svPPA semantic variant PPA.

MRI & FDG-PET: The results of both imaging meta-analyses on svPPA were projected together onto the same MNI template, which revealed only small conjunctions between MRI and FDG-PET studies in the left inferior and middle temporal gyrus (see Figure 4 on the top). To validate the specificity between imaging modalities, we conducted additionally subtraction analyses between both meta-analyses on svPPA. As shown in Figure 4 in the middle upper part, right inferior, middle and superior temporal gyri, right fusiform gyrus, and bilateral hippocampus/parahippocampal gyri/amygdalae were specifically related to atrophy as measured with MRI, while left thalamus and left inferior temporal gyrus/fusiform gyrus were more specifically related to hypometabolism as measured by FDG-PET. A detailed overview is given in Supplementary Table A.2.

2.3.2.2 Progressive nonfluent aphasia

MRI: An overview of the results for nfvPPA is given in Table 3 and the relevant clusters are depicted in red in Figure 3, third row. The meta-analysis on nfvPPA across the 11 MRI studies (101 foci, 90 subjects) revealed clusters of significant atrophy solely in the left hemisphere, in particular in the putamen, anterior and middle insula, inferior, middle, and superior frontal gyri, as well as middle and superior temporal gyri. This result was in essence replicated in an analysis including only the seven studies that explicitly excluded subjects with lvPPA.

FDG-PET: As illustrated in orange color in Figure 4, fourth row, the meta-analysis on nfvPPA across the three PET studies including 26 foci and 26 subjects yielded significant clusters of hypometabolism bilaterally in the caudate nuclei as well as in the left hemisphere in the thalamus, middle and superior temporal gyri, insula/inferior frontal gyrus, pars opercularis, lateral orbital gyrus, and middle frontal gyrus.

MRI & FDG-PET: The results of both imaging meta-analyses on nfvPPA were projected together onto the same MNI template to visualize possible conjunct atrophy and hypometabolism to identify common networks. As shown in Figure 4 on the bottom, the results of both meta-analyses were disjunct. Note however that due to the small number of studies in the meta-analysis on nfvPPA across PET studies, no subtraction analysis was performed.

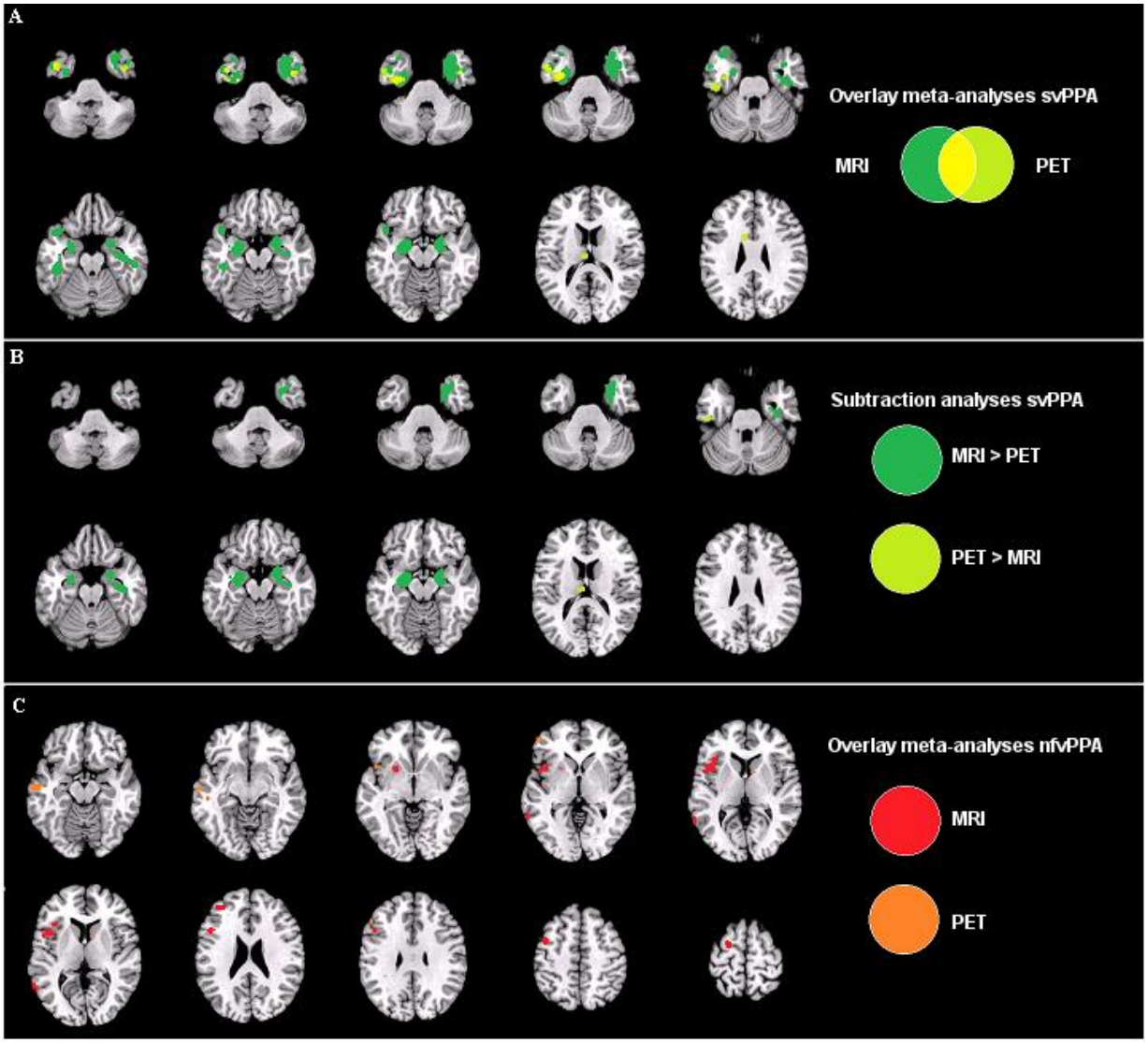

Figure 4: Comparison between the anatomical likelihood estimation (ALE) meta-analyses across different imaging modalities for semantic variant PPA (svPPA) and nonfluent variant PPA (nfvPPA) to identify method-specific and -common neural networks. Conjunction/overlap between atrophy (magnetic resonance imaging, MRI), and glucose hypometabolism (fluorodeoxyglucose positron emission tomography, PET) (A) in svPPA, and (C) in nfvPPA. (B) Results of the subtraction analysis between both meta-analyses on svPPA. False discovery rate (FDR) corrected $p < 0.05$. Left side is left.

2.3.2.3 Logopenic progressive aphasia

MRI: As illustrated in blue color in Figure 3 on the bottom, the meta-analysis on lvPPA (6 MRI studies) encompassing 70 foci and 58 subjects yielded significant clusters of atrophy exclusively in the left hemisphere in middle and superior temporal gyri, parallel sulcus, supramarginal gyrus, superior temporal gyrus, and dorsal posterior cingulate gyrus. The respective MNI coordinates, cluster sizes, ALE values

and Bas are shown in Table 3. For FDG-PET, we did not find any study in the literature investigating lvPPA.

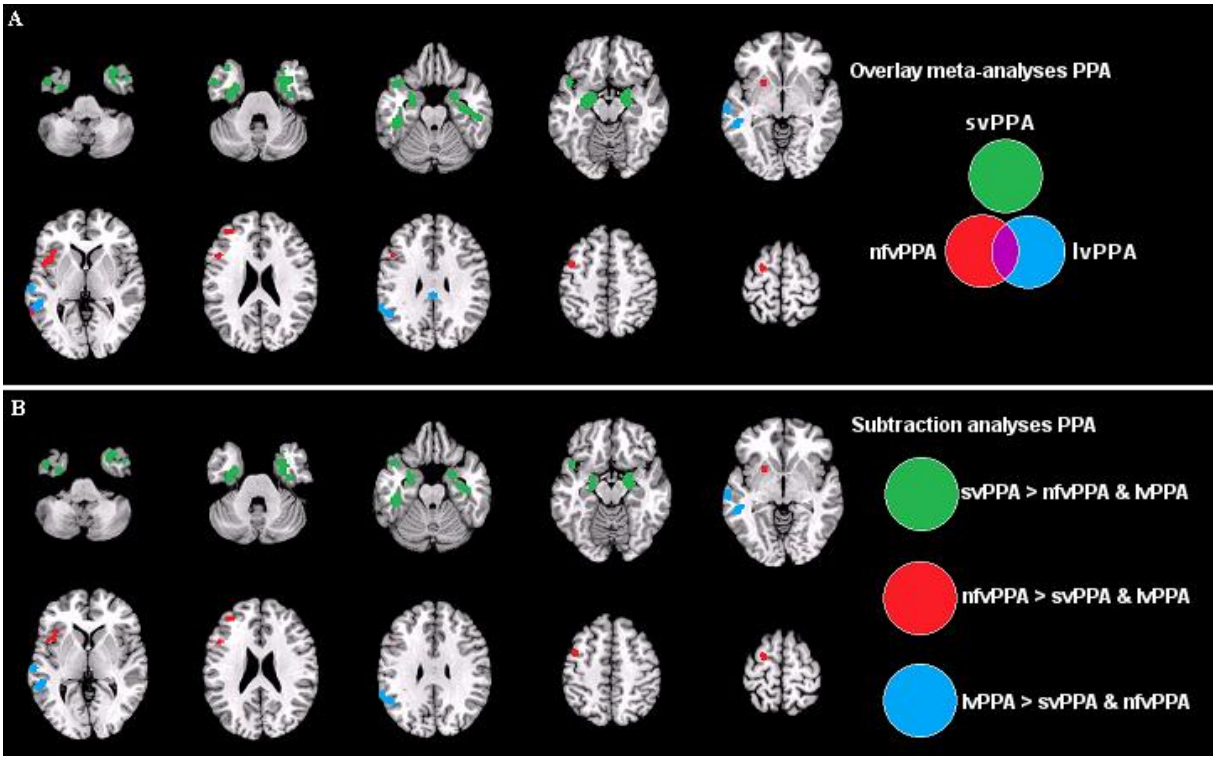

Figure 5: Comparison between the meta-analyses on the different variants of primary progressive aphasia for atrophy as measured with magnetic resonance imaging (MRI). (A) Conjunction/overlap between semantic variant PPA (svPPA), nonfluent variant PPA (nfvPPA), and logopenic variant PPA (lvPPA). (B) Results of the subtraction analyses to identify PPA variant-specific networks. False discovery rate (FDR) corrected $p < 0.05$. Left side is left.

2.3.2.4 Comparison between the meta-analyses on the different variants of primary progressive aphasia

The results of the three MRI meta-analyses on the different variants of PPA were projected together onto an MNI template to investigate the variant-specificity. For FDG-PET such an analysis was not possible due to limited study numbers. As shown in Figure 5 at the top, there was no overlap between the results of the meta-analyses across MRI studies on svPPA (dark green), nfvPPA (red), and lvPPA (blue), except for a small conjunction (64 mm^3, purple) between nfvPPA and lvPPA in the left posterior middle temporal gyrus. To validate the regional specificity for each PPA variant, we conducted additionally subtraction analyses (nfvPPA > svPPA & lvPPA, svPPA > nfvPPA & lvPPA, lvPPA > svPPA & nfvPPA) between the meta-analyses on

the different PPA variants. The results of the subtraction analyses are shown in Figure 5 at the bottom and details on the respective MNI coordinates, cluster sizes, ALE values, and BAs are reported in Supplementary Table A.2. The analysis revealed that almost all atrophic brain regions as identified in the ALE meta-analysis for each PPA variant separately (see Figure 3) were also specific for this variant (see anatomical description above).

2.4 Discussion

The present work validated the recently proposed imaging criteria for the three variants of PPA using ALE meta-analyses. In the following, we will first focus on the results of the variant-specific meta-analyses. Thereafter, we will emphasize the distinctiveness of the networks of atrophy for svPPA, nfvPPA, and lvPPA and discuss future clinical implications of the relative disjunction between the meta-analyses on svPPA (and nfvPPA) across different imaging modalities.

2.4.1 Validation and refinement of diagnostic imaging criteria for primary progressive aphasia

The new diagnostic imaging criteria for svPPA include anterior (ventral and lateral) temporal lobes (Gorno-Tempini et al., 2011). Our meta-analyses on svPPA across MRI studies confirmed atrophy bilateral in anterior ventral temporal lobe (inferior temporal gyrus) and anterior lateral temporal lobe (middle/superior temporal gyri, fusiform gyrus), but extended the proposed regions towards the anterior medial temporal lobe (right amygdala and bilaterally hippocampus/parahippocampal gyri). Similarly, the results of our meta-analysis on nfvPPA across MRI studies confirmed insula, inferior frontal gyrus, premotor (inferior, middle, and superior frontal gyrus), and supplementary motor areas (superior frontal gyrus) as useful diagnostic imaging criteria for nfvPPA (Gorno-Tempini et al., 2011). The results of our meta-analysis on nfvPPA across MRI studies additionally showed consistent atrophy in middle and superior temporal gyri, putamen, and precentral gyrus, thus emphasizing the role of these regions for the diagnosis of nfvPPA.

The proposed imaging criteria for lvPPA encompass posterior perisylvian/parietal areas, supramarginal gyrus, and angular gyrus (Gorno-Tempini et al., 2011). The

results of our meta-analysis on lvPPA support the supramarginal gyrus and posterior perisylvian regions (superior temporal gyrus), but not the angular gyrus as consistently atrophied regions across studies. Interestingly, our meta-analysis on lvPPA showed additionally atrophy in the dorsal posterior cingulate gyrus and in superior/middle temporal gyrus, thus highlighting the importance of these regions for future MRI based diagnosis of lvPPA. Furthermore, atrophy in the posterior cingulate cortex in lvPPA supports the assumption that lvPPA is pathologically closely related to AD (Rabinovici et al., 2008; Schroeter et al., 2009). Interestingly, the conjunction of the different meta-analyses across MRI studies showed a regional overlap in the posterior middle temporal gyrus between nfvPPA and lvPPA, which suggests that this region might play an important role in both PPA variants. However, given that this overlap was very small, a high clinical specificity and usability of the diagnostic imaging criteria for PPA variants is still guaranteed. This was further supported by the subtraction analysis identifying specific atrophic networks related to each PPA variant.

Although the new diagnostic criteria contain also brain perfusion markers, we could not detect any studies with this imaging modality in PPA. Interestingly, recent studies for AD revealed regionally coinciding reductions in glucose metabolism and perfusion (e.g., Dubois et al., 2007). In analogy, we assume that changes of these imaging modalities coincide regionally in PPA variants as well, although this hypothesis has to be proofed by future meta-analyses.

2.4.2 Open up the road to method-specific diagnostic imaging criteria for primary progressive aphasia

Interestingly, there were only small conjunctions (in inferior and middle temporal gyrus) between the results of the meta-analysis on svPPA across MRI studies and the one across FDG-PET studies. The meta-analysis on svPPA across FDG-PET studies furthermore extended the relevant regions for this PPA variant towards limbic regions, in particular the posterior midcingulate gyrus, and the thalamus. This implicates on the one hand that the posterior midcingulate gyrus and thalamus might play a larger role as diagnostic imaging criteria for svPPA as formerly assumed. However, the specificity of these regions is hampered by the fact that comparable

meta-analyses have identified these regions as relevant for bvFTD and AD as well (Dubois et al., 2007; Schroeter et al., 2008). On the other hand, results suggest different diagnostic imaging criteria for FDG-PET than for MRI as has already been proposed for bvFTD and AD (Dubois et al., 2007; Schroeter et al., 2014; Schroeter et al., 2008). There was no overlap between the meta-analysis on nfvPPA across MRI studies and the one across FDG-PET studies, which further supports this idea. Note however, that this descriptive disjunction should be considered with caution as only three FDG-PET studies had been included, and, accordingly, no method-specific subtraction analysis could be conducted. There were no FDG-PET studies available for lvPPA. Therefore, no conclusions can be drawn regarding potential differences for FDG-PET and MRI in lvPPA. Future meta-analyses on nfvPPA and lvPPA across FDG-PET studies (when more data are available) will show whether the disjunction between hypometabolism and atrophy found in svPPA can be replicated in other PPA variants.

2.5 Limitations

Results of the pilot meta-analysis on nfvPPA across FDG-PET studies and the descriptive disjunction between atrophy and hypometabolism in nfvPPA are considered to show trends based on the present state of knowledge, but should be interpreted cautiously as only three FDG-PET studies were included. Also for the meta-analysis on svPPA across FDG-PET studies and the meta-analysis on lvPPA, the number of clusters might be increased by future additionally involved studies. However, a previous ALE meta-analysis including MRI studies with svPPA and nfvPPA identified comparable clusters (Schroeter et al., 2008), supporting generally the stability and reliability of our findings. The clinical Neary criteria are not completely interchangeable with the clinical Gorno-Tempini criteria (see Supplementary Table A.3). Therefore, some of the patients diagnosed with nfvPPA according to the Neary criteria may actually have suffered from lvPPA. However, as in seven of the 11 MRI studies and in one of the three PET studies the authors explicitly differentiated between both variants of PPA, this bias had, if ever, a minor impact on our results. This assumption was confirmed by an analysis including only the seven MRI studies on nfvPPA that explicitly excluded subjects with lvPPA. As the

foci included in the ALE meta-analyses were reported by different research groups using different statistical approaches and thresholds, the results might be influenced by the methodological quality (e.g., sample size) of the single studies. This problem is partly addressed in the ALE meta-analysis method by modeling results of studies with smaller sample sizes by smaller Gaussian probability distributions than those of studies reporting larger sample sizes (Eickhoff et al., 2009).

2.6 Conclusion

We used anatomical likelihood estimation meta-analyses to validate and refine the new diagnostic imaging criteria for the different variants of PPA. As there was almost no overlap between the meta-analyses on semantic variant PPA, nonfluent variant PPA, and logopenic variant PPA across MRI studies, the new imaging criteria are highly distinctive. Limbic regions, in particular the posterior midcingulate gyrus and thalamus might play a larger role for logopenic variant PPA and semantic variant PPA as has been assumed until now. Finally, our results on semantic variant PPA suggest different diagnostic imaging criteria for FDG-PET than for MRI scans. Future meta-analyses on nonfluent variant PPA and logopenic variant PPA across FDG-PET studies will show whether this disjunction between hypometabolism and atrophy also concerns the other variants of PPA.

3 Predicting Primary Progressive Aphasia with Support Vector Machine Approaches in structural MRI data

3.1 Introduction

Primary progressive aphasia (PPA) is a neurodegenerative disease with insidious onset mainly characterized by a language dysfunction that remains isolated for at least two years without significant impairment in other cognitive domains (Gorno-Tempini et al., 2011; Mesulam, 1982; Neary et al., 1998). PPA subsumes three gradually progressive language disorders, namely semantic variant PPA (svPPA) or semantic dementia, nonfluent/agrammatic variant PPA (nfvPPA) or progressive nonfluent aphasia, and logopenic variant PPA (lvPPA) or logopenic progressive aphasia (Gorno-Tempini et al., 2008; Gorno-Tempini et al., 2004; Gorno-Tempini et al., 2011). SvPPA is mainly characterized by impairments in confrontation naming, single-word comprehension, and object-knowledge, as well as surface dyslexia or dysgraphia (Gorno-Tempini et al., 2011). The imaging supported diagnosis of svPPA is given when patients additionally show atrophy and/or hypometabolism in the anterior (ventral and lateral) temporal lobe. Patients suffering from nfvPPA show predominantly agrammatism, effortful halting speech with inconsistent speech sound errors and distortions (apraxia of speech), and impaired comprehension of syntactically complex sentences. These language deficits are often associated with atrophy or hypometabolism in left inferior frontal gyrus, insula, premotor, and supplementary motor areas. LvPPA is characterized by impaired single-word retrieval in spontaneous speech and naming as well as impaired repetition of sentences. Patients suffering from lvPPA furthermore often show phonologic paraphasias in spontaneous speech and naming. The imaging supported diagnosis of lvPPA is given when patients additionally show atrophy and/or hypometabolism in left posterior parietal, supramarginal, and angular gyri (Gorno-Tempini et al., 2011). The suggested imaging criteria have recently been validated by comprehensive meta-analyses (Bisenius et al., 2016).

The prevalence of PPA is roughly estimated to range from 3-15/100,000 in the US population (Grossman, 2010; Harvey et al., 2003; Ratnavalli et al., 2002). PPA is thus a rare disease, which makes it very difficult for neurologists outside specialized clinics to correctly recognize and differentiate between the three PPA variants in routine hospital practice (e.g., Wilson et al., 2009). Given that the current imaging criteria are only supportive for the diagnosis of PPA, magnetic resonance imaging (MRI) scans are often not included as standard in the clinical assessment of PPA, but mainly used to exclude differential diagnoses (e.g., Wilson et al., 2009). It has been shown for other types of dementia like for instance, AD that changes in atrophy as visualized by MRI are an especially good biomarker for correct early diagnosis and furthermore even predictive for individuals with mild cognitive impairment to decline into AD (e.g., Frisoni et al., 2010; McEvoy and Brewer, 2010; Schroeter et al., 2009; Weiner et al., 2010). Therefore, it might be highly interesting to investigate whether MRI scans have a similar predictive value for the correct early diagnosis of PPA and to investigate which brain regions contribute the most to the classification of its three variants.

On the one hand, it seems plausible that brain regions proposed in the current diagnostic imaging criteria and based on a large range of imaging studies (Bisenius et al., 2016; Gorno-Tempini et al., 2011) enable the correct diagnosis of the three PPA variants. On the other hand, most of the current imaging studies report comparisons of the three variants of PPA with age-matched healthy controls at a group-level and it has been critically discussed that statistical differences at group level might not necessarily reveal the most important regions to correctly diagnose individual cases (Davatzikos et al., 2008a; Davatzikos et al., 2008b; Wilson et al., 2009). Therefore, it might advance our knowledge in this field crucially to investigate whether brain regions contributing the most to the correct diagnosis of the three PPA variants indeed correspond to regions that are especially atrophied in these three variants. Moreover, it might be highly interesting to explore whether disease-specific regions of interest (ROIs) in comparison with whole brain approaches even enhance the predictive power of MRI scans for the correct PPA classification.

To address these issues, we investigated here atrophy, namely changes in grey matter density, with voxel-based morphometry (VBM) in patients suffering from one

of the PPA variants in comparison with healthy controls as well as by comparing patients with different PPA variants at a group level. Subsequently, we used linear support vector machine (SVM) classification of the individual grey matter density maps to investigate their discriminative or predictive power for the correct classification of single subjects as belonging to one of the PPA variants or healthy controls. A number of recent studies have used similar pattern classification methods to classify patients with AD, FTD, and mild cognitive impairment (Davatzikos et al., 2008a; Davatzikos et al., 2008b; Dukart et al., 2013; Dukart et al., 2011; Fan et al., 2008; Klöppel et al., 2008b; Lerch et al., 2008; Misra et al., 2009; Teipel et al., 2007; Vemuri et al., 2008). Wilson and colleagues (2009) investigated the utility of structural MRI scans for SVM classification in PPA variants in a single center study. Here, we investigated patients included in the multi-center study of the German consortium for frontotemporal lobar degeneration (FTLD; Otto et al., 2011) to replicate and generalize previously reported results, where the multi-center design is a precondition for application in clinical routine in the future. Additionally, we compared a whole-brain approach to a disease-specific ROI approach based on comprehensive anatomical likelihood estimation meta-analyses on the three variants of PPA (Bisenius et al., 2016). These ROIs represent the prototypical networks consistently affected in the three variants of PPA across MRI studies reporting group-level statistics. Note that these ROIs are based on a totally different cohort avoiding circularity. In order to better understand possible differences between the whole brain and the regions-of-interest approach, we furthermore computed and visualized the voxels that contributed the most to the SVM classification in the whole brain approach. To reveal whether the brain regions that contributed the most to the SVM classification in the whole brain approach corresponded to the regions that were especially atrophic in the three PPA variants, we also report pairwise group-level comparisons of grey matter probability maps between patients and healthy controls, respectively between PPA variants. For the pairwise group-level comparisons, we hypothesized that, according to the current imaging criteria and previously published VBM studies, atrophy is focused to left fronto-insular regions in nfvPPA, to the (mainly left) anterior temporal lobe in svPPA, and to the (predominantly left) posterior perisylvian or parietal cortex in lvPPA (e.g., Bisenius et al., 2016; Desgranges et al.,

2007; Gorno-Tempini et al., 2011; Grossman et al., 2004; Mummery et al., 2000). Furthermore, we hypothesized that the same brain regions would mainly contribute to the correct SVM classification in PPA variants and healthy controls and that disease-specific ROI approaches would reveal a higher predictive power for the SVM classification than whole-brain approaches.

3.2 Materials and methods

3.2.1 Subjects

Patients and healthy controls were recruited within seven centers (located in Ulm, Munich, Leipzig, Homburg, Erlangen, Bonn, and Goettingen) of the German consortium for FTLD (http://www.ftld.de). All subjects gave written consent. The research protocol was in accordance with the latest version of the Declaration of Helsinki and approved by the universities' ethics committees. For each center, the clinical evaluation and the assessment of the MRI scans were done on site according to standard operating procedures. That is, all of these centers used the same study protocol (diagnostic criteria, demographic, neuropsychological and language assessment, and scanning parameters), except for one center, where different scanning parameters were used (see section 2.2). The diagnosis of PPA required progressive deterioration of speech and that the main deficits were restricted to speech and language for at least two years. Patients were diagnosed more specifically with nfvPPA, svPPA, or lvPPA according to the newest diagnostic criteria (Gorno-Tempini et al., 2011). Note that data from the patient's first visit in the multi-centric FTLD consortium's study was included guaranteeing the relevance of our results for early diagnosis of PPA syndromes. None of the patients included in this study had any comorbid psychiatric or neurodegenerative disease. The degree of clinical impairment of the patients was assessed using the Clinical Dementia Rating scale (CDR) and the FTLD-modified Clinical Dementia Rating scale (FTLD-CDR). We compared 44 right-handed patients suffering from a variant of PPA (16 nfvPPA, 17 svPPA, and 11 lvPPA) with 20 right-handed healthy controls. We report all possible pairwise comparisons between PPA variants. Subjects from the larger group of a given group comparison were matched as closely as possible to the smaller group for 1) number, 2) scanning parameter, 3) age, and where possible 4) gender.

3.2.2 Image acquisition

All structural images were acquired on Siemens Magnetom 3T scanners (2xVerio, 2xSkyra, 2xTrio, 1xAllegra, Erlangen, Germany). 47 T1-weighted images (12 svPPA, 11 nfvPPA, ten lvPPA, 14 healthy controls) were acquired using a magnetization prepared rapid gradient echo sequence with a matrix=240x256x176, resolution=1x1x1 mm, field of view=240 mm, repetition time=2300 ms, echo time=2.98 ms, inversion time=900 ms, and flip angle=9°. For 17 subjects (five nfvPPA, five svPPA, one lvPPA, six healthy controls), T1-weighted images were acquired using a magnetization prepared rapid gradient echo sequence with a matrix=208x256x256, resolution=1x1x1 mm, field of view=256 mm, repetition time=2200 ms, echo time=4.38 ms, inversion time=1200 ms, and flip angle=8°. The distribution of the two sequences (scanning parameters) did not differ significantly, neither between patient groups nor between patient groups and healthy control groups (see Table 4). The very first MRI scans that were assessed as soon as the subjects were enrolled in the study, were used for analyses.

3.2.3 Data analysis

3.2.3.1 Clinical characteristics

We used SPSS version 22 (IBM Corporation, Armonk, NY) to compute descriptive group scores (mean and standard deviation) for the overall patient and healthy control groups as well as for the respective subsets after matching for sample size, age, gender, and scanning parameters. Group comparisons for age, disease duration, education, and total grey matter density between all patient and healthy control groups as well as between PPA variants were performed using one-way ANOVAs, Kruskal-Wallis tests, and post-hoc t-tests in SPSS. Group comparisons for demographic and clinical characteristics between the matched subsets were performed using independent t tests (normally distributed data) and Mann-Whitney U tests (not normally distributed data) in SPSS. Group comparisons for gender and scanning parameter were done using chi-square tests in SPSS.

3.2.3.2 Voxel-based morphometry

Images were processed with the VBM toolbox (http://dbm.neuro.uni-jena.de/vbm/) in SPM 8 (Wellcome Department of Imaging Neuroscience, London, UK; http://www.fil.ion.ucl.ac.uk/spm/software/spm8/) running in a MATLAB 8.5 environment (Mathworks, Inc., Sherbon, MA, USA) using the default parameters. MRI images were segmented into grey matter, white matter, and cerebrospinal fluid using the unified segmentation module (Ashburner and Friston, 2005) and normalized to the standard Montreal Neurological Institute template including affine and non-linear modulation to account for local compression and expansion during transformation. The normalized segmented grey matter density maps were smoothed with a Gaussian kernel of 8 mm full-width-at-half-maximum. The group comparisons between the three variants of PPA and healthy controls as well as between PPA variants were performed in FSL (FMRIB Analysis Group, Oxford University, UK., http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSL) using permutation-based non-parametric testing (5000 permutations) with the Threshold-Free Cluster Enhancement (TFCE) method (Smith and Nichols, 2009; Winkler et al., 2014). Age, gender, and total grey matter were entered as covariates in the general linear model and results are reported at a family-wise error (FWE) corrected $p < 0.05$.

SVM classification (Vapnik, 1995; Vapnik, 1998) was performed using libsvm version 3.18 (Chang and Lin, 2001; https://www.csie.ntu.edu.tw/~cjlin/libsvm) in a MATLAB 8.5 environment (Mathworks, Inc., Sherbon, MA, USA). Analyses were done using a linear kernel and the default solver C-SVC with C=1. In the training step, SVM assigns a weight to the scan of each subject which indicates its importance for the discrimination between groups. This weight is multiplied by a label vector which indicates the group of the scan (e.g., patient or healthy control). The cross-validation of the trained SVM was performed using the leave-one (subject)-out method. This procedure iteratively leaves-out the information of one subject of each group and trains the model on the remaining subjects for subsequent class assignment of the respective subject that was not included in the training procedure. This validation method allows the generalization of the trained SVM to data that have not been presented to the SVM algorithm previously and avoids the danger of inflating accuracies

In the whole brain approach, we included all voxels that had a probability for grey matter higher than 0.2 (because voxels lying between white matter and ventricular cerebrospinal fluid tend to be misclassified as grey matter (e.g., Ashburner and Friston, 2000; Dukart et al., 2011). In the ROI approach, we used the results from a recently published anatomical likelihood estimation meta-analysis on the three variants of PPA ($p < 0.05$ false discovery rate corrected) across MRI studies as a prototypical disease-specific template (Bisenius et al., 2016). The original meta-analytic clusters were coregistered to the Montreal Neurological Institute template of the VBM results using SPM 8 and dilated by two voxels using the 3 D dilation function implemented in the WFU PickAtlas (Maldjian, http://www.nitrc.org/projects/wfu_pickatlas). Non-parametric statistical comparisons were calculated between the performance (as indicated by the area under the receiver operating characteristic curve, AUC) of the ROI approach and the whole brain approach for all pairwise comparisons at $p<0.05$ in StAR (Vergara et al., 2008; www.melolab.org/star/home.php). In order to determine and visualize the importance of each voxel for the discrimination between groups in the whole brain approach, we multiplied each grey matter probability map (containing only voxels where $p > 0.2$) by the product of weight and label and summed on a voxel basis (Klöppel et al., 2008b).

3.3 Results

3.3.1 Demographic and clinical characteristics

The demographic and clinical characteristics of the overall patient and healthy control groups are shown in Table 1. The patient and healthy control groups did not differ significantly from each other in age, education, or disease duration. The patient and healthy control groups differed however significantly in total grey matter density ($F(3,63)=4.06$, $p=0.01$) with svPPA and lvPPA showing lower values than healthy controls. The three PPA variants did not differ significantly from each other in age, education, disease duration, or total grey matter density.

Table 4 Demographic and clinical characteristics of patients and healthy controls

	nfvPPA	svPPA	lvPPA	HC
number	16	17	11	20
gender (m/f)	8/8	11/6	4/7	11/9
scanning parameter	11/5	12/5	10/1	14/6
age (years)	67.50 ± 7.42	62.53 ± 7.77	65.36 ± 6.25	67.05 ± 6.61
education (years)	13.19 ± 4.29	15.35 ± 3.37	13.27 ± 3.35	14.10 ± 3.04
disease duration (years)	2.19 ± 1.60	3.59 ± 2.45	3.64 ± 2.66	-
total grey matter densitiy (dm^3)	0.54 ± 0.08	0.52 ± 0.08	0.51 ± 0.09	0.59 ± 0.05
CDR	3.44 ± 3.20	5.32 ± 4.19	4.64 ± 4.43	0.03 ± 0.11
FTLD-CDR	5.94 ± 4.07	7.88 ± 5.44	6.86 ± 5.81	0.05 ± 0.15
CERAD Plus (test battery)				
MMSE	19.94 ± 7.25	19.31 ± 8.35	22.10 ± 6.03	28.70 ± 0.92
word list memory (trials 1-3)	13.07 ± 6.61	13.92 ± 7.62	11.64 ± 8.93	23.40 ± 3.03
word list recall	4.33 ± 2.62	3.77 ± 3.30	3.73 ± 3.88	8.20 ± 2.38
word list recognition (yes)	8.57 ± 2.41	8.85 ± 1.41	9.10 ± 1.20	9.80 ± 0.52
word list recognition (no)	9.57 ± 0.65	7.69 ± 2.63	8.40 ± 3.34	10.00 ± 0.00
constructional praxis	9.06 ± 1.95	10.00 ± 2.08	8.18 ± 3.31	11.00 ± 0.00
constructional praxis recall	6.75 ± 2.86	6.31 ± 4.31	4.55 ± 4.28	9.45 ± 1.91
Trail Making Test A (s)	94.38 ± 46.95	75.69 ± 51.56	75.80 ± 51.33	35.80 ± 9.01
Trail Making Test B (s)	220.18 ± 91.33	123.70 ± 72.24	201.13 ± 84.47	74.50 ± 19.12
Boston Naming Test	9.93 ± 4.76	6.47 ± 4.26	10.18 ± 3.89	14.85 ± 0.49
Verbal Fluency Test	8.06 ± 7.34	8.00 ± 5.01	12.09 ± 8.49	26.75 ± 5.50
Phonemic Fluency Test	3.87 ± 4.09	7.23 ± 5.29	6.80 ± 4.52	18.20 ± 4.63
Repeat and Point Test				
Repeat task	7.93 ± 2.34	8.93 ± 1.98	6.80 ± 3.36	10.00 ± 0.00
Point task	8.53 ± 1.55	6.14 ± 2.85	8.10 ± 1.91	9.88 ± 0.49

CDR clinical dementia rating scale, global score, CERAD Consortium to Establish a Registry for Alzheimer's Disease, FTLD frontotemporal lobar degeneration, HC healthy controls, lvPPA logopenic variant PPA, MMSE Mini-Mental State Examination, nfvPPA nonfluent/agrammatic variant PPA, PPA primary progressive aphasia, svPPA semantic variant PPA. Note age, education, disease duration, CDR, FTLD-CDR, CERAD Plus, and Repeat and Point Test are indicated as mean ± standard deviation. Note that data was missing for a few subjects on some subtests of the CERAD Plus and the Repeat and Point Test.

A detailed description of each of the pairwise comparisons between the matched subsets is given in Supplementary Table B.1. As shown in Table B.1, no pair of groups differed significantly in age, gender, and education and none of the patient groups differed significantly from the other patient groups in age, gender, education, duration of disease, CDR, and FTLD-CDR. PPA variants differed significantly from healthy controls in CDR, FTLD-CDR, and most of the subtests of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Plus test battery. NfvPPA and

svPPA additionally differed significantly from healthy controls in the Repeat and Point Test. In the pairwise comparisons between PPA variants, svPPA showed a significantly lower test score in the Point task than nfvPPA and a significantly higher test score in the Repeat task than lvPPA (see Supplementary Table B.1).

3.3.2 Voxel-based morphometry results

Significant results of the statistical comparison between grey matter density maps of healthy controls and patients are shown in red (nfvPPA), light green (svPPA), and blue (lvPPA) color in Figures 6-8 on the top left (for more details, see Supplementary Table B.2). All results are reported at an FEW corrected significance level of $p < 0.05$. The results of the statistical comparison between grey matter density maps of svPPA and nfvPPA are shown in Figure 9 on the top left (svPPA < nfvPPA in light green color, nfvPPA < svPPA in red color). The results for the statistical comparison between lvPPA and svPPA are shown in Figure 10 on the top left (svPPA < lvPPA in light green color, lvPPA < svPPA no significant results at $p < 0.05$). There were no significant results for the comparison between lvPPA and nfvPPA at a FEW corrected significance level of $p < 0.05$ (therefore not shown). More details on the pairwise comparisons between PPA variants are given in Supplementary Table B.2.

3.3.3 Support vector machine classification results

SVM classification was applied separately to each group comparison: 1) nfvPPA vs. healthy controls, 2) svPPA vs. healthy controls, 3) lvPPA vs. healthy controls, and 4) svPPA vs. nfvPPA. The reported accuracy is the percentage of subjects correctly assigned to the clinical diagnosis (patient/healthy control or svPPA/nfvPPA). Sensitivity refers to the proportion of patients correctly classified as patients and specificity to the proportion of healthy controls correctly classified as healthy controls. Positive predictive value refers to the number of correctly classified patients out of all subjects classified as patients and negative predictive value refers to the number of correctly classified healthy controls out of all subjects classified as healthy controls.

3.3.3.1 Group comparisons between patients and healthy controls

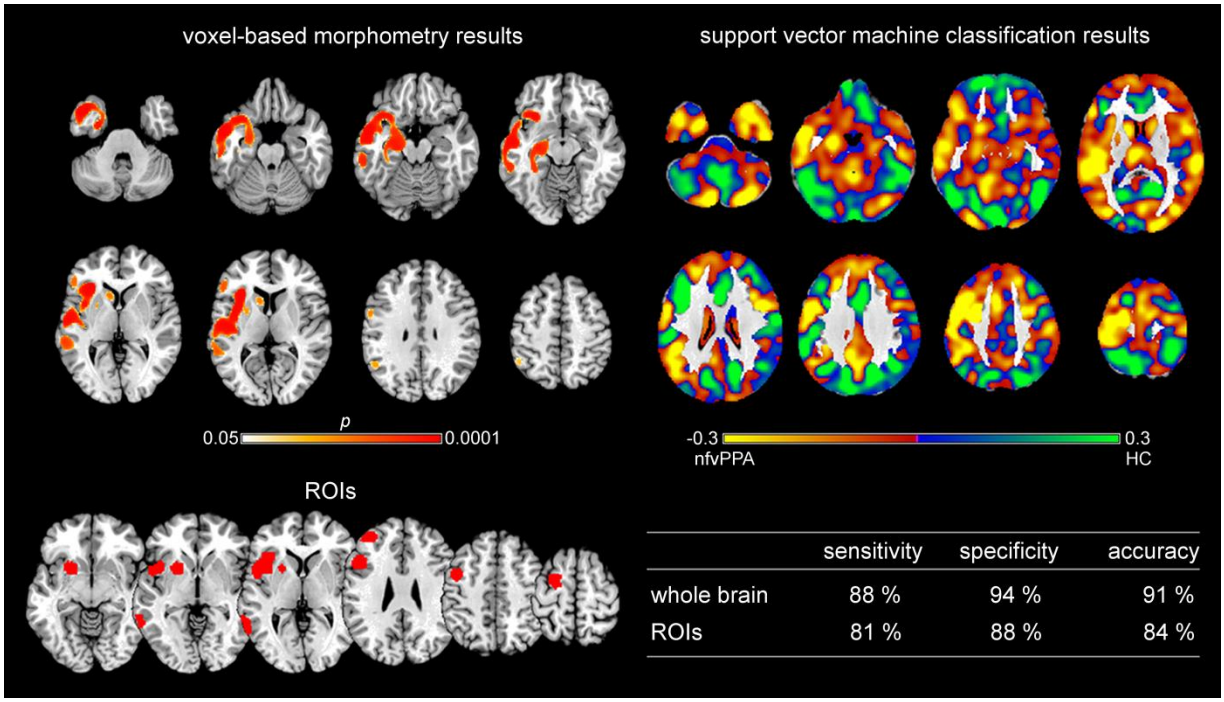

Figure 6: Voxel-based morphometry and support vector machine classification results for nonfluent/agrammatic variant PPA as compared to healthy controls. Top left: voxel-based morphometry (VBM) results for the comparison between nonfluent/agrammatic variant PPA (nfvPPA) and healthy controls (HC) (family-wise error corrected $p < 0.05$). Bottom left: Regions of interest (ROIs) based on independent meta-analyses. Right: Results of support vector machine classification (SVM) classification. Top: Regions most relevant for classification as patients in yellow, HC in light green. Note that the scale of the distance weights has no applicable units. Bottom: Sensitivity, specificity, and accuracy for the ROI approach and the whole brain approach in SVM classification.

The accuracy for the classification between different variants and healthy controls using the leave-one-out approach ranged from 91 to 97 % for the whole brain approach and from 82 to 100 % for the ROI approach. Details on the respective sensitivity, specificity, and accuracy are given in Figures 6-8 on the bottom right and details on positive and negative predictive values are shown in Supplementary Table B.3. The results of the SVM classification between patients and healthy controls for the whole brain approach are shown on the top right of Figures 6-8. Here, values range between -1 and 0 or 0 and 1 and reflect the relative importance of these voxels in the discrimination between both groups. Voxels that contributed the most to the classification of subjects as patients (i.e., had a higher negative value) are depicted in yellow and the voxels that contributed the most to the classification of subjects as healthy controls (i.e., had a higher positive value) are shown in light green. A value

near 0 indicates that this voxel was neither indicative for the classification as patient nor as healthy control.

Brain regions that contributed the most to the classification of subjects as nfvPPA vs. control subjects (Figure 6 on the top right) encompass bilaterally cerebellum, inferior, middle, and superior temporal gyri, middle occipital gyrus, parahippocampal gyrus, crus cerebri, thalamus, precuneus, inferior and superior frontal gyri, as well as in the left hemisphere orbital gyrus, insula, pre- and postcentral gyri, middle frontal gyrus, and angular gyrus. Classification accuracy was 91 % for the whole brain approach and 84 % for the ROI approach. The statistical comparison between both approaches revealed high AUC values, but without significant differences (AUC_{ROI}=0.90, $AUC_{whole\ brain}$=0.94, p=0.48).

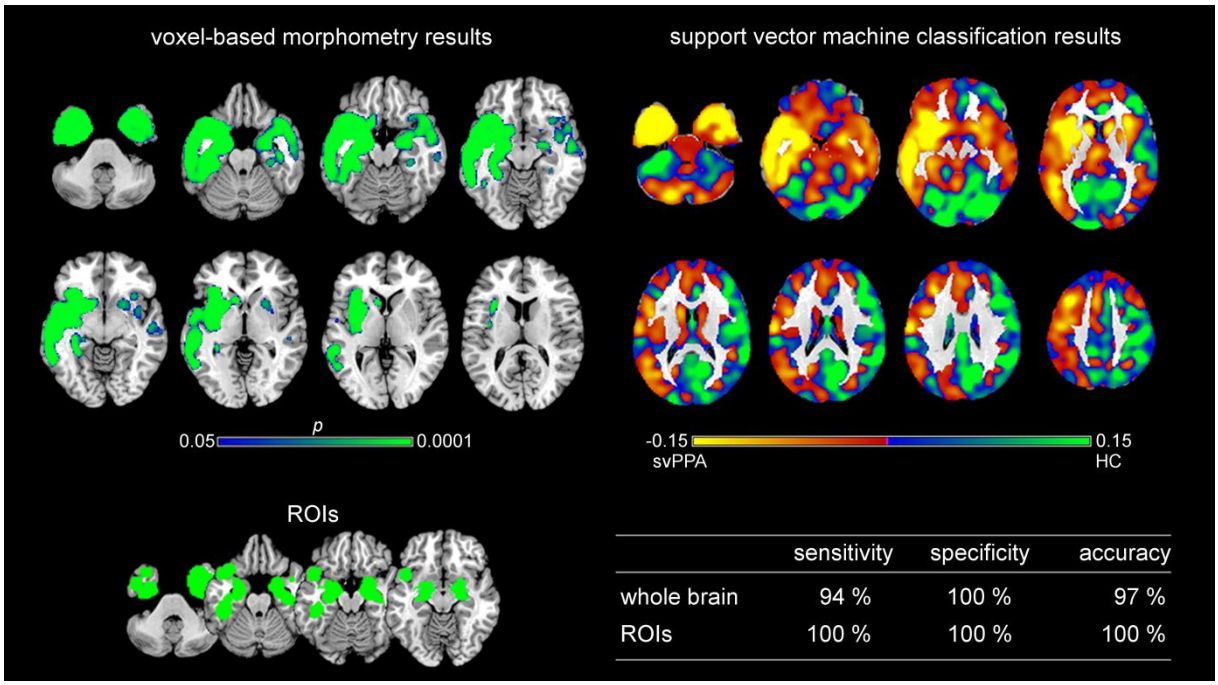

Figure 7: Voxel-based morphometry and support vector machine classification results for semantic variant PPA as compared to healthy controls. Top left: voxel-based morphometry (VBM) results for the comparison between semantic variant PPA (svPPA) and healthy controls (HC) (family-wise error corrected $p < 0.05$). Bottom left: Regions of interest (ROIs) based on independent meta-analyses. Right: Results of support vector machine (SVM) classification. Top: Regions most relevant for classification as patients in yellow, HC in light green. Note that the scale of the distance weights has no applicable units. Bottom: Sensitivity, specificity, and accuracy for the ROI approach and the whole brain approach in SVM classification.

Regions that contributed the most to the classification of subjects as svPPA vs. control subjects included bilaterally (although predominantly in the left hemisphere) cerebellum, inferior, middle and superior temporal gyri, middle occipital gyrus, parahippocampal gyrus, hippocampus, amygdala, putamen, insula, precentral and postcentral gyri, middle frontal gyrus, inferior parietal gyrus, and cingulate gyrus (see Figure 7 on the top right). Classification accuracy was very high for both approaches (97 % for the whole brain approach and 100 % for the ROI approach). The statistical comparison between approaches showed very high AUC values for both, but without significant differences (AUC_{ROI}=1.00, $AUC_{whole\ brain}$=0.97, p=0.32).

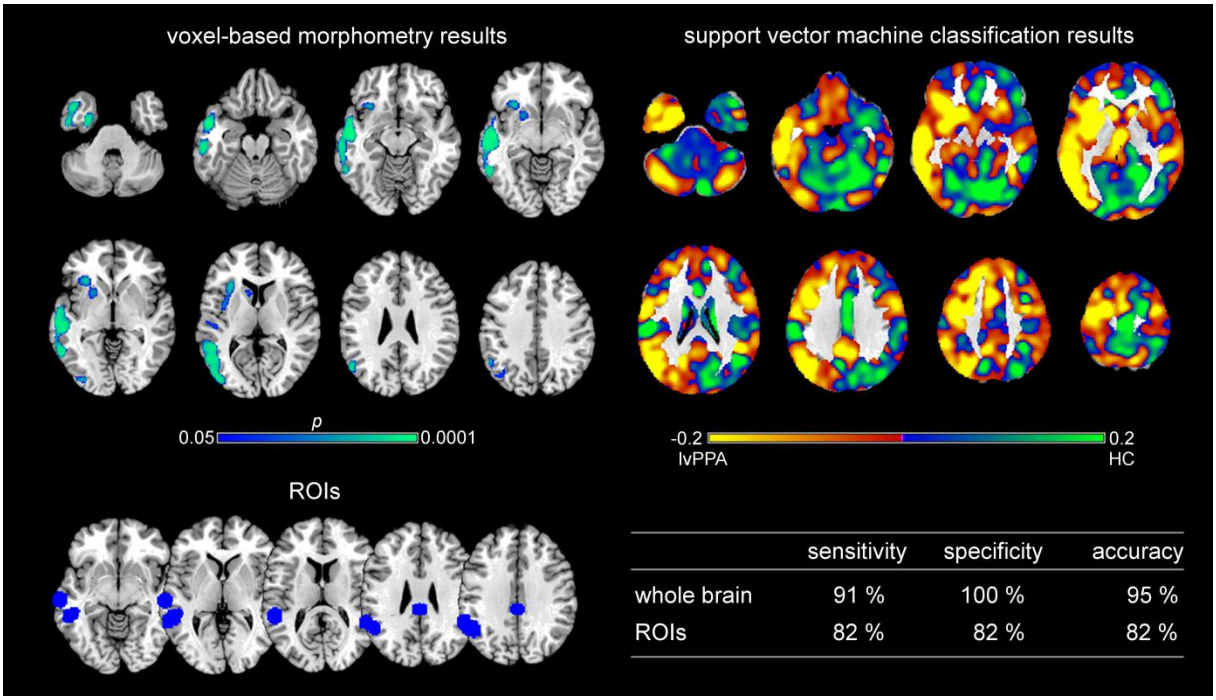

Figure 8: Voxel-based morphometry and support vector machine classification results for logopenic variant PPA as compared to healthy controls. Top left: voxel-based morphometry (VBM) results for the comparison between logopenic variant PPA (lvPPA) and healthy controls (HC) (family-wise error corrected $p < 0.05$). Bottom left: Regions of interest (ROIs) based on independent meta-analyses. Right: Results of support vector machine (SVM) classification. Top: Regions most relevant for classification as patients in yellow, HC in light green. Note that the scale of the distance weights has no applicable units. Bottom: Sensitivity, specificity, and accuracy for the ROI approach and the whole brain approach in SVM classification.

Regions that contributed the most to the classification of subjects as lvPPA patients vs. control subjects are shown in yellow in Figure 8 on the top right and encompass left inferior temporal gyrus, fusiform gyrus, middle occipital gyrus, parahippocampal

gyrus, hippocampus, putamen, insula, thalamus, precentral gyrus, middle and superior frontal gyri, angular gyrus, supramarginal gyrus, and cingulate gyrus as well as bilaterally cerebellum, middle and superior temporal gyri, caudate nucleus, thalamus, middle and superior frontal gyri, precuneus, and superior parietal gyrus. Classification accuracy was high for both, the whole brain approach (95 %) and the ROI approach (82 %). The statistical comparison between both approaches did show high AUC values without significant differences (AUC_{ROI}=0.91, $AUC_{whole\ brain}$=0.95, *p*=0.38).

3.3.3.2 Group comparisons between PPA variants

Figure 9 illustrates on top right in yellow the regions that contributed the most to the classification as svPPA and in green the regions that contributed the most to the classification as nfvPPA. Here, sensitivity refers to the ratio of correctly classified svPPA patients and specificity to the ratio of correctly classified nfvPPA patients. Details on positive and negative predictive values are given in Supplementary Table B.3. The regions that contributed the most to the classification of a subject as svPPA included bilaterally cerebellum, inferior, middle and superior temporal gyri, middle occipital gyrus, fusiform gyrus, parahippocampal gyrus, hippocampus, putamen, insula, cuneus, precuneus, inferior frontal gyrus, superior parietal gyrus, cingulate gyrus, and left precentral gyrus. Regions that contributed the most to the classification of nfvPPA included bilateral cerebellum, middle and superior occipital gyrus, superior temporal gyrus, gyrus rectus, posterior orbital gyrus, caudate nuclei, thalamus, inferior, middle, and superior frontal gyrus, precentral gyrus, postcentral gyrus, inferior parietal gyrus, angular gyrus, supramarginal gyrus, right precuneus, right superior parietal gyrus, and right cingulate gyrus. Classification accuracy was 78 % for both, the whole brain and the ROI approach. Both approaches revealed high AUC values without significant differences between them (AUC_{ROI}=0.87, $AUC_{whole\ brain}$=0.88, p= 0.72).

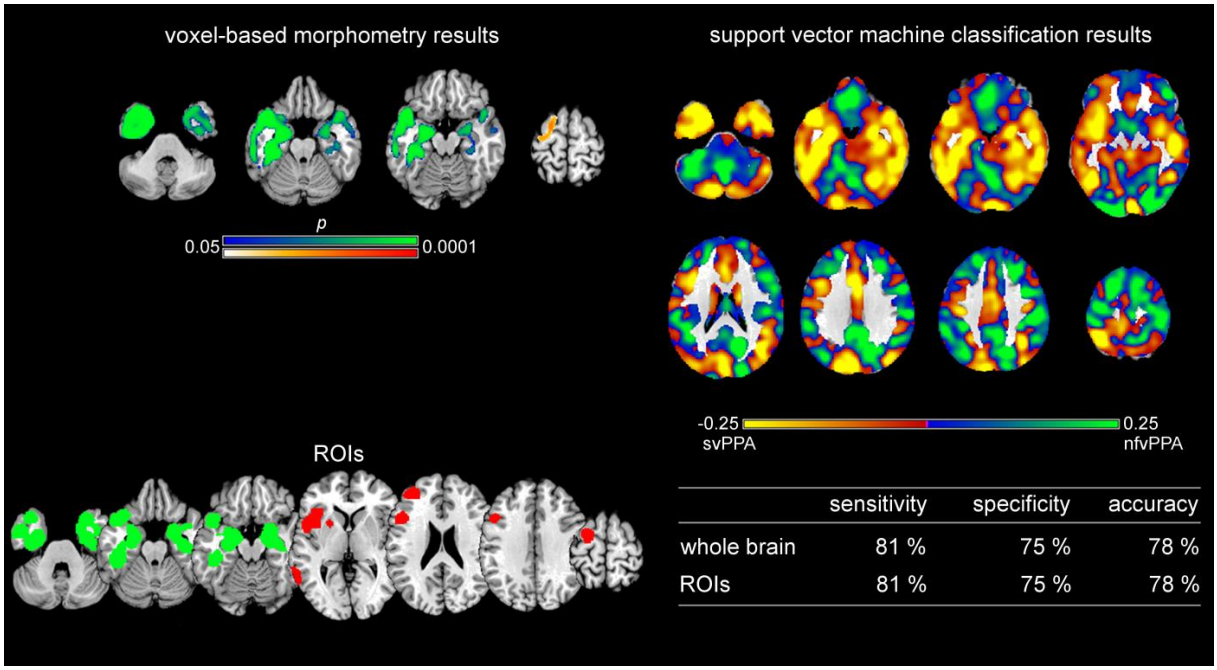

Figure 9: Support vector machine classification results for the comparison and discrimination between semantic variant PPA and nonfluent/agrammatic variant PPA. Top left: VBM results for the comparison between semantic variant PPA (svPPA) and nonfluent/agrammatic variant PPA (nfvPPA) (svPPA<nfvPPA green, nfvPPA<svPPA red, family-wise error corrected $p < 0.05$). Bottom left: Regions of interest (ROIs) based on independent meta-analyses. Right: Results of support vector machine (SVM) classification. Top: Regions most relevant for classification as svPPA in yellow, nfvPPA in light green. Note that the scale of the distance weights has no applicable units. Bottom: Sensitivity, specificity, and accuracy for the ROI approach and the whole brain approach in SVM classification.

Figure 10 illustrates on top right in yellow the regions that contributed the most to the classification as lvPPA and in green the regions that contributed the most to the classification as svPPA. Sensitivity refers to the ratio of correctly classified lvPPA patients and specificity to the ratio of correctly classified svPPA patients. Positive and negative predictive values are given in Supplementary Table B.3. The regions that contributed the most to the classification of a subject as lvPPA included bilateral cerebellum, middle occipital gyrus, middle and superior temporal gyri, caudate nuclei, thalamus, superior frontal gyrus, supramarginal gyrus, angular gyrus, precuneus, cingulate gyrus, right lateral orbital gyrus, inferior and middle frontal gyrus, and superior parietal gyrus. Regions that contributed the most to the classification of svPPA included bilateral cerebellum, inferior, middle, and superior temporal gyrus, parahippocampal gyrus, hippocampus, insula, and right putamen. Classification accuracy was 95 % for both, the whole brain and the ROI approach. Both

approaches reached high AUC values without significant differences between them (AUC_{ROI}=0.91, $AUC_{whole\ brain}$=0.93, p=0.41).

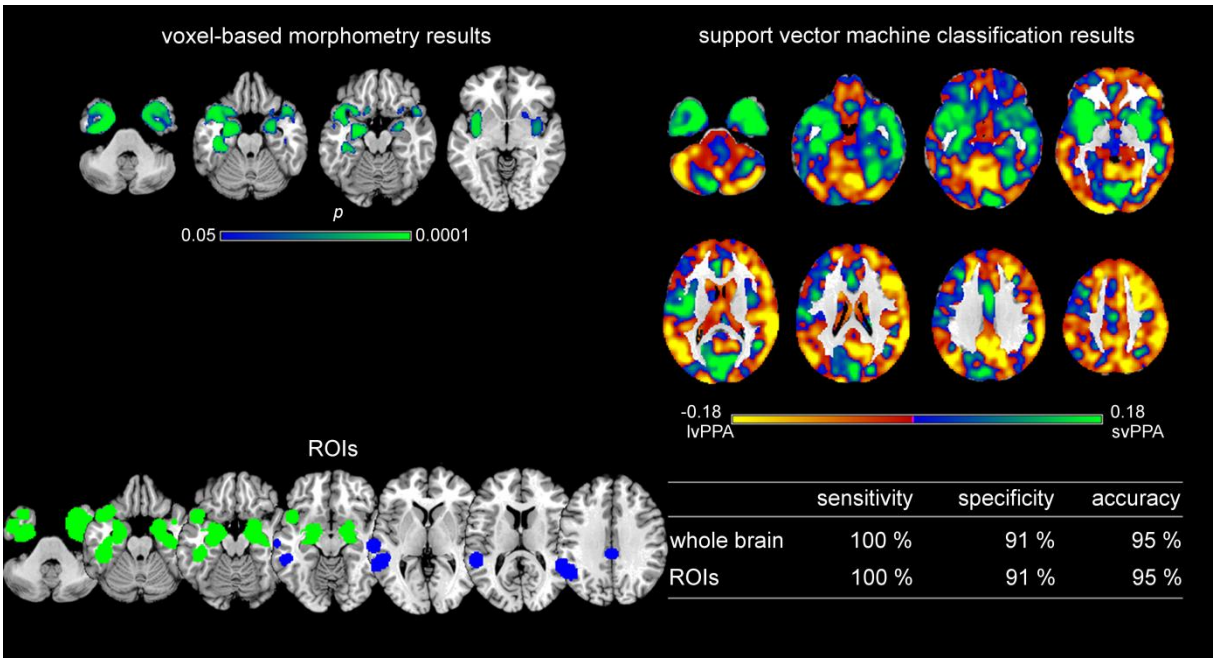

Figure 10: Support vector machine classification results for the comparison and discrimination between logopenic variant PPA and semantic variant PPA. Top left: VBM results for the comparison between logopenic variant PPA (lvPPA) and semantic variant PPA (svPPA) (svPPA<lvPPA family-wise error corrected $p < 0.05$). Bottom left: Regions of interest (ROIs) based on independent meta-analyses. Right: Results of support vector machine (SVM) classification. Top: Regions most relevant for classification as lvPPA in yellow, svPPA in light green. Note that the scale of the distance weights has no applicable units. Bottom: Sensitivity, specificity, and accuracy for the ROI approach and the whole brain approach in SVM classification.

Figure 11 illustrates on top in yellow the regions that contributed the most to the classification as lvPPA and in green the regions that contributed the most to the classification as nfvPPA. Sensitivity refers to the ratio of correctly classified lvPPA patients and specificity to the ratio of correctly classified nfvPPA patients. For details on positive and negative predictive values see Supplementary Table B.3. The regions that contributed the most to the classification of a subject as lvPPA included bilateral cerebellum, inferior, middle occipital gyrus, middle and superior temporal gyri, thalamus, putamen, middle and superior frontal gyrus, supramarginal gyrus, angular gyrus, precentral gyrus, cingulate gyrus, precuneus, superior parietal gyrus. Regions that contributed the most to the classification of nfvPPA included right inferior temporal gyrus, bilateral middle and superior temporal gyri, gyrus rectus,

lateral orbital gyrus, insula, caudate nuclei, cuneus, cingulate gyrus, middle and superior frontal gyri, postcentral gyrus, supramarginal gyrus, and superior parietal gyrus. Classification accuracy was low with 55 % for the whole brain approach and higher with 64 % for the ROI approach. AUC values were comparable, namely higher for the ROI than the whole brain approach, but without significant differences between them (AUC_{ROI}=0.64, $AUC_{whole\ brain}$=0.59, p=0.50).

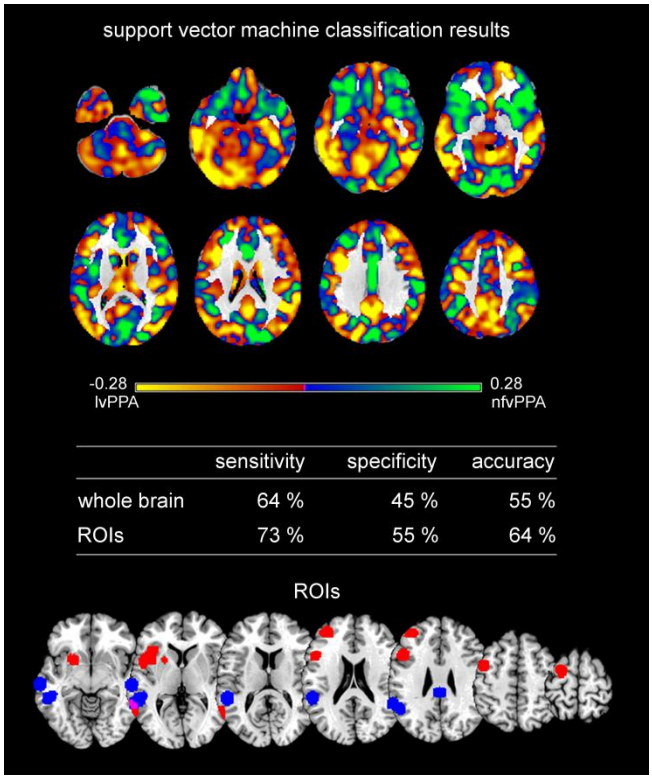

Figure 11: Support vector machine classification results for the discrimination between logopenic variant PPA and nonfluent/agrammatic variant PPA. Top: Regions most relevant for support vector machine classification as logopenic variant PPA (lvPPA) in yellow, nonfluent/agrammatic variant PPA (nfvPPA) in light green. Note that the scale of the distance weights has no applicable units. VBM results are not shown for the group comparisons, because no significant results were obtained. Middle: Sensitivity, specificity, and accuracy for the ROI approach and the whole brain approach in SVM classification. Bottom Regions of interest (ROIs) based on independent meta-analyses.

3.4 Discussion

To our knowledge, this is the first study demonstrating that SVM classification in multi-center MRI data can be used to diagnose and dissociate PPA subtypes, where the multi-center design is a precondition for application in clinical routine in the future. Moreover, we compare a whole brain vs. data-driven disease-specific ROI approach for SVM classification. We used ROIs reported in a recent comprehensive meta-analysis on PPA (Bisenius et al., 2016). In order to reveal whether the regions that contributed the most to the whole brain SVM classification of the three variants of PPA corresponded to the regions that were especially atrophic in the respective

variant, we additionally conducted statistical group-level comparisons between patient groups and healthy control groups. In the following, we are going to introduce the results of these group-level comparisons, before we discuss in more detail the results of the SVM classification for the whole brain approach and the ROI approach as well as possible further implications.

3.4.1 Atrophy in the different variants of primary progressive aphasia

The group comparisons in our study revealed regional brain atrophy that included the disease-specific brain areas identified in comprehensive systematic and quantitative meta-analyses across imaging studies from the literature, if one compares this data for each PPA variant (see left top and bottom images in Figures 6-8). Beyond that our group-level comparisons are in line with studies showing that, with the progression of the disease, the atrophic networks in the three subtypes of PPA partly converge (e.g., Gorno-Tempini et al., 2011; Rogalski et al., 2011). Mild and early svPPA has been shown to involve atrophy in (predominantly left) anterior temporal lobe, with extension to the adjacent temporoparietal junction, hippocampus and amygdala and posterior orbital cortex as well as in the right anterior temporal lobe (Czarnecki et al., 2008; Grossman, 2010 Krueger et al., 2010; Mesulam et al., 2012; Rohrer et al., 2008) and to progress bilaterally into posterior and superior temporal lobe, left temporoparietal junction, bilateral cingulate cortex and orbitofrontal gyri, left superior orbitofrontal gyrus, left inferior and superior frontal gyri (e.g., Grossman, 2010; Kumfor et al., 2016; Rogalski et al., 2011). Early and mild stages of nfvPPA, on the other hand, have been shown to be characterized by atrophy in left inferior frontal gyrus, temporoparietal junction, anterior superior temporal gyrus, posterior middle frontal gyrus and precentral gyrus (Mesulam et al., 2012) and to progress into left anterior temporal lobe, orbital cortex, dorsolateral prefrontal cortex, anterior cingulate cortex, and along the perisylvian fissure into the parietal lobe (e.g., Grossman 2010; Rogalski et al., 2011). For lvPPA, atrophy has been shown to progress from (predominantly left) posterior superior temporal cortex, inferior parietal cortex, posterior cingulate cortex and medial temporal cortex into the anterior and lateral temporal cortex, caudate nucleus, insula, inferior frontal gyrus and dorsal frontal

cortex as well as into the temporo-parietal junction, posterior cingulate and precuneus of the right hemisphere. (e.g., Rogalski et al., 2011; Rohrer et al., 2013).

3.4.2 Support vector machine classification is a useful tool to differentiate between healthy controls and primary progressive aphasia variants

Accuracies for the whole brain approach in SVM classification between patients and healthy controls ranged from 91 % for nfvPPA over 95 % for lvPPA to 97 % for svPPA. The between-subtype whole brain SVM classification enabled high accuracy of 78 and 95 % for the discrimination between svPPA vs. nfvPPA and svPPA vs. lvPPA variant. Only for the discrimination between nfvPPA and lvPPA variants accuracy was low with 55 %. These numbers are in line with previously reported accuracies ranging from 58-100 % in studies on neurodegenerative diseases like AD (e.g., (e.g., Chetelat and Baron, 2003; Davatzikos et al., 2008b; Dukart et al., 2013; Dukart et al., 2011; Klöppel et al., 2008b; Lerch et al., 2008; Teipel et al., 2007; Vemuri et al., 2008), mild cognitive impairment (e.g., Davatzikos et al., 2008a; Teipel et al., 2007), FTD (e.g., Davatzikos et al., 2008b; Dukart et al., 2011; Klöppel et al., 2008a), and PPA (Wilson et al., 2009; Zhang et al., 2013).

Until now, there has only been one study investigating the three variants of PPA with SVM classification (Wilson et al., 2009). These authors performed a principal component analysis on MRI scans from one study center and subsequently used the results for the pairwise SVM classification between patients and healthy controls as well as between the three patient groups. Wilson et al. (2009) found an accuracy of 100 % for the discrimination between svPPA patients and healthy controls, 100 % for the classification between lvPPA patients and healthy controls, and an accuracy of 89 % for the discrimination between nfvPPA and healthy controls. These authors report an accuracy of 89 % for the discrimination between svPPA and nfvPPA patients, 93.8 % for svPPA vs. lvPPA, and 81.3 % for lvPPA vs. nfvPPA. Our SVM results using the whole brain approach on grey matter density maps in the multi-center cohort of the FTLD consortium are thus comparable with the results of Wilson et al. (2009) with regard to the classification between patients and healthy controls showing higher accuracies for svPPA and lvPPA than for nfvPPA and the

classification between lvPPA and nfvPPA showing a lower classification accuracy than the other classifications between PPA variants.

Additionally, we performed group-level comparisons on the grey matter density maps between patients and healthy controls as well as between PPA variants in order to investigate whether the regions that contributed the most to the SVM classification of patients also corresponded to the regions mostly atrophied in these patients. Figures 7 and 8 show that brain regions that were most consistently atrophied in svPPA and lvPPA indeed also contributed the most to the SVM classification of these patients. For nfvPPA, on the other hand, brain regions that contributed the most to the SVM classification as patients were not constrained to the regions that were atrophied in our nfvPPA patients, but also encompassed very similar regions in the contralateral (right) hemisphere (see Figure 6). A possible explanation for the importance of the additional brain regions in the right hemisphere might be that they were affected to a lesser extent (and thus not significant in the group-level comparison) and that SVM classification as a more sensitive method already took into account early atrophy in these regions. There is a general consensus that the results of group-level statistics might not be applicable to individual scans, because their sensitivity and specificity at early stages of brain pathology is insufficient for the prediction of the status of individual scans (Davatzikos et al., 2008b; Fan et al., 2008; Wilson et al., 2009).

Interestingly, for the discrimination between svPPA and nfvPPA, the regions that contributed to the SVM classification as svPPA patients (see Figure 9 on the top), corresponded to the regions that were most consistently atrophied in these patients (see Figure 7 on the top left). The regions that contributed to the SVM classification as nfvPPA, on the other hand, were (except for two characteristic regions in the inferior and middle frontal gyri) rather spread. This might be due to the fact that the group comparisons between patients and healthy controls showed for both, svPPA and nfvPPA, significant atrophy in the superior temporal gyrus, parahippocampal area, hippocampus, insula, and inferior frontal gyrus (see Figures 6 and 7 on the top left). Although atrophy in the superior temporal gyrus, parahippocampal area, and hippocampus have been discussed to be rather specific for svPPA, while insula, and inferior frontal gyrus have been discussed to be rather characteristic for nfvPPA, it has been shown in longitudinal studies that with the progression of the disease, the

atrophic networks in the three variants of PPA partly converge (e.g., Gorno-Tempini et al., 2011; Rogalski et al., 2011). Given that on the one hand several regions might be affected similarly in nfvPPA and svPPA depending upon the current stage of the respective disease and on the other hand structural MRI scans do not provide any information regarding the temporal dynamic pattern of brain atrophy, the SVM classification method, given its high sensitivity, might not always be able to perfectly discriminate between these two variants. For both subtype-specific classifications, svPPA vs. nfvPPA and svPPA vs. lvPPA, we reached a high classification accuracy, although the number of patients was rather low for lvPPA and the respective comparison. The high accuracy might be related to a relatively strong (in the sense of high t-values) and regionally focused atrophy in svPPA. This is obvious in the group comparisons revealing much higher atrophy in svPPA than nfvPPA or lvPPA, whereas nfvPPA showed stronger atrophy only in a very small area and lvPPA did not show any atrophy in comparison with svPPA. Note that disease duration and severity did generally not significantly differ between PPA subtypes excluding these factors as explanation for differences in classification accuracy.

As stated before the whole-brain SVM classification between nfvPPA and lvPPA variants reached only a low accuracy. This might be related to relatively small and rather distributed atrophy in these two PPA variants or to conceptual issues. In a prospective data-driven study, Sajjadi et al. (2012) examined to which extent PPA patients would be classifiable according to the revised clinical diagnostic criteria and which linguistic impairments would cluster together (and thus form distinct syndromes) using principal factor analysis. In this cohort, 58.7 % of the patients could be assigned to one of the three variants of PPA proposed by Gorno-Tempini et al. (2011), while 41.3 % of the patients were classified as mixed PPA because their deficits either extended beyond a single PPA variant or they met the diagnostic criteria for more than one variant. The principal factor analysis identified two clear syndromes corresponding to the proposed syndromes of svPPA and nfvPPA as well as a residual miscellany. Interestingly, impaired sentence repetition, which has been proposed as a cardinal diagnostic feature for lvPPA, aligned with the factor corresponding to nfvPPA. One might therefore speculate that low classification accuracy between nfvPPA and lvPPA in imaging data might not only be related to the

rather relatively small and distributed atrophy, but possibly also to problems in clinically distinguishing both PPA syndromes.

3.4.3 Regions-of-interest approach or whole brain approach?

We compared the whole brain approach for SVM classification with an ROI approach using ROIs from a recent meta-analysis on the three variants of PPA (Bisenius et al., 2016). A similar approach has already been adopted by Dukart and colleagues who compared the whole brain versus ROI approach for SVM classification between FTD and AD as well as between these patient groups and healthy controls using structural MRI and PET scans (Dukart et al., 2013; Dukart et al., 2011). These authors reported that for MRI scans, the ROI approach was comparable to the whole brain approach for the discrimination between patients and healthy controls, but had a lower accuracy for the discrimination between patient groups (AD vs. FTD) (Dukart et al., 2013; Dukart et al., 2011). In the current study, the ROI approach reached generally a high accuracy in diagnosis and, at least mainly, differential diagnosis/classification of PPA syndromes, comparable to the whole-brain approach. In detail, it showed a higher accuracy as compared to healthy controls for svPPA patients and a slightly lower accuracy for nfvPPA and lvPPA patients, while it showed a similar accuracy for svPPA vs. nfvPPA and svPPA vs. lvPPA patients as compared to the whole brain approach. Remarkably, for the lvPPA vs. nfvPPA comparison the ROI approach showed a higher accuracy than the whole brain approach, may be due to the diffusivity and similar strength (in the sense of t-values) of brain atrophy requiring higher regional specificity for the analysis. One might speculate that ROI-based classification might be given preference for special questions in differentiating between syndromes in the future. Given however that none of these trends was statistically significant, we consider both approaches as equally valid.

The visual comparison between the whole brain approach and the ROI approach raises however the question about the optimal method to choose ROIs for SVM classification in PPA. The optimal number of ROIs for SVM classification needs to be such as to accurately capture all subtleties of the structural abnormality in these patients and thus achieve a sufficient predictive accuracy without however reducing predictive accuracy through the increase of noise that possibly accompanies

additional ROIs that are less relevant to the classification. Selecting ROIs based on group-level comparison between patients and healthy control groups might for instance provide a higher discriminative power for the SVM classification in the same study sample. These ROIs would however be biased to at least some extent by the specific study sample and might therefore not necessarily lead to similar good results in other study samples. Another possibility to find the optimal ROIs for the SVM classification between nfvPPA (or lvPPA) and healthy controls might consist in rerunning meta-analyses on the three variants of PPA across MRI studies using a less conservative statistical threshold. This methodological approach might no longer exclusively reveal the brain regions that are specific to a given variant (and to some extent possibly even false positive results), but due to the higher sensitivity, also common networks between variants that become usually only visible in longitudinal studies monitoring the progression of the disease (e.g., Rogalski et al., 2011). For the ROI approach of SVM classification between the different variants of PPA, on the other hand, it might be rather promising to only consider ROIs that are either more severely impaired in one variant as in the other variants as for instance the inferior and middle temporal gyri in svPPA, or rather specific to the given variant (e.g., middle frontal gyrus in nfvPPA as compared to svPPA). The considerations regarding the optimal ROI for SVM classification in PPA are however purely hypothetical and need to be investigated in future studies.

Furthermore, it might be interesting to compare the ROI approach to the whole brain approach using combined imaging data as for instance MRI and PET as has already been done for AD and FTD (e.g., Davatzikos et al., 2008b; Dukart et al., 2013; Dukart et al., 2011) or using MRI and diffusion tensor imaging data as has been done by Zhang et al. (2013), who showed, in a small sample, higher accuracies for whole brain SVM classification of diffusion tensor imaging data than of MRI data for nfvPPA and svPPA versus healthy controls. Moreover, the potential of ROI approaches for disease classification has to be validated in longitudinal studies, where one would assume higher accuracy in early stages.

3.5 Limitations

The relatively small number of subjects might hamper the generalization of the results to the overall population of PPA patients. Given however that our results are very similar to another study including more patients but using a different approach (Wilson et al., 2009) this should not really constitute a major issue. A problem that might occur in pattern classification methods is the risk of overfitting the data due to the high-dimensionality of the data, which can however be reduced by using the leave-one out approach as has been done in the current study. Segmentation and normalization processes are not always perfect which might result in underestimation of atrophy in patients or underestimation of grey matter in healthy controls, which leads to lower accuracies in the SVM classification. This issue should however at least partly be addressed in the current study as that our data have been acquired on different scanners and were well balanced between patient and healthy control groups. Finally, the classification between pairs of groups was a highly idealized situation that does not reflect the problem in the real world of differential diagnosis between several neurological diseases with different prevalence rates – an issue that has to be addressed in future studies validating the application of SVM approaches in every day diagnostic life.

3.6 Conclusion

Our study aimed at validating the potential of structural multi-center MRI data for disease classification in PPA. We compared the whole brain approach with a disease-specific ROI approach for SVM classification in the three variants of PPA. Generally, both the whole brain and the disease-specific approach reached high classification accuracy in diagnosis and differential diagnosis of PPA syndromes without significant differences. Our results showed that for svPPA, the ROI approach using prototypical disease-related networks as revealed by meta-analyses across MRI studies revealed a higher accuracy (perfect discrimination of 100 %) than the whole brain approach. For nfvPPA and lvPPA on the other hand, the SVM classification showed higher accuracies when using the whole brain approach. The regions contributing to the correct SVM classification of patients mostly corresponded to regions that were consistently atrophied in these patients as shown by the VBM

results. For the discrimination between svPPA and nfvPPA, and between svPPA and lvPPA the whole brain approach and the ROI approach showed similar results. The ROI approach increased accuracy in classification between lvPPA and nfvPPA in comparison with the whole brain approach, which might be related to the diffusivity and similar strength (in the sense of t-values) in these PPA syndromes requiring higher regional specificity for the analysis. Given that the accuracies for SVM classification using the ROI approach were still quite high despite the relatively small size of the chosen ROIs as compared to the regions that were taken into account in the whole brain SVM classification of the respective patients, future studies shall further explore the potential of the ROI approach using different ROIs for SVM classification of PPAs.

4 General Discussion

In the revised diagnostic criteria for PPA (Gorno-Tempini et al., 2011), more importance is attributed to the assessment of imaging scans as has been the case in the previous consensus diagnostic criteria for PPA (Neary et al., 1998). The current imaging criteria have been proposed based on a qualitative evaluation of the literature in this field. Here, we provided a quantitative evaluation of the currently available MRI and PET studies in order to statistically validate the proposed diagnostic imaging criteria using ALE meta-analyses. Thereafter, we investigated the diagnostic value of MRI scans for early individual diagnosis of PPA in clinical routine using support vector machine classification and explored whether focusing exclusively on prototypical networks for the single PPA variants would ameliorate the diagnostic value of MRI scans. In the following, we are not going to discuss in detail the results of the two studies presented on the previous pages as this has already been done extensively in section 2.3 and section 2.4, but rather discuss the usefulness of these findings for clinicians within a broader framework.

4.1 Evaluation of the validity of the current diagnostic criteria for primary progressive aphasia

To a great extent, the results of our separate meta-analyses on nfvPPA, svPPA, and lvPPA studies validated the revised diagnostic imaging criteria. Interestingly, the results of our meta-analyses across MRI studies even extended the proposed imaging criteria by showing additional atrophy in the anterior medial temporal lobe (right amygdala and bilaterally hippocampus/parahippocampal gyri) for svPPA and in the middle temporal gyrus, superior temporal gyrus, putamen, and precentral gyrus for nfvPPA. Furthermore, the results of our meta-analysis on lvPPA showed that the angular gyrus might not be as consistently atrophied in these patients as has been assumed so far, while the dorsal posterior cingulate gyrus and superior/middle temporal gyrus most probably constitute additional diagnostic imaging marker for lvPPA. We suggest that these findings should be considered in future revisions of the diagnostic criteria for PPA.

Another highly interesting finding resulted from the comparison between the results of both meta-analyses (one across MRI and one across PET studies) on svPPA. This comparison showed that it might be useful, at least for this PPA variant, to define separate diagnostic imaging criteria for FDG-PET and MRI scans. Future studies will show whether separate imaging criteria for FDG-PET and MRI should be applied similarly to nfvPPA and lvPPA. Separate imaging modality-specific diagnostic criteria have also already been proposed for other types of dementia (Dubois et al., 2007; Schroeter et al., 2014; Schroeter et al., 2008). We suggest that future revisions of the diagnostic criteria for PPA should include the current knowledge about separate imaging markers for FDG-PET and MRI scans.

While we evaluated and validated the revised diagnostic imaging criteria, other authors evaluated the revised diagnostic clinical criteria for PPA (Harris et al., 2013; Mesulam, Wieneke, Thompson, Rogalski, & Weintraub, 2012; Sajjadi, Patterson, Arnold, Watson, & Nestor, 2012; Wicklund et al., 2014). In a prospective data-driven study, Sajjadi et al. (2012) examined to which extent 46 consecutively recruited patients would be classifiable according to the revised clinical diagnostic criteria for PPA. Additionally, these authors investigated which linguistic impairments would cluster together (and thus form distinct syndromes) using principal factor analysis. In this patient cohort, 58.7 % of the patients could be assigned to one of the three variants of PPA proposed by Gorno-Tempini et al. (2011), while 41.3 % of the patients were classified as mixed PPA because their deficits either extended beyond a single PPA variant (i.e., showed also linguistic impairments expected to be spared in this syndrome) or they met the diagnostic criteria for more than one variant (whithout showing differences in disease duration). The principal factor analysis identified two clear syndromes corresponding to the proposed syndromes of svPPA and nfvPPA as well as a residual miscellany. Interestingly, impaired sentence repetition which has been proposed as a cardinal diagnostic feature for lvPPA aligned with the factor corresponding to nfvPPA (Sajjadi et al., 2012). Similarly, Wicklund et al. (2014) showed that 31 % of 84 PPA patients were unclassifiable according to the current diagnostic criteria (some fulfilled simultaneously the diagnostic criteria for more than one PPA variant and some fulfilled the criteria for lvPPA except for the core feature of impaired repetition).

It has been proposed that some of the problems of unclassifiable patients according to the diagnostic criteria of Gorno-Tempini et al. (2011) might be circumvented if impaired repetition would be regarded as an ancillary rather than a core feature of lvPPA and if the “absence of definite grammar and comprehension impairment” would be regarded as a core feature of lvPPA (Mesulam & Weintraub, 2014). Mesulam and Weintraub (2014) furthermore proposed that the recognition of a “mixed” PPA variant might highly decrease the number of unclassifiable cases because some patients already show at very early stages of the disease a combination of agrammatism and semantic impairment. It is thus highly probable that the diagnostic criteria for PPA will be revised within the next years.

Changes in consensus diagnostic criteria can have a major impact as has for instance been shown for the shift from the previous consensus criteria on PPA proposed by Neary et al. (1998) to the current diagnostic criteria for PPA of Gorno-Tempini et al. (2011). Chare and colleagues showed that the comparison of the diagnostic criteria of Neary et al. (1998) and the revised criteria of Gorno-Tempini et al. (2011) revealed no changes in the diagnosis of 87 % of the svPPA patients, but that 51 % of the nfvPPA patients were reclassified as suffering from lvPPA (Chare et al., 2014). These reclassifications of patients were due to several reasons (Mesulam & Weintraub, 2014). Altough Neary et al. (1998) did not explicitly claim to cover and characterize all possible variants of PPA in their diagnostic criteria, most researchers and clinical practicioners used these diagnostic criteria as such (Mesulam & Weintraub, 2014). Consequently, lvPPA was not recognized as a distinct syndrome and PPA patients with a pathology different from FTLD were previously implicitly excluded from the diagnosis of PPA. Furthermore, in the revised diagnostic criteria of Gorno-Tempini et al. (2011) impaired repetition is no longer one of the supportive criteria for nfvPPA, but is included as a core diagnostic criterium for lvPPA. Anomia, which has previously been part of the diagnostic features for nfvPPA (Neary et al., 1998), is meanwhile attributed to svPPA if it is accompagnied with loss of word meaning and to lvPPA if it appears without loss of word meaning (Mesulam & Weintraub, 2014). By first diagnosing PPA according to Mesulam (2001) before further specifying the concrete variant of PPA, patients whose most prominent problem is prosopagnosia and/or an associative agnosia (and would therefore have

been classified as svPPA according to the criteria of Neary et al. (1998)) are now explicitly excluded from the diagnosis of svPPA (Mesulam & Weintraub, 2014).

The changes from the diagnostic criteria for PPA proposed by Neary et al. (1998) to the current diagnostic criteria for PPA of Gorno-Tempini et al. (2011) lead to a relatively large number of reclassified patients (Chare et al., 2014). One might wonder how importantly the suggested revisions of the diagnostic criteria of Gorno-Tempini et al. (2011) might affect the current diagnoses of PPA patients. The suggested revisions for future consensus diagnostic criteria concern mostly lvPPA (i.e., regard impaired repetition as ancillary feature and the absence of definite grammar and comprehension impairment as core features for lvPPA) and the recognition of patients showing a combination of agrammatism and semantic impairment as distinct “mixed” PPA variant (Mesulam & Weintraub, 2014; Mesulam et al., 2014).

In the following, we will discuss possible implications of future revisions of the diagnostic criteria for the validity and informative value of the two imaging studies presented in this thesis. As svPPA and nfvPPA are not affected by the recommended revisions, we do not expect that future imaging results (after revision of the current diagnostic criteria) for svPPA and nfvPPA will differ importantly from the ones presented here. For lvPPA on the other hand, we expect larger study samples (including lvPPA with and without impaired repetition), which will enhance the statistical power of future studies and thus provide more solid results. Sajjadi, Patterson, and Nestor (2014) showed that PPA patients that were unclassifiable according to the diagnostic criteria of Gorno-Tempini et al. (2011) showed at group-level atrophy similar to the currently proposed imaging criteria for lvPPA. Therefore, we assume that also for lvPPA, the results of future imaging studies (after revision of the current diagnostic criteria) will not differ drastically from the ones presented here. Note however, that it is not sure yet, whether the diagnostic criteria of Gorno-Tempini et al. (2011) will indeed be revised in near future. The assumptions regarding imaging results for PPA variants after the revision of the current diagnostic criteria are thus purely speculative and need to be substantiated by future studies.

4.2 How useful are the current diagnostic imaging criteria for clinical routine?

In the following, we are going to discuss the usefulness of the current diagnostic imaging criteria (respectively their quantification via ALE meta-analysis) for clinical routine. The comparison of the separate meta-analyses across MRI studies (via conjunction and subtraction analyses) showed that the imaging criteria for the PPA variants are highly distinct. The conjunction analysis showed a small regional overlap in the posterior middle temporal gyrus between nfvPPA and lvPPA, which suggests that this region might play an important role in both PPA variants. Nevertheless, as this overlap was very small, a high clinical distinctiveness is still guaranteed. At first sight, studies comparing PPA patients to healthy controls at group-level thus suggest that these imaging markers constitute useful guidelines for clinicians to correctly distinguish between PPA variants in clinical routine.

We used support vector machine classification to investigate statistically how useful MRI scans are actually for the individual diagnosis of PPA patients. In order to represent the situation in clinical routine as closely as possible, we considered scans assessed at initial presentation for each subjet. Our SVM results showed accuracies (in the whole brain approach) ranging from 55 % to 97 %. In a second step, we investigated whether it would be sufficient to only consider brain regions corresponding to the proposed diagnostic imaging criteria (respectively their quantification via ALE meta-analysis) or whether additional brain regions should be taken into account. Our results showed that for svPPA, focusing only on the (quantification of the) proposed diagnostic imaging criteria lead to a perfect discrimination (of 100 %) between patients and healthy controls. For nfvPPA and lvPPA on the other hand, the SVM classification showed slightly higher accuracies when considering the whole brain. For the discrimination between svPPA and nfvPPA/lvPPA, both approaches showed similar results. For the discrimination between lvPPA and nfvPPA, the ROI approach showed a higher accuracy than the whole brain approach. Given that none of the differences between both approaches were statistically significant, we consider both approaches as equally valid. Our accuracies for SVM classification considering only the (quantification of the)

proposed diagnostic imaging criteria were (except for the discrimination between lvPPA and nfvPPA) quite high despite the relatively small size of the chosen brain regions. These findings thus provide empirical evidence that (except for the differential diagnosis between lvPPA and nfvPPA) the proposed supportive imaging criteria constitute (not only at group-level, but) also at individual subject level useful guidelines for clinicians to correctly diagnose PPA variants in clinical routine.

Besides providing a sound statistical method to evaluate the discriminative power (and thus the usefulness) of single features (e.g., MRI scans) for the correct diagnosis of patients in clinical routine, the SVM method has the practical advantage that its algorithm (used to classify subjects after the classifier has been trained), can be implemented in an imaging software. SVM is a highly sensitive method which takes into account early changes in atrophy that cannot easily be perceived by the naked eye. Providing such a software might thus ensure the best use of imaging scans to support the diagnosis of PPA patients in clinical routine. Before such a software can be put on the market, the algorithm needs however to be optimized in order to provide classification accuracies of approximatively 100 %. In the following, we are going to discuss possible ways to improve the algorithm and thereby the accuracy of support vector machine classification for PPA.

One possibility to improve the accuracy of the SVM classification using MRI might consist in further exploring the optimal number and size of brain regions to be taken into account (see section 3.4.3). Regarding this our results unveiled matters of a rather technical nature. The SVM classification method is highly sensitive and therefore takes into account also very early atrophy. Supposed that several regions might be affected similarly in the three PPA variants depending upon the current stage of the respective disease (e.g., Rogalski et al., 2011) and structural MRI scans do not provide any information regarding the temporal dynamic pattern of brain atrophy, SVM classification might not always be able to perfectly discriminate between PPA variants. In order to address this rather technical issue, it might be highly interesting to investigate in future studies, whether considering disease-specific networks including also very early atrophy and additionally weighting more importantly the brain regions that are rather specific for a given PPA variant as

compared to the other PPA variants, would increase the accuracy of SVM classification significantly.

Another possibility to improve the accuracy of the SVM classification using MRI might consist in including further parameters like for instance additional imaging data (e.g., FDG-PET or diffusion tensor imaging) or language test scores (e.g., Dukart et al., 2011; Wilson et al., 2009; Zhang et al., 2013) or constructing dynamic disease models based on longitudinal data. Wilson et al. (2009) showed for instance, that at least for the discrimination between svPPA and nfvPPA, adding linguistic variables to MRI data improved significantly the accuracy of the SVM classification. In this regard, it might be highly interesting to further investigate which standard language tests used in clinical routine provide the most promising results. It has for instance been proposed that the Repeat and Point Test (Hodges, Martinos, Woollams, Patterson, & Adlam, 2008) assessing single word repetition and comprehension might be especially useful for the discrimination between svPPA and nfvPPA. Other authors in contrast proposed that considering language tests assessing comprehension and grammaticality might discriminate best between PPA variants (Mesulam & Weintraub, 2014; Mesulam et al., 2014). It might thus be of interest to investigate whether these assumptions can be empirically supported using SVM classification and to provide a good overview for clinicians regarding the informative value of standard language tests used in clinical routine.

Note however that including further parameters like language test scores and additional imaging data into SVM classification for PPA is most probably rather of scientific interest than of practical benefit in the sense of realistically implementable into an imaging software for clinical purposes. This is due to the fact that different clinics use partly different standard tests to evaluate language impairments in their PPA patients. Furthermore, most clinics are rather in the possession of an MRI scanner than of a PET scanner, because of the great expenses of PET and invasiveness of the radioactive tracers (e.g., Berns, 1999). Similarly, diffusion tensor imaging sequences on MRI scanners are usually run for scientific purposes only and not included as standard sequences in clinical routine.

4.3 General limitations

The main limitations of the work presented in this thesis are the relatively small number of studies included in the ALE meta-analyses as well as the relatively small number of patients included in the SVM study. Small sample sizes in this research field are due to the fact that PPA is an orphan disease with an estimated prevalence of approximately 1.1-6.0 per 100,000 in the population (Grossman, 2014). Although the cooperation between several clinics and research centers within national and international consortia has already largely alleviated this problem, the number of subjects recruited over a period of several years is still relatively low.

Another reason for the relatively small sample sizes in cross-sectional studies is that it is advisable to include patients at a relatively early stage of the disease, because it has been shown in longitudinal studies that with the progression of the disease, the language impairments as well as the atrophic networks in the three variants of PPA partly converge (Gorno-Tempini et al., 2011; Rogalski et al., 2011). Furthermore, it has been shown that there are considerable longitudinal shifts in PPA variant classification while the disease progresses (Mesulam et al., 2014). This seems to concern especially lvPPA where seven out of 11 patients progressed over time into nfvPPA, svPPA, or mixed PPA (Mesulam et al., 2014). Other authors showed that these longitudinal shifts are not limited to the diagnosis of PPA variants, but also include other FTLD syndromes (Knibb & Hodges, 2005). Whereas svPPA patients frequently develop characteristical features of bvFTD, nfvPPA patients often show similarities to patients with corticobasal syndrome (Knibb & Hodges, 2005). In order to gain new insights into PPA, it is thus necessary to include patients at a relatively early or middle stage of the disease and recruit them over a longer period of time.

4.4 General conclusion

The aim of the two studies presented in this thesis was to evaluate the validity of the new diagnostic imaging criteria for PPA variants using anatomical likelihood estimation meta-analysis and to investigate the usefulness of these criteria for the individual diagnosis of PPA patients in clinical routine. To a great extent, the results of our separate meta-analyses on nfvPPA, svPPA, and lvPPA studies validated and

even extended the revised diagnostic imaging criteria. Furthermore, our results suggest that at least for svPPA, it might be useful to define separate diagnostic imaging criteria for FDG-PET and MRI scans. Our support vector machine classification results showed that the accuracies for SVM classification considering only the (quantification of the) proposed diagnostic imaging criteria were (except for the discrimination between lvPPA and nfvPPA) quite high despite the relatively small size of the chosen brain regions. Our findings thus suggest that (except for the differential diagnosis between lvPPA and nfvPPA) the proposed supportive imaging criteria constitute (not only at group-level, but) also at individual subject level useful guidelines to correctly diagnose PPA variants in clinical routine.

5 Summary (Zusammenfassung)

Zusammenfassung der Arbeit

Dissertation zur Erlangung des akademischen Grades Dr. rer. med.

Validation of diagnostic imaging criteria for PPA

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5.1 German summary

Primär progrediente Aphasien (PPA) sind neurodegenerative Erkrankungen, die zu einer alltagsrelevanten Beeinträchtigung von Sprachfunktionen führen können. Die ersten Studien, die zu PPA und ihren Varianten veröffentlicht wurden, berichteten Ergebnisse über sehr geringe Stichprobengrößen oder aber waren Fallbeispiele. Dies lag daran, dass es sich bei PPA um eine seltene Erkrankung handelt, deren Prävalenz auf circa 1.1-6.0 pro 100.000 Personen in der Bevölkerung geschätzt wird (Grossman, 2014). Erst der Zusammenschluss von mehreren Studienzentren zu nationalen und internationalen Konsortien machte es möglich größere Stichproben zu erheben, welche für repräsentative inferenzstatistische Erkenntnisse unabdinglich sind. Weitere Ziele solcher Konsortien sind die Verbesserung der Früherkennung der Erkrankung, die Erhebung des Krankheitsverlaufs, das Sammeln von epidemiologischen Daten, das Aufdecken von möglichen Risikofaktoren, die Evaluation von möglichen Therapien, sowie die Etablierung von einheitlichen Diagnosekriterien (z.B., Otto et al., 2011; Brun et al., 1994).

Während zwei Jahrzehnten wurden die allgemeinen Diagnosekriterien für frontotemporale Demenz (Brun et al., 1994; McKhann et al., 2001) herangezogen, um Patienten mit PPA zu diagnostizieren. Die anschließende Spezifizierung des Subtyps als progressive nichtflüssige Aphasie oder semantische Demenz erfolgte nach den Diagnosekriterien von Neary und Kollegen (Neary et al., 1998). Es stellte sich jedoch mit der Zeit heraus, dass nicht alle PPA Patienten eindeutig einem der beiden Subtypen zugeordnet werden konnten (z.B., Gorno-Tempini et al., 2004), was eine Revision der Diagnosekriterien für PPA zur Folge hatte (Gorno-Tempini et al., 2011). PPA wurde neu definiert als eine neurodegenerative Erkrankung mit schleichendem Beginn, welche sich in den ersten zwei Jahren hauptsächlich als isolierte, progrediente Sprachstörung (ohne bedeutsame Beeinträchtigung in anderen kognitiven Bereichen) bemerkbar macht. PPA umfasst drei Varianten: die semantische Variante (svPPA, früher als semantische Demenz bezeichnet), die nichtflüssige Variante (nfvPPA, früher als progressive nichtflüssige Aphasie bezeichnet), und die logopenische Variante (lvPPA). Das klinische Erscheinungsbild der svPPA ist hauptsächlich gekennzeichnet durch Beeinträchtigungen im Benennen und im Verständnis von einzelnen Wörtern, zunehmenden Verlust des Wissens um die Bedeutung von Wörtern, Oberflächendyslexie und Oberflächendysgraphie. Die Diagnose gilt als bildgebungsgestützt, wenn Patienten zusätzlich Atrophie, Hypometabolismus oder Hypoperfusion im anterioren Temporallappen aufzeigen. Die nfvPPA ist charakterisiert durch eine nichtflüssige Spontansprache mit Sprechanstrengung und langen Pausen, Agrammatismus, Sprechapraxie (Störung der Initiierung und Exekution der für das Sprechen notwendigen Bewegungsabläufe), sowie beeinträchtigtes Verständnis von grammatikalisch komplexen Sätzen. Diese Sprachstörung geht häufig mit Schädigungen in links posterioren frontoinsulären Gehirnregionen einher. Die lvPPA ist hauptsächlich gekennzeichnet durch beeinträchtigten Wortabruf in der Spontansprache und beim Benennen, sowie beeinträchtigtes Nachsprechen von längeren Sätzen. Die Diagnose der lvPPA gilt als bildgebungsgestützt, wenn die Patienten zusätzlich zu den genannten klinischen Symptomen ebenfalls Atrophie, Hypometabolismus oder Hypoperfusion in links posterioren perisylvischen oder parietalen Gehirnregionen aufzeigen.

In den revidierten Diagnosekriterien für PPA wird den Ergebnissen aus Bildgebungsverfahren ein größerer Wert beigemessen, als es in den vorherigen Diagnosekriterien der Fall war (Gorno-Tempini et al., 2011 vs. Neary et al., 1998). Die neuen bildgebenden Diagnosekriterien wurden jedoch auf Grund einer rein qualitativen Evaluation der Literatur vorgeschlagen. Ziel der beiden im Folgenden dargestellten Studien war es, die Validität der neuen bildgebenden Diagnosekriterien für PPA zu evaluieren (erste Studie) und ihren praktischen Nutzen für die individuelle Diagnosestellung von PPA-Patienten im klinischen Alltag zu untersuchen (zweite Studie).

Die erste Studie befasste sich mit der inferenzstatistischen (quantitativen) Evaluierung der Validität der neuen bildgebenden Diagnosekriterien für PPA. Zu diesem Zweck wurden Metaanalysen über alle verfügbaren MRT und PET Studien durchgeführt (Kapitel 2). Ziel war es die in den einzelnen PPA-Varianten konsistent (über mehrere Studien hinweg) betroffenen Gehirnregionen auszumachen und mit Hilfe von Subtraktions- und Konjunktionsanalysen herauszufinden, wie subtypspezifisch oder überlappend diese Regionen zwischen den einzelnen Varianten sind. Ein weiteres Ziel bestand darin zu untersuchen, ob die vorgeschlagenen bildgebenden Diagnosekriterien gleichermaßen für alle Bildgebungsverfahren gelten, oder ob unterschiedliche Diagnosekriterien für MRT und PET angewendet werden sollten, wie es bereits für andere Demenzen vorgeschlagen wurde (Dubois et al., 2007; Schroeter et al., 2014). Unsere systematische Literaturrecherche ergab 22 Studien (15 MRT, sechs FDG-PET, eine MRT & FDG-PET) für svPPA, 14 Studien (11 MRT, drei FDG-PET) für nfvPPA, und sechs Studien (sechs MRT, null FDG-PET) für lvPPA. Die Ergebnisse unserer Metaanalysen bestätigten größtenteils die vorgeschlagenen bildgebenden Diagnosekriterien ($p < 0.05$, False Discovery Rate korrigiert). Interessanterweise zeigten unsere Metaanalysen über MRT-Studien zusätzliche bedeutsame Gehirnareale für die einzelnen PPA-Varianten auf. So fanden wir zusätzliche Atrophie im anterioren medialen Temporallappen (rechte Amygdala und beidseitig Hippocampus) für svPPA sowie im mittleren und superioren Gyrus temporalis, Putamen und Gyrus praecentralis für nfvPPA. Des Weiteren zeigten unsere Ergebnisse zu lvPPA, dass der Gyrus angularis nicht so konsistent in dieser Variante

betroffen ist, wie bislang angenommen wurde, während der dorsale posteriore Gyrus cinguli sowie der mittlere und superiore Gyrus temporalis möglicherweise weitere bildgebende Marker für lvPPA darstellen. Die Ergebnisse der Subtraktions- und Konjunktionsanalysen zeigten, dass (bis auf eine kleine regionale Überlappung zwischen nfvPPA und lvPPA im posterioren mittleren Gyrus temporalis), die betroffenen Regionen in hohem Maße spezifisch für die einzelnen Varianten sind. Der Vergleich zwischen beiden Metaanalysen zu svPPA (eine über MRT- und eine über PET-Studien) zeigte nur sehr kleine Überlappungen im inferioren und mittleren Gyrus temporalis auf. Diese Ergebnisse legen nahe, dass für svPPA, ähnlich wie für andere Demenzen (z.B., Dubois et al., 2007), separate bildgebende Diagnosekriterien für PET und MRT von Nutzen sein könnten. Zukünftige Studien werden zeigen, ob dies ebenfalls für nfvPPA und lvPPA zutrifft.

Die vorgeschlagenen bildgebenden Diagnosekriterien für PPA scheinen folglich (zumindest für die Beurteilung von MRT-Scans) nützliche Richtlinien für Kliniker darzustellen. Es besteht jedoch genereller Konsens, dass Studienergebnisse, die auf Gruppenvergleichen basieren, nicht unbedingt zur Evaluierung einzelner individueller MRT-Scans herangezogen werden können, weil die Sensitivität und Spezifizität von Gruppenvergleichen nicht ausreichend sind, um anfängliche Atrophie zu erfassen.

In der zweiten Studie wollten wir mittels Support Vektor Maschinen (SVM)-Klassifikation statistisch untersuchen, wie nützlich MRT-Scans allgemein für die Diagnosestellung von PPA-Patienten im klinischen Alltag sind (Kapitel 3). Des Weiteren wollten wir gezielter untersuchen, ob hierbei die ausschließliche Fokussierung auf die vorgeschlagenen bildgebenden Diagnosekriterien (bzw. deren Quantifizierung mittels Metaanalysen, welche in der ersten Studie berichtet wurde) den diagnostischen Wert von MRT-Scans verbessern würde. Wir verglichen hier 44 rechtshändige PPA Patienten (16 nfvPPA, 17 svPPA und 11 lvPPA) mit 20 rechtshändigen gesunden älteren Kontrollen, welche für Stichprobengröße, Alter, Geschlecht und Scanning-Parameter gematcht waren. Alle Probanden wurden im Rahmen des Deutschen und Italienischen Konsortiums für Frontotemporale Lobärdegeneration erhoben (Otto et al., 2011). Die verglichenen Gruppen unterschieden sich nicht signifikant in Alter, Geschlecht, Bildungsstand, oder Krankheitsdauer. Die Vorhersagegenauigkeit für die Analysen, die das gesamte

Gehirn umfassten, variierten für die SVM-Klassifikationen zwischen PPA-Patienten und Kontrollen von 91 % für nfvPPA über 95 % für lvPPA zu 97 % für svPPA. Die SVM Klassifikation zeigte eine Genauigkeit von 78 % für svPPA versus nfvPPA und eine Genauigkeit von 95 % für lvPPA versus svPPA. Für die Unterscheidung zwischen lvPPA und nfvPPA zeigte die SVM Klassifikation eine Genauigkeit von 55 %. Diese Zahlen sind im Einklang mit SVM Studien zu anderen neurodegenerativen Erkrankungen (z.B. Alzheimer-Krankheit oder leicht kognitive Einschränkung; Davatzikos, Resnick, et al., 2008; Dukart et al., 2011). Um herauszufinden ob die Gehirnregionen, die am meisten zur SVM-Klassifikation zwischen Patienten und Kontrollen beitragen, den Gehirnregionen entsprechen, die am meisten in diesen Patientengruppen atrophisch sind, haben wir zusätzlich statistische Gruppenvergleiche zwischen Patienten und gesunden Kontrollen gerechnet. Unsere Ergebnisse zeigten, dass die Regionen, die am meisten zur SVM-Klassifikation zwischen Patienten und Kontrollen beitrugen, in der Tat größtenteils den Regionen entsprachen, die in den entsprechenden Patientengruppen atrophisch waren. Die ausschließliche Fokussierung auf die (Quantifizierung mittels Metaanalysen der) bildgebenden Diagnosekriterien zeigte für svPPA eine höhere Vorhersagegenauigkeit auf (100 %) als wenn das gesamte Gehirn berücksichtigt wurde (97 %). Die Vorhersagegenauigkeiten für nfvPPA (84 %) und lvPPA (82 %) hingegen waren leicht geringer, wenn ausschließlich die bildgebenden Diagnosekriterien in Betracht gezogen wurde. Für die Klassifikation zwischen svPPA und nfvPPA bzw. lvPPA war die Vorhersagegenauigkeit bei beiden Methoden gleich (78 % bzw. 95 %). Für die Klassifikation zwischen lvPPA und nfvPPA war die Vorhersagegenauigkeit leicht höher (64 %), wenn ausschließlich auf die bildgebenden Diagnosekriterien fokussiert wurde. Zusammengefasst waren die Vorhersagegenauigkeiten der SVM-Klassifikationen, wo ausschließlich die (Quantifizierung der) bildgebenden Diagnosekriterien berücksichtigt wurde, trotz der geringen Größe der betrachteten Regionen, (außer für die Unterscheidung zwischen lvPPA und nfvPPA) recht hoch. Unsere Ergebnisse untermauern den praktischen Nutzen der vorgeschlagenen bildgebenden Diagnosekriterien für die Beurteilung von MRT-Scans zur Diagnosestellung von PPA-Patienten im klinischen Alltag (mit Ausnahme für die Differentialdiagnose zwischen lvPPA und nfvPPA).

5.2 English summary

Primary progressive aphasias (PPA) are neurodegenerative diseases that lead to profound impairments in language functions. For almost a decade, most studies on PPA and its variants were either case reports or single-center studies reporting very small sample sizes. Until now, there are no community-based prevalence estimates for PPA available, but based on autopsy-proven cases, the prevalence for PPA is estimated at approximately 1.1-6.0 per 100,000 in the population (Grossman, 2014). PPA is thus an orphan disease. Only the cooperation between several study centers within national and international consortia in recent years made it possible to gather sufficiently large sample sizes making deductive statistical research in this field possible. Further aims of these consortia are to improve disease recognition along with its management, evaluate disease progression, collect data on epidemiology, find risk factors and early disease markers, evaluate possible therapeutic approaches as well as to discuss and establish standard diagnostic criteria (e.g., Otto et al., 2011; Brun et al., 1994).

For two decades, researchers and clinicians have been using the diagnostic criteria for frontotemporal dementia (Brun et al., 1994; McKhann et al., 2001) to generally diagnose a patient as suffering from PPA and the criteria of Neary et al. (1998) to further specify the diagnosis as progressive nonfluent aphasia or semantic dementia. However, there were a number of PPA cases that could not be classified according to the criteria of Neary and colleagues (Gorno-Tempini et al., 2004; Grossman & Ash, 2004; Neary et al., 1998), which led to a revision of the diagnostic criteria for PPA (Gorno-Tempini et al., 2011). PPA has been redefined as a neurodegenerative disease with insidious onset mainly characterized by a language dysfunction that remains isolated for at least two years without significant impairment in other cognitive domains. PPA subsumes three gradually progressive language disorders, namely the semantic variant PPA (svPPA, formerly also known as semantic dementia), nonfluent variant PPA (nfvPPA, formerly also known as progressive nonfluent aphasia), and the logopenic variant PPA (lvPPA). SvPPA is clinically mainly characterized by impairments in confrontation naming, single-word comprehension, and object-knowledge, as well as surface dyslexia or dysgraphia.

The imaging supported diagnosis of svPPA is given when patients additionally show atrophy and/or hypoperfusion/-metabolism in the anterior (ventral and lateral) temporal lobe. Patients suffering from nfvPPA show predominantly agrammatism, effortful halting speech with inconsistent speech sound errors and distortions (apraxia of speech), as well as impaired comprehension of syntactically complex sentences. These language deteriorations are often conjoined with atrophy or hypoperfusion/-metabolism in left posterior fronto-insular regions (e.g., inferior frontal gyrus, insula, premotor, and supplementary motor areas). LvPPA is characterized by impaired single-word retrieval in spontaneous speech and naming as well as impaired repetition of sentences. The imaging supported diagnosis of lvPPA is given when patients additionally show atrophy and/or hypoperfusion/-metabolism in left posterior perisylvian or parietal areas (e.g., posterior parietal, supramarginal, and angular gyri).

In the revised diagnostic criteria for PPA, more importance is attributed to the diagnostic assessment of imaging scans as has been the case in previous diagnostic criteria (Neary et al., 1998). The diagnostic imaging criteria were however proposed based on a qualitative evaluation of the literature and have not been validated so far. The aim of the two studies presented in this thesis was to evaluate the validity of the new diagnostic imaging criteria for PPA (first study) and to investigate the usefulness of the diagnostic imaging criteria for the individual diagnosis of PPA patients in clinical routine (second study).

The aim of the first study was to validate the proposed diagnostic imaging criteria for PPA at a deductive statistical level. Therefore, we quantitatively evaluated all currently available PET and MRI studies using anatomical likelihood estimate meta-analyses (chapter two). Our objective was to identify the neural networks affected in the three PPA variants and examine their regional specificity in subtraction and conjunction analyses identifying specific and overlapping networks, respectively. A further objective was to investigate whether the proposed imaging criteria would apply similarly to PET and MRI scans or whether separate, imaging modality-specific imaging criteria should be applied for PPA as has been suggested for other types of dementia (Dubois et al., 2007; Schroeter et al., 2014). Our systematic literature search yielded 22 studies (15 MRI, six FDG-PET, one MRI & FDG-PET) for svPPA, 14 studies (11 MRI, three FDG-PET) for nfvPPA, and six studies (six MRI, zero FDG-

PET) for lvPPA. Analyses were conducted using a false discovery rate corrected threshold of $p < 0.05$. To a great extent, the results of our separate meta-analyses on nfvPPA, svPPA, and lvPPA studies validated the revised diagnostic imaging criteria. Interestingly, our meta-analytic results across MRI studies even extended the proposed imaging criteria by showing additional atrophy in the anterior medial temporal lobe (right amygdala and bilaterally hippocampus/parahippocampal gyri) for svPPA and in the middle temporal gyrus, superior temporal gyrus, putamen, and precentral gyrus for nfvPPA. Furthermore, the results of our meta-analysis on lvPPA showed that the angular gyrus might not be as consistently atrophied in these patients as has been assumed so far, while the dorsal posterior cingulate gyrus and superior/middle temporal gyrus most probably constitute additional diagnostic imaging markers for lvPPA. The conjunction and subtraction analyses between the separate meta-analyses on PPA variants across MRI studies showed that except for a very small regional overlap in the posterior middle temporal gyrus between nfvPPA and lvPPA, the neural networks affected in the three PPA variants were highly distinct. The comparison between the results of both meta-analyses (one across MRI and one across PET studies) on svPPA showed only small conjunctions in inferior and middle temporal gyrus, which suggest that it might be useful to define separate diagnostic imaging criteria for FDG-PET and MRI. Future studies will show whether separate imaging modality-specific criteria apply similarly to nfvPPA and lvPPA.

At first sight, these results thus suggest that the current imaging criteria indeed constitute useful supportive guidelines for clinicians to correctly distinguish between PPA variants in clinical routine. There is however a general consensus that the results of group-level statistics might not be applicable to individual scans, because their sensitivity and specificity at early stages of brain pathology is insufficient for the prediction of the status of individual scans (Davatzikos, Resnick, et al., 2008; Fan et al., 2008; Wilson et al., 2009).

In the second study presented in this thesis, we therefore aimed at investigating statistically how useful MRI scans are for the individual diagnosis of PPA patients using support vector machine (SVM) classification. Furthermore, we raised the question whether focusing exclusively on the diagnostic imaging criteria (respectively their quantification via anatomical likelihood estimate meta-analyses presented in the

first study) would improve the diagnostic value of MRI scans for the individual diagnosis. We compared 44 right-handed patients suffering from a variant of PPA (16 nfvPPA, 17 svPPA, and 11 lvPPA) with 20 right-handed healthy controls that were matched as closely as possible for sample size, age, gender, and scanning parameters. All data were acquired within the German and Italian Consortium for FTLD (Otto et al., 2011). No pair of groups differed significantly in age, gender, education, or disease duration (if applicable). Accuracies for the whole brain approach in SVM classification between patients and healthy controls ranged from 91 % for nfvPPA over 95 % for lvPPA to 97 % for svPPA. The SVM classification of svPPA vs. nfvPPA showed an accuracy of 78 %. The SVM classification for lvPPA vs. svPPA showed an accuracy of 95 % and the SVM classification for lvPPA vs. nfvPPA showed an accuracy of 55 %. These numbers are in line with previously reported accuracies ranging from 58-100 % in studies on neurodegenerative diseases as Alzheimer's disease and mild cognitive impairment (e.g., Davatzikos, Resnick, et al., 2008; Dukart et al., 2011; Klöppel, Stonnington, Barnes, et al., 2008). In order to reveal whether the regions that contributed the most to the whole brain SVM classification of the three variants of PPA corresponded to the regions that were especially atrophied in the respective variants, we additionally conducted statistical group-level comparisons between patients and healthy controls. Brain regions that were most consistently atrophied in svPPA and lvPPA indeed also contributed the most to the SVM classification of these patients. For nfvPPA, on the other hand, brain regions that contributed the most to the SVM classification as patients were not constrained to the regions that were atrophied in our nfvPPA patients, but also encompassed very similar regions in the contralateral hemisphere. A possible explanation for the importance of the additional brain regions in the right hemisphere might be that they were affected to a lesser extent (and thus not significant in the group-level comparison) and that SVM classification as a more sensitive method already took into account early atrophy in these regions. For the discrimination between svPPA and nfvPPA, the regions that contributed to the SVM classification as svPPA patients corresponded to the regions that were most consistently atrophied in these patients, while the regions that contributed to the classification as nfvPPA were rather spread. Our results showed that for svPPA, focusing only on the

(quantification using anatomical likelihood estimate meta-analyses of the) diagnostic imaging criteria for PPA showed a higher accuracy (100 %) than the whole brain approach (94 %). The accuracy for nfvPPA (84 %) and lvPPA (82 %) was slightly lower when focusing only on the (quantification of the) diagnostic imaging criteria as compared to the whole brain approach. For svPPA versus nfvPPA (78 %) as well as for svPPA versus lvPPA patients (95 %), the accuracy remained unchanged. For lvPPA versus nfvPPA, the accuracy was slightly higher when focusing only on the (quantification of the) diagnostic imaging criteria (64 %). All in all, the accuracies for SVM classification considering only the (quantification of the) proposed diagnostic imaging criteria were (except for the discrimination between lvPPA and nfvPPA) quite high despite the relatively small size of the chosen brain regions. These findings suggest that (except for the differential diagnosis between lvPPA and nfvPPA) the diagnostic imaging criteria constitute (not only at group-level, but) also at individual level useful guidelines for clinicians to correctly diagnose PPA variants in clinical routine.

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7 Appendix

7.1 Supplementary material

7.1.A Supplementary material for "Validating New Diagnostic Imaging Criteria for Primary Progressive Aphasia via ALE Meta-analyses"

Supplementary Table A.1

Overview of the studies included in the separate meta-analyses on semantic variant PPA, nonfluent variant PPA, and logopenic variant PPA

Study	N	Diagnostic criteria	Age	Disease duration	MMSE
SvPPA MRI					
Adlam et al. (2006)	7 svPPA	Gorno-Tempini et al. (2004)	62.8 (57-72)	n.a.	26.0 (23-29)
	12 HC		65.0 (55-75)		28.8 (27-30)
Agosta et al. (2012)	7 svPPA	Gorno-Tempini et al. (2011)	71.5 ± 6.5	5.6 ± 1.5	20.4 ± 8.6
	27 HC		68.9 ± 5.9		
Boxer et al. (2003)	11 svPPA	Neary et al. (1998)	66.2 ± 9.8	n.a.	21.7 ± 7.1
	15 HC		65.1 ± 8.3		29.5 ± 0.5
Brambati et al. (2009)	13 svPPA	Neary et al. (1998)	62.0 ± 6.3	3.2 ± 1.1	22.0 ± 6.9
	6 svPPA		63.1 ± 6.3	5.7 ± 3.7	27.0 ± 2.6
	25 HC		64.8 ± 6.9		29.6 ± 0.8
Desgranges et al. (2007)	10 svPPA	Neary et al. (1998)	65.7 ± 8.6	3.3 ± 2.5	24.2 ± 3.08
	17 HC		65.8 ± 7.4		n.a.
Gorno-Tempini et al. (2004)	10 svPPA	Neary et al. (1998)	63.0 ± 5.8	4.0 ± 1.2	23.1 ± 6.5
	64 HC	Gorno-Tempini et al. (2004)	68.2 (56-81)		n.a.
Grossman et al. (2004)	8 svPPA	McKhann et al. (2001)	65.5 ± 13	3.46 ± 3.27	23.8 ± 4.6
	12 HC	Neary et al. (1998) The L&MG (1994)	68.5 ± 9.4		n.a.
Halpern et al. (2004)	3 svPPA	McKhann et al. (2001)	67.73 ± 8.75	4.72 ± 1.73	22.87 ± 3.72
	12 HC	Neary et al. (1998) The L&MG (1994)	matched		
Josephs et al. (2008)	15 svPPA	Neary et al. (1998)	64 (54-74)	3.7´(0.7-0.5)	21 (9-28)
	12 svPPA		64 (49-77)	3.4 (1.2-5.4)	26 (18-29)
	27 HC		64 (53-75)		29 (27-30)
Josephs et al. (2009)	8 svPPA	Neary et al. (1998)	68 (56-73)	n.a.	26 (20-27)
	30 HC		matched		
Mummery et al. (2000)	6 svPPA	Neary et al. (1998)	60.5 (58-65)	n.a.	n.a.
	14 HC		62 (60–65)		
Noppeney et al. (2007)	6 svPPA	The L&MG (1994)	61.17 (59-66)	n.a.	21.83
	60 HC				
Pereira et al. (2009)	8 svPPA	Neary et al. (1998)	62.9 ± 6.40	5.0 ± 2.52	21.0 ± 5.86
	25 HC		63.8 ± 7.20		29.3 ± 0.84

Schwindt et al. (2011)	9 svPPA 16 HC	Neary et al. (1998) Gorno-Tempini et al. (2011)	67.6 ±7.6	6.4 ± 2.7	19.9 ± 8.4
Wilson et al. (2009)	5 svPPA 48 HC	Neary et al. (1998)	61.4 ± 4.8 61.5 ± 10.3	5.9 ± 1.7	24.2 ± 4.8 n.a.
Wilson et al. (2010)	25 svPPA 10 HC	Neary et al. (1998)	66.7 ± 6 68.5 ± 5.9	8.9 ± 3.1	22 ± 6.2 29.5 ± 0.5
SvPPA PET					
Desgranges et al. (2007)	10 svPPA 17 HC	Neary et al. (1998)	65.7 ± 8.6 65.8 ± 7.4	3.3 ± 2.5	24.2 ± 3.08 n.a.
Diehl et al. (2004)	9 svPPA 15 HC	The L&MG (1994)	62.1 ± 3.6 61.8 ± 9.1	4 ± 4.05	25.00 ± 3.55 n.a.
Diehl-Schmid et al. (2006)	8 svPPA 15 HC	Neary et al. (1998)	62.8 ± 3.8 61.8 ± 9.1	4.38 ± 3.34 4.4 ± 3.1	25.1 ± 4.8 n.a.
Drzezga et al. (2008)	8 svPPA 26 HC	Neary et al. (1998)	66.4± 4.9 65.4 ± 10.5	n.a.	19.9 + 6.7 n.a.
Nestor et al. (2006)	9 svPPA 14 HC	Neary et al. (1998)	63.4 ± 7.0 61.4 ± 6.9	3.6 ± 2.1	25.8 ± 3.3 29.8 ± 0.4
Raczka et al. (2010)	7 svPPA 9 HC	The L&MG (1994) Neary et al. (1998)	64.6 ± 3.0 59.3 ± 8.0	n.a.	20.0 ± 10.0 n.a.
Suh et al. (2010)	6 svPPA 13 HC	Neary et al. (1998)	65.0 ± 9.6 71.5 ± 2.0	n.a.	21.7 ± 3.7 n.a.
NfvPPA MRI					
Agosta et al. (2011)	9 nfvPPA	Gorno-Tempini et al. (2011)	67.7 ± 5.1	2.0 ± 1.0	20.0 ± 7.0
Gorno-Tempini et al. (2004)	11 nfvPPA 64 HC	Neary et al. (1998) Gorno-Tempini et al. (2004)	67.9 ± 8.1 68.2 (56-81)	4.4 ± 2.5	26.0 ± 3.4
Gorno-Tempini et al.	6 nfvPPA	Gorno-Tempini et al. (2004)	69.2 ± 8.2	4.5 ± 2.1	26.8 ± 1.3
(2006)	5 nfvPPA 40 HC		62.4 ± 9.5 65.1	4.3 ± 2.1	29.2 ± 0.8
Grossman et al. (2004)	7 nfvPPA	McKhann et al. (2001)	68.9 ± 11.4	3.25 ± 1.88	21.9 ± 7.1
	12 HC	Neary et al. (1998) The L&MG (1994)	68.5 ± 9.4		
Hu et al. (2010)	11 nfvPPA 24 HC	Neary et al. (1998) McKhann et al. (2001) Gorno-Tempini et al. (2008)	65.16 ± 0.45 65.2 ±8.6	3.11.± 1.66	22.58 ± 5.78
Josephs et al. (2006)	3 nfvPPA 12 HC	Neary et al. (1998)	63.3 ± 7.1 matched	5.7 ± 1.2	n.a.
Nestor et al. (2003)	7 nfvPPA 10 HC	Neary et al. (1998)	68.8 ± 7.8 65.9 ± 6.1	3.4 ± 1.4	22.1 ± 7.0 29.8 ± 0.4
Pereira et al. (2009)	3 nfvPPA 25 HC	Neary et al. (1998)	68.33 ± 9.02 63.8 ± 7.20	3.3 ± 2.52	17.7 ± 4.51 29.3 ± 0.84
Schwindt et al. (2011)	9 nfvPPA 16 HC	Neary et al. (1998) Gorno-Tempini et al. (2011)	65.2 ±10.8 70.1 ± 8.7	4.1 ± 2.0	20.0 ± 10.1
Wilson et al. (2010)	14 nfvPPA	Gorno-Tempini et al. (2011)	67.8 ± 8.1	6.3 ± 1.9	25.9 ± 4.1
	10 HC		68.5 ± 5.9		29.5 ± 0.5
Zahn et al. (2005)	5 nfvPPA 10 HC	Neary et al. (1998)	65.0 ± 7.4 65.8 ± 7.8	n.a.	23.0 ± 5.3

NfvPPA PET					
Nestor et al. (2003)	7 nfvPPA 10 HC	Neary et al. (1998)	68.8 ± 7.8 65.9 ± 6.1	3.4 ± 1.4	22.1 ± 7.0 29.8 ± 0.4
Perneczky et al. (2007)	11 nfvPPA 16 HC	Neary et al. (1998)	69.91 ± 8.10 67.88 ± 9.99	3.20 ± 2.04	18.91 ± .76 30.00 ± 0.00
Zahn et al. (2005)	5 nfvPPA 12 HC	Neary et al. (1998)	65.0 ± 7.4 48.0 ± 16.0	n.a	23.0 ± 5.3 n.a.
LvPPA MRI					
Agosta et al. (2011)	4 lvPPA 27 HC	Gorno-Tempini et al. (2011)	66.8 ± 6.4 68.9 ± 5.9	2.5 ± 0.7	19.5 ± 5.2
Gorno-Tempini et al. (2004)	10 lvPPA 64 HC	Neary et al. (1998) Gorno-Tempini et al. (2004)	72.0 ± 8.5 68.2(56–81)	4.5 ± 0.8	22.2 ± 4.6
Gorno-Tempini et al. (2008)	4 lvPPA 40 HC	Gorno-Tempini et al. (2004)	58.75 ± 2.9 matched	3 ± 0	21.5 ± 2.87
Hu et al. (2010)	12 lvPPA 24 HC	Neary et al. (1998) McKhann et al. (2001) Gorno-Tempini et al. (2008)	62.74 ± 8.36 65.2 ±8.6	3.05 ± 1.9	22.28 ± 7.73
Migliaccio et al. (2009)	10 lvPPA 65 HC	Gorno-Tempini et al. (2004)	63.5 ± 7.2 60.7 ± 10.1	3.3 ± 2.1	20.5 ± 4.4 28 ± 1.5
Wilson et al. (2010)	11 lvPPA 10 HC	Gorno-Tempini et al. (2011)	63.5 ± 7.3 68.5 ± 5.9	6 ± 2.8	22.3 ± 6.2 29.5 ± 0.5

Note. HC healthy controls, lvPPA logopenic variant PPA, L&MG Lund and Manchester groups, MMSE Mini-Mental State Examination, MRI magnetic resonance imaging, nfvPPA nonfluent variant PPA, n.a. not available, N number of subjects, PET positron emission tomography, svPPA semantic variant PPA. Age (years), disease duration (years), and MMSE are indicated either as mean (range) or mean ± standard deviation as reported in the respective single studies. The diagnostic criteria were taken as they were from the original studies.

Supplementary *Table A.2*

Results of the subtraction analyses between meta-analyses on semantic variant PPA (magnetic resonance imaging studies versus positron emission tomography studies) and between meta-analyses on different variants of primary progressive aphasia (magnetic resonance imaging studies)

Region	Lat.	BAs	MNI coordinates			Volume (mm^3)	ALE-value
			x	y	z		
SvPPA MRI > PET							
Inferior, middle, & superior temporal gyri/fusiform gyrus/ hippocampus/parahippocampal gyrus/amygdala	R	28/34/38	27	-0	-21	6592	3.2389
Hippocampus/parahippocampal gyrus/amygdala	L	28/34	-26	-4	-20	3504	2.9478
SvPPA PET > MRI							
Thalamus	L		-7	-18	15	280	1.8807
Inferior temporal gyrus /fusiform gyrus	L	20	-48	-22	-32	240	2.2903
SvPPA > nfvPPA & lvPPA							
Inferior, middle, & superior temporal gyri/fusiform gyrus/ hippocampus/parahippocampal gyrus/amygdala	R	28/34/38/	27	-1	-1	8952	3.7190
Inferior temporal gyrus/hippocampus/parahippocampal gyrus	L	20/28	-28	-4	-7	5304	3.7190
Fusiform & parahippocampal gyri	L	20/36	-38	-30	-22	1432	3.1559
Superior temporal gyrus	L	38	-44	15	-3	912	1.9881
Inferior temporal gyrus	L	21/38	-42	-2	-44	664	2.5366
Middle temporal gyrus	R	21	48	10	-44	472	2.9112
Superior temporal gyrus	L	38	-36	14	-42	248	2.1200
NfvPPA > svPPA & lvPPA							
Insula/inferior frontal gyrus	L	6	-42	22	2	944	3.2388
Middle frontal gyrus	L	13/44	-35	42	21	448	2.2903
Superior frontal gyrus	L		-21	-7	62	448	2.9478
Insula	L	13	-40	4	49	424	1.8694
Putamen	L	10	-24	10	-4	416	2.8208
Insula	L	9	-52	14	18	368	1.9172
LvPPA > svPPA & nfvPPA							
Middle & superior temporal gyri	L	13/21/22	-55	-39	9	3352	3.7190
Supramarginal gyrus	L	39/40	-55	-52	33	2184	3.5401
Temporal gyrus	L	21/22	-65	-22	1	1192	3.7190

Note. ALE anatomical likelihood estimation, BAs Brodmann areas, FDG-PET fluorodeoxyglucose positron emission tomography, Lat. lateralization, L left, lvPPA logopenic variant PPA, MNI Montreal Neurological Institute, MRI magnetic resonance imaging, nfvPPA nonfluent variant PPA, R right, svPPA semantic variant PPA.

Supplementary Table A.3

Former diagnostic criteria for primary progressive aphasia

Diagnostic criteria for frontotemporal dementia	
The Lund and Manchester Group (1994) This article focused on the diagnostic features for the behavioral variant of frontotemporal dementia and referred the reader to previous literature (Neary et al., 1993a, 1993b; Snowden et al., 1992) for a more detailed description of the diagnostic features of the language variant of frontotemporal dementia. **Neary and colleagues (1993a, 1993b) & Snowden and colleagues (1992)** *Profile A (anomia/nonfluent)* omission or incorrect use of prepositions and other filler words nonfluent aphasia with a hesitant, broken, telegrammatic style of speech relatively spared comprehension (however difficulties in the understanding of spatial prepositions and of complex syntax) dyslexia and dysgraphia impaired repetition with sound-based/phonemic errors word-finding difficulty, with literal and verbal paraphasias *Profile B (anomia + comprehension disorder/fluent)* impaired confrontation naming and understanding of word meaning relatively preserved reading aloud and writing to dictation spared repetition fluent aphasia with normal articulation, prosody, and syntax naming difficulties a proportion of these patients develops visual associative agnosia verbal paraphasias *Profile C (shared features of profiles A and B*)	**Mc Khann and colleagues (2001)** The development of behavioral or cognitive deficits is manifested by • early and progressive change in personality, characterized by difficulty in modulating behavior, often resulting in inappropriate responses or activities or • early and progressive change in language, characterized by problems with expression of language or severe naming difficulty and problems with word meaning The deficits cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning The course is characterized by a gradual onset and continuing decline in function. The deficits are not due to other nervous system conditions, systemic conditions, or substance-induced conditions The deficits do not occur exclusively during a delirium The disturbance is not better accounted for by a psychiatric diagnosis

Supplementary Table A.3 (continued)

Former diagnostic criteria for primary progressive aphasia

<table>
<tr><th colspan="2">Diagnostic criteria for primary progressive aphasia ((Mesulam, 2001)</th></tr>
<tr><td colspan="2">

Insidious onset and gradual progression of word finding, object-naming, or word-comprehension impairments as manifested during spontaneous conversation or as assessed through formal neuropsychological tests of language
All limitation of daily living activities attributable to the language impairment, for at least 2 years after onset
Intact premorbid language function
Absence of significant apathy, disinhibition, forgetfulness for recent events, visuospatial impairment, visual recognition deficits or sensory-motor dysfunction within the initial 2 years of the illness
Acalculia and ideomotor apraxia may be present even in the first 2 years
Other domains possibly affected after the first 2 years but with language remaining the most impaired function throughout the course of the illness and deteriorating faster than other affected domains
Absence of “specific” causes such as stroke or tumor as ascertained by neuroimaging

</td></tr>
<tr><th colspan="2">Diagnostic criteria for the subtypes of primary progressive aphasia (Neary et al., 1998)</th></tr>
<tr><td>
Progressive nonfluent aphasia

Core diagnostic features

Insidious onset and gradual progression
Nonfluent spontaneous speech with at least one of the following: agrammatism, phonemic paraphasias, anomia

</td><td>
Semantic dementia
Core diagnostic features

Insidious onset and gradual progression
Language Disorder characterized by

Progressive, fluent, empty spontaneous speech
Loss of word meaning, manifest by impaired naming and comprehension
Semantic paraphasias and or

Perceptual disorder characterized by

Prosopagnosia: impaired recognition of identity of familiar faces and/or
Associative agnosia: impaired recognition of object identity

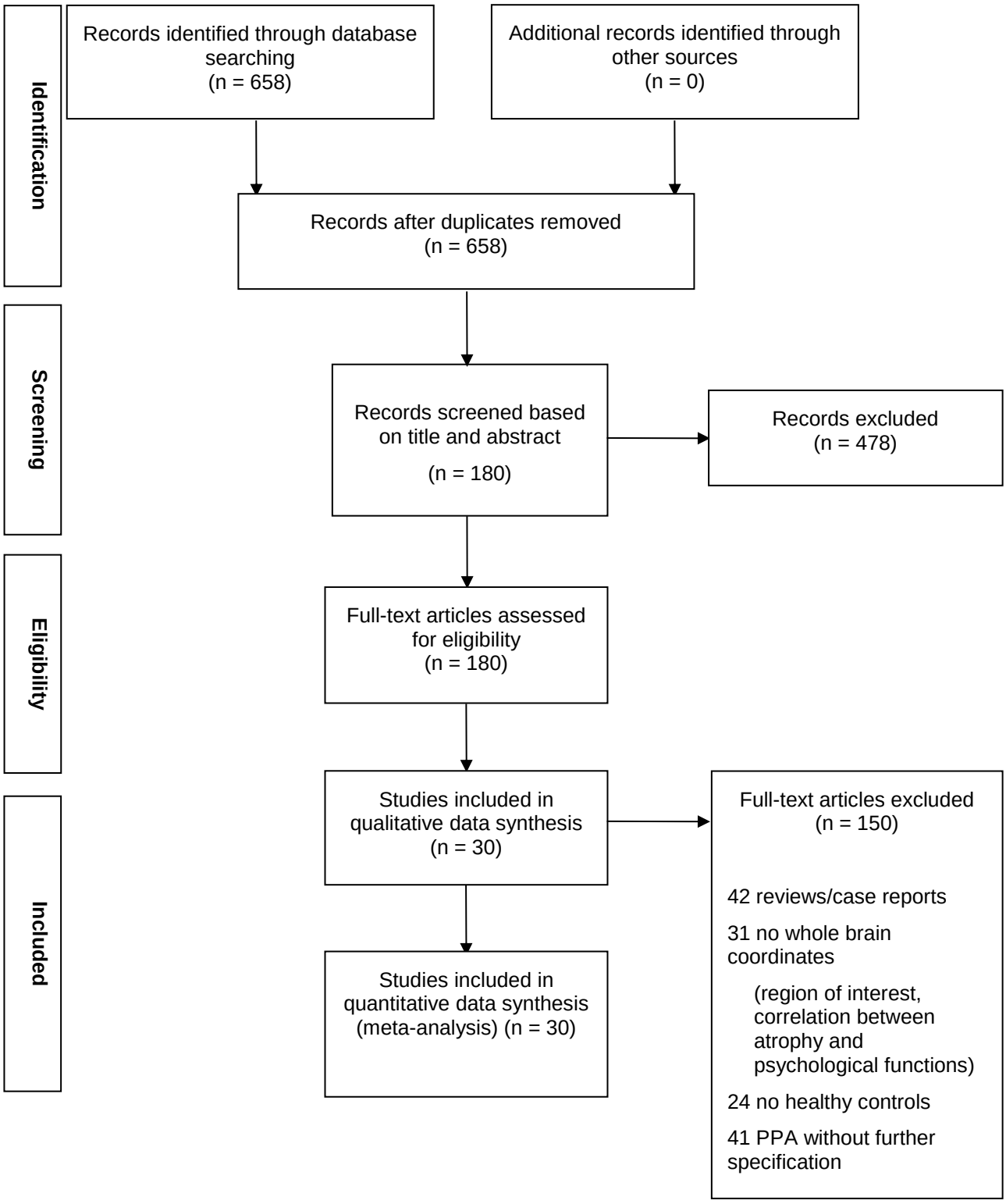
Preserved perceptual matching and drawing reproduction
Preserved single-word repetition
Preserved ability to read aloud and write to dictation orthographically regular words

</td></tr>
</table>

Supplementary Table A.3 (continued)

Former diagnostic criteria for primary progressive aphasia

Diagnostic criteria for the subtypes of primary progressive aphasia (Neary et al., 1998) (continued)	
Supportive diagnostic features • Speech and language ◦ Stuttering or oral apraxia ◦ Impaired repetition ◦ Alexia, agraphia ◦ Early preservation of word meaning ◦ Late mutism • Behavior ◦ Early preservation of social skills ◦ Late behavioral changes similar to FTD • Physical signs ◦ late contralateral primitive reflexes, akinesia, rigidity, and tremor • Investigations ◦ Neuropsychology: nonfluent aphasia in the absence of severe amnesia or perceptuospatial disorder ◦ Electroencephalography: normal or minor asymmetric slowing ◦ Brain imaging (structural and/or functional): asymmetric abnormality predominantly affecting dominant (usually left) hemisphere	Supportive diagnostic features • Speech and language ◦ Press of speech ◦ Idiosyncratic word usage ◦ Absence of phonemic paraphasias ◦ Surface dyslexia and dysgraphia ◦ Preserved calculation • Behavior ◦ Loss of sympathy and empathy ◦ Narrowed preoccupations ◦ Parsimony • Physical signs ◦ Absent or late primitive reflexes ◦ Akinesia, rigidity, and tremor • Investigations • Neuropsychology ◦ Profound semantic loss, manifest in failure of word comprehension and naming and/or face and object recognition ◦ Preserved phonology and syntax, and elementary perceptual processing, spatial skills, and day-to-day memorizing • Electroencephalography: normal • Brain imaging (structural and/or functional): predominant anterior temporal abnormality (symmetric or asymmetric)



Supplementary Figure A: PRISMA 2009 Flow Diagram of the study selection for the meta-analyses on primary progressive aphasia

Supplementary references A

Reference list of the studies included in the ALE meta-analyses on primary progressive aphasia.

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7.1.B Supplementary material for "Validating New Diagnostic Imaging Criteria for Primary Progressive Aphasia via ALE Meta-analyses"

Supplementary Table B.1
Demographic and clinical characteristics of the investigated subject groups

	nfvPPA (HC_{nfvPPA})	svPPA (nfvPPA)	svPPA (lvPPA)	lvPPA (HC_{lvPPA})	nfvPPA (lvPPA)	svPPA (HC_{svPPA})	HC_{svPPA}	HC_{nfvPPA}	HC_{lvPPA}
number	16	16	11	11	11	17	17	16	11
gender (m/f)	8/8	10/6	5/6	4/7	5/6	11/6	9/8	9/7	5/6
scanning	11/5	11/5	10/1	10/1	10/1	12/5	12/5	11/5	10/1
age(years)	67.50 ± 7.42	63.38 ± 7.17	64.36 ± 7.66	65.36 ± 6.25	67.27 ± 7.21	62.53 ± 7.77	66.00 ± 7.79	68.38 ± 7.15	63.45 ± 7.01
education (years)	13.19 ± 4.29	15.13 ± 3.34	14.82 ± 3.66	13.27 ± 3.35	13.82 ± 3.71	15.35 ± 3.37	14.59 ± 2.96	13.88 ± 3.24	14.36 ± 3.33
disease duration	2.19 ± 1.60	3.56 ± 2.53	3.66 ± 2.69	3.64 ± 2.66	2.45 ± 1.75	3.59 ± 2.45	-	-	-
Total grey matter	0.54 ± 0.08	0.50 ± 0.09	0.54 ± 0.08	0.51 ± 0.09*	0.57 ± 0.07	0.52 ± 0.08***	0.59 ± 0.05	0.59 ± 0.05	0.60 ± 0.05
CDR	3.44 ± 3.20***	5.09 ± 4.22	4.86 ± 4.43	4.64 ± 4.43**	4.23 ± 3.58	5.32 ± 4.19***	0.00 ±0.00	0.03 ± 0.13	0.00 ±0.00
FTLD-CDR	5.94 ± 4.07***	7.50 ± 5.37	7.45 ± 5.71	6.86 ± 5.81**	7.09 ± 4.25	7.88 ± 5.44***	0.03 ± 0.12	0.06 ± 0.17	0.05 ± 0.15
CERAD Plus									
MMSE	19.94 ± 7.25**	19.31 ± 8.35	19.09 ± 9.76	22.10 ± 6.03**	19.09 ± 8.07	19.31 ± 8.35***	28.71 ± 0.92	28.06 ± 2.84	28.91 ± 0.83
word list memory	13.07 ± 6.61***	13.92 ± 8.35	16.00 ± 7.57	11.64 ± 8.93**	12.90 ± 7.74	13.92 ± 7.62***	23.56 ±3.14	22.33 ± 4.08	22.73 ± 3.13
word list recall	4.33 ± 2.62**	3.77 ± 3.30	4.56 ± 3.32	3.73 ± 3.88*	4.10 ± 2.85	3.77 ± 3.30 ***	8.25 ± 2.49	7.47 ± 2.90	7.55 ± 2.73
word list	8.57 ± 2.41	8.85 ± 1.41	9.00 ± 1.50	9.10 ± 1.20	8.00 ± 2.85	8.85 ± 1.41***	9.81 ± 0.54	9.73 ± 0.59	9.73 ± 0.65
word list	9.57 ± 0.65	7.69 ± 2.63	7.78 ± 2.99	8.40 ± 3.34	9.67 ± 0.50	7.69 ± 2.63***	10.00 ± 0.00	9.87 ± 0.52	10.00 ± 0.00
constructional praxis	9.06 ± 1.95***	10.00 ± 2.08	10.30 ± 1.34	8.18 ± 3.31*	9.45 ± 1.51	10.00 ± 2.08	11.00 ± 0.00	11.00 ± 0.00	11.00 ± 0.00
constructional praxis recall	6.75 ± 2.86*	6.31 ±4.31	7.22 ± 3.77	4.55 ± 4.28**	7.0 ± 2.93	6.31 ± 4.31***	9.69 ±1.70	9.20 ± 2.15	9.27 ± 1.90
Trail Making Test A (s)	94.38 ± 46.95***	67.00 ± 42.76	74.56 ± 47.51	75.80 ± 51.33*	102.64 ± 52.90	75.96 ± 51.56***	35.94 ± 9.36	41.80 ± 17.62	38.45 ± 10.41
Trail Making Test B (s)	220.18 ± 91.33***	123.70 ± 72.24	130.57 ± 87.21	201.13 ± 84.47**	222.71 ± 85.76	123.70 ± 72.24	75.44 ± 20.37	77.29 ± 20.23	78.64 ± 21.77
Boston Naming Test	9.93 ± 4.76**	6.47 ± 4.26	6.50 ± 4.58	10.18 ± 3.98**	8.64 ± 4.93	6.47 ± 4.26***	14.81 ± 0.54	14.00 ± 2.83	14.73 ± 0.65
Verbal Fluency Test	8.06 ± 7.34***	8.00 ± 5.01	8.50 ± 5.74	12.09 ± 8.49***	6.27 ± 5.68	8.00 ± 5.01***	26.76 ± 4.88	25.06 ± 7.68	25.82 ± 5.65
Phonemic Fluency Test	3.87 ± 4.09***	7.23 ± 5.29	7.78 ± 5.93	6.80 ± 4.52***	3.50 ± 3.78	7.23 ± 5.29***	17.59 ± 5.06	16.85 ± 6.56	17.36 ± 5.22
Repeat and Point									
Repeat Task	7.93 ± 2.34*	8.93 ± 1.98	9.44 ± 1.33*	6.80 ± 3.36*	9.00 ± 1.25	8.93 ± 1.98	9.93 ± 0.26	9.79 ± 0.58	10.00 ± 0.00
Point Task	8.53 ± 1.55*	6.14 ± 2.85**	6.22 ± 2.64	8.10 ± 1.91*	8.10 ± 1.60	6.14 ± 2.85	10.00 ± 0.00	9.71 ±0.73	

CDR clinical dementia rating scale, global score, CERAD Consortium to Establish a Registry for Alzheimer's Disease; FTLD frontotemporal lobar degeneration, HC healthy controls, lvPPA logopenic variant PPA, MMSE Mini-Mental State Examination, nfvPPA nonfluent/agrammatic variant PPA, PPA primary progressive aphasia, svPPA semantic variant PPA. Note age, education, disease duration, CDR, FTLD-CDR, CERAD Plus, and Repeat and Point Test are indicated as mean ± standard deviation. Note that data was missing for a few subjects on some subtests of the CERAD Plus and the Repeat and Point Test. Pairwise group-level comparisons were performed using independent t tests (normally distributed data) and Mann-Whitney U tests (not normally distributed data). Asterisks denote the level of significance *p≤0.05; **p≤0.01; ***p≤0.001.

Supplementay Table B.2

Voxel-based morphometry results for the three variants of PPA as compared to healthy controls

region	Lat.	MNI coordinates			*p*-value	T-value
		x	y	z		
Nonfluent variant PPA < healthy controls						
Inferior, middle, and superior temporal gyri/parahippocampal gyrus/hippocampus/amygdala/orbital gyri/putamen/insula/inferior frontal gyrus/angular gyrus/supramarginal gyrus	L	-42	-16	10	< 0.0001	6.92
		-42	-12	18		6.14
		-18	-15	-12		6.09
Inferior frontal gyrus/precentral gyrus/middle frontal gyrus	L	-52	8	31	< 0.0001	5.86
		-28	5	52		5.43
		-30	-10	63		4.68
Middle frontal gyrus/superior frontal gyrus	L	-26	48	21	< 0.0001	5.82
		-6	63	12		5.80
		-21	41	24		5.61
Inferior frontal gyrus, pars orbitalis/insula		34	24	9	0.036	4.82
Semantic variant PPA < healthy controls						
Inferior, middle, and superior temporal gyri/fusiform gyrus/parahippocampal gyrus/hippocampus/amgdala/gyrus rectus/orbital gyrus/insula /inferior frontal gyrus/cingulate gyrus/putamen/caudate nucleus/angular gyrus	L/R	-27	2	-36	< 0.0001	13.98
		-15	3	-45		11.98
		-44	-15	-45		11.58
Superior frontal gyrus/cingulate gyrus	L	-3	15	34	0.009	4.65
		-3	2	42		4.30
		-3	44	19		4.30
Logopenic variant PPA < healthy controls						
Inferior, middle, and superior temporal gyri/fusiform gyrus/middle occipital gyrus/gyrus rectus/orbital gyrus/putamen/caudate nucleus/thalamus/insula/inferior frontal gyrus, pars orbitalis/middle frontal gyrus/superior frontal gyrus/cingulate gyrus/precentral gyrus/postcentral gyrus/angular gyrus/precuneus/supramarginal gyrus	L	-32	26	9	< 0.0001	10.29
		-46	-52	4		8.41
		-30	3	52		7.72
Middle and superior temporal gyri	R	69	-40	9	< 0.0001	5.75
		54	-25	-11		5.36
		50	-27	1		5.25
Cingulate gyrus/precuneus	L	-12	-54	27	0.040	6.08
		-15	-49	42		5.14
Semantic variant PPA < nonfluent variant PPA						
Inferior, middle, and superior temporal gyri/fusiform gyrus/parahippocampal gyrus/hippocampus/amgydala/insula	L	-16	3	-44	< 0.0001	7.99
		-33	-25	-30		7.92
		-22	12	-32		7.22
Inferior, middle, and superior temporal gyri/fusiform gyrus/parahippocampal gyrus/hippocampus/amgydala/insula	R	42	-4	-29	< 0.0001	6.50
		36	4	-32		6.16
		45	27	-33		5.93

Note. Lat. Lateralization, MNI Montreal Neurological Institute, PPA primary progressive aphasia.

Supplementary Table B.3

Positive and negative predictive values for the support vector machine classification results between the three variants of primary progressive aphasia and healthy controls as well as between PPA variants

	Positive predictive value	Negative predictive value
nfvPPA versus healthy controls		
regions-of-interest	87 %	82 %
whole brain	93 %	88 %
svPPA versus healthy controls		
regions-of-interest	100 %	100 %
whole brain	100 %	94 %
lvPPA versus healthy controls		
regions-of-interest	82 %	82 %
whole brain	100 %	92 %
svPPA versus nfvPPA		
regions-of-interest	76 %	80 %
whole brain	76 %	80 %
lvPPA versus svPPA		
regions-of-interest	92 %	100 %
whole brain	92 %	100 %
lvPPA versus nfvPPA		
regions-of-interest	62 %	67 %
whole brain	54 %	56 %

Note. LvPPA logopenic variant PPA, nfvPPA nonfluent/agrammatic variant PPA, PPA primary progressive aphasia, svPPA semantic variant PPA. Positive predictive value=true positives (patients that were correctly classified as patients)/all subjects that were (correctly or incorrectly) classified as patients. Negative predictive value=true negatives (healthy controls that were correctly classified as healthy controls)/all subjects that were (correctly or incorrectly) classified as healthy controls. For svPPA versus nfvPPA, the positive predictive value refers to the number of correctly classified svPPA patients/all patients that were (correctly or incorrectly) classified as svPPA patients, while the negative predictive value refers to the number of correctly classified nfvPPA patients/all patients that were (correctly or incorrectly) classified as nfvPPA patients. For lvPPA versus svPPA/nfvPPA, the positive predictive value refers to the number of correctly classified lvPPA patients/all patients that were (correctly or incorrectly) classified as lvPPA patients, while the negative predictive value refers to the number of correctly classified svPPA/nfvPPA patients/all patients that were (correctly or incorrectly) classified as svPPA/nfvPPA patients.

7.2 Declaration of contribution (Erklärung über den Beitrag zur Publikation)

Erklärung über den wissenschaftlichen Beitrag des Promovenden zur Publikation

Hiermit erkläre ich in meinem Namen und dem Namen aller Koautoren, folgenden Beitrag zur Publikation „Validating New Diagnostic Imaging Criteria for Primary Progressive Aphasia via ALE Meta-analyses“ geleistet zu haben: (Mit)Konzeption der Studie, Durchführung der Literaturrecherche sowie der statistischen Analysen, Erstellung der Abbildungen und Tabellen, Interpretation der Ergebnisse, Verfassen der Publikation.

Leipzig, 05.02.2017 ....

Datum Unterschriften

Hiermit erkläre ich in meinem Namen und dem Namen aller Koautoren, folgenden Beitrag zur Publikation „Predicting Primary Progressive Aphasia with Support Vector Machine Approaches in structural MRI data“ geleistet zu haben: (Mit)Konzeption der Studie, Beitrag zur Datenerhebung, Durchführung der statistischen Analysen, Erstellung der Abbildungen und Tabellen, Interpretation der Ergebnisse, Verfassen der Publikation.

Leipzig, 05.02.2017 ....

Datum Unterschriften

7.3 Declaration of authenticity (Eigenständigkeitserklärung)

Erklärung über die eigenständige Abfassung der Arbeit

Hiermit erkläre ich, dass ich die vorliegende Arbeit selbstständig und ohne unzulässige Hilfe oder Benutzung anderer als der angegebenen Hilfsmittel angefertigt habe. Ich versichere, dass Dritte von mir weder unmittelbar noch mittelbar eine Vergütung oder geldwerte Leistungen für Arbeiten erhalten haben, die im Zusammenhang mit dem Inhalt der vorgelegten Dissertation stehen, und dass die vorgelegte Arbeit weder im Inland noch im Ausland in gleicher oder ähnlicher Form einer anderen Prüfungsbehörde zum Zweck einer Promotion oder eines anderen Prüfungsverfahrens vorgelegt wurde. Alles aus anderen Quellen und von anderen Personen übernommene Material, das in der Arbeit verwendet wurde oder auf das direkt Bezug genommen wird, wurde als solches kenntlich gemacht. Insbesondere wurden alle Personen genannt, die direkt an der Entstehung der vorliegenden Arbeit beteiligt waren. Die aktuellen gesetzlichen Vorgaben in Bezug auf die Zulassung der klinischen Studien, die Bestimmungen des Tierschutzgesetzes, die Bestimmungen des Gentechnikgesetzes und die allgemeinen Datenschutzbestimmungen wurden eingehalten. Ich versichere, dass ich die Regelungen der Satzung der Universität Leipzig zur Sicherung guter wissenschaftlicher Praxis kenne und eingehalten habe.

Leipzig, 07.04.2017 .....

Datum Unterschrift

7.4 Curriculum vitae

Personal data

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Education

since 04/2012	department of Neurology, Max-Planck-Institute for Human Cognitive and Brain Sciences (MPI), Leipzig PhD: *Validation of diagnostic imaging criteria for primary progressive aphasia* (Prof. Dr. Dr. Matthias L. Schroeter)
05/2011-04/2012	diploma thesis: *Neural correlates of visual consciousness* (Prof. Dr. Dr. Matthias L. Schroeter, MPI Leipzig, Prof. Dr. Julius Kuhl, University of Osnabrück)
10/2006-04/2012	diploma in Psychology, Department of Psychology, University of Osnabrück
06/2006	Abitur, Lycée Hubert Clément Esch (Esch/Alzette in Luxembourg)

7.5 List of publications

2017

Bisenius, S., Mueller, K., Diehl-Schmid, J., Fassbender, K., Grimmer, T., Jessen, F., Kassubek, J., Kornhuber, J., Landwehrmeyer, B., Ludolph, A., Schneider, A., Anderl-Straub, S., Stuke, K., Danek, A., Otto, M., Schroeter, M. L., & FTLDc study group. (2017). Predicting primary progressive aphasias with support vector machine approaches in structural MRI data. *NeuroImage: Clinical, 14*, 334–343.

Albrecht, F., **Bisenius, S.,** Schaack, R. M., Neumann, J., & Schroeter, M. L. (2017). Disentangling the neural correlates of corticobasal syndrome & corticobasal degeneration with systematic & quantitative ALE meta-analyses. *npj Parkinson's Disease, 3*(12), 1–8.

Meyer, S., Mueller, K., Stuke, K., **Bisenius, S.,** Diehl-Schmid, J., Jessen, F., Kassubek, J., Kornhuber, J., Ludolph, A.C., Prudlo, J., Schneider, A., Schuemberg, K., Yakushev, I., Otto, M., Schroeter, M.L., & FTLDc study group (2017). Predicting behavioral variant frontotemporal dementia with pattern classification in multi-center structural MRI data. *NeuroImage: Clinical, 14*, 656–662.

2016

Bisenius, S., Neumann, J., & Schroeter, M. L. (2016). Validating new diagnostic imaging criteria for primary progressive aphasia via anatomical likelihood estimation meta-analyses. *European Journal of Neurology, 23*(4), 704–712.

Bisenius, S., Neumann, J., & Schroeter, M. L. (2016). Response to the letter on 'Validating new diagnostic imaging criteria for primary progressive aphasia via anatomical likelihood estimation meta-analyses'. *European Journal of Neurology, 23*(8), e52–3.

Teipel, S., Raiser, T., Riedl, L., Riederer, I., Schroeter, M.L., **Bisenius, S.,** Schneider, A., Kornhuber, J., Fliessbach, K., Spottke, A., Grothe, M.J., Prudlo, J., Kassubek, J., Ludolph, A., Landwehrmeyer, B., Straub, S., Otto, M.,* Danek, A.,* & the FTLDc study group (2016). Atrophy and structural covariance of the cholinergic basal forebrain in primary progressive aphasia. *Cortex, 83*,124–135.

2015

Bisenius, S., Trapp, S., Neumann, J. & Schroeter, M.L. (2015) Identifying neural correlates of visual consciousness with ALE meta-analyses. *Neuroimage, 122*, 177–187.

7.6 List of conference contributions

Talks

2016

Bisenius, S. Imaging data in PPA: Results from meta-analyses and support vector machine classification in patients enrolled in the study of the FTLD-consortium. Paper presented at the colloquium of the Disease oriented competence network degenerative dementias (KNDD), Göttingen, Germany.

2015

Bisenius, S., Müller, K., Danek, A., Diehl-Schmid, J., Fassbender, K., Foerstl, H., Giese, A., Jahn, H., Jessen, F., Kassubek, J., Landwehrmeyer, B., Lauer, M., Ludolph, A. C., Otto, M., Prudlo, J., Schneider, A., Stuke, K., & Schroeter, M. L. (2015, November). Support vector machine classification enables detection of primary progressive aphasia subtypes with MRI. Paper presented at the Annual Meeting of the German Association for Psychiatry, Psychotherapy and Psychosomatics, Berlin, Germany.

Schroeter, M. L., Meyer, S., Stuke, K., **Bisenius, S.,** Neumann, J., Mueller, K., Otto, M., & FTLD-Konsortium Germany (2015, November). Meta-analyses and pattern classification of imaging data enable prediction of behavioral variant frontotemporal dementia. Paper presented at the Annual Meeting of the German Association for Psychiatry, Psychotherapy and Psychosomatics, Berlin, Germany.

Stuke, K., Holiga, S., **Bisenius, S.,** Kassubek, J., Prudlo, J., Otto, M., & Schroeter, M. L. (2015, November). Behavioral Variant Frontotemporal Dementia Patients Reveal Changes in Functional Connectivity in Cingulate Cortex – Data from the German FTLD Consortium. Paper presented at the Annual Meeting of the German Association for Psychiatry, Psychotherapy and Psychosomatics, Berlin, Germany.

2014

Bisenius, S., Neumann, J., Schroeter, M. L. (2014, November). Validation of the new diagnostic imaging criteria for the subtypes of primary progressive aphasia using ALE meta-analyses. Paper presented at the Annual Meeting of the German Association for Psychiatry, Psychotherapy and Psychosomatics, Berlin, Germany.

Stuke, K., Mueller, K., Bisenius, S., Danek, A., Diehl-Schmid, J., Fassbender, K., Foerstl, H., Giese, A., Jahn, H., Jessen, F., Kassubek, J., Kornhuber, J., Landwehrmeyer, B., Lauer, M., Ludolph, A. C., Otto, M., Prudlo, J., Schneider, A., Schroeter, M. L., & FTLD Study Group Germany. (2014, November). Voxel-based morphometry in behavioral variant frontotemporal dementia – Data from the multicentric FTLD consortium's study Germany. Paper presented at the Annual Meeting of the German Association for Psychiatry, Psychotherapy and Psychosomatics, Berlin, Germany.

Müller, K., Bisenius, S., Danek, A., Diehl-Schmid, J., Fassbender, K., Foerstl, H., Giese, A., Jahn, H., Jessen, F., Kassubek, J., Kornhuber, J., Landwehrmeyer, B., Lauer, M., Ludolph, A. C., Otto, M., Prudlo, J., Schneider, A., Stuke, K., Schroeter, M. L., & FTLD Study Group Germany (2014, November). Investigating brain structure in different FTLD subtypes using voxel-based morphometry – Data from the multicentric FTLD consortium's study Germany. Paper presented at the Annual Meeting of the German Association for Psychiatry, Psychotherapy and Psychosomatics, Berlin, Germany.

Poster

2016

Bisenius, S., Mueller, K., Diehl-Schmid, J., Fassbender, K., Jessen, F., Kassubek, J., Kornhuber, J., Schneider, A., Stuke, K., Danek, A., Otto, M., Schroeter, M. L., & FTLD Study Group Germany. (2016, August/September). Classifying primary progressive aphasias individually with support vector machine approaches in MRI data. Poster presented at the 10th International Conference on Frontotemporal Dementias (ICFTD), Munich, Germany.

Albrecht, A., **Bisenius, S.,** Schaack, R. M., & Schroeter, M. L. (2016, August/September). Disentangling the neural correlates of corticobasal syndrome & corticobasal degeneration with systematic & quantitative ALE meta-analyses. Poster presented at the 10th International Conference on Frontotemporal Dementias (ICFTD), Munich, Germany.

Meyer, S., Mueller, K., **Bisenius, S.,** Diehl-Schmid, J., Foerstl, H., Fassbender, K., Kassubek, J., Landwehrmeyer, B., Ludolph, A. C., Kornhuber, J., Prudlo, K., Schneider, A., Stuke, K., Schroeter, M. L. (2016, August/September). Neurofilament light chain protein concentration in CSF and atrophy are correlated in bvFTD patients –Data from the multicentric FTLD consortium's study. Poster presented at the 10th International Conference on Frontotemporal Dementias (ICFTD), Munich, Germany.

2015

Mueller, K., **Bisenius, S.,** Danek, A., Diehl-Schmid, J., Fassbender, K., Foerstl, H., Giese, A., Jahn, H., Jessen, F., Kassubek, J., Kornhuber, J., Landwehrmeyer, B., Lauer, M., Ludolph, A. C., Otto, M., Prudlo, J., Schneider, A., Stuke, K., Schroeter, M. L. (2015, May/June). Characterizing Neurodegeneration in Progressive Supranuclear Palsy Using VBM and SVM Classification. Poster presented at the ISMRM 23rd Annual Meeting and Exhibition, Toronto, Ontario, Canada.

Schroeter, M. L., Meyer, S., Stuke, K., **Bisenius, S.,** Otto, M., Neumann, J., Mueller, K. (2015, June). Predicting behavioral variant FTD with metaanalyses & pattern classification of imaging data. Poster presented at the 21th Annual Meeting of the Organization for Human Brain Mapping, Honolulu, Hawai.

Stuke, K., Holiga, S., **Bisenius, S.,** Kassubek, J., Prudlo, J., Otto, M., Schroeter, M. L. (2015, June). Reduced Functional Connectivity in Cingulate Cortex in Behavioral Variant Frontotemporal Dementia. Poster presented at the 21th Annual Meeting of the Organization for Human Brain Mapping, Honolulu, Hawai.

2014

Bisenius, S., Neumann, J., Schroeter, M. L. (2014, October). Validation of the new diagnostic imaging criteria for primary progressive aphasia by ALE meta-analyses. Poster presented at the 9th International Conference on Frontotemporal Dementias (ICFTD), Vancouver, Canada.

Bisenius, S., Müller, K., Danek, A., Diehl-Schmid, J., Fassbender, K., Foerstl, H., Giese, A., Jahn, H., Jessen, F., Kassubek, J., Kornhuber, J., Landwehrmeyer, B., Lauer, M., Ludolph, A. C., Otto, M., Prudlo, J., Schneider,A., Stuke, & K., Schroeter, M. L. (2014, October). Voxel-based morphometry in primary progressive aphasia and its subtypes–data from the multicentric FTLD consortium's study Germany. Poster presented at the 9th International Conference on Frontotemporal Dementias (ICFTD), Vancouver, Canada.

Bisenius, S., Müller, K., Danek, A., Diehl-Schmid, J., Fassbender, K., Foerstl, H., Giese, A., Jahn, H., Jessen, F., Kassubek, J., Kornhuber, J., Landwehrmeyer, B., Lauer, M., Ludolph, A. C., Otto, M., Prudlo, J., Schneider, A., Stuke, & K., Schroeter, M. L. (2014, November). Investigating primary progressive aphasia with MRI in the multicentric FTLD consortium's study. Poster presented at the Annual Meeting of the German Association for Psychiatry, Psychotherapy and Psychosomatics, Berlin, Germany.

Mueller, K., **Bisenius, S.,** Danek, A., Diehl-Schmid, J., Fassbender, K., Foerstl, H., Giese, A., Jahn, H., Jessen, F., Kassubek, J., Kornhuber, J., Landwehrmeyer, B., Lauer, M., Ludolph, A. C., Otto, M., Prudlo, J., Schneider, A., Stuke, K., Schroeter, M. L., & FTLD Study Group Germany. (2014, October) Investigating brain structure in different FTLD subtypes using voxel-based morphometry – data from the multicentric FTLD consortium's study Germany. Poster presented at the 9th International Conference on Frontotemporal Dementias (ICFTD), Vancouver, Canada.

Stuke, K., Mueller, K., **Bisenius, S.,** Danek, A., Diehl-Schmid, J., Fassbender, K., Foerstl, H., Giese, A., Jahn, H., Jessen, F., Kassubek, J., Kornhuber, J., Landwehrmeyer, B., Lauer, M., Ludolph, A. C., Otto, M., Prudlo, J., Schneider, A., Schroeter, M. L., & FTLD Study Group Germany. (2014, October). Voxel-based morphometry in behavioral variant frontotemporal dementia – data from the multicentric FTLD consortium's study Germany. Poster presented at 9th International Conference on Frontotemporal Dementias (ICFTD), Vancouver, Canada.

2013

Bisenius, S., Trapp, S., Neumann, J. & Schroeter, M. L. (2013, June). Identifying neural correlates of visual consciousness with ALE meta-analyses. Poster presented at the 19th Annual Meeting of the Organization for Human Brain Mapping, Seattle, WA, USA.

Bisenius, S., Trapp, S., Neumann, J. & Schroeter, M. L. (2013, November). Identifying neural correlates of visual consciousness with ALE meta-analyses. Poster presented at the Annual Meeting of the German Association for Psychiatry, Psychotherapy and Psychosomatics, Berlin, Germany.

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