Structural and Physiological Observations in Biomarker-Defined Primary Progressive Aphasia

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Chapter 1 Introduction

1.1 A Historical View on Primary Progressive Aphasia

Besides Alzheimer dementia (AD) as the most common form of dementia, other rare forms of dementia exist that have very distinct deficits. Those can help to understand the fundamentals of cognition. Primary progressive aphasia (PPA) is an umbrella term for forms of dementia that are characterised by a prominent loss of language function while initial preservation of other cognitive domains. In modern medical science, Mesulam was the first to report PPA patients. He published a case series of six patients with aphasic symptoms and a progressive, neurodegenerative disorder without impairment of other cognitive domains (Mesulam, 1982). Even before, reports about single cases of PPA have been published but the authors did not know the term PPA at that time (Pick, 1892; Sérieux, 1893). Nevertheless, the description of symptoms and atrophy patterns gave rise to today's diagnosis PPA. The first historical publication reported a patient with progressive language disturbance in late life (Pick, 1892). In addition, the patient presented with behavioural symptoms and progressive memory loss besides the language impairment. In post-mortem examination of the brain, Pick found a frontotemporal atrophy pattern and claimed this causative for symptoms in the patient. One year later, Paul Sérieux reported a patient with similar post-mortem atrophy (Sérieux, 1893). In contrast to the Pick case, his patient presented with isolated and progressive language impairment without additional cognitive deficits. Sérieux's patient is the first description of a patient suffering from primary progressive aphasia. Even though, Mesulam's 1982 publication was not the first description of a patient with progressive aphasia it channelled a research interest

in PPA syndromes in modern medicine. After his first PPA publication Mesulam and other authors published more cases of slowly progressive aphasia (Chawluk et al., 1986; Heath et al., 1983). On the basis of available histological information it was stated that non-Alzheimer (AD) pathology was causative for the progressive aphasia (Mesulam, 1987). While most of the described PPA patients were non-fluent, other authors described a fluent, progressive aphasic entity, namely semantic dementia (Snowden, 1989). The semantic dementia (SD) patients had fluent speech with a profound loss of semantic knowledge, arising from a modality-unspecific loss of conceptual knowledge. Nearly one decade later, a consensus meeting on frontotemporal lobar degeneration (Neary et al., 1998) proposed three distinct clinical entities in the spectrum of frontotemporal lobar degeneration (FTLD); namely frontotemporal dementia (FTD), semantic dementia (SD), and progressive nonfluent aphasia (PNFA). While FTD was a behavioural syndrome, SD and PNFA presented with language deficits, putting those together under the umbrella term PPA. The commonality of the three FTLD syndromes was neurodegeneration in frontal and temporal lobe structures and a strong association with non-Alzheimer pathology. The clinical appearance of each entity was believed to depend on the distribution of pathology.

A consequence of two definite PPA variants was patients with the root diagnosis PPA who did not fulfil criteria for SD and PNFA. In 2004, a third clinical entity in the PPA spectrum was proposed, described, and named logopenic progressive aphasia (LPA; Gorno-Tempini et al. 2004). Further studies found a link between LPA and Alzheimer pathology (Kas et al., 2012; Leyton et al., 2011) and LPA was suspected to represent an atypical form of Alzheimer's disease (Ahmed et al., 2012; Rohrer et al., 2012). In 2011, clinical diagnostic recommendations for the diagnosis of PPA and its subtypes

were published (Gorno-Tempini et al., 2011) and provided a framework for uniform diagnosis of PPA variants. The published clinical consensus criteria for PPA defined three syndromes; namely the semantic variant (svPPA), the agrammatic/nonfluent variant (nfvPPA), and the logopenic variant of PPA (lvPPA). Since this publication, some authors have speculated that lvPPA, as defined by strictly applying the diagnostic criteria, is extremely rare (Giannini et al., 2017; Hoffman et al., 2017; Mesulam et al., 2012; Sajjadi et al., 2014). Recently, the term "lvPPA+" was introduced for PPA patients with AD pathology who presented with more extensive language features than captured by the definition lvPPA (Giannini et al., 2017). Another proposed redefinition is the term AD-related PPA (AD-PPA), which is defined by the absence of the clinical diagnoses svPPA and nfvPPA and the presence of Alzheimer pathology (Sajjadi et al., 2012a). In summary, the debate about a distinct clinical entity besides svPPA and nfvPPA is ongoing and research focuses on behavioural features, structural alterations, and biological underpinnings of PPA syndromes.

1.2 Primary Progressive Aphasia: Clinical Variants and Pathological Substrates

This section provides a description of the core diagnosis primary progressive aphasia and its subtypes. The clinical diagnoses can be supported by the presence of atrophy in anatomical magnetic resonance imaging (MRI) and hypometabolism in positron emission tomography (PET). In addition, the relationship of clinical subtypes and pathological substrates will be outlined. The provided description of PPA subtypes was derived from current clinical consensus criteria (Gorno-Tempini et al., 2011) and other relevant publications. As mentioned before, the terms lvPPA and AD-PPA are subject to ongoing research and, therefore, will be presented in one paragraph.

1.2.1 The Core Diagnosis PPA

The name primary progressive aphasia encompasses the three core features of the clinical diagnosis. Deficits in the language domain must be the salient feature of the disease [aphasia], e.g. language comprehension, syntax, object naming, or word production. Impairment of activities of daily living must lean strongest on these deficits [primary] and symptoms initially are isolated and must remain the dominant impairment while disease progresses [progressive] (Weintraub et al., 1990). Other cognitive domains are initially preserved but can deteriorate with disease progression, e.g. episodic memory. Activities of daily living should be unaffected as long as language is not a prerequisite for the activity (e.g. one of our patients performed cost calculation for the family's organization but was not able to take incoming calls). Ultimately, PPA will lead to mutism, the end-stage of all forms of FTLD (Neary et al., 1988).

Exclusion criteria for PPA are alternative explanations for the aphasic symptoms like cerebrovascular lesions or other non-degenerative nervous system, psychiatric or medical disorders. Furthermore, initial deficits in visuospatial processing, visual memory, and episodic memory must result in exclusion of the diagnosis primary progressive aphasia. These symptoms can occasionally occur in later stages of the disease. Once the core diagnosis PPA is established subtyping is recommended. This can be accomplished on three different levels; namely clinical-syndromic, image-supported, and on a pathological level. Subtyping is driven by the absence and presence of clinical symptoms. Image support and pathological classification are additional, yet subordinate, features and must not always correspond to clinical subtypes for two reasons. The first reason is partial insensitivity of imaging biomarkers (Sajjadi et al., 2017). The second reason is missing one-to-one correspondence of

clinical subtypes and pathological substrates (Alladi et al., 2007; Leyton et al., 2011; Pereira et al., 2009; Rabinovici et al., 2008).

1.2.2 The Semantic Variant of PPA

The seminal description of semantic dementia encompassed three patients with deficits in visual and verbal semantic memory (Warrington, 1975). Only a few years later, three patients with a fluent, progressive aphasic condition were described and coined semantic dementia (SD; Snowden, 1989). Semantic dementia was an ambiguous term, referring to, on the one hand, a syndrome with progressive aphasia and agnosia and, on the other hand, a syndrome with fluent aphasia and decreased comprehension (Mesulam et al., 2003). Contemporary research states, that the dominant symptom, which is either naming or comprehension, correlates with the hemispheric dominance of atrophy in anterior temporal lobe structures (Snowden et al., 2017; Woollams and Patterson, 2017). With increasing disease severity, the two "supposedly" different clinical entities converge to a unitary, clinical entity.

Clinical Features

The semantic variant of PPA (svPPA; also known as semantic dementia or PPA semantic) is characterised by anomia and prominent single-word comprehension deficits (Gorno-Tempini et al., 2011). The before-mentioned symptoms arise from degradation of the semantic memory system. Degradation of the semantic memory system follows a frequency-by-typicality-interaction (Funnell, 1995; Jefferies et al., 2010; Knibb et al., 2006; Rogers and Patterson, 2007). Other factors associated with the naming performance of svPPA patients are imageability (Jefferies et al., 2009) and

familiarity (Nestor et al., 2002) of words. The imageability effect is the advantage to identify concrete nouns better than abstract nouns (dog VS hope). The advantage for concrete nouns emerges from their multimodal representation in the semantic memory system. The familiarity effect arises from a personal object advantage in naming performance. Personal items are recognised easier compared to perceptual similar, but unfamiliar, items. As for the imageability effect, the personal object advantage arises from the increased multimodal representation of patients' personal items over perceptual similar items (Giovannetti et al., 2006). The status of semantic knowledge can be investigated with graded-difficulty naming tasks (e.g. the Boston Naming Task). Omissions are more common to low frequency items, while semantic errors are more common for high frequency items (Woollams et al., 2008). Another prominent finding is the frequent use of circumlocutions in speech. Circumlocutions are easy to detect in naming tasks. However, naming tasks lack sensitivity for morpho-syntactic abnormalities. Appropriate tasks for the detection of morpho-syntactic abnormalities are picture description and interviews. Interviews are superior to picture description tasks in eliciting natural connected speech (Sajjadi et al., 2012b). Typical features of connected speech in svPPA are increased use of closed-class words (e.g. prepositions and conjunctions) relative to open-class words (e.g. nouns and verbs) and increased use of embedded sentences (Wilson et al., 2010). Both features are driven by the degradation of semantic knowledge, where embedded sentences are used to hide missing knowledge of words. Closed-class words are preferred because of their higher overall frequency-of-use, relative to open-class words.

Another striking feature of svPPA is surface dyslexia. Surface dyslexia is an acquired dyslexia where patients suffer from irregular grapheme-to-phoneme conversion (Marshall and Newcombe, 1973). In practice, patients cannot pronounce irregular

words correctly. To give an example, hint is transcribed in international phonetic alphabet (IPA) as [*hɪnt*], whereas the irregular pint is IPA translated [*paɪnt*]. SvPPA patients, however, will read the words as [*hɪnt*] and [*pɪnt*] because they tend to use the regular rules of pronunciation. The symptom is present in all svPPA patients, although some patients initially preserve irregular pronunciation (Woollams et al., 2007).

Imaging Abnormalities

Structural and metabolic changes are dominant in bilateral anterior temporal lobes (ATL) of svPPA patients and incorporates grey and white matter atrophy (Acosta-Cabronero et al., 2011), as well as hypometabolism (Diehl et al., 2004). Atrophy starts asymmetrically (Hodges et al., 2010; Kumfor et al., 2016; Mion et al., 2010; Woollams and Patterson, 2017) and is left-dominant in approximately 70 percent of the cases (Chan et al., 2009). The cause of predilection for the anterior temporal lobe is not known. The structural changes were found to be associated with clinical subtype rather than pathological substrate (Pereira et al., 2009) and anterior fusiform atrophy showed the strongest correlation with clinical symptoms (Mion et al., 2010). The temporal lobe atrophy in svPPA is qualitatively and quantitatively different from the atrophy in amnestic Alzheimer's dementia (AD) in the way that an anterior-posterior gradient of temporal lobe atrophy is setting it apart from the hippocampal and medial temporal lobe atrophy in AD (Chan et al., 2001; Davies et al., 2004; Galton et al., 2001).

Pathological Substrates

Several pathological substrates were found in post-mortem examination of svPPA patients. The most often found pathology in svPPA is ubiqitin-positive inclusions with

an overrepresentation of transactive response DNA-binding protein 43 (TDP-43) pathology (Davies et al., 2005; Kumfor et al., 2016). Consequently, AD pathology is rarely found in cerebrospinal fluid biomarkers (CSF) of svPPA patients (Kas et al., 2012) and histopathological confirmed svPPA cases (Alladi et al., 2007; Davies et al., 2005; Gil-Navarro et al., 2013). An additional molecular underpinning for the absence of AD is the extremely low frequency of the ApoE4-allele (Gorno-Tempini et al., 2004) and normal AD-CSF biomarker ($A\beta_{42}$,p-tau,t-tau; Cruz de Souza et al. 2011) in svPPA patients.

1.2.3 The Non-Fluent/Agrammatic Variant of PPA

Clinical Features

The speech of nfvPPA patients is effortful and halting, defining the nonfluent character of patients' speech. Core diagnostic criteria are the presence of agrammatism and/or apraxia of speech (Gorno-Tempini et al., 2011). The halted character of speech can be objectified with story-telling and semi-structured interviews (Ash et al., 2010; Sajjadi et al., 2012c). Hallmarks of impaired spontaneous speech in nfvPPA are reduced number of words per minute and reduced spontaneity, as well as increased speech sound errors and phonological paraphasia (Sajjadi et al., 2012c; Wilson et al., 2010). Speech sound errors can emerge from two different sources; namely a motor planning deficit and a language-processing deficit. The seminal study on speech sound errors in nfvPPA patients (Croot et al., 1998) described two patients with a nonfluent progressive aphasia and related the speech sound errors to a deficit called 'phonetic disintegration', thus circumnavigated to prescribe a motor deficit or cognitive deficits to cause speech sound errors. A later study directly investigated the difference between

phonetic and phonemic errors in nfvPPA, where the dominant error type was phonemic errors (Ash et al., 2010). However, the authors stated that the patient sample did not present with major apraxia of speech (AOS), which might, as consequence of a motor planning deficit, account for the phonetic errors produced by nfvPPA patients. Besides speech sound errors, nfvPPA patients lack the ability to process complex syntax and produce simplified grammatical structures (Ash et al., 2010; Peelle et al., 2008). Because of those symptoms, patients' speech is often described as telegraphic speech.

Imaging Abnormalities

Atrophy and hypometabolism in nfvPPA are maximal in and around the left frontal operculum (Gorno-Tempini et al., 2004; Nestor et al., 2003; Sajjadi et al., 2013). Additional atrophy in dorsomedial and dorsolateral frontal, as well as superior temporal areas has been reported in past imaging studies (Caso et al., 2014; Josephs et al., 2006; Leyton et al., 2016). Although key areas of atrophy in nfvPPA are well-described, atrophy in individual nfvPPA patients can often be unspecific (Sajjadi et al., 2017).

Pathological Substrates

The most common pathological substrate in nfvPPA is Tau pathology, yet TDP-43 and AD pathology can occur (Grossman, 2010). The presence of motor speech deficits is associated with tau pathology, whereas agrammatism is associated with TDP-43 pathology in nfvPPA (Caso et al., 2014). Another, less frequent, pathological substrate for nfvPPA is AD pathology. Metabolic imaging with PET or SPECT was found to be an *in vivo* marker for the differentiation of underlying pathology in nfvPPA (Nestor et

al., 2007). The authors found decreased metabolic activity in bilateral temporoparietal association cortices to be specific for AD-pathology, whereas no metabolic lesion was present in the temporoparietal association cortices of non-AD pathology nfvPPA. One study comprised non-SD, non-fluent PPA patients under the umbrella-term Progressive non-fluent aphasia (Knibb et al., 2009). Isolated AOS and LPA were integrated in this patient pool and data pointed towards a continuum in the PNFA spectrum, where AOS and LPA are at the opposite endings of the continuum. This idea might work for a subset of symptoms but the association of AOS/PNFA and LPA with different pathological substrates is speaking against such a continuum.

1.2.4 The Logopenic Variant of PPA and AD-related PPA

In 2004, the logopenic progressive aphasia (LPA) was proposed (Gorno-Tempini et al., 2004). The initial description LPA, which was renamed lvPPA later on, highlighted the logopenic speech of those patients.

Clinical Features

Characteristics of logopenic speech are slow rate of speech and frequent word-finding pauses. Diagnostic recommendations defined impaired word retrieval, present as word-finding difficulty in confrontation naming and spontaneous speech, and deficient sentence- and phrase-repetition as diagnostic hallmarks of lvPPA (Gorno-Tempini et al., 2011). Reported symptoms and neuroimaging results proposed a phonological loop deficit as the core mechanism underlying lvPPA (Gorno-Tempini et al., 2008). While the link of AD pathology and lvPPA is established, neuropsychological data remain ambiguous. The linguistic abnormalities of nfvPPA and lvPPA cannot be

distinguished by interviews, whereas interview analysis can differentiate svPPA from the other PPA variants (Sajjadi et al., 2012c). Both, nfvPPA and lvPPA, present with an increased frequency of phonological errors and hesitations, while reduction of mean length of utterances and rate of speech (Sajjadi et al., 2012c). Some authors speculated that the digit span forward can differentiate lvPPA and amnestic AD (Meyer et al., 2015), as well as lvPPA and the other subtypes of PPA (Giannini et al., 2017). That investigation of PPA-subtypes, however, had one pitfall. The authors included svPPA and nfvPPA in the non-AD-PPA group, which made that group ambiguous in terms of cognitive deficits. Chapter 3 of this thesis will provide contrary data, that reveal that the digit span forward, as a suggested clinical marker for AD pathology, cannot differentiate AD-PPA from non-AD nfvPPA.

Imaging Abnormalities

An early VBM study found atrophy in the posterior perisylvian cortex of an LPA group (Gorno-Tempini et al., 2004). Later studies found the same pattern in lvPPA patients (Rohrer et al., 2010) and in PPA patients with probable underlying AD (Sajjadi et al., 2014). As for nfvPPA, sensitivity of imaging abnormalities is low for individual lvPPA patients (Sajjadi et al., 2017). The reason might be the reporting method of imaging abnormalities in group-averaged studies. Peak areas of atrophy are the statistically strongest differences between groups. However, significant degeneration is defined by a statistical threshold and by increasing that threshold, abnormal brain regions might appear unaffected while there is degeneration present. To investigate the extent of degeneration in PPA subtypes, Chapter 3 will analyse MRI data from the present patient cohort and compare the atrophy in reported key atrophy sites.

Pathological Substrate

In addition to the symptomatic description, the initial description provided CSF-data that were mostly abnormal in LPA patients and infrequently abnormal in SD and PNFA (Gorno-Tempini et al., 2004). The APOe4 frequency, a genetic risk factor for sporadic AD (Corder et al., 1994; Hauser and Ryan, 2013), of the LPA group was 67% which clearly differed from 20% in the PNFA and 0% in the SD group. The finding of possible AD pathology in lvPPA patients was unexpected, given the fact that PPA and AD pathology were proposed a very rare combination (Mesulam, 2001). The assumption was based on earlier pathology-confirmed reports of PPA patients where authors consistently found PPA patients with underlying FTLD-spectrum pathology (Mesulam, 1987; Snowden et al., 1992). However, PPA patients with underlying AD pathology have been described before the invention of lvPPA (Kempler et al., 1990). After 2004, several post mortem studies reported up to one third of PPA patients with underlying Alzheimer pathology (Alladi et al., 2007; Forman et al., 2006; Knibb et al., 2006; Rabinovici et al., 2008). In addition to post-mortem studies, CSF data show that lvPPA and AD pathology are associated with each other(Cruz de Souza et al., 2011; Kas et al., 2012). The p-tau/$A\beta_{42}$-ratio was the best CSF marker to distinguish amnestic AD and atypical forms of AD from non-AD dementias (Cruz de Souza et al., 2011). As mentioned previously, several publications dealt with the controversy of diagnosing lvPPA patients (Giannini et al., 2017; Leyton and Hodges, 2013; Mesulam et al., 2012; Sajjadi et al., 2014, 2012a). Before the invention of lvPPA in consensus recommendations (Gorno-Tempini et al., 2011), clinico-pathological studies found that approximately one third of PPA patients had underlying AD pathology (Forman et al., 2006; Knibb et al., 2006) but were not able to associate an explicit clinical subtype to the pathology. One might argue here that PPA with underlying AD pathology

resembles a pathology-defined subtype rather than lvPPA as a syndrome-defined subtype of PPA. A second point to consider is the occurrence of positive PET-amyloid scans in cognitively normal elderly (Aizenstein et al., 2008; Mosconi et al., 2010; Pike et al., 2007) and non-lvPPA patients (Leyton et al., 2011). The reported proportion of 10 - 20 % of cognitively normal elderly with a positive amyloid-PET is weakening the association of beta amyloid and cognitive impairment.

In summary, the controversial debate about lvPPA will not be a defining moment of this thesis. We will work with the assumption, that clinically mixed PPA with underlying AD pathology is AD-PPA and lvPPA is a rare syndromic subtype.

1.3 Electrophysiology in PPA: The Missing Modality

In past decades, PPA research focused on neuropsychology, neuroimaging and pathological substrates. However, minor interest was present for high-temporal resolution processing of language in PPA. This means, behavioural measures, structural changes of the brain and protein malfunction in PPA are very well known but the spread of information between cortical regions is poorly understood in PPA. EEG is a technique that visualises the spread of information in both, time and space. Unravelling this information can gain critical insights into the fundamentals of cognitive deficits and to the source rather than the consequence of cognitive decline in PPA patients.

1.3.1 A Short Introduction to Electroencephalography

Electroencephalography (EEG) is a non-invasive measurement of electrical brain activity recorded with surface-electrodes on the scalp. The aim of EEG measurements is detection of the brain's electrical activity amongst external electrical noise. In comparison to other imaging techniques (e.g. magnetic resonance imaging (MRI) or positron emission tomography (PET) EEG has a millisecond-to-millisecond temporal resolution. However, the number of electrodes restricts the spatial resolution of EEG, which is inferior to MRI and PET.

EEG signal uptake differs from other electrophysiological measures. It reflects the synchronous activity of consortia of neurons with similar spatial orientation, while intracellular recordings detect single cell behaviour and extracellular recordings measure the signal of neurons surrounding an electrode (Luck, 2014). The synchronous activity of consortia of neurons with similar spatial orientation is mainly composed of cortical pyramidal cells' post-synaptic potentials. This gives rise to two disadvantages. First, measuring the activity of subcortical structures is hardly possible with EEG. Second, the detected signal under every single electrode is a composite of many cortical and non-cortical signal generators. As a result, the spatial position of a signal source can only be approximated. This "inverse problem" can be solved analytically but strongly relies on *a priori* information from computational models (Hansen et al., 2010).

The primary external activity in EEG is non-neuronal background activity. Most brain activity is hidden in statistical-random, noisy background signal. Based on its random occurrence, background-signal can be downgraded substantially by averaging multiple

epochs of EEG. Those epochs are time-locked to events. Averaging epochs around events creates event-locked neuronal activity, so called event-related potentials (ERPs). The time course of ERPs is the ERP signature. Artefacts in ERPs must be prevented by noise rejection and noise-reduction techniques to obtain noise-free data. Only noise-free data can give insight to the electrophysiological behaviour of the brain. Sources that corrupt detected brain activity are commonly continuous with small EEG amplitudes (e.g. human heartbeat, line noise from electrical devices) or spontaneous events with massive EEG amplitudes (e.g. eye blinks and head movement).

Many ERP studies have aimed to understand the brain's function by manipulating stimulus properties and experimental conditions. Those manipulations are associated with changes in the ERP signature. Generally, three different effects on an ERP signature can be investigated:

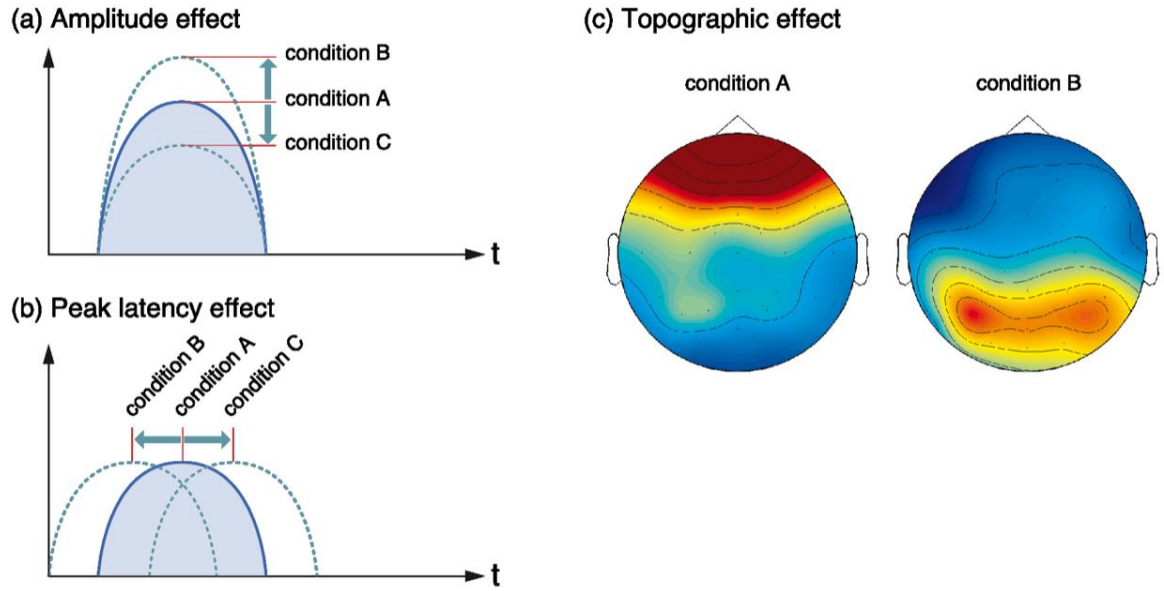

Figure 1.1 A schematic representation of three ERP effects; (a) and (b) are effects related to the change of an ERP peak and (c) is visible in a 2D representation of the electrode arrangement

(i) Amplitude effect: The amplitude of electrode peaks differs between conditions or groups (Fig. 1.1a). If the effect is present in several electrodes a global Field Power

(GFP) analysis can display such an effect. Local changes below single electrodes are hardly detectable in GFP analysis.

(ii) Peak latency effect: The peak latency of a signal shifts (Fig. 1.1b). Searching for maximum/minimum voltages in time ranges detects such a change in latency of maximal and minimal voltages.

(iii) Topographic effect: The pattern of voltage distributions differs between conditions or groups (Fig. 1.1c). This pattern is visualised by plotting voltage distributions on a two- or three-dimensional representation of the head surface. Cortical reorganization and strong atrophy can cause topographical effects.

1.3.2 Classical ERP-Components of Language Processing

In ERP research, a component is conceptually defined as 'scalp-recorded neural activity that is generated in a given neuroanatomical module when a specific computational operation is performed' (Luck, 2014). All components in ERP research are labelled. Three different nomenclatures for component labelling have emerged. First, a component is defined by its polarity (negative or positive) and approximate peak latency (e.g. the N400 component is a negative deflection that peaks 400 milliseconds after stimulus-onset). Second, a component is named after the deflection's polarity and indexed by the position in the number of deflections (e.g. the P3 component is the third positive deflection in an ERP signature). Third, components are named generically by characteristics like location, polarity, time of appearance or experimental condition (e.g. late posterior negativity [Mecklinger et al. 2016], left anterior negativity [Meltzer & Braun 2013], mismatch negativity [Näätänen et al. 2007]). All three nomenclatures co-exist and several components exist in more than one

nomenclature. The first and second nomenclatures ignore the spatial location of a voltage deflection. This might lead to confusion if polarity and latency are similar for more than one component. The second nomenclature heavily relies on a fixed sequence of deflections, meaning, if an additional deflection occurs in the ERP signature or a deflection diminishes all subsequent deflections change names. The third nomenclature gives a name that specifies random characteristics of a component. Figure 1.2 illustrates the labelling of components according to the three nomenclatures.

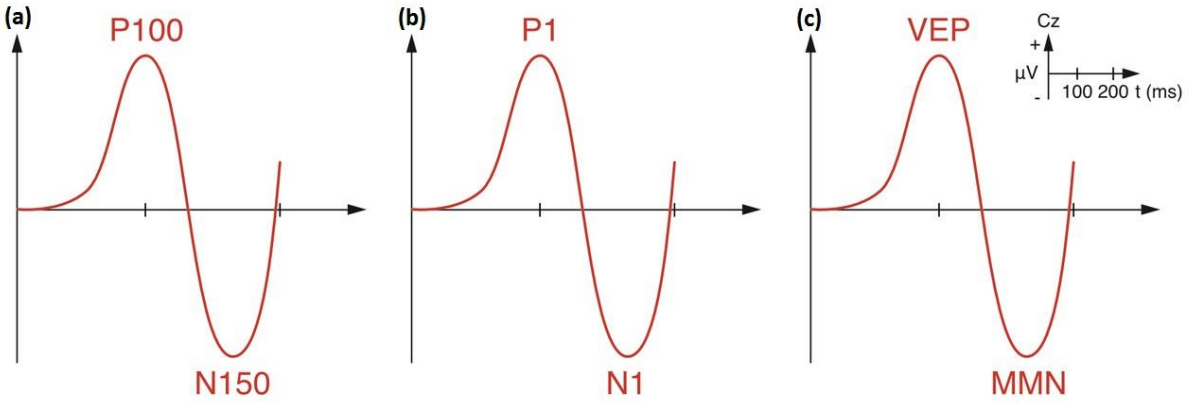

Figure 1.2 Illustration of an ERP signature and labels according to different nomenclatures; (a) = nomenclature 1, (b) = nomenclature 2, (c) = nomenclature 3, VEP = visual evoked potential, MMN = mismatch negativity

The following paragraph will introduce the most relevant ERP components for this thesis. In the field of neurolinguistics, several components have been identified. Components, here, are associated with processing stages of receptive and productive language. Manipulation of stimuli and task demands, as well as the experimental setup can alter the appearance of such components. The probably most studied component in neurolinguistics is the N400 component (Kutas and Hillyard, 1980). The component was first described in a sentence-reading task where the final word of a sentence was either congruous (*He spread the bread with butter*) or incongruous (*He spread the bread with socks*). The semantically incongruent words produced stronger N400 potentials than the congruous words. Since this seminal experiment, the N400 has been interpreted as marker for the integration of lexico-semantic information (Kutas

and Federmeier, 2000; Lau et al., 2008). A second, later-occurring component in neurolinguistics is the P600 component, which is associated with the identification of syntactic anomalies, e.g. comparing the grammatical ‘the broker hoped to sell the stock’ and the ungrammatical ‘the broker persuaded to sell the stock’ (Hagoort et al., 1993; Osterhout and Holcomb, 1992). However, two components that occur about 500 ms after the onset of a written word are unlikely to represent the initial stages of lexico-semantic and syntactic information processing. The average reading speed of healthy adults is 185 words per minute (Trauzettel-Klosinski and Dietz, 2012), which translates to 320 milliseconds per word. The average reading speed is faster than the peak latency of both, N400 and P600, components. Therefore, earlier components must be critical for the initial integration of linguistic information. In addition, effects on N400 and P600 components have mostly been elicited with the help of additional non-linguistic tasks (for a review, see Van Berkum 2009). Those secondary tasks have probably attenuated the components (Egorova et al., 2013).

Several authors manipulated word parameters and investigated the effect on ERP components prior to N400 and P600. The earliest effects manifest as early as 100 milliseconds after visual word presentation (Miozzo et al., 2015; Moseley et al., 2013; Pulvermüller et al., 2001, 1995; Sereno et al., 2003; Sereno and Rayner, 2000). The very early effects, around 100 ms, were attributed to visual processing because word length was manipulated (Assadollahi and Pulvermüller, 2003). The earliest differences between the processing of words and pseudowords was found 110 milliseconds after stimuli onset (Sereno et al., 1998). In addition, components peaking at approximately 160, 210, and 280 milliseconds revealed effects of lexicality and typicality prior to N400 and P600 components (Hauk et al., 2006; Hinojosa et al., 2001; Martín-Loeches et al., 1999). This short introduction to early effects of stimulus parameters on language

processing clearly indicates that initial stages of language processing take place before the occurrence of N400 and P600 components. A detailed introduction to relevant components will be given in Chapters 5 and 6.

1.3.3 Cortical Sources of Word Processing

The first models of cortical organization of language derived from lesion reports. The seminal reports were from Broca and Wernicke, reporting Broca's area, Wernicke's area, and their association to language impairment (Broca, 1861; Wernicke, 1874). The emerging knowledge from Broca's and Wernicke's initial lesion studies paved the way for neuroanatomical models of language. Lesion studies, however, are confounded by cortical reorganisation, which deteriorates the localisation of functional regions. Therefore, studies in healthy, non-lesioned participants are an important source of information. This section attempts to give a short overview of cortical regions that are associated with language processing. The language network overlaps with the key areas of neurodegeneration in the PPA spectrum (see Chapter 1.2 for details), thus giving an anatomical basis to emerging symptoms in PPA patients (Gorno-Tempini et al., 2011; Mesulam et al., 2008).

In the 80s and 90s of last century, pioneering imaging studies in neurolinguistics identified cortical sources of word processing. The authors acquired PET data while healthy participants performed language tasks. In 1988, Petersen and colleagues were the first to investigate language processing in combination with functional imaging. From the seminal set of experiments it was concluded that left temporoparietal, extrastriate, ventral premotor, and ventral prefrontal cortices, as well as, bilateral dorsolateral prefrontal cortex, anterior cingulate, anterior insula, and rolandic cortex

are involved in reception and production of language (Petersen et al., 1988). Based on these findings, a new anatomical model of lexical processing, incorporating most proposed areas and associating functions, was postulated (Petersen et al., 1989). Later studies identified specific function for some of the areas, e.g. the left extrastriate cortex was associated with early visual processing (Indefrey et al., 1997), semantic processing with the angular gyrus (Vandenberghe et al., 1996), and the abstract representation of visual words was attributed to the left occipitotemporal cortex (Cohen et al., 2000; Dehaene et al., 2001). Today, a huge and ever-growing body of research investigates the association of language function and cortical structures (for a review, consider Price 2012).

Some publications created the picture that every language function activates a defined cortical locus. While this is partially true for simple functions, complex language functions are associated with specific regions but rather utilise a distributed language network, where each area contributes a certain aspect to the resulting complex language function. Keeping the before mentioned facts in mind, it is absolutely reasonable that not deduction of single experiments but rather the integration of results from many experiments facilitates the understanding of the functional cortical language network (Petersen and Fiez, 1993).

1.3.4 Currently Available Studies about Electrophysiology in PPA

In the past decades of PPA research, much effort has focused on neuropsychological assessment, to detect and objectify clinical symptoms, and MR imaging, which can identify group-level atrophy patterns in various sub-groups but often fails at a single-subject diagnostic level (Sajjadi et al., 2017). Virtually no work

has been conducted with physiological measures such as electroencephalography (EEG) and magnetoencephalography (MEG). Both methods record very accurate temporal information about the spread of neuronal depolarisation inside and throughout the language network. Besides the high temporal resolution, which is essential for understanding mechanisms underlying neuronal processing, both methods are completely non-invasive and harm-free. Although these methods have been successful in detecting changes in chronic stroke aphasia (Breier et al., 2009; Ofek et al., 2013; Zipse et al., 2011), only two ERP studies in PPA patients exist today. The first report is a longitudinal study of a single PPA patient using ERPs recorded with EEG (Giaquinto and Ranghi, 2009). The authors did not subtype the PPA patient but the patient provided description resembled a mixed PPA. In an auditory oddball, the patient presented increased N400 latency while duration and amplitude of that ERP component decreased. This pattern of N400 malformation increased in the first follow-up examination and, co-occurring with the inability to perform the task, the N400 component was absent in the last follow-up examination. This was a first attempt to show that spatio-temporal properties of language processing in PPA patients are altered and the authors claimed to have found a potential biomarker of cognitive change in PPA patients. The second study was an EEG investigation of 20 PPA patients without details of further syndromic subtyping (Hurley et al., 2009). The participants attended an object-word-matching task with two modulatory conditions; namely a mismatch-effect and a category-effect for the N400 component. The PPA group produced a delayed mismatch-effect and no category-effect. Although alterations in spatio-temporal processing of language-based tasks in the PPA group were reported, the results are difficult to interpret because a non-subtyped PPA group contains different aphasic syndromes, different neural substrates and underlying pathologies.

While some effort regarding ERP signatures of PPA patients was performed, knowledge about the basic neuronal processing of visually presented words in PPA patients is still missing. Alterations of the N400 component have been described and clinical implication was suggested for other neurological conditions (Cruse and Owen, 2010; Owen, 2013) but the relevance of this component is still a matter of debate (Kutas and Federmeier, 2011). One strong argument against the use of the N400 is the human use of visually presented words. When fluent, adult readers are confronted with text, the reading speed for a single word is faster than 400 milliseconds, favouring earlier processing steps to be heavily influential for differences between PPA patients and healthy participants. As explained earlier in the chapter, this suggestion is undermined by a huge body of linguistic research that found alterations of earlier ERP components in response to experimental-controlled manipulation of linguistic parameters, e.g. lexical frequency and word length.

1.4 Aims and Objectives

As being shown before, the PPA spectrum is very well described in terms of neuropsychology, neuropathology, and neuroimaging. However, basic electrophysiological signatures of language processing remain unclear. The aim of this thesis is the description of language-related electrophysiological signatures of PPA subtypes. While many classical language experiments concentrated on later/endogenous components like N400 and P600, some authors found effects of word manipulations in earlier/exogenous components (Hauk et al., 2009; Martín-Loeches et al., 1999). It is assumed that the pathological substrate and clinical subtypes of PPA lead to different maladaptation of ERP components, which, in turn,

will influence the appearance of ERP signatures. Today, most ERP studies incorporate heavily demanding tasks. However, one will not gain critical information with this approach in PPA (Pulvermüller et al., 2010). Therefore, in this thesis, a low-demand task (silent reading) will be administered to retrieve the most basic, language-related ERP signatures in PPA patients.

In the second set of experiments, participants will perform language tasks with more emphasis on active language processing. Therefore, oddball paradigms were utilised and a linguistic and a non-linguistic oddball paradigm were compared. Oddball paradigms focus on specific features of stimuli by presenting many standard stimuli and few rare stimuli (oddballs) and contrasting the reaction to both types of stimuli. The advantage of acquiring data on tasks with almost identical experimental settings offers the possibility to compare the influence of language on processing in PPA patients. It is believed that the processing of non-linguistic stimuli is not affected in PPA while processing of linguistic stimuli is affected in PPA. Ultimately, the thesis will present and compare electrophysiological data and response time data from both oddball experiments.

The rationale for conducting this project is the increase of knowledge about the temporal signature of language processing in PPA patients, thus adding critical information for future therapeutic, interventional strategies. Some authors applied non-invasive brain stimulation (transcranial magnetic stimulation) in PPA patients and AD patient to increase patients' language performance (Cotelli et al., 2012, 2011). Another study successfully decreased the reading ability of healthy participants by setting a temporary lesion with TMS in the left anterior temporal lobe, the key area of atrophy in svPPA (Woollams et al., 2017). While the before mentioned studies successfully reduced the symptoms in PPA patients and increased language-related deficits in

healthy participants by setting a temporary lesion, other investigators were not able to replicate such findings with similar stimulation protocols (McConathey et al., 2017). By adding temporal information with the help of EEG investigation, targets for future therapeutic interventions with TMS might be uncovered.

In addition to the electrophysiological results, this project incorporates structural, as well as, neuropsychological data from a prospective cohort of PPA patients that was recruited in Magdeburg.

Chapter 2 Materials & Methods

This chapter presents methods that apply to all experiments of the thesis. All data, presented in this thesis, were acquired at the German Center for Neurodegenerative Diseases (DZNE) in Magdeburg, Germany. Data were collected in a prospective, cross-sectional, neuropsychological, neurophysiological, and neuroimaging cohort study of 31 consecutively recruited PPA patients. Throughout this chapter, cross references to other chapters are given and chapters three, five and six will provide cross references to this chapter.

2.1 Ethical Approval

Ethical approval for the study was obtained from the local ethics committee at the university clinic in Magdeburg in July 2014. The ethics approval was given for the study "Verständnis der klinischen Heterogenität und Herstellung einer Pathologie-spezifischen Diagnostik bei primär progressiver Aphasie" and all experiments that are presented here were administered as part of the study program. Written informed consent was obtained from all participants or, where appropriate, their legal representative.

2.2 Participants

Healthy participants were recruited from a pool of volunteering elderly people. Patients were referred to the DZNE Magdeburg from several cooperating institutions, namely:

- 21 patients from the neurology department at the university clinic in Magdeburg
- 7 patients from the clinical dementia center at the university medical center in Göttingen
- 3 patients from the department neurodegenerative diseases and gerontopsychiatry at the university clinic in Bonn
- 1 patient from the neurological clinic at the university clinic in Dresden
- 1 patient from the neurology department at the university clinic in Leipzig
- 1 patient from the memory clinic in Munich

Patients were diagnosed by an experienced neurologist (PJN) according to internationally agreed guidelines for the diagnosis primary progressive aphasia (Gorno-Tempini et al., 2011). All patients fulfilled the core diagnostic features for PPA. Sv- and nfvPPA patients were classified according to consensus recommendations (Gorno-Tempini et al., 2011) and by having a negative Florbetaben-PET result. The diagnosis AD-related PPA was given when the criteria for either svPPA or nfvPPA were not fulfilled and the Florbetaben-PET result was positive.

The following conditions led to patients' exclusion from the study:

- German was not the patients' native language
- neuropsychological assessment was not possible as a consequence of cognitive impairment
- history of current alcohol or illegal drug abuse
- other neurological or major psychiatric illnesses

Healthy participants were included with the following criteria:

- German was the native language
- Mini Mental State Examination (MMSE) score was in the healthy range (McKhann et al., 1984)
- no history of alcohol and drug abuse
- no history of neurological or major psychiatric illnesses

2.3 Neuropsychological Assessments

All patients underwent a battery of neuropsychological tests, probing different aspects of cognitive function with special emphasis on the language domain. Healthy participants had a brief cognitive examination to ensure a neurological normal state.

2.3.1 General Neuropsychological Tests

Mini Mental State Examination (MMSE)

The MMSE is a brief questionnaire consisting of 30 tasks and questions (Folstein et al., 1975). It evaluates the degree of cognitive impairment in several cognitive domains, e.g. recall, language, memory, and orientation. A score of 27 or more points accounts for normal cognition. Lower scores indicated mild (19-24 points), moderate (10-18 points) and severe (≤9 points) cognitive impairment. The score is no equivalent to a diagnosis of dementia because it is a screening tool and not a diagnostic test battery.

Geriatric Depression Scale (GDS)

A brief evaluation of depressive symptoms (Yasavage and Sheikh, 1986). The examiner asks 15 questions about mood and feelings that need to be answered with *YES* or *NO*. Scores between zero and six indicate no depressive state. Six to ten points indicate mild to moderate depression and 11 to 15 points indicate a severe depressive state.

Verbal and Visual Span

The span tests examine visual and verbal working memory capacity. Outcome parameter is the longest span examinees can recall. For the verbal span, the examiner gives a sequence of digits for immediate reproduction. The verbal span is a subtest of the WAIS-III: Wechsler Adult Intelligence Scale—3rd (Wechsler, 1997a). The visual span is the Corsi block-tapping test (Kessels et al., 2000). A board with nine mounted blocks is presented to the examinee. The examiner tapes a sequence of blocks that have to be repeated by the examinee immediately. Both, visual and verbal span tasks were administered as forward- and backward-version. In the backward version, examinees have to reproduce the sequence in reversed order.

Digit Symbol Substitution (DSS)

The DSS consists of nine digit-symbol pairs and a list of digits without corresponding symbols from the WAIS-III: Wechsler Adult Intelligence Scale—3rd Edition(Wechsler, 1997b). The examinee has to fill the list of digits with corresponding symbols, obtained from digit-symbol pairs, as fast as possible. The examinee has to stop the task after 120 seconds.

Rey Complex Figure Test (RFT)

The RFT is a complex line drawing (Osterrieth, 1944; Rey, 1941). The test consists of three conditions; namely "copy", "immediate recall", and "delayed recall". In the "copy" condition, the figure is placed in front of the examinee and needs to be reproduced on a blank sheet of paper. The instruction is:" Draw every detail and take as much time as you need." In the recall conditions, examinees have to reproduce the figure from memory to the best of their ability. The "immediate recall" starts approximately three minutes after the "copy" condition and the "delayed recall" condition after approximately 30 minutes. The RFT evaluates visuo-constructive ability which incorporates several mental abilities such as spatial reasoning, memory, attention, and planning.

2.3.2 Linguistic Neuropsychological Tests

Letter Fluency and Category fluency

Examinees have to produce as many words as possible in 60 seconds in the fluency tasks (Aschenbrenner et al., 2000). Two conditions were administered. The "letter" condition examines the influence of phonemic/pre-lexical knowledge and demanded the examinee to produce words beginning with the letter K. In the second condition, the influence of semantic knowledge on verbal fluency is investigated by asking for words that belong to the category animals.

Boston Naming Test (BNT)

The BNT is a graded naming task consisting of 30 line drawings of objects and examinees have to name the drawings (Merten, 2004). The selection of drawings

includes 10 frequent, 10 less frequent, and 10 rare objects. An object is scored correct if it is named correct within 10 seconds after presentation.

"Kaffee & Kuchen" Test

The "Kaffee & Kuchen" test is a German adaptation of the Camel & Cactus test (Bozeat et al., 2000). It is a four-alternatives semantic-association test based on the principles of the Pyramids & Palm trees test (Howard and Patterson, 1992). Patients with degraded semantic knowledge usually have an inferior performance in the test. In the "Kaffee & Kuchen" test, examinees see a picture and have to decide, out of four alternatives pictures, which alternative suits the picture best.

Repeat & Point Test (R&P)

The R&P test is designed to distinguish svPPA and nfvPPA (Hodges et al., 2008). It has two conditions; a repeating condition and a pointing condition. First the examinee has to repeat a word that is given by the examiner. After the repetition, the examinee will see seven pictures and has to point to the picture that represented the word.

Sentence Comprehension Task - Visual Version (SECT-V)

The SECT-V is designed to detect problems in sentence comprehension (Billette et al., 2015). The examiner visually presents 24 sentences with varying syntactic complexity that can be embedded, passive, and comparative sentences. After the presentation of each sentence a question about the content was asked to assess the comprehension of that sentence. Patients with problems in understanding complex grammar are

susceptible to giving wrong answers because the content of the sentences is defined by the grammatical complexity.

Sentence Repetition

The sentence repetition comprises five sentences that have to be repeated by the examinee. The sentences are syntactically complex. Sentences are scored correct if the examinee is able to reproduce the complete sentence without major hesitations and pronounces all words correctly.

2.4 Electro- and Magnetoencephalography

The experiments from Chapters 5 and 6 were performed in an electrically and acoustically shielded chamber. The chamber contained a combined MEG and EEG setup. After conduction of the experiment in chapter 5, the MEG setup was replaced by a more modern MEG setup, resulting in increased sampling rate in chapter 6. For completeness, parameters for both setups will be provided. Pre-processing was identical in all experiments. Therefore, chapter 2.4.2 provides pre-processing details for all experiments. Post-processing was slightly different in the experiments and will be provided in the respective method section of Chapters 5 & 6.

2.4.1 EEG and MEG Recording

All data from Chapter 5 were recorded in a Magnes 3600 whole-head magnetoencephalographic system with 248 magnetometers. The data for Chapter 6 were recorded in a Neuromag TRIUX whole-head magnetoencephalographic system

with 102 triplet-sensors. Here, each triplet combines one magnetometer and two gradiometers. The set of 32 EEG channels was identical in both setups.

Continuous EEG and EOG data were recorded with Ag/AgCl electrodes. EEG electrode impedances were kept below five kΩ and EOG electrode impedances below 10 kΩ. The EOG-setup consisted of two bipolar electrodes placed horizontally to the eyes' orbital angles and one electrode placed on the right inferior orbita. The EEG electrodes contained an online-reference on the right mastoid bone and a frontopolar, central-placed ground electrode. The 29 active electrodes consisted of 12 left-hemispheric electrodes (Fp1, F3, F7, FC1, C3, T7, CP1, P3, P7, PO3, PO7, O1), 12 right-hemispheric electrodes (Fp2, F4, F8, FC2, C4, T8, CP2, P4, P8, PO4, PO8, O2) and 5 midline electrodes (Fz, Cz, Pz, Oz, Iz). Electrode positions were derived from 10-20 and 10-10 montage and locations were predefined on elastic caps with electrode holders.

The MEG and EEG signal from the Magnes 3600-setup was digitised with a sampling rate of 290.64 Hz and a band-pass frequency of 0.01 to 150 Hz. The MEG/EEG signal of the Neuromag TRIUX system was digitised with a sampling rate of 1000 Hz and online band-pass filtered from direct current (DC) to 300 Hz.

2.4.2 EEG and MEG Data Pre-Processing

EEG and MEG data were pre-processed with Fieldtrip (Oostenveld et al., 2011), an open source EEG and MEG analysis toolbox running under MATLAB. The EEG data were offline re-referenced to an average electrode. An initial inspection of overall data quality was performed for MEG and EEG separately. All channels were inspected in one-minute epochs to identify major artefacts. In the case of major artefacts (e.g.

permanent movement of the head or eyes, signal distortion by metal, a permanent artefact of breathing) data were considered unfeasible for further processing. Details on data quality and artefacts will be provided in Chapter 4. Following initial inspection, an ICA transformation of all datasets was performed and the resulting components were visually inspected for heartbeat artefacts. If a heartbeat was visible in single component, those were erased and the remaining components were back-projected into native MEG and EEG signal. This step was performed for EEG channels and MEG sensors separately.

As a next step, eye blink detection was performed with two consecutive analysis steps; a fully automated detection algorithm and a subsequent visual inspection of the data. The fully automated detection algorithm transformed the electrodes Fp1, Fp2, and the horizontal EOG into absolute values. A new, virtual channel was created by multiplying the transformed channels. The virtual channel was scanned for signal amplitudes higher than five standard deviations of the virtual channel. Epochs with values higher than the threshold were defined as artefacts. This relative threshold considered individual differences in eye blink amplitude and seemed superior to standard eye blink detection techniques. Standard eye blink detection techniques (e.g. peak-to-peak amplitude) utilise absolute detection thresholds. Absolute thresholds are insensitive to channels with low signal amplitude and, consequently, cannot detect eye blinks in low-signal channels. After automatic detection, the virtual channel was inspected visually for remaining artefacts with values below five standard deviations. Figure 2.1 depicts the magnification of eye blinks over other signal with the automated detection algorithm. After eye blink detection, all data were bandpass filtered from 0.5 Hz to 50 Hz. Explicit duration of trials and conditions, as well as post-processing options will be described in the method sections of Chapters 5 & 6.

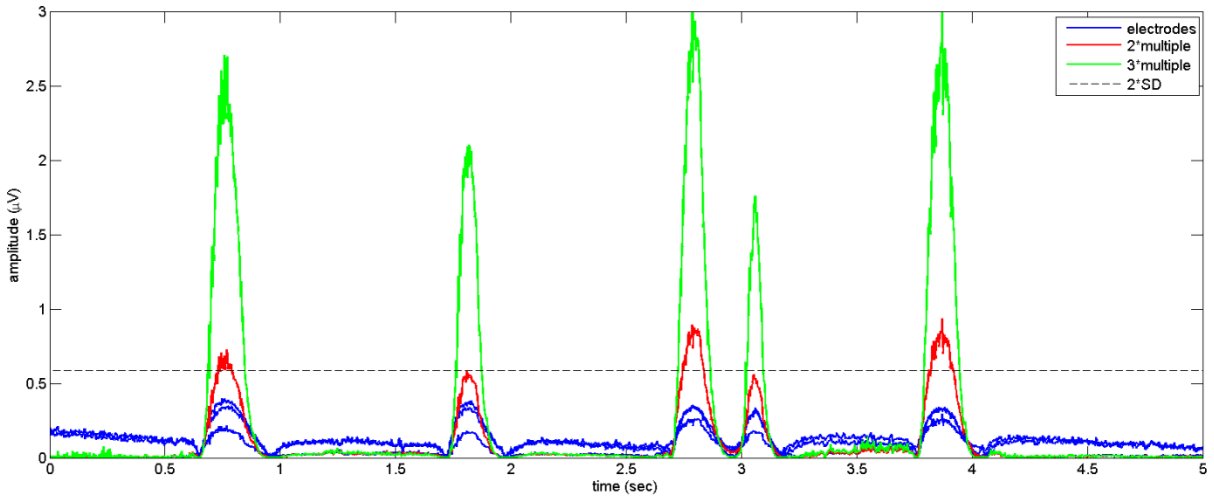

Figure 2.1 The effect of the eye blink detection algorithm; signal of the vertical EOG, FZ1, and Fz2 channels (blue), the product of two channels (red) and the product of all three channels (green). The dotted line represents the detection threshold for the 3*multiple. Note the emerging difference between eyeblink activity and the non-eyeblink activity.

2.4.3 Global Field Power

The Global Field Power (GFP) is the standard deviation of all channels at one time point. Stringing together all GFP values of a dataset results in a GFP signature. All individuals' GFP signatures where pooled to obtain group GFP signatures. Such a signature reflects the global activity as a function of time. GFP signatures are a tool to investigate the temporal dimension of ERP signatures by reducing all spatial information (information of all electrodes) into a single value. Zero GFP value resembles an equal voltage distribution while higher GFP values resemble increasing inequality of voltages. Figure 2.2 shows the topographical representation of low and high GFP values. As being evident from Figure 2.2, higher GFP values correspond to interesting pattern of activity. The GFP approach is one of three possibilities to investigate overall neural dynamics. While GFP was used in this project, other authors preferred the signal-to-noise-ratio (SNR) or the root mean square (RMS) as unbiased estimate for overall neural dynamics. If one assumes perfect shielding from external

noise GFP, RMS, and SNR are identical. The assumption translates into the definition, that the mean voltage of all combined electrodes is zero plus external noise plus neural activity.

$$\text{Standard deviation} = \sqrt{\sum_{i=1}^{N}(x_i - \bar{x})^2} \quad (1)$$

$$\text{Root mean square} = \sqrt{\sum_{i=1}^{N}(x_i)^2} \quad (2)$$

$$\text{Signal-to-Noise-Ratio} = \sqrt{\sum_{i=1}^{N}(x_i - STD_{Baseline})^2} \quad (3)$$

Implementing the theoretical cancellation of external noise, formula (1) simplifies to formula (2); in other words, GFP and RMS are identical under perfect noise cancellation. For the SNR, every electrode value is divided by the standard deviation of the baseline and the obtained values are afterwards transferred to an RMS calculation, represented in formula (3). The baseline does not contain event-related

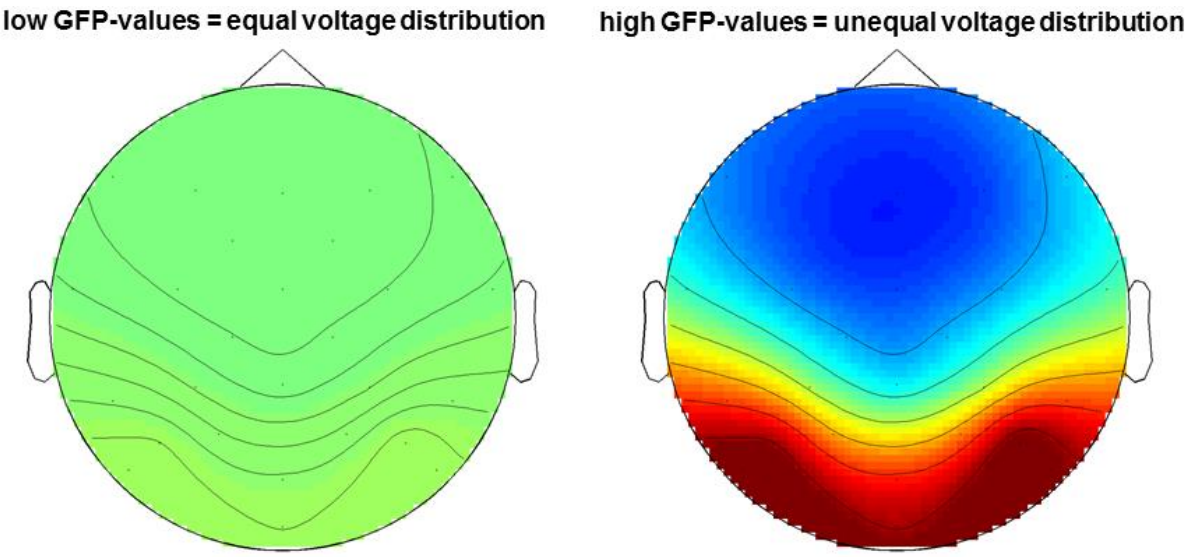

Figure 2.2 Topographical representations of low (left) and high (right) GFP values; the representations reveal that low GFP reveal no difference between electrodes while high GFP values results from differences in voltages of several electrodes.

activity in a well-designed experiment and, therefore, only external noise (which is zero under perfect cancellation of external noise) can occur in the baseline. In practice, voltage fluctuations arising from external noise diminish when averaging of a sufficient amount of trials, which makes the use of GFP, RMS, or SNR a personal preference.

2.4.4 Response Time Analysis

For chapter 6, response times were recorded. Response time (RT) distributions are often insufficiently characterised by the classical two-parameter model with mean (M) and standard deviation (STD) of a response time distribution (Luce, 1986). However, probabilistic functions offer a description of RT distributions that are adaptive and multifactorial, making those more suitable for producing interpretable results. To solve the problem of non-normal distributed RTs, a three-parameter model, modelling an ex-Gaussian distribution over RTs was proposed (Lacouture and Cousineau, 2008).

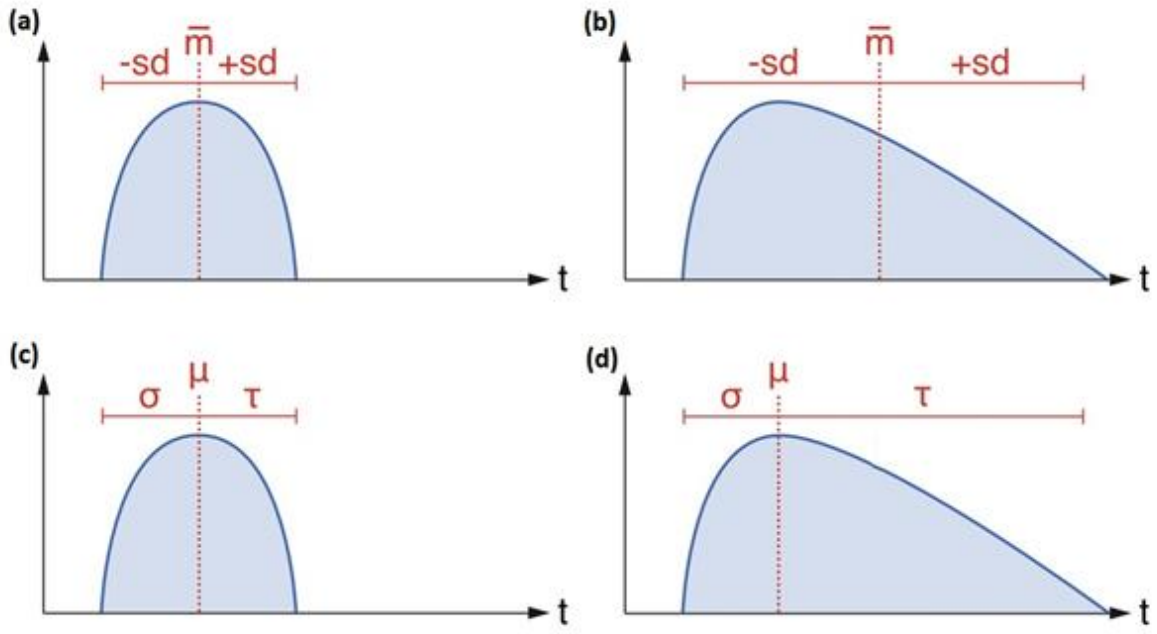

Figure 2.3 Influence of response time distributions on the parameter fit of response time models; (a) and (c) represent the model fit on a normal distribution, (b) and (d) represent the model fit on a non-normal distribution of response times

The parameter-fitting to an ex-Gaussian distribution is implemented in the MATLAB toolbox DISTRIB (http://www.psy.ulaval.ca/~yves/distrib.html). Parameters for the ex-Gaussian distribution are estimated with a maximum likelihood approach to model the best fit of parameters to the empirical data distribution. The ex-Gaussian distribution is a convolution of an exponential distribution and a Gaussian distribution. The parameters μ and σ are the mean and the standard deviation of the Gaussian distribution, while τ is the mean of the exponential distribution. Therefore, σ represents the left tail of the distribution and τ represents the right tail of the distribution. A projection of the two- and three-parameter models on normal and non-normal distributions is depicted in Figure 2.3. An example for an empirical RT distribution from this thesis is shown in Figure 2.4. The shape of the empirical RT distribution is clearly non-normal distributed.

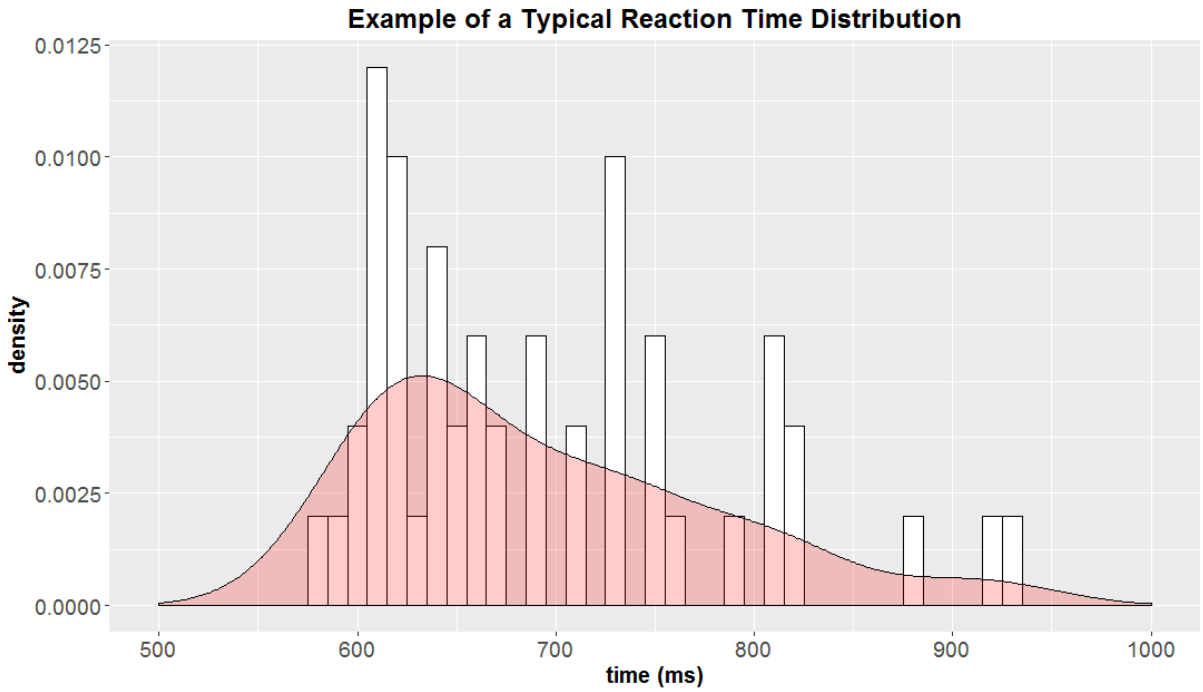

Figure 2.4 An example for a typical response time distribution; the distribution is from a healthy participant's data in chapter 5

All response times in Chapter 6 were recorded with a button box. response latency was the time between appearance of a stimulus and the button press. For every

participant, all recorded response latencies were processed with the DISTRIB toolbox to obtain the parameters μ, σ and τ.

2.5 Imaging

2.5.1 Image Acquisition

MRI scanning was performed on a 3 Tesla MR Scanner (Siemens Magnetom Verio syngo MR B19, Erlangen, Germany) with an equipped gradient coil capable of 45 mT/m and a slew rate of 200 T/m/s. A standard 32-channel phased array imaging head coil in receive mode (Siemens Medical System, Erlangen, Germany) was used. To decrease motion and increase inter-subject reproducibility in head positioning a thin pillow was placed in the head coil, surrounding the back and sides of the head. All eligible PPA participants (N=25) and all healthy participants (N=42) had to fill a safety-questionnaire before entering the MR-laboratory.

The exclusion criteria for magnetic resonance imaging were:

- any metallic, electronic or magnetic implants, e.g. endoprostheses, cardiac pacemakers, neurostimulators or implanted defibrillators, which could be affected by the magnetic field
- loose metallic objects in the body which could be heated up or moved by the magnetic field
- any medical condition that will prevent participants from lying comfortably in the scanner for a maximum of 90 minutes.

2.5.2 T1-weighted Anatomical Imaging

The T1-weighted anatomical images (from here on referred to as T1 images) were acquired using a 3D magnetisation-prepared rapid gradient-echo (MPRAGE) sequence. The imaging parameters were TR = 2500 ms, TE = 4.37 ms, TI = 1100 ms, flip angle = 7°, 192 slices with 1 mm isotropic voxels in a 256 x 256 voxel matrix. Receiver bandwidth was 140 Hz/pixel and echo spacing was 11.1 ms, GRAPPA mode was enabled with 24 reference lines and an acceleration factor of two. The scan was complete after five minutes and eight seconds.

2.5.3 T2 Imaging

Whole brain T2-weighted images were acquired with TR/TE/flip angle = 8160ms/96ms/150° and 45 slices (transversal plane) with a matrix dimension of 320 x 320 and voxel resolution 0.7/0.7/3.0 mm. Receiver bandwidth and echo spacing were 220 Hz/pixel and 9.64 ms, respectively. GRAPPA mode was enabled with an acceleration factor of two and 51 reference lines. The total scan time was one minute and 56 seconds.

2.5.4 MRI Analysis

For visual inspection, further processing of T1- and T2-weighted MR images was not conducted. On the one hand, visual inspection was performed to register structural abnormalities, infarcts, and other incidents that can comprise the diagnosis

PPA and would have led to exclusion from the study. On the other hand, visual rating of atrophy was performed to acquire image-support for subtyping of the patients.

To compare patient groups to published data, group-atrophy patterns were created. For this purpose, T1-weighted images were processed and analysed with open source software suite Freesurfer (version 6.0.0, https://surfer.nmr.mgh.harvard.edu). Details of the standard Freesurfer processing pipeline can be found elsewhere (Fischl et al., 2004; Fischl and Dale, 2000). To summarise the process, automatic cortical reconstruction, including automatic cortical parcellation (Fischl et al., 2004), was performed (Fischl and Dale, 2000). Cortical thickness is defined as the estimated distance between pial surface and grey/white matter boundary. The one exception from standard processing is application of a 20mm full width at half-maximum (FWHM) smoothing kernel. The higher-than-normal smoothing level was used for the whole brain analyses (Diaz-De-Grenu et al., 2014).

To create data for the experimental hypothesis, regions of interest (ROIs) were defined. ROIs were automatically extracted from the cortical ribbon and parcellation of the Desikan-Killiany atlas (Desikan et al., 2006) and the Destrieux atlas (Destrieux et al., 2010) was utilised. The ROIs correspond to the three cortical sites of maximal atrophy in the PPA subtypes. From the Desikan-Killiany atlas, pars triangularis and pars opercularis were combined to represent the left inferior frontal gyrus (IFG), the site of maximal degeneration in nfvPPA. The supramarginal gyrus and the inferoparietal gyrus were combined to create a left posterior perisylvian ROI (PPS), representing the main site of degeneration in AD-related PPA. The structural hallmark of svPPA is massive atrophy in bilateral temporal poles. However, the peak atrophy site is the anterior fusiform area (AFA) (Chan et al., 2001). This region has been identified as the neural substrate for the cognitive deficit in svPPA (Mion et al., 2010). To this end, the

region designated anterior transverse collateral sulcus in the Destrieux atlas was chosen as it corresponds to the AFA; this also meant that the ROI was of a similar size order to those for IFG and PPS. The average cortical thickness for the three defined ROIs, was extracted and entered statistical analysis.

2.5.5 PET Acquisition and Interpretation

Positron emission tomography (PET) data were recorded at the nuclear medicine department of the university clinic Magdeburg. Patients had one PET acquisition with ^{18}F-Florbetaben. ^{18}F-Florbetaben (florbetaben) is a PET-tracer that visualises Aβ plaques in the human brain. All PET scans were acquired according to the standard protocol for the tracer (Sabri et al., 2015). In short, 300 MBq florbetaben were injected intravenous and a 20 minutes acquisition was recorded after a 90-minute waiting period. To assess the amyloid-status, visual rating of the PET scans was performed by raters who had undergone the tracer manufacturer's rater-training course.

Chapter 3 Neuropsychology and Imaging of the Present PPA Cohort

3.1 Introduction

This chapter introduces neuropsychological and imaging results of the patient cohort. The essence of this chapter is twofold. First, to conceptualise the patient cohort as basis for investigating electrophysiological signatures in PPA subtypes. Second, the current debate about lvPPA and AD-related PPA is missing pathologically proven underpinning of imaging results. The patient cohort is pathologically described by definite amyloid status (amyloid PET scan) and structural imaging & neuropsychological data are provided to reveal core deficits of the PPA subtypes.

As mentioned previously, clinical subtypes are associated to different pathologies. SvPPA and nfvPPA are typically associated with pathologies in the spectrum of frontotemporal lobar degeneration (FTLD), where svPPA has the strongest association to TDP-43 pathology and nfvPPA to tau pathology (Hodges et al., 2004; Yokota et al., 2009). In contrast to the FTLD-associated subtypes, lvPPA has the strongest association to Alzheimer pathology (Grossman, 2010; Harris and Jones, 2014). As formulated in Chapter 1, the exact definition lvPPA is currently being discussed in the PPA community. It is a matter of fact that PPA is often found with underlying Alzheimer pathology (Villarejo-Galende et al., 2017). If this happens, the clinical presentation rarely corresponds the definition sv- and nfvPPA (Josephs et al., 2008; Rabinovici et al., 2008). Some studies have struggled to identify the precise clinical profile of lvPPA when strictly applying proposed lvPPA criteria (Mesulam et al., 2012; Sajjadi et al.,

2014). Resonating with before mentioned studies, a clinico-pathological study found that most patients with PPA and AD pathology had more extensive language features than is captured by the criteria for lvPPA leading the authors to coin the term “lvPPA+” (Giannini et al., 2017). This finding resonates with an earlier clinical series that found a large number of patients presenting a “mixed” PPA that was separate from nfvPPA and svPPA, while patients meeting criteria for lvPPA were mostly absent (Sajjadi et al., 2012a). Another study proposed a hierarchical diagnostic algorithm that defined lvPPA by the absence of sv- and nfvPPA; largely abandoning the proposed criteria for lvPPA (Leyton et al., 2011).

To mention a last study to support the redundancy of the recent definition of lvPPA, a data-driven analysis of clinical features suggested that the proposed features of nfvPPA and svPPA cluster together as they were expected, whereas those for lvPPA did not (Sajjadi et al., 2012a).

The three proposed subtypes of PPA and characteristic loci of neurodegeneration have been described in Chapter 1.2. To recapitulate, maximal atrophy and/or hypometabolism has been localised around the left frontal operculum in nfvPPA (Gorno-Tempini et al., 2004; Nestor et al., 2003; Sajjadi et al., 2013); in the left rostral temporal lobe in svPPA (Acosta-Cabronero et al., 2011; Diehl et al., 2004; Gorno-Tempini et al., 2004); and in left posterior perisylvian region in lvPPA (Gorno-Tempini et al., 2004; Mesulam et al., 2012). The reported lesion of lvPPA was found in those designated ‘mixed PPA’. The term ‘mixed PPA’ underpinned that their deficits extended beyond that, which can be captured with the strict consensus definition of lvPPA. Nonetheless, this finding suggests that such cases are conceptually identical to those labelled ‘lvPPA’ by others (Sajjadi et al., 2014).

Although these imaging findings are highly replicated, it should be noted that they refer to peak areas of neurodegeneration as defined by the most statistically significant

abnormalities in group-averaged data. Therefore, it does not exclude additional areas of significant degeneration. The method of reporting is a biasing problem, when it comes to understanding the full extent of cortical degeneration associated with any particular syndrome; whole-brain studies typically report maps of statistical significance. However, this approach means that, by increasing the statistical threshold, abnormal brain regions can appear unaffected. The present chapter intends to investigate cortical thinning in the three peak atrophy sites associated with PPA subtypes. The specific hypothesis is that, although the maximal site of damage is the left posterior perisylvian region, degeneration affects the left hemisphere language network more diffusely in AD-related PPA, compared to sv- and nfvPPA. This, in turn, would offer a possible explanation for why patients in this category often have a more mixed aphasic syndrome (including semantic and grammatic deficits) and fail to meet strict lvPPA criteria. In contrast, we predicted that in svPPA and nfvPPA degeneration would be more restricted to the respective sites of peak degeneration.

3.2 Material & Methods

Details on acquisition and processing of T1-weighted MR images, T2-weighted MR images, and amyloid-PET data were described in detail in Chapter 2.5.

3.2.1 Participants

Data from 31 patients with the root diagnosis primary progressive aphasia were collected. Patients underwent the full battery of neuropsychological assessment (Chapter 2.3), magnetic resonance imaging, and, as part of their clinical diagnostic

work-up, ^{18}F-Florbetaben PET. Six patients were excluded from the final analyses, three because of contraindication to MRI; two with amyloid-negative PET whose PPA syndrome was unclassifiable (i.e. neither sv- nor nfv-PPA); and one who did not have PET, leaving 25 patients in this study.

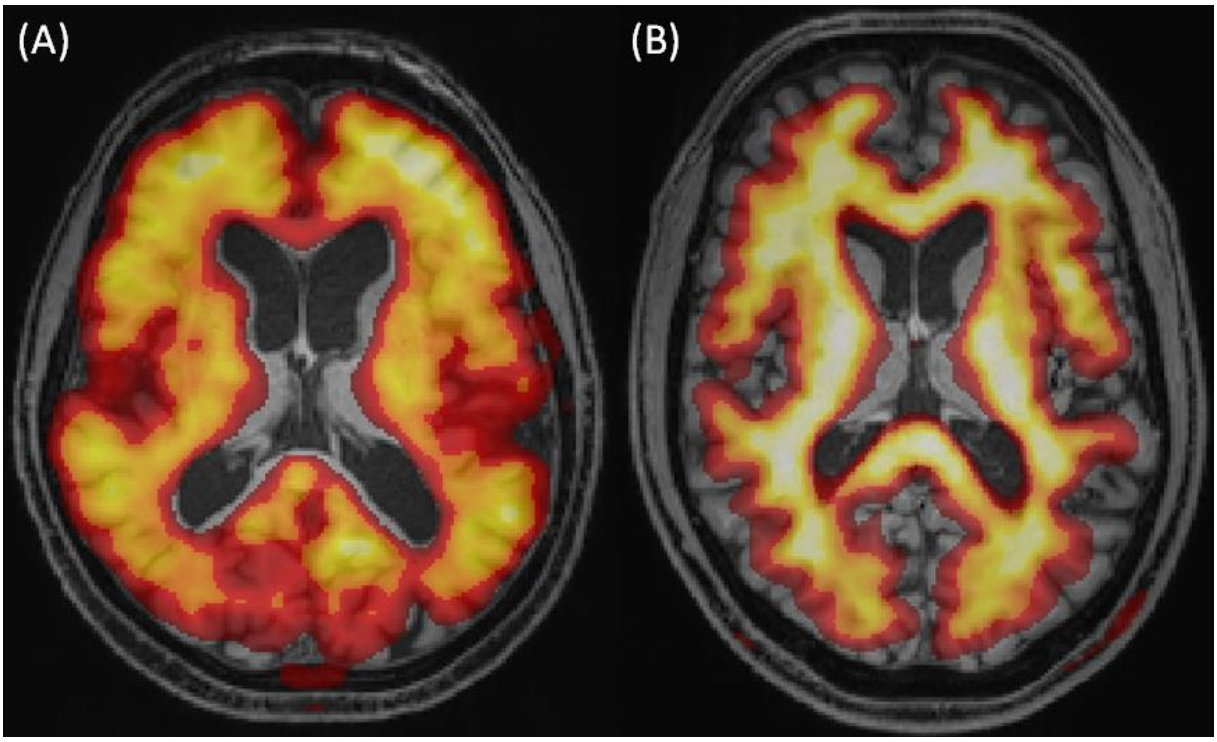

Figure 3.1 Examples of (A) an amyloid-positive 18F-Florbetaben scan in comparison to (B) an amyloid-negative scan.

The age-matched healthy control group (N=42) was recruited from a pool of local MRI participants. These participants had no history of neurological disorders or major psychiatric illness. All participants scored in the normative range in cognitive testing. Demographics of all groups are collected in Table 3.1.

Table 3.1 Demographic variables from the MRI control group and the three patient groups

group	Control (N=42)	AD-PPA (N=9)	svPPA (N=10)	nfvPPA (N=6)
Age	68.4(+/-4.9)	68.8(+/- 6.4)	65.3(+/-6.4)	68.2(+/-7.0)
Sex (M/F)	19/23	4/5	5/5	6/0
Symptom Duration (years)	-	2.3(+/-0.9)	4.6(+/-2.5)	3.2(+/-1.7)

3.2.2 Neuropsychological Assessment

Applied neuropsychological tests are described in chapter 2.3. The general neuropsychological assessment comprised Mini Mental State Examination (MMSE), Geriatric Depression Scale (GDS), Digit Symbol Substitution test (DSS), as well as copy, immediate recall, and delayed recall of the Rey complex figure. Linguistic neuropsychology included Boston Naming test, verbal digit span test, category and letter fluency test, “Kaffee & Kuchen”-test, the Repeat & Point test, a sentence repetition task, and the visual version of the Sentence Comprehension Test (SECT-V).

3.2.3 Statistical Analysis

Neuropsychological test results were analysed with one-way ANOVAs with $\alpha = 0.05$. For multiple comparisons adjustment was applied a Bonferroni correction with the significance level set at $p < 0.05$. Whole brain analysis of cortical thickness was performed to contextualise the current cohorts with previous group studies. Analysis of vertex-wise whole-brain cortical thickness was performed with a general linear model; multiple comparisons were adjusted with a false discovery rate (FDR) at $p < 0.001$. Statistical analyses of cortical thickness in ROIs were performed using SPSS version 21 (IBM, Chicago, IL).

Shapiro-Walk test assessed the ROI data for normality and subsequently Kruskal-Wallis test followed by pair-wise comparison with Dunn’s test were performed. For multiple comparisons adjustment a Bonferroni correction with the significance level set at $p < 0.05$ was applied.

3.3 Results

3.3.1 Subtyping and Demographic Data of the Patient Cohort

This chapter reports data from a new prospective cohort of PPA patients. Subtyping of all 25 patients resulted in 10 svPPA, 6 nfvPPA, and 9 PPA patients that misfit the definition svPPA, nfvPPA, and lvPPA. Examples of amyloid-positive and amyloid-negative PET scans are depicted in Figure 3.1. All sv- and nfvPPA patients had negative 18F-Florbetaben scans, meaning none of them had neocortical Aβ deposition. In contrast, the 9 remaining patients had a positive PET scan, making them AD-PPA patients. Demographic data for all groups is displayed in Table 3.1. Gender distribution was balanced in controls, svPPA, and AD-PPA, whereas nfvPPA consisted exclusively of males. AD-PPA patients presented with the shortest symptom duration, follow by nfvPPA and svPPA, which presented with the longest symptom duration. However, these differences were not significant ($X^2(2) = 3.77$, $p = 0.15$). Mean age was similar in all groups.

3.3.2 Neuropsychological Performance

Table 3.2 provides the detailed results of the neuropsychological data. A mild-to-moderate depressive state was indicated by the GDS, scores were similar across all patient groups. MMSE, as well, was similar in the three patient groups and, in comparison with normative data, decreased, suggesting cognitive deficit in the patients. As expected, the three patient groups presented with subtype specific deficits. Deficits in the svPPA group manifested in tests connected to semantic knowledge: category fluency; Boston naming test; Kaffee & Kuchen-test; and the semantic (point)

component of the Repeat & Point test. The svPPA group's scores in BNT, point component of the Repeat & Point test, and 'Kaffee & Kuchen' test is significantly worse than the scores of all three other groups. These tests rely strongly on semantic knowledge because knowledge for explicit objects must be available. Although, the svPPA group's score in category fluency was worst it was not statistically significant from the other patient groups' scores.

NfvPPA deficits were most pronounced in tests tapping on repetition and grammatical comprehension, namely the span tests, repetition of single words (repeat component of the Repeat & Point test) and sentences; as well as grammatical comprehension in the SECT-V. The AD-PPA group produced significantly worse scores in all tests except the point component of the Repeat & Point. The group's performance was intermediate to svPPA and nfvPPA in category fluency, BNT, 'Kaffee & Kuchen' test, span tests, and the repeat component of the Repeat & Point test.

3.3.3 Whole Brain Analysis of Cortical Thinning

Significant atrophy was present in all three patient groups (FDR-corrected $p<0.001$). In addition, the atrophy was asymmetric and left hemisphere dominant in all three groups but with subtype-specific peak atrophy sites (Fig. 3.2). The site of significant cortical thinning in the svPPA group was bilateral (left worse than right) temporal cortex, in particularly in fusiform, inferior temporal, middle temporal, and the anterior portion of the superior temporal gyrus. Significant atrophy in the nfvPPA group encompassed dorsolateral prefrontal cortex (left worse than right), left dorsomedial, and opercular frontal regions, as well as the left superior temporal gyrus. The AD-PPA group had most significant cortical thinning at the left temporoparietal junction (posterior perisylvian area), encompassing the superior and middle temporal lobe as

well as inferior parietal lobe, left dorsolateral prefrontal cortex and inferior frontal gyrus. The same analysis but with a Freesurfer standard 10mm smoothing kernel is shown in Figure 3.4. Although the quantity of atrophy pattern is reduced, the same cortical areas presented with significant cortical atrophy.

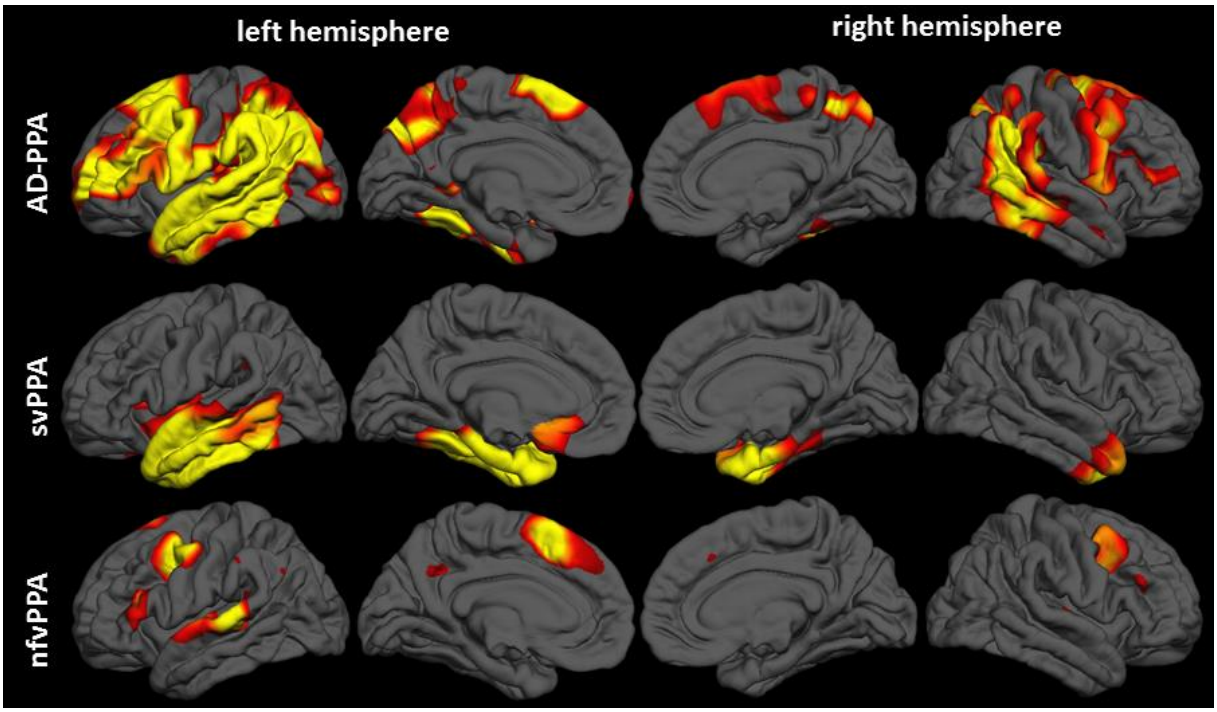

Figure 3.2 Whole-brain cortical thinning displayed on the pial surface for every PPA variant compared to a cohort of healthy age-matched volunteers; FDR-corrected ($p < 0.001$) with a 20 mm FWHM smoothing kernel; reprinted with permission by Elsevier (Preiß et al. 2019)

Table 3.2 Results from the neuropsychological assessment; normative data are collapsed from cognitive healthy participants in the range 60-80 years (N= 25-33); data = mean (SD); "Kaffee & Kuchen"-test for one nfvPPA patient was not recorded due to technical problems; Source (Preiß et al. 2019)

	Normative data	AD-PPA (N=9)	SvPPA (N=10)	NfvPPA (N=6)	Omnibus significance
General Neuropsychological Assessment					
MMSE /30*	29.1 (0.8)	19.3 (5.0)[a]	21.0 (5.9)[a]	20.8 (67.4)[a]	F(3,54)=23.542, p < 0.001
GDS /15*	0.6 (0.8)	4.2 (4.5)[a]	2.4 (1.7)	4.0 (4.0)[c]	F(3,54)=8.079, p < 0.001
Digit Symbol Substitution	11.3 (1.8)	6.2 (1.8)[a]	9.7 (1.6)[d]	6.3 (2.3)[a,h]	F(3,54)=25,324, p < 0.001
Rey copy /36*	32.3 (2.7)	22.6 (8.5)[a]	33.6 (1.6)[d]	27.9 (5.2)	F(3,53)=13.784, p < 0.001
Rey immediate recall /36*	18.5 (5.8)	7.5 (4.9)[a]	14.0 (4.2)	14.8 (4.3)	F(3,53)=10.571, p < 0.001
Rey delayed recall /36*	17.8 (5.0)	7.1 (5.7)[a]	12.0 (4.1)[c]	14.3 (5.3)[f]	F(3,53)=11.895 p < 0.001
Linguistic Neuropsychological Assessment					
Letter Fluency	12.8 (2.3)	6.4 (4.5)[a]	5.7 (3.3)[a]	2.7 (1.8)[a]	F(3,49)=32.135, p < 0.001
Category Fluency	18.2 (4.1)	7.4 (3.1)[a]	5.9 (3.5)[a]	7.8 (4.4)[a]	F(3,44)=34.802, p < 0.001
Boston Naming /30*	27.4 (2.4)	16.4 (6.3)[a]	4.7 (4.5)[a,d]	22.7 (4.4)[c,f,g]	F(3,54)=97.082, p < 0.001
Kaffee & Kuchen /30*	27.8 (1.6)	22.9 (2.0)[a]	17.0 (5.0)[a,d]	24.7 (2.4)[g]	F(3,45)=37.486, p < 0.001
Digit Span forward /8*	6.2 (1.0)	4.1 (0.9)[a]	5.6 (1.0)[e]	3.3 (0.8)[a,g]	F(3,54)=23.313, p < 0.001
Digit Span backward /7*	4.4 (0.7)	2.8 (1.2)[a]	4.2 (0.9)[f]	2.2 (1.5)[a,g]	F(3,54)=14.087, p < 0.001
Sentence Repetition /5*	4.9 (0.3)	2.5 (1.3)[a]	4.5 (0.7)[d]	1.5 (2.1)[f]	F(3,49)=15.840, p < 0.001
Repeat & Point (Repeat) /10*	9.9 (0.4)	6.6 (2.4)[a]	9.6 (0.7)[e]	4.5 (3.7)[a,g]	F(3,46)=21.860, p < 0.001
Repeat & Point (Point) /10*	9.8 (0.4)	8.7 (1.3)	5.8 (2.6)[a,d]	9.0 (2.0)[h]	F(3,46)=13.597, p < 0.001
SECT-V /48*	45.2 (2.2)	36.1 (3.1)[a]	43.0 (5.1)[d]	36.0 (5.1)[a,h]	F(3,42)=22.119, p < 0.001

Abbreviations: MMSE = Mini-Mental State Examination, GDS = Geriatric Depression Scale, SECT-V = visual version of the Sentence Comprehension Test, AD-PPA = Alzheimer-related PPA, svPPA = semantic variant of PPA, nfvPPA = nonfluent/agrammatic variant of PPA

*represents the maximum score for the test

[a] p<0.001 compared with normative data

[b] p<0.01 compared with normative data

[c] p<0.05 compared with normative data

[d] p<0.001 compared with AD-PPA

[e] p<0.01 compared with AD-PPA

[f] p<0.05 compared with AD-PPA

[g] p<0.001 compared with svPPA

[h] p<0.01 compared with svPPA

[I] p<0.05 compared with svPPA

3.3.4 ROI Analysis

The analysis of cortical thickness in three ROIs produced statistically significant differences between groups in all ROIs: the IFG ($X^2(3) = 25.6$, $p < 0.001$), the PPS ($X^2(3) = 34.6$, $p < 0.001$), and the AFA ($X^2(3) = 39.8$, $p < 0.001$). Post-hoc pairwise comparisons with Dunn's test ($p < 0.05$, corrected) was performed to reveal the exact differences. The IFG showed a significant mean thickness reduction of 16% in the nfvPPA group ($p < 0.001$); 9% in the AD-PPA group ($p < 0.05$); and a non-significant 4% reduction in svPPA, compared to the control mean (Fig. 3.3 left). In the AFA, mean reduction was 31% for svPPA ($p < 0.001$); 14% for AD-PPA group ($p < 0.005$); and a non-significant 8% for nfvPPA (Fig. 3.3 middle). Severe reduction of PPS thickness was detected in the AD-PPA group (15%, $p < 0.001$). However, with reductions also reaching significant reduction of PPS thickness was also present in nfvPPA (8%, $p< 0.05$) and in svPPA (5%, $p< 0.05$) (Fig. 3.3 right).

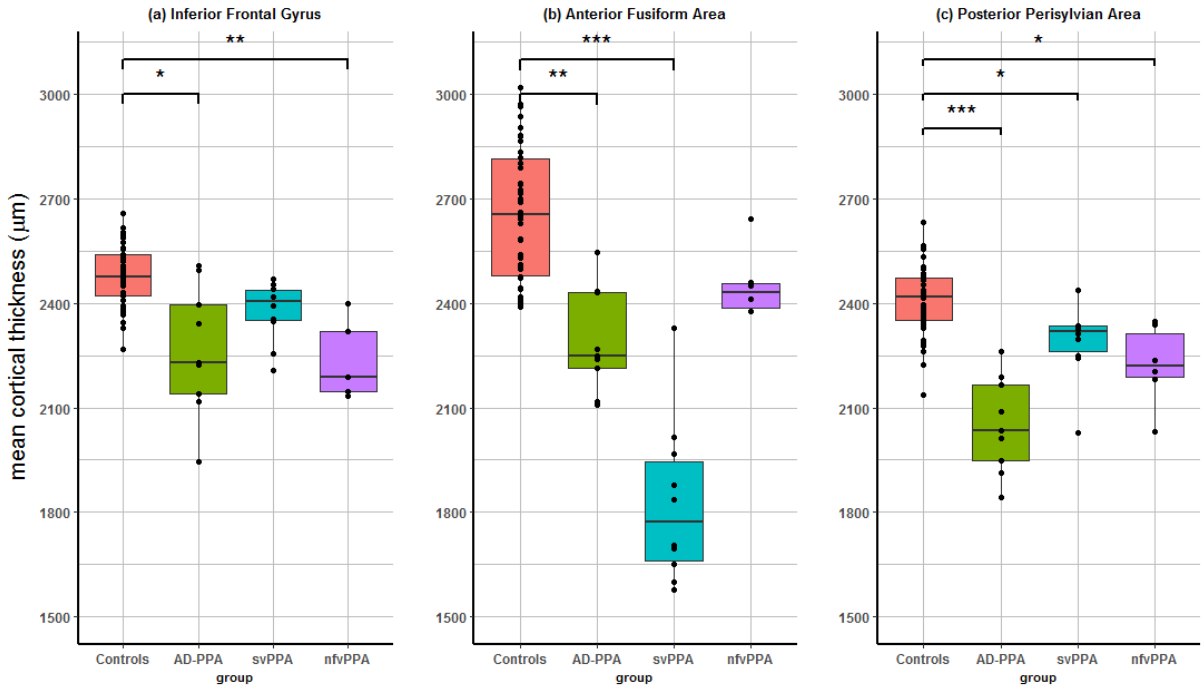

Figure 3.3 Results from the ROI analysis for the ROIs a) IFG, b) PPS and c) AFA; boxplot= 1st, 2nd, 3rd quartile; whiskers 95% CI; * = p<0.05; ** = p<0.005; *** = p<0.001; reprinted with permission by Elsevier (Preiß et al. 2019)

3.4 Discussion

The results of the ROI analysis are in line with prior knowledge. Most extreme cortical thinning in each region corresponded to the expected syndrome: the most severe IFG thinning was in the nfvPPA group; likewise, for AFA thinning and svPPA; and, PPS thinning and AD-PPA. As hypothesised, statistically significant cortical thickness reduction was evident in all three ROIs in the AD-PPA group. This result confirmed the prediction that the left hemisphere language network is diffusively affected by degeneration, while the left posterior perisylvian region is the most severely affected area in AD-related PPA. In contrast, nfvPPA did not present with significant AFA abnormality and, vice versa, svPPA with significant IFG abnormality. Both nfvPPA and svPPA did, however, show mild, but statistically significant, thickness reductions in the PPS. In line with the ROI analysis, the whole-brain analyses highlighted diffuse left hemispheric changes in AD-PPA, whereas the other two patient groups revealed focal cortical thinning.

The present analysis revealed a pattern similar to earlier whole-brain analyses of cortical thickness in pathologically confirmed AD-PPA groups (Rohrer et al., 2012, 2010). Likewise, the voxel-based morphometry method also identified reduced grey matter density to be maximal in the posterior temporoparietal region in AD-PPA (Josephs et al., 2008) although this analysis method is less sensitive than the cortical thickness approach at capturing degeneration in the cortical ribbon (Diaz-De-Grenu et al., 2014; Rohrer et al., 2010). Whether it is whole-brain cortical thinning or voxel-based morphometry, both methods produce statistical maps with methodological limitations. The major limitation is the degree of arbitrariness in what gets defined as the extent of the degenerated region; for instance, the stringency of the applied statistical threshold, and the degree of smoothing influence the quantity of detected abnormality. Another

author (Diaz-De-Grenu et al., 2014) reported that the default smoothing kernel in the Freesurfer method of 10mm appears to underestimate the extent of neurodegeneration in AD by giving patchy, and thus non-biological-looking blobs [compare Figs. 3.2 & 3.4 and consider (Diaz-De-Grenu et al., 2014) for further discussion]. In contrast, studies using large smoothing kernels (20mm FWHM), such as the present study and others (Leyton et al., 2016; Rohrer et al., 2012, 2010) yield confluent areas of cortical thinning. The novelty of the present study was in quantifying the severity of cortical thinning in the key loci for each of the three PPA groups. This approach was also employed in a post-mortem study although the "semantic" ROI was the temporal pole rather than the anterior fusiform gyrus (Leyton et al., 2016). Nonetheless, similar atrophy pattern emerged in that AD-PPA showed significant atrophy at the putative svPPA and nfvPPA loci.

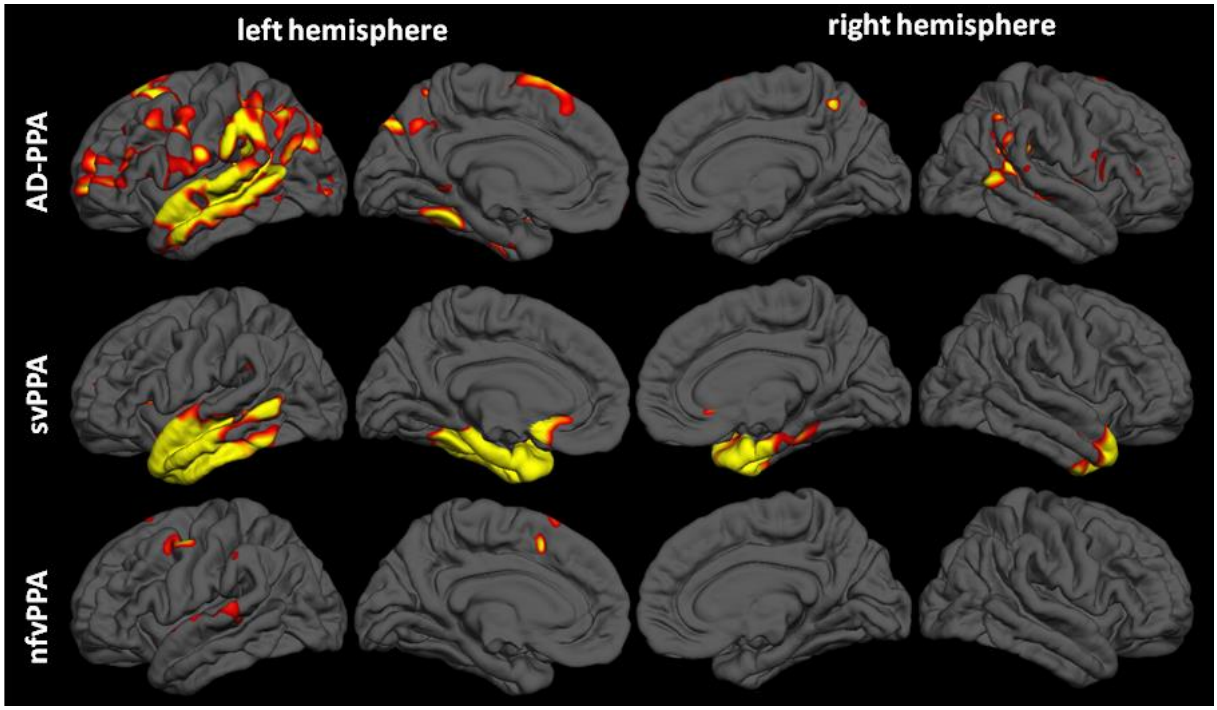

Figure 3.4 Whole-brain cortical thinning displayed on the pial surface for every PPA variant compared to a cohort of healthy age-matched volunteers with a 10 mm smoothing kernel; FDR-corrected ($p < 0.001$), this is the same analysis and statistical threshold as presented in Fig. 3.2, except that the default FreeSurfer 10 mm smoothing kernel is applied; reprinted with permission by Elsevier (Preiß et al. 2019)

Involvement of regions characteristically associated with nfvPPA and svPPA has been significant in the AD-PPA group. From a neuropsychological perspective, deficits in

semantic knowledge, as well as grammatical abilities in the AD-PPA group became present. In contrast, inability in nfvPPA and svPPA focused on grammatical abilities and semantic knowledge, respectively. This finding offers a plausible explanation for why the language deficit in AD-PPA is often more extensive than is captured in the current conceptualisation of lvPPA (Gorno-Tempini et al., 2011). To this end, it is notable that in this new, prospective cohort study, both the AD-PPA and the nfvPPA groups showed significant impairments in grammatical comprehension (the SECT-V test) whereas svPPA did not; similarly, the AD-PPA and svPPA groups showed significant impairments in semantic associative knowledge whereas the nfvPPA group did not. In other words, there was evidence for a double dissociation between grammatical and semantic comprehension between nfvPPA and svPPA whereas AD-PPA showed impairments in both domains.

With 31 % cortical thinning, the AFA atrophy in the svPPA group was the most extreme lesion across all groups. The well-documented finding of extreme rostroventral atrophy in this group resonates with the finding. The major atrophy in svPPA patients manifests in individual patients. A recent diagnostic study found, that while visual rating of MRI scans was insensitive for the atrophy pattern of the other clinical PPA subtypes it was highly sensitive for atrophy in svPPA (Sajjadi et al., 2017). Although the key area of degeneration in nfvPPA is the IFG, additional smaller spots of atrophy were found in dorsomedial, dorsolateral frontal, and superior temporal cortices. All of these findings have been reported in past nfvPPA groups (Caso et al., 2014; Josephs et al., 2006; Leyton et al., 2016). The small number of patients in the nfvPPA group (N = 6) was the main limitation of this study. Nevertheless, cognitive deficits and the atrophy pattern of the cohort corresponds to previously published data.

In conclusion, the analysis in this prospective cohort indicates diffuse involvement of the left hemisphere language network in AD-PPA. The results likely explain why the

broader spectrum of deficits in AD-PPA cannot be covered by the consensus recommendations for lvPPA, which are frequently associated with AD pathology. This opens up a deeper understanding of degeneration patterns in the PPA spectrum in addition to the highly-replicated loci of maximal atrophy for each syndrome. We have proven that the heterogeneity of language deficits in AD-PPA co-exists with diffuse structural changes, compared to much more focal atrophy in FTLD-related PPAs.

Chapter 4 Attempting Neurophysiology: Are MEG and EEG applicable in PPA?

4.1 Introduction

While the previous chapter focused on neuropsychology and structural imaging, this and subsequent chapters will investigate electrophysiology in PPA patients. Electroencephalography (EEG) and magnetoencephalography (MEG) are two electrophysiological measurement techniques and only two EEG studies were conducted with PPA patients (Giaquinto and Ranghi, 2009; Hurley et al., 2009). The studies presented data from 20 patients (Hurley et al., 2009) and from a single patient (Giaquinto and Ranghi, 2009) but did not report the number of patients that were excluded because of poor data quality recordings. From these studies one cannot infer the feasibility of EEG and MEG in PPA patients. The exclusion rate of EEG and MEG depends on the level of noise in individual data sets and both techniques are highly susceptible to noise. Noise can have two sources, namely external sources or internal sources. A detailed overview of types of noise and sources can be found elsewhere (Cohen, 2014; Hansen et al., 2010; Luck, 2014).

This paragraph will introduce the most typical sources of noise. External sources are from the environment, e.g. line noise or noise from other electrical devices. These kinds of noise can be circumnavigated with an electrically shielded setup and well isolated electrical conductors inside the setup. Internal sources derive from participants and the experimental design. Three internal sources are described below. First, participants can have metallic objects that are not detachable (e.g. tooth implants or pace makers). These objects will produce constant artefacts or acute artefacts when participants move. Second, muscle artefacts like tension, eye rolling or tongue movement. The

amount of muscle artefacts can be reduced by sitting participants comfortably and including resting breaks in the experiment. Participants that cannot control movement or sit still for a certain period of time are likely to produce a tremendous amount of muscle artefacts. Third, task-induced movement like strong eye movement or head movement in response to task instructions or task demands. A well-designed experiment does not force participants to move their head or eyes extensively. All described artefacts contaminate data sets and reduce the amount of noise-free trials. Once too many trials of a data set are contaminated by artefacts, the dataset needs to be discarded from post-processing.

4.2 Results

The results section will summarise the amount of recorded and processed EEG and MEG datasets for this thesis, in total, 102 datasets were recorded with both EEG and MEG. Table 4.1 and Table 4.2 summarize the number of recorded and processable datasets. Processable datasets refer to those which were not discarded because of artefacts or disrupted recording.

EEG datasets

In the control group, 55 of 56 datasets had sufficient quality. Only one dataset in the passive reading experiment was contaminated by permanent eye blinks and rejected from the analysis. In the patient groups, the number of datasets with sufficient quality was lower. Eleven datasets from the passive reading experiment and three datasets from each oddball experiment did not enter post-processing because of insufficient data quality. The insufficient data quality resulted from contamination by permanent

eye blinks, metal artefacts, repeated and substantial movement or technical problems while recording.

Table 4.1 Total numbers of recorded and processed EEG datasets

EEG groups	All Datasets		Datasets for the passive reading		Datasets for the visual oddball		Datasets for the semantic oddball	
	recorded	processed	recorded	processed	recorded	processed	recorded	processed
Controls	56	55	24	23	16	16	16	16
Patients	46	31	22	13	12	9	12	9
Total	102	86	46	36	28	25	28	25

MEG datasets

The rejected datasets from EEG were automatically rejected from MEG analysis because the disruption of data, especially from movement, was worse in MEG than in EEG. The additional technical problems related to measured signal fluctuations in MEG sensors. Once amplitudes are too strong, MEG sensors are at risk of shutting down until system reset, which results into break-up of an experiment. The amount and intensity of metal artefacts was bigger in patient-datasets leading to an increased risk of strong signal fluctuations. Only six patient datasets had sufficient quality in the passive reading experiment and only three datasets in both oddball experiments.

Table 4.2 Total numbers of recorded and processed MEG datasets

MEG groups	All Datasets		Datasets for the passive reading		Datasets for the visual oddball		Datasets for the semantic oddball	
	recorded	processed	recorded	processed	recorded	processed	recorded	processed
Controls	56	44	24	18	16	13	16	13
Patients	46	12	22	6	12	3	12	3
Total	102	56	46	24	28	16	28	16

4.3 Conclusion

This initial, descriptive analysis revealed that electrophysiological methods in PPA patients are at high risk of contamination by artefacts. The amount of processable

datasets was substantially lower in PPA patients than in healthy participants. While in EEG 98% of healthy participants and 67% of patient datasets had sufficient quality, in MEG 79% of healthy participant and 25% of patient datasets had sufficient quality for post-processing. The increased number of discarded MEG datasets arises primarily from metal artefacts in MEG, which are not detected by EEG. The difference between patients and healthy participants is partly explained by a recruiting bias. Healthy participants were recruited from a pool of volunteers for MRI experiments; therefore, most of them did not have metal implants that would create a risk in MRI experiments. However, because of the general small pool of available PPA patients, patients were recruited even though they had metal implants.

In summary, MEG data quality was inferior to EEG data quality. The reason is MEG's greater sensitivity to all sources of movement and increased intensity of metal-induced artefacts. Participants must reduce movement to an absolute minimum to decrease artefacts, which, based on the low amount of MEG datasets with sufficient data quality, seemed impossible for most PPA patients in this cohort. External artefacts like line noise or noise from other electrical sources can corrupt the datasets as well but were not the primary cause for rejection of datasets. In Chapters 5 & 6, MEG data were discarded because of the small number of datasets with sufficient data quality.

In general, electrophysiological investigations can help to gain insight into the temporal development of cortical processing but might not become a clinical marker for individual PPA patients due to the restrictions that come naturally with this recording technique, especially with MEG. In addition, more complex tasks are likely to increase the amount of task-induced movement artefacts and, therefore, complex tasks combined with electrophysiological measures are unlikely to be applicable in PPA cohort studies.

Chapter 5 ERP Signatures of Reading in Pathology-Defined Subtypes of PPA

Up until now, most studies in the PPA spectrum focussed on neuropsychology, imaging and pathology. High-resolution temporal information of cortical processing in PPA is virtually non-existent. Two recording techniques, namely electroencephalography (EEG) and magnetoencephalography (MEG), can detect cortical activity in millisecond-to-millisecond resolution. By investigating electrophysiological signatures in PPA, critical information about functional consequences of the disease will be added to the existing knowledge and add further insight for biomarker development and interventions in PPA research.

5.1 Introduction

As described in Chapter 1, ERP studies in PPA patients are rare and focused on manipulation of the N400 component (Giaquinto and Ranghi, 2009; Hurley et al., 2009). Those studies reported signal alterations in the N400 time range but did not investigate earlier components of the ERP signature. The N400 component was proposed as a marker for several linguistic processes, e.g. word comprehension, semantic access and syntactic analysis (Hinojosa et al., 2001; Kutas and Federmeier, 2011; Lau et al., 2008). However, many psycholinguistic investigations revealed that ERP components prior to the N400 are influenced by word properties, such as word length and lexical frequency (Chetail et al., 2012; Dambacher et al., 2006; Hauk et al., 2009; Sereno et al., 1998). One of those studies postulated the N400 component to reflect post-lexical processes rather than lexical access (Sereno et al., 1998). In that study, words and non-words with four to six letters were presented to young participants and the recorded ERP signatures diverged approximately 100 ms and 130

ms after stimulus onset with strongest amplitudes recorded under occipital electrodes. Those ERP peaks were identified as the components P1 and N1 and revealed processing of lexicality several hundred milliseconds earlier than the N400. At around the same time, another team of researchers applied MEG measures to locate cortical sources of language processing (Tarkiainen et al., 1999). Their main findings were two language-related peaks at around 100 and 150 milliseconds after stimulus onset. The first signal was generated in the occipital lobe, namely in the V1 area and surrounding neocortex; the second signal was generated in the inferior occipitotemporal cortex. The described signal peaks were the MEG-analogues to P1 and N1 in EEG and, again, revealed that processing of language-relevant information takes place prior to the N400. The early ERP components are affected by word length and lexical frequency of words (Hauk and Pulvermüller, 2004a). However, those properties are naturally correlated (Zipf, 1935). In the early 20th century, some authors disentangled the issue of inverse correlation of word length and lexical frequency and the accompanying interaction of both word properties. Word length and lexical frequency are naturally correlated ($r \approx -0.9$), meaning that the shorter a word, the higher is the lexical frequency (Osterhout et al., 1997). This natural correlation makes it difficult to differentiate the effect of both properties on processing of words. In two studies, word sets with uncorrelated word length and lexical frequency were presented to participants to distinguish the effects of those variables (Assadollahi and Pulvermüller, 2003; Pulvermüller et al., 2001). The authors found, in a single case study (Pulvermüller et al., 2001) and in a group study (Assadollahi and Pulvermüller, 2003), differential effects of word length and lexical frequency on word processing, namely a word length effect in the P1 component and a lexical frequency effect in the N1 component. Source estimation revealed that P1 was generated in the occipital lobe and N1 in the inferior occipitotemporal cortex (Assadollahi and Pulvermüller, 2003). Later studies found

effects in identical time ranges of global field power (GFP) signatures for silent reading (Hauk and Pulvermüller, 2004b) and lexical decision (Hauk and Pulvermüller, 2004a).The latter study postulated lexical access happening, at the latest, 150 milliseconds after visual presentation of words.

The referenced studies identified time ranges and spatial locations that are critical for visual word processing. Results were obtained with different tasks in healthy participants but, unfortunately, not every task is practical in neurodegenerative diseases. One example in the field of PPA is a study in svPPA patients (Pulvermüller et al., 2010). Patients performed a forced-choice lexical-decision task and response times were recorded. In that task, participants had to respond whether a word is a lexical entry (real word) or has no meaning (pseudoword). Even though, patients were able to understand and perform the task they were not able to press one of two buttons, corresponding to their decision, and verbalise the answer. As a result, the experimenter had to push buttons after receiving the answer from patients. In this scenario, response times were not representative for the patients' performance but rather a composite of patients' response time and the examiner's response time. The problem was attributed to the "dual-task" situation. Here, "dual-task" refers to the lexical decision task and the task to press one of two buttons, corresponding to the correct response. If a secondary task is demanding for participants it will influence the resulting data, making the subsequent interpretation redundant. Besides this study, no data regarding dual tasks situations in PPA are available to estimate appropriate task demands for PPA patients. A simple language task with minimal task demands is a good starting point. The most simplistic task in psycholinguistics is a passive reading task, where participants have to read words silently. The simplicity bares the risk of not activating the relevant neuronal circuits and not producing ERP signatures that are representative for visual

word processing. This knowledge creates two critical questions for the design of the present experiment:

1. Is the passive reading task, as the most simplistic task in psycholinguistics, suitable for patients suffering from PPA?
2. Even though the passive reading task is very simple, will it still elicit ERP signatures that are representative for visual word processing?

A task is considered suitable, if patients can perform the task and interpretable data are generated. The automaticity of reading (Flaudias and Llorca, 2014) in a passive reading task creates virtually non-existent task demands. This makes passive reading ideal for the investigation of visual word processing in neurodegenerative diseases. To answer the second question, ERP signatures in response to different tasks must be compared. The effect of different tasks on ERP signatures of visual word processing was investigated before by others (Chen et al., 2013). The authors compared the activation when passive reading, lexical decision (Does the word exist?) and semantic decision (Does the word belong to a category?) were performed. Every task added more complexity to the task demands. The basic task of silently reading words (passive reading) was extended by access to lexicality of a word (lexical decision) and retrieval of word meaning from the mental lexicon (semantic decision). Task-induced effects appeared 150 ms after word presentation and lasted until 500 ms in frontal and temporal cortices. Overall activation was smaller in the passive reading task, where no decision-making was involved, compared to lexical and semantic decision. Although task-specific effects occurred, all three tasks produced similar patterns of activation. The focus on specific properties of stimuli, as in lexical decision and semantic decision, attenuates task-specific components of signatures. However, the additional activation emerges with the penalty of increased task demands. Therefore, it is reasonable to

believe that passive reading will elicit ERP signatures which are representative for visual word processing in healthy participants and PPA patients. Another team compared the ERPs of healthy participants and neurological patients. Here, passive reading was applied in healthy participants (Moseley et al., 2013) and, subsequently, the same task was applied in patients with autism spectrum disorder (Moseley et al., 2014). The authors reported relevant activation in time ranges from 70 to 130, from 140 to 160, from 170 to 250 milliseconds and two later activity peaks that were associated with N400 activity. Activations were localised in perisylvian regions, posterior fusiform gyri and in the visual cortex. The studies revealed that passive reading can be applied in neurological patients and detect differences to ERP signatures of healthy participants. The activation as described by the previously mentioned studies is a proof that passive reading, even though it is a very simple task, elicits ERP signatures that are representative for visual word processing in healthy participants and in neurological patients. The present experiment aims to identify ERP signatures of language processing in PPA patients. Data from a passive reading experiment, incorporating high lexical frequency words, low lexical frequency words, and pseudowords, will be presented. The experiment was followed by an offline forced-choice lexical decision task containing all words from the passive reading experiment. The following questions will be addressed by this experiment:

1. Do ERP signatures (EEG) and ERF signatures (MEG) of PPA patients diverge from signatures of the healthy control group?
2. Do ERP signatures (EEG) and ERF (MEG) signatures of PPA subtypes diverge from each other in relevant time ranges?
3. Will behavioral data of the control group and patient groups show different error rates in the lexical decision task?

5.2 Methods

5.2.1 Participants

For the EEG/MEG experiment, 24 healthy participants and 22 patients with the core diagnosis PPA were recruited. Healthy participants were recruited from a pool of volunteering elderly citizens. Further details about recruitment can be found in chapter 2.2. All patients underwent neuropsychological assessment, magnetic resonance imaging (MRI), and ^{18}F-Florbetaben positron emission tomography (PET). Amyloid PET scans were rated visually and classified as AD-positive or AD-negative. PPA patients were classified by an experienced neurologist. SvPPA and nfvPPA patients were classified according to consensus recommendations for the respective syndromes (Gorno-Tempini et al., 2011) and by a negative amyloid-PET scan. In this cohort, no svPPA and nfvPPA patient had a positive amyloid-PET scan. All patients with a positive amyloid-PET scan who did not meet the criteria for svPPA and nfvPPA were diagnosed AD-PPA. All AD-PPA patients presented with anomia and additional grammatical and/or semantic deficits. The classification AD-PPA corresponded to descriptions “mixed PPA” (Sajjadi et al., 2014, 2012a) or “lvPPA+” (Giannini et al., 2017) in previous studies. After pre-processing of EEG data (further details on pre-processing of data can be found in chapter 2.4.2) two healthy participants and 13 PPA patients were rejected from post-processing because of major artefacts in continuous EEG, leading to a final pool of 23 healthy participants, eight AD-PPA patients, three nfvPPA patients and two svPPA patients. The nfvPPA and svPPA patients were collapsed into an FTLD-PPA group for two reasons. First, comparing groups of two and three patients against bigger groups will not give interpretable results and, second, both groups share the negative amyloid-PET scan and major atrophy in frontal and

temporal cortices but not in occipital cortex (see Figure 3.2). For MEG, 18 datasets from healthy participants and only six datasets from PPA patients had sufficient quality for analysis. The low number of PPA datasets and the further splitting into AD-PPA (N = 4) and FTLD-PPA (N = 2) was not sufficient for statistical analysis. Therefore, MEG analysis was discarded in this chapter. Patients' neuropsychological data were compared to reference data from healthy age-matched participants (Table 5.1).

Table 5.1 Neuropsychological test results from the control group, the AD-PPA group and the FTLD-PPA group

Neuropsychological test	Normative data	AD-PPA (N = 8)	FTLD-PPA (N = 5)
MMSE /30	29.1 (0.8)	18.8 (5.3)	27.6 (1.6)
GDS /15	0.6 (0.8)	3.5 (3.0)	1.8 (1.0)
Digit Symbol Substitution	11.3 (1.8)	6.1 (2.1)	8.6 (1.6)
Rey copy /36	32.3 (2.7)	21.4 (8.6)	31.0 (3.6)
Rey immediate recall /36	18.5 (5.8)	6.3 (4.4)	15.1 (4.7)
Rey delayed recall /36	17.8 (5.0)	5.3 (4.1)	14.5 (3.6)
Letter Fluency	12.8 (2.3)	5.4 (3.1)	6.4 (3.2)
Category Fluency	18.2 (4.1)	8.1 (2.9)	10.4 (3.5)
Boston Naming /30	27.4 (2.4)	14.3 (7.0)	19.2 (10.5)
Kaffee & Kuchen /30	27.8 (1.6)	23.9 (2.4)	26.6 (4.1)
Digit Span forward /8	6.2 (1.0)	3.6 (1.6)	5.0 (1.8)
Digit Span backward /7	4.4 (0.7)	2.9 (1.2)	3.4 (1.5)
Sentence Repetition /5	4.9 (0.3)	2.2 (1.5)	3.0 (1.9)
Repeat & Point (Repeat) /10	9.9 (0.4)	6.4 (2.2)	8.0 (2.1)
Repeat & Point (Point) /10	9.8 (0.4)	8.9 (1.3)	8.6 (2.0)
SECT-V /48	45.2 (2.2)	34.5 (3.8)	40.0 (5.6)

5.2.2 Experimental Design

The experiment took place in an electrically and acoustically shielded chamber. Participants were seated comfortably in a MEG setup with simultaneously recorded EEG. Prior to the experiment, participants had to read instructions and were encouraged to ask questions. Experimental instruction stated that single words would be presented to participants and are to be read silently. Instructions stressed that some words would have no meaning. Besides the experiment-specific instructions,

participants were instructed to keep their head still and to reduce blinking while the experiment was running. In addition, they were told that breaks would occur every 1.5 minutes. During the breaks, they were able to close their eyes and relax.

5.2.3 Procedure

Passive Reading Task

Participants were instructed outside the scanner, then seated comfortably inside the scanner and instructed again before the experiment started. Presentation took place on a screen, one meter in front of the participant. The experiment consisted of 15 blocks, each containing 40 stimuli. Between blocks, participants had an eye-resting period of 15 seconds and the start of the subsequent block was indexed by a five-second countdown. Every stimulus was presented for 1000 milliseconds in the center of the screen and followed by a fixation cross of 800 to 1200 milliseconds (Fig. 5.1). Stimuli were presented in randomised order. The experiment comprised 600 stimuli and took 23 minutes and 30 seconds, in total. Stimuli were presented with Psychopy software (version, 1.80.03 Peirce 2007; Peirce 2008).

Lexical Decision Task

Subsequent to the passive reading experiment, participants had to perform a forced-choice lexical decision task outside the scanner. A handout contained all words that were presented before in the passive reading task in alphabetical order. All words had to be categorised as real word or pseudo word. The percentage of correct answers was calculated for every condition, separately.

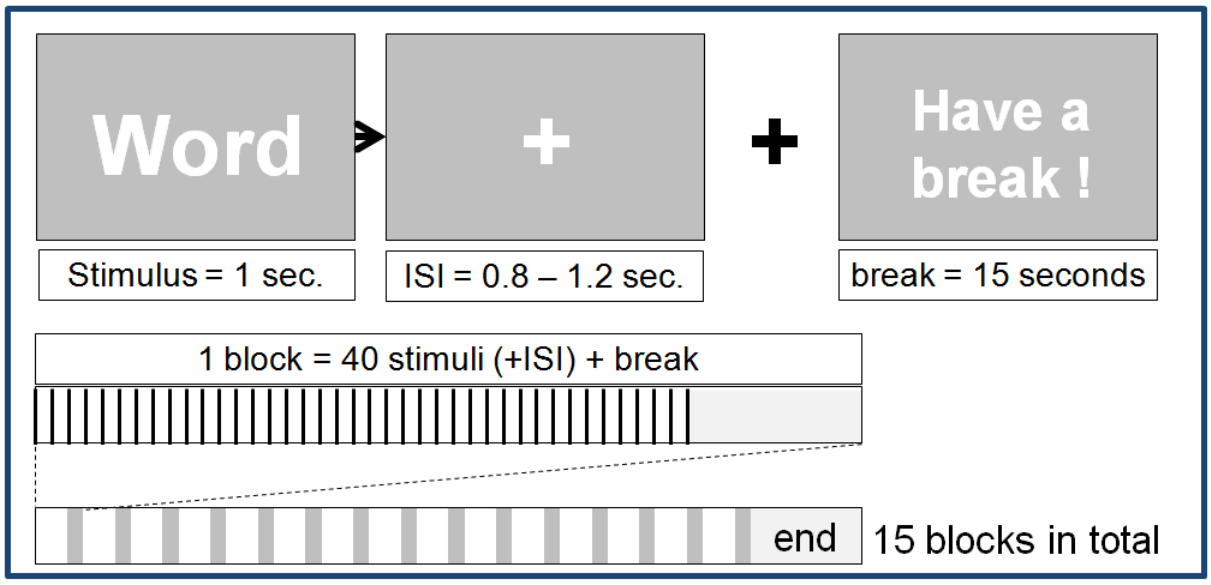

Figure 5.1 Illustration of the experimental procedure in the passive reading experiment; Abbreviation: ISI = inter-stimulus interval

5.2.4 Stimulus Set

For the passive reading experiment a list of 400 German nouns was created. All words were two-syllable nouns of five to seven letters. The 400 words were chosen to group into two equally sized conditions: high lexical frequency words and low lexical frequency words. Lexical frequency indexes the relative occurrence of a word in a representative corpus of literature. It is defined as items per one million words. Items for the pseudoword condition were created by exchanging the second syllables of words from the two real-word conditions. Non-existence was assessed for all pseudowords and the list was reduced to 200 randomly selected pseudowords. The aim of the three conditions was experimental control of attendance and the introduction of a lexicality effect, which is known from active tasks (Hauk and Pulvermüller, 2004a). Lexical frequency was derived from the online database dlexDB (http://www.dlexdb.de). In addition, orthographic properties, namely initial sign frequency, initial bigram frequency and initial trigram frequency, were extracted for all

words. Those frequencies index the relative occurrence of the initial one, initial two and initial three letters, which are known to affect ERPs (Chetail et al., 2012).

5.2.5 Post-Processing of EEG data

A detailed description of data acquisition (Chapter 2.4.1) and pre-processing (Chapter 2.4.2) of EEG and MEG data is given in Chapter 2. Following pre-processing, trials were defined from 200 ms prior until 600 ms after stimulus onset. The 200 ms epoch pre-stimulus was used as a baseline for trials. Grand average ERPs and GFP signatures were created by averaging all trials per individual and collapsing all individuals of a group.

5.2.6 Global Field Power Analysis

The GFP analysis elucidates the global temporal information of EEG datasets, similar to signal-to-noise ratio (SNR) and root mean square error (RMS). A detailed explanation of GFP, SNR and RMS is to be found in chapter 2.4.3. To generate GFP signatures, GFP values were calculated from all trials that survived EEG pre-processing and were rated correct in the lexical decision task. Those trials were averaged for every individual separately. GFP group signatures were created by averaging individual GFP signatures for the control group, the AD-PPA group and the FTLD-PPA group separately. Characteristic peaks in group signatures where analysed with a full-width quarter-maximum (FWQM) approach to generate time ranges of interest (TOIs) for later analysis steps. For the FWQM analysis, the cut-off for time range definition was set to 75% (instead of 50 % in FWHM) of maximal amplitude. In

addition to the GFP analysis, GFP signatures of FTLD subgroups, namely svPPA and nfvPPA, were generated to elucidate the impact of both subgroups on the appearance of the FTLD-PPA group's GFP signature.

5.2.7 Topographical Analysis

Electrode values in TOIs were visualised on a 2-dimensional representation of the head to investigate topographic voltage distribution. The primary purpose was identification of the spatial distribution of voltages. The selection of electrodes for subsequent analyses was based on the spatial patterns, which are derived from topographical analysis. The electrode selection concentrated on the polarity that dominated each voltage distribution (positive/negative polarity). In case of additional activation, additional electrode clusters were analysed in subsequent analysis steps.

5.2.8 Electrode Space Analysis

The electrode space analysis is based on information from GFP and topographical analysis and collapses temporal and spatial information to elucidate maximum differences between experimental groups and conditions. The four maximum electrodes, derived from the topographical analysis, for every TOI separately, were collapsed for every condition in every experimental group and statistical analysis was performed. If additional clusters emerged in topographical analysis those electrodes were averaged as well.

Furthermore, the N400, as the classical component in language research, was investigated by collapsing the signal of centro-parietal electrodes (CP1, CP2, Pz, P3

and P4) in the time range 300 to 500 milliseconds post-stimulus (Kutas and Federmeier, 2011).

5.2.9 Statistical Considerations

Word Properties

Properties (lexical frequency and orthographic frequencies) of real word conditions were compared with Shapiro-Wilk tests for assessment of normal distribution and with parametric independent samples t-test or non-parametric Mann-Whitney-U test for independent samples. Tests were applied with the alpha-level set to 0.05. The pseudoword condition was not included in the analysis because lexical frequency was zero for all items and the orthographic frequencies were a mix of the real word conditions' frequencies.

GFP Data & Electrode Data

To compare conditions in the control group, Levene tests for the evaluation of homoscedasticity and subsequent one-way ANOVAs or non-parametric alternatives were performed for all identified TOIs. For comparison of groups, two-way ANOVAs with factors group and condition were performed with post-hoc pairwise comparison (Bonferroni corrected, $p < 0.05$), where appropriate. All tests were administered with the alpha-level set to 0.05.

Forced-Choice Lexical Decision Task

First, Kolmogorov Smirnoff test was performed for every experimental group, followed by two-way ANOVA with the factors group and condition with post-hoc pairwise

comparison (Bonferroni corrected, $p < 0.05$), where appropriate, or non-parametric Wilcoxon tests. All tests were administered with the alpha-level set to 0.05.

5.3 Results

5.3.1 Word Properties

Descriptive data and statistical analyses of the word sets are presented in Table 5.2. Shapiro-Wilk tests revealed non-normal distribution of all word properties of the real word sets.

Table 5.2 Descriptive data and statistical analyses of word sets; high = high lexical frequency, low = low lexical frequency, pseudo = pseudoword, descriptive data are mean and standard deviation

Condition	Lexical frequency	Initial sign frequency	Initial bigram frequency	Initial trigram frequency
High	0.88/0.52	13882/5845	2385/2148	433/920
Low	-0.50/0.36	13703/5986	2218/2164	370/755
Pseudo	0/0	13779/5816	2263/2142	335/765
Analysis of normal distribution (Shapiro-Wilk test)				
High	W = 0.953 p < 0.001	W = 0.945 p < 0.001	W = 0.858 p < 0.001	W = 0.437 p < 0.001)
Low	W = 0.977 p = 0.002)	W = 0.948 p < 0.001	W = 0.822 p < 0.001	W = 0.490 p < 0.001
Nonparametric statistical Analysis of high lexical frequency and low lexical frequency word sets (Mann-Whitney-U test)				
High VS Low	U = 0.000 p < 0.001	U = 19.695 p = 0.792	U =18.809 p = 0.303	U = 17.869 p = 0.065

Since normality was violated in all conditions Mann-Whitney-U tests were applied to statistically compare both word sets. A statistically significant difference between high and low frequency words was present in lexical frequency but not in orthographic frequencies.

5.3.2 Forced Choice Lexical Decision Task

The forced-choice lexical decision task was administered directly after the passive reading experiment to compare error rates in lexical decision. The percent of correct answers entered a two-way ANOVA with factors group (healthy controls, AD-PPA patients, and FTLD-PPA patients) and condition (high lexical frequency words, low lexical frequency words, pseudowords). Statistically significant differences in the factor group ($F_{(2,114)} = 14.239$ $p < 0.001$) and the factor condition ($F_{(2,114)} = 21.523$, $p > 0.001$) emerged without statistically significant interaction ($p = 0.63$). Post-hoc pair-wise comparison revealed that more correct answers were given in the control group compared to the AD-PPA group and the FTLD-PPA group ($p < 0.001$). The percentage of correct answers was highest in the high frequency word condition compared to the low lexical frequency word condition ($p < 0.001$) and to the pseudoword condition ($p < 0.001$). Data are visualised in Figure 5.2 and collected in Table 5.3.

Table 5.3 Error rates in the force-choice lexical decision task; sorted by group and word type/condition

Group	**Controls (N=23)**	**AD-PPA (N=10)**	**FTLD-PPA (N=8)**
% correct answers (M / SD)	95.5 % / 4.8	91 % / 7.4	87.5% / 11.8
Word Type	**high frequency words (N=41)**	**low frequency words (N=41)**	**pseudowords (N=41)**
% correct answers (M / SD)	98 % / 3.3	89.5 % / 7.9	90.5% / 8.5

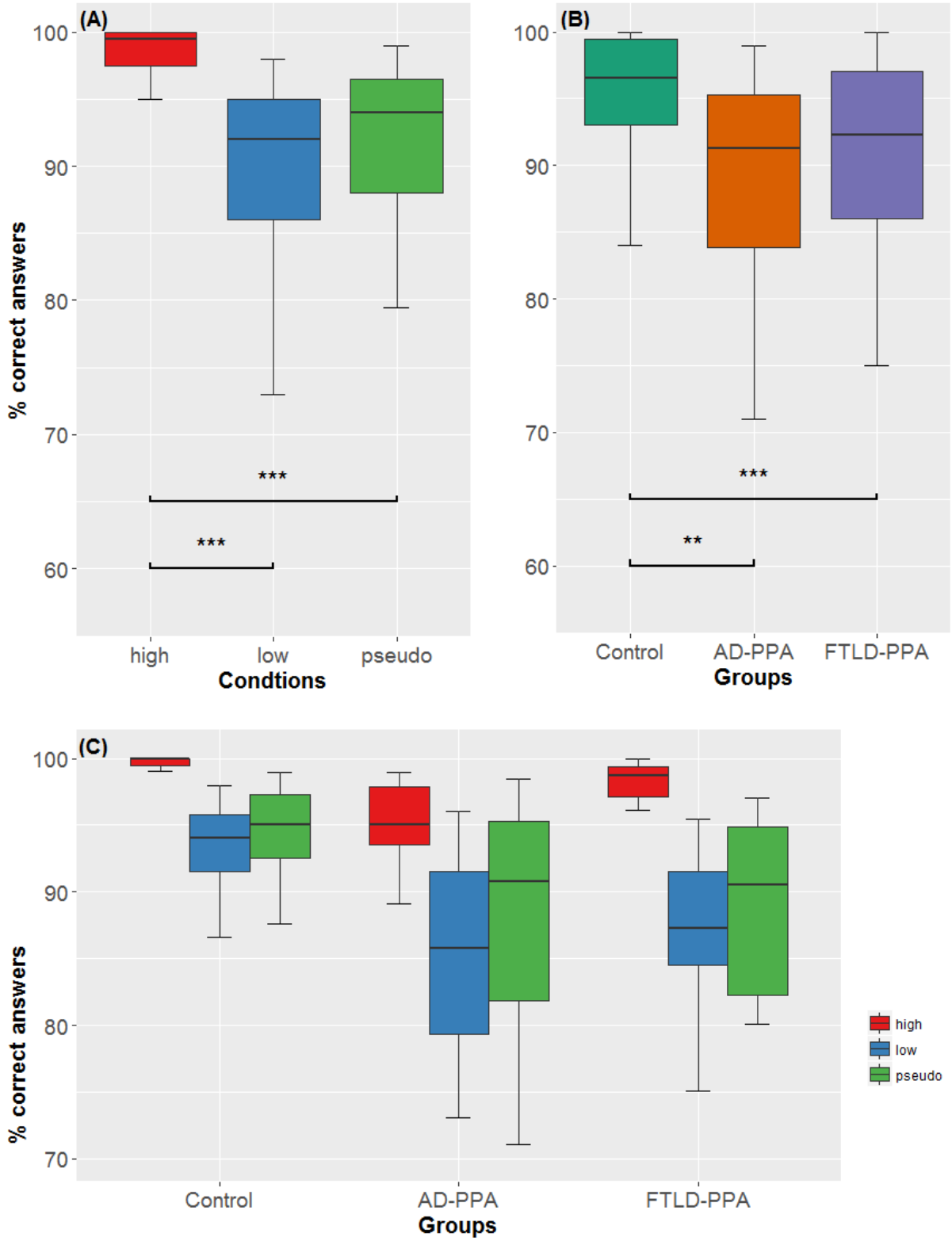

Figure 5.2 Percentage of correct answers in the forced-choice lexical decision task sorted by condition (A), group (B) and conditions in individual groups (C); ** p < 0.01, *** p < 0.001, results from the statistical analysis are depicted in (A) and (B)

5.3.3 Global Field Power Analysis

A Global Field Power analysis was performed to define time ranges of interest (TOIs). As a first step, GFP data were calculated for all word types in the healthy control group. Three characteristic peaks occurred in GFP time courses (Fig. 5.3). A full-width quarter maximum (FWQM) calculation was performed to estimate the temporal expansion of GFP peaks. The 1st range was identical for all three conditions, ranging from 110 to 127 ms and the 2nd range was identical with 169 to 200 ms in all conditions. The 3rd range was 251 to 337 ms in the high lexical frequency condition and shifted to 255 to 348 ms and 251 to 341 ms in low and pseudo conditions, respectively. Maximum and minimum latencies were combined to produce the time range 251 to 348 ms for TOI 3. Resulting TOIs are summarised in Table 5.4 and Figure 5.3 displays GFP signatures of all three groups with highlighted TOIs.

Table 5.4 Selected mean amplitude ranges from the healthy control groups' GFP data

Word type	TOI 1 (ms)	TOI 2 (ms)	TOI 3 (ms)
High	110 – 127	169 – 200	251 – 337
Low	110 – 127	169 – 200	255 – 348
Pseudo	110 – 127	169 – 200	251 – 341
combined TOI	110 – 127	169 – 200	251 – 348

Mean GFP signals, elicited by the three different word types, in the control group were compared in all TOIs. Descriptive and statistical data for this comparison is summarised in Table 5.5. Levene-tests were non-significant and, therefore, one-way ANOVAs were conducted. Also, one–way ANOVAs were non-significant in all three TOIs.

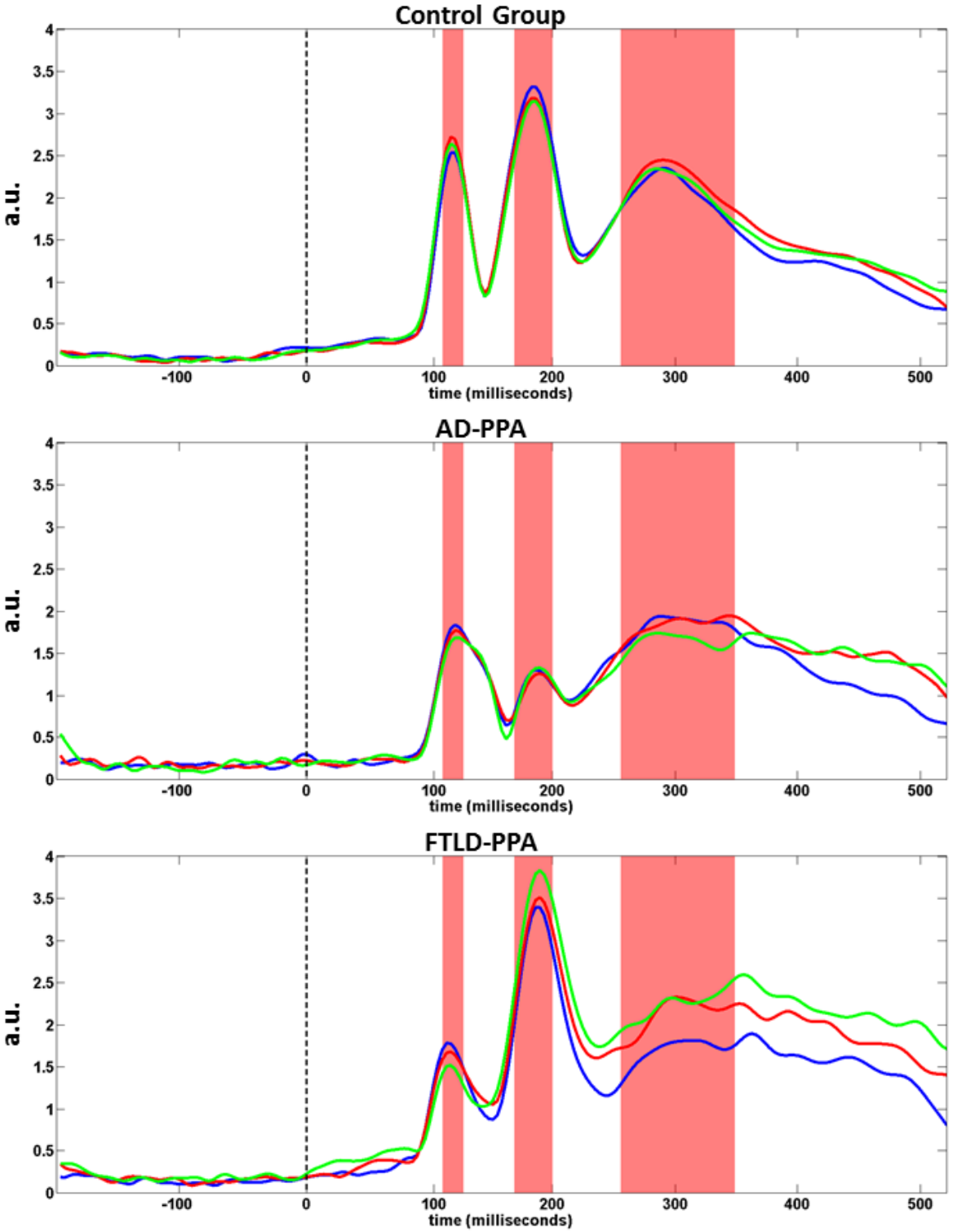

Figure 5.3 GFP signatures elicited by the three conditions in the control group (upper panel), the AD-PPA group (middle panel) and the FTLD-PPA group (lower panel); red areas indicate the TOIs, blue = high frequency words, red = low frequency words, green = pseudowords, a.u. = arbitrary unit

Table 5.5 Summary of statistical and descriptive data for comparison of GFP values of word conditions in the control group

TOI	GFP High (M/SD)	GFP Low (M/SD)	GFP Pseudo (M/SD)	Levene Test	One-way ANOVA
1	2.73 (1.19)	2.92 (1.31)	2.83 (1.23)	$F_{(2,66)} = 0.102$ $p = 0.90$	$F_{(2,66)} = 0.12$ $p = 0.89$
2	3.68 (1.37)	3.56 (1.40)	3.54 (1.44)	$F_{(2,66)} = 0.048$ $p = 0.95$	$F_{(2,66)} = 0.64$ $p = 0.94$
3	2.76 (1.26)	2.86 (1.28)	2.80 (1.35)	$F_{(2,66)} = 0.015$ $p = 0.99$	$F_{(2,66)} = 0.34$ $p = 0.97$

For group comparison, mean GFP amplitudes of all groups and conditions entered two-way ANOVAs with factors group (healthy controls, AD-PPA and FTLD-PPA) and condition (high lexical frequency words, low lexical frequency words, pseudowords). Descriptive data are collapsed in Table 5.6 and visualised in Figure 5.4. In TOI 1, a significant main effect of the factor group ($F_{(2,99)} = 7.664$, $p < 0.001$) emerged. Pairwise comparison revealed that the AD-PPA group ($M = 1.85$, $SD = 0.88$) produced significantly smaller GFP values ($p_{corrected} < 0.001$) than the control group ($M = 2.83$, $SD = 1.26$). In addition, the FTLD-PPA group ($M = 2.08$, $SD = 0.64$) produced smaller GFP values than the control group but did not reach statistical significance after multiple comparison correction ($p_{corrected} = 0.07$). In TOI 2, a significant main effect of the factor group ($F_{(2,99)} = 11.640$, $p < 001$) was present. Pairwise comparison revealed that the AD-PPA group ($M = 2.11$, $SD = 0.55$) produced significant smaller GFP values than the control group ($M = 3.60$, $SD = 1.38$; $p_{corrected} < 0.001$) and the FTLD-PPA group ($M = 3.51$, $SD = 1.64$; $p_{corrected} < 0.005$). In TOI 3, no statistically significant difference emerged in both factors.

Table 5.6 Mean GFP values of the groups in the three TOIs

Group	GFP TOI 1 (M/SD)	GFP TOI 2 (M/SD)	GFP TOI 3 (M/SD)
Control	2.83/1.26	3.60/1.38	2.81/1.31
AD-PPA	1.85/0.88	2.11/0.55	2.36/0.63
FTLD-PPA	2.08/0.64	3.51/1.64	3.04/1.04

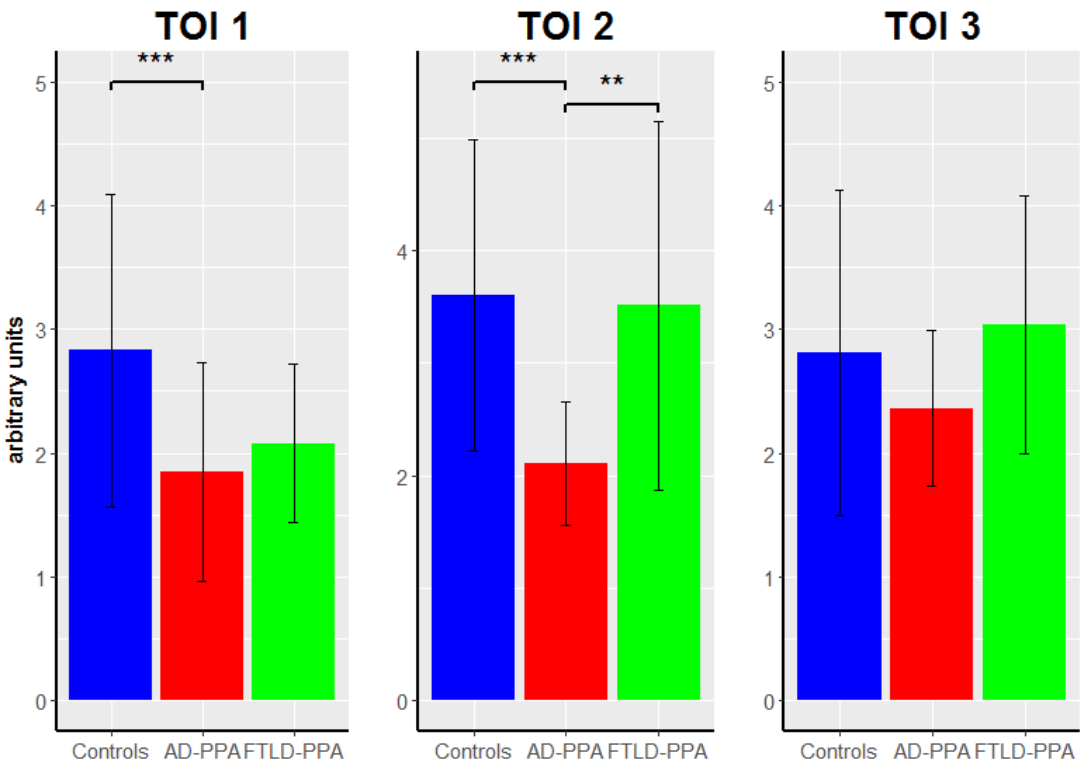

Figure 5.4 Mean GFP values in the three TOIs from GFP analysis; blue = healthy controls, red = AD-PPA, green = FTLD-PPA bars represent mean values, whiskers represent standard deviation, abbreviation: ** = p<0.01, ***= p<0.001

To evaluate the homogeneity of the FTLD-PPA group, GFP signatures of the svPPA subgroup and the nfvPPA subgroup were visualised separately and displayed together with the FTLD-PPA group (Fig. 5.5). Different amplitudes were present in the signature, where the nfvPPA subgroup had highest GFP amplitudes from 100 – 200 milliseconds and the svPPA subgroup had highest amplitudes from 200 – 500 milliseconds.

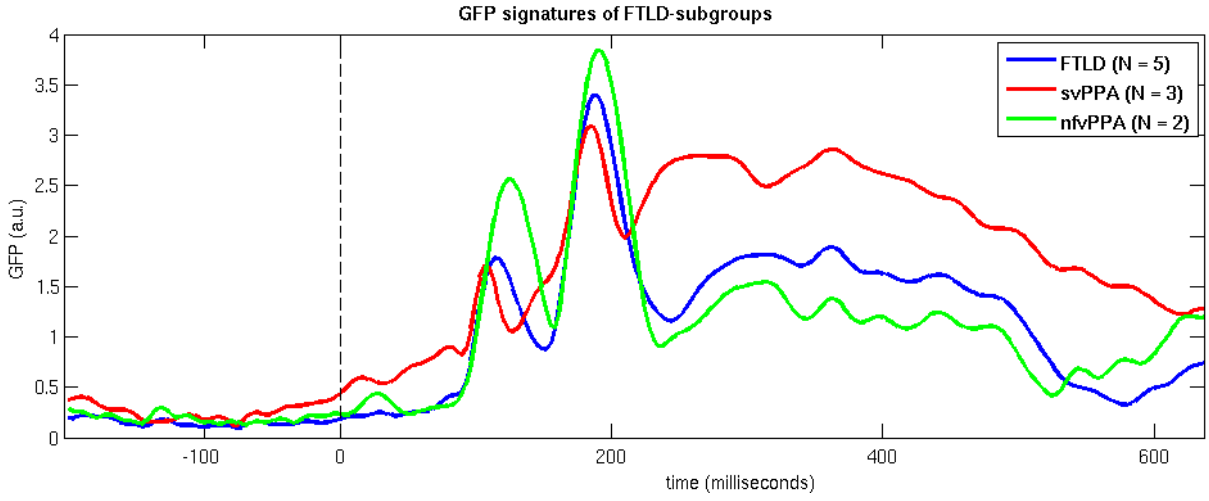

Figure 5.5 GFP signature of the FTLD-PPA group and its subgroups, namely svPPA and nfvPPA

5.3.4 Topographical Analysis

Topographical distributions were investigated in the three identified TOIs. In TOI 1, the control group presented a distinct bilateral posterior-temporal positivity (Fig. 5.6, upper row), which is identical to P1 from previous investigations (Di Russo et al., 2002). Topographical distributions of voltages were similar in both patient groups but, in comparison to the control group, signal attenuation was present. The AD-PPA group showed bilateral signal attenuation while the FTLD-PPA group presented with a left-dominant reduction of the occipital positivity. In TOI 2, a posterior-temporal negativity was present in the control group. This pattern and time range were described before as N1 component (Hopf et al., 2002; Schindler et al., 2018). The FTLD-PPA group presented a similar pattern, while overall signal reduction was present in the AD-PPA group (Fig 5.6, middle row). In TOI 3, a bilateral posterior parietal positivity and a small string of positivity, elongating over left frontotemporal electrodes, occurred. The dominant posterior-parietal positivity was identical to the P3 component (Polich, 2007).The left frontotemporal positivity was mostly absent in the AD-PPA group and was increased in the FTLD-PPA group, while the latter group presented with decreased posterior positivity (Fig. 5.6 lower row). For the left frontotemporal positivity, a left frontal electrode cluster (Fp1, F3, F7) and the right-hemispheric frontotemporal cluster (Fp2, F4, F8) were added to the subsequent analysis.

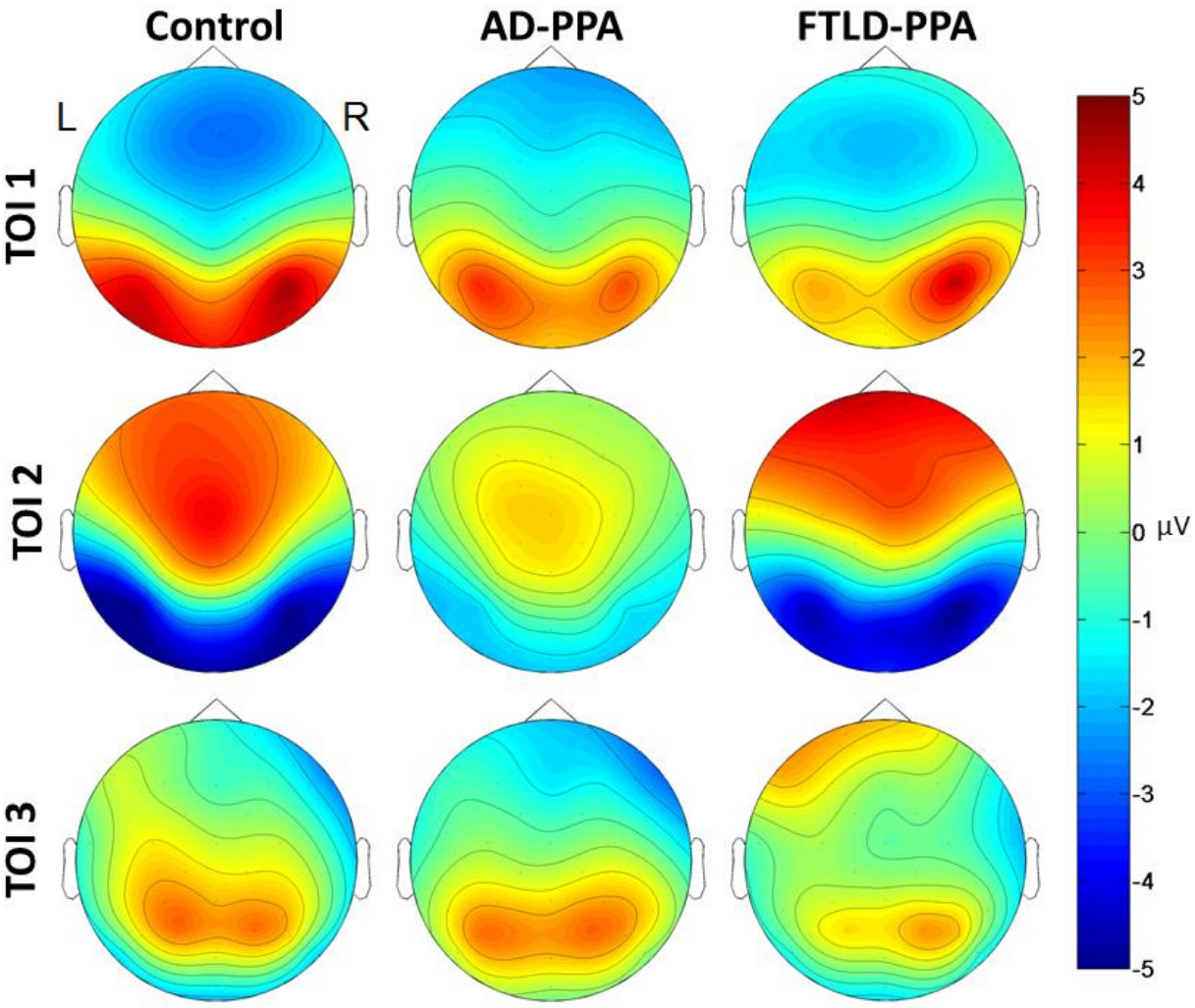

Figure 5.6 Topographic voltage distribution in all TOIs for the healthy control group (left column), the AD-PPA group (middle column), and the FTLD-PPA group (right column)

Visualisation of voltage distribution in the three TOIs revealed three distinct patterns of activation. The four electrodes with maximal voltage were selected for later analyses in electrode space. The dominant feature in every TOI assigned the maximum electrodes' polarity. In TOI 1, based on the occipital bilateral positivity the four most positive electrodes were pooled. A prominent bilateral posterior-temporal negativity was present in TOI 2. Therefore, the four most negative electrodes, which were identical to electrodes in TOI 1, were selected. In TOI 3, a prominent bilateral posterior

parietal positivity was visible. Table 5.7 contains the electrodes for subsequent analyses.

Table 5.7 Electrodes with maximum voltages in TOI1, TOI 2 and TOI3 of the passive reading experiment

Condition	TOI 1 (positive polarity)	TOI 2 (negative polarity)	TOI 3 (positive polarity)
High	PO7, PO8, O1, O2	PO7, PO8, O1, O2	P3, P4, PO3, PO4
Low	PO7, PO8, O1, O2	PO7, PO8, O1, O2	P3, P4, PO3, PO4
Pseudo	PO7, PO8, O1, O2	PO7, PO8, O1, O2	P3, P4, PO3, PO4

5.3.5 Electrode Space Analysis

The four maximum electrodes from topographical analyses were pooled and mean amplitudes were extracted for the electrode space analysis. Fig. 5.7 & 5.8 illustrate pooled ERPs for selected electrodes in TOI 1, TOI 2 and TOI 3.

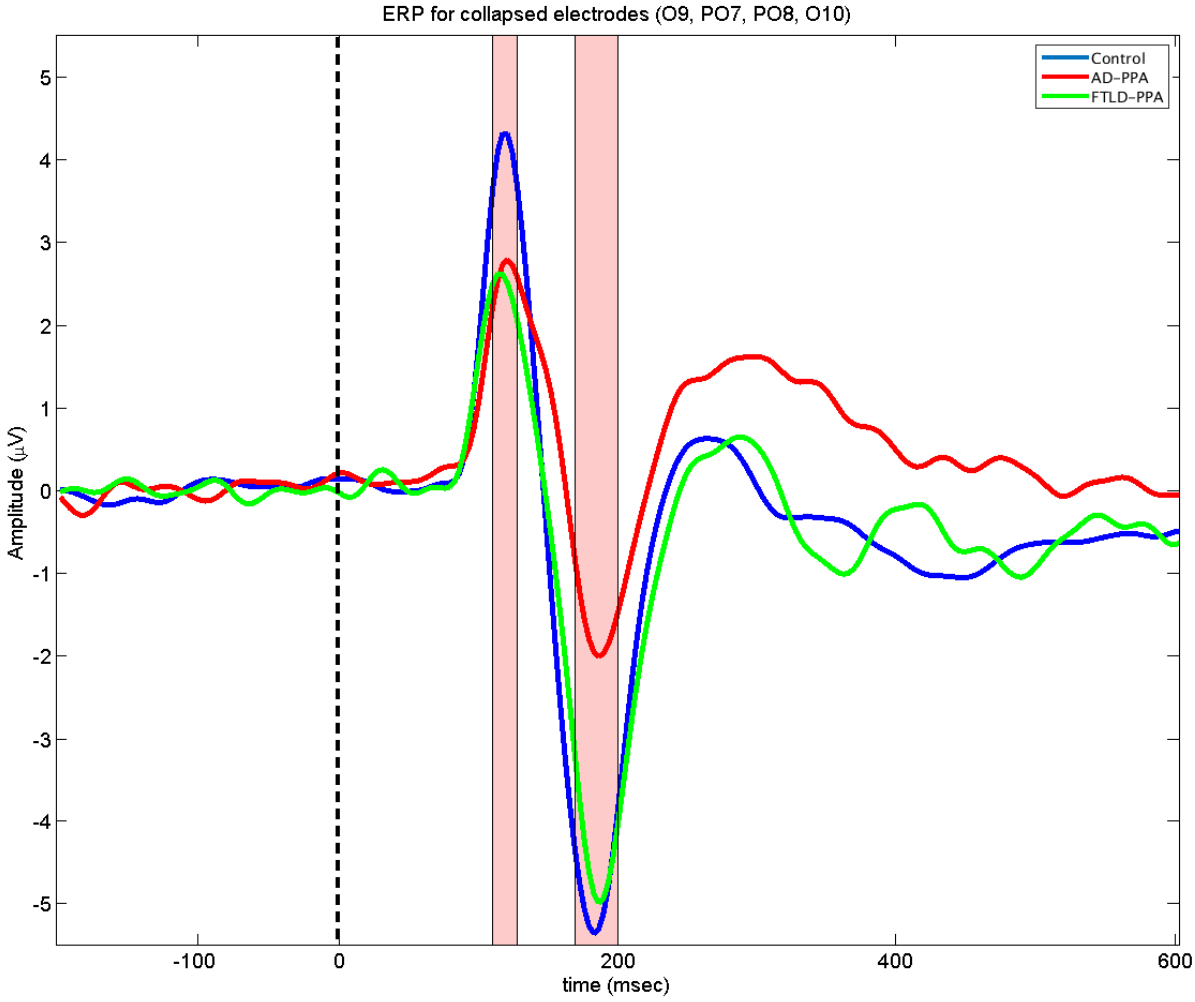

Figure 5.7 Pooled ERP data for the maximum electrodes in TOI 1 and TOI 2; data of electrodes PO7, PO8, O1, and O2 are pooled; TOIs are indicated in light red

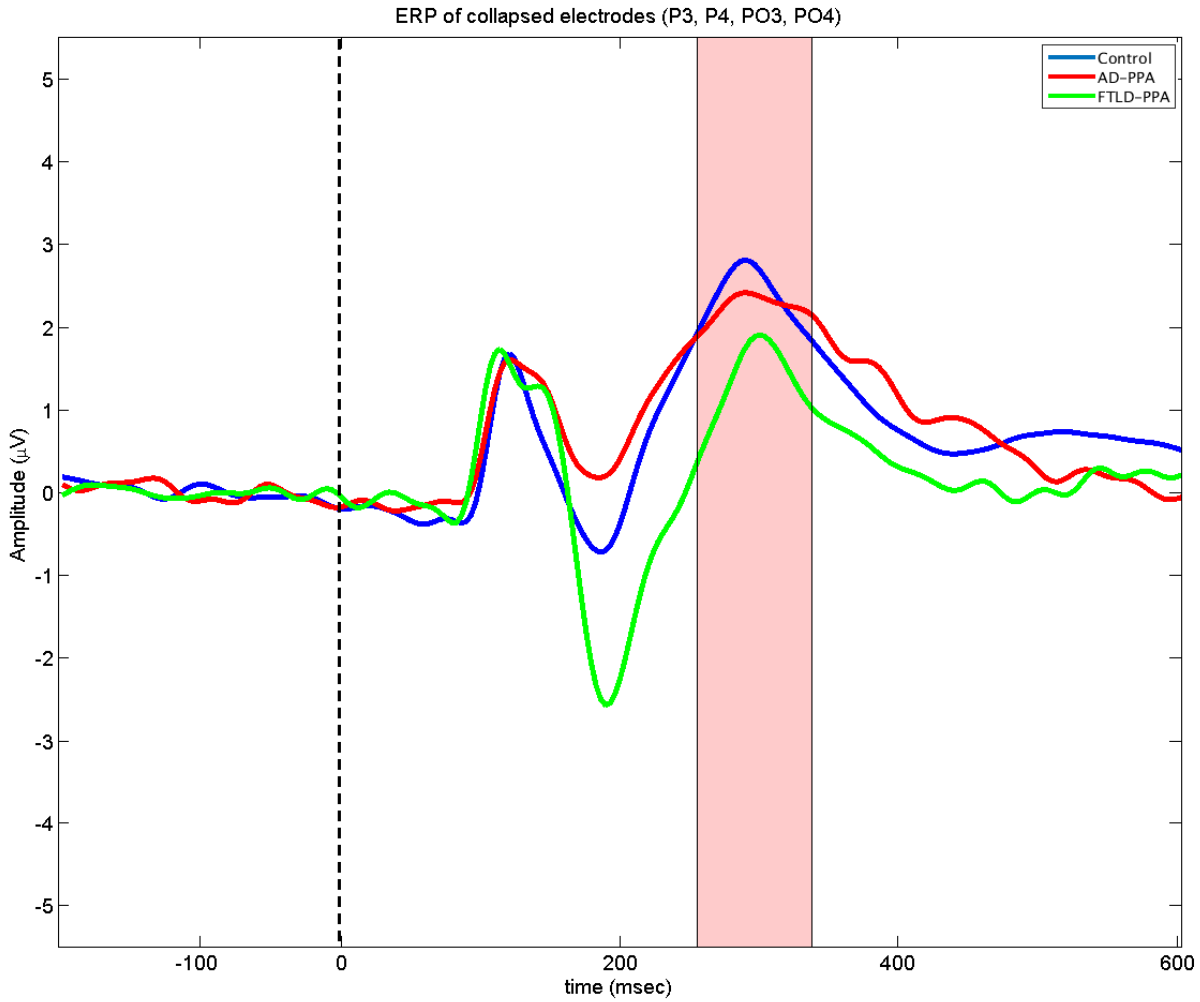

Figure 5.8 Pooled ERP data for the maximum electrodes in TOI 3; data from electrodes P3, P4, PO3, and PO4 are pooled, the TOI is indicated in light red

In addition to identified TOIs, the N400 potential, as a highly-investigated marker in neurolinguistics, was analyzed. Figure 5.9 shows the ERP signature from electrodes

CP1, CP2, Pz, P3, and P4 between 300 to 500 milliseconds, referred to as N400 potential (Van Petten, 1993).

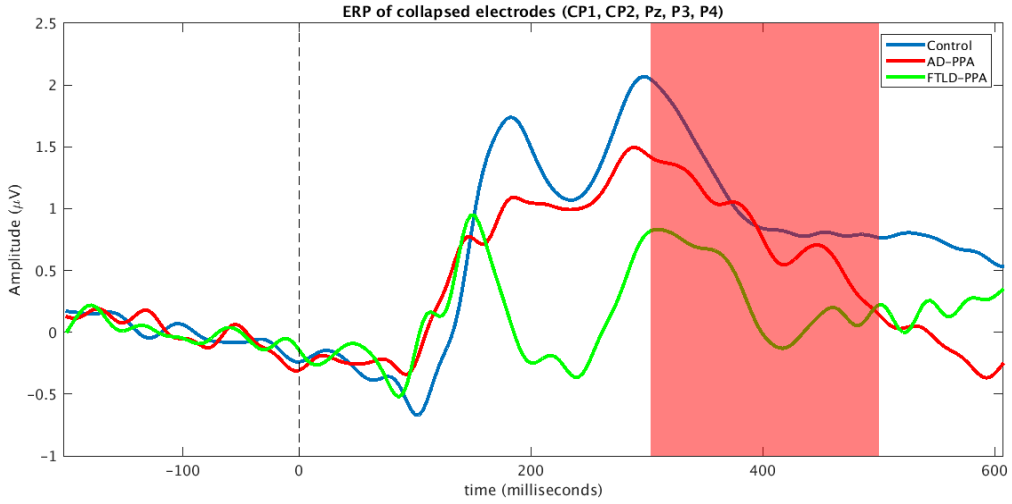

Figure 5.9 Pooled ERP data for the N400; data from electrodes CP1, CP2, Pz, P3, and PO4 are pooled, the TOI is indicated in light red

First, data from the control group were analysed to compare the effect of word type on ERP signatures. Statistical data for intra-group comparison are summarised in Table 5.8. Levene-tests and one-way ANOVAs were non-significant in all three TOIs and the N400 time range.

Table 5.8 Summary of statistical results from the electrode space analysis of the healthy control group

TOI	Levene Test	One-way ANOVA
1	$F_{(2,66)} = 0.007$, $p = 0.99$	$F_{(2,66)} = 0.05$, $p = 0.95$
2	$F_{(2,66)} = 0.002$, $p = 0.99$	$F_{(2,66)} = 0.06$, $p = 0.94$
3	$F_{(2,66)} = 0.206$, $p = 0.81$	$F_{(2,66)} = 0.01$, $p = 0.99$
N400	$F_{(2,66)} = 0.079$, $p = 0.93$	$F_{(2,66)} = 0.34$, $p = 0.72$

In the next step, all groups' mean amplitudes were compared with a two-way ANOVA with factors group (healthy controls, AD-PPA patients, and FTLD-PPA patients) and condition (high lexical frequency words, low lexical frequency words, pseudowords). In TOI 1 was a significant main effect in the factor group ($F_{(2,99)} = 7.602$, $p = 0.001$)

present. Compared to the control group, pair-wise comparison revealed that in both, the FTLD-PPA group ($p_{corrected}$ = 0.008) and the AD-PPA group ($p_{corrected}$ = 0.01), the mean amplitude was significantly reduced. In TOI 2 was a significant main effect of the factor group ($F_{(2,99)}$ = 9.806, p < 0.001) present. Compared to the AD-PPA group, pair-wise comparison revealed that the control group ($p_{corrected}$ < 0.001) and the FTLD-PPA group ($p_{corrected}$ < 0.001) had increased mean amplitudes. In TOI 3 was a significant main effect of the factor group ($F_{(2,99)}$ = 4.402, p = 0.015) present. Pair-wise comparison revealed that FTLD-PPA patients had a significantly increased mean amplitude compared to the control group ($p_{corrected}$ = 0.011). The left frontotemporal cluster in the P3 time range had a main effect of the factor group ($F_{(2,99)}$ = 5.208, p = 0.007). Pair-wise comparison revealed that the FTLD-PPA group had a significantly increased mean amplitude compared to the control group ($p_{corrected}$ = 0.006). In the right-hemispheric frontotemporal control region, no statistically significant differences emerged for main factors group ($F_{(2,99)}$ = 0.458, p > 0.6) and condition ($F_{(2,99)}$ = 0.486, p > 0.6). In the N400 time range was a significant main effect of the factor group ($F_{(2,99)}$ = 5.337, p = 0.006) present. Pair-wise comparison revealed that, in comparison to the FTLD-PPA group, the mean amplitude of the control group ($p_{corrected}$ = 0.004) was significantly decreased and the mean amplitude of the AD-PPA group ($p_{corrected}$ = 0.06) was marginally decreased. All data are summarised in Table 5.9 and visualised in Figure 5.10.

Table 5.9 Mean amplitudes and standard deviations (M/SD) for all analyzed electrode clusters. Note: TOI 3 o refers to data from the occipital electrode cluster in TOI 3, while lf and rf refer to the left frontal and right frontal clusters, respectively.

Group	TOI 1	TOI 2	TOI 3 o	TOI 3 lf	TOI 3 rf	N400
Control	4.14/2.35	-4.64/3.06	2.38/1.34	-1.35/0.93	0.33/0.70	1.01/0.90
AD-PPA	2.60/1.55	-1.63/2.09	2.14/0.98	-1.11/0.44	0.18/0.32	0.87/0.61
FTLD-PPA	2.26/1.43	-4.60/2.85	1.28/1.35	-0.55/0.93	0.34/0.72	0.23/0.69

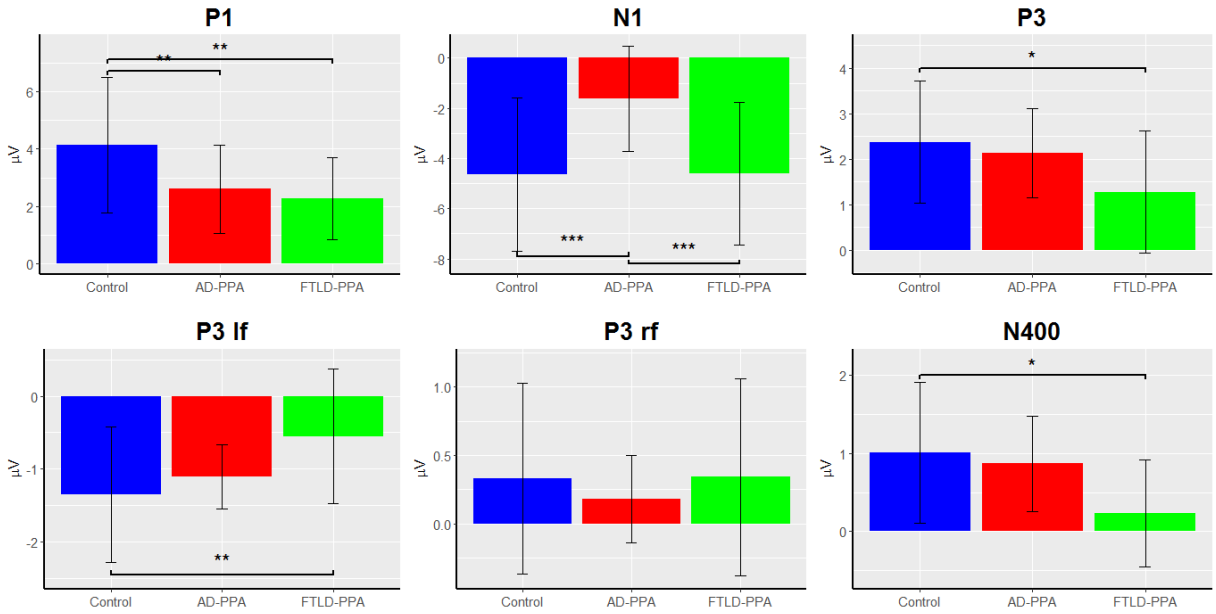

Figure 5.10 Mean amplitudes of all group comparisons in electrode space; * p < 0.05, ** p < 0.01, *** p < 0.001, P3l = left frontal electrode cluster in P3, P3r = right frontal electrode cluster in P3

5.4 Discussion

In this experiment, electrophysiological signatures of language processing were investigated in a cohort of PPA patients and compared to a cognitively healthy control group. All participants performed a passive reading experiment and a subsequent forced-choice lexical decision task, which contained the full set of stimuli from the passive reading experiment. Differences between healthy control participants and PPA patients as well as between patient groups were present in all analysis steps, namely GFP analysis, topographical analysis, electrode space analysis, and behavioural results. To the author's knowledge, this is the first study investigating early EEG components of language processing in the PPA spectrum.

5.4.1 Subjective Experience of Lexical Frequency and the Lexicality Effect

Stimuli were constructed in three sets with high, low, and zero lexical frequency and the forced-choice lexical decision task was performed to validate the subjective recognition of lexical frequency. Orthographic frequencies were not statistically different between real word conditions. The pseudowords were constructed by intermixing real words from both real word conditions. Therefore, orthographic frequencies of pseudowords were in-between those of real words and lexical frequency was zero. The three sets of stimuli differed solely in lexical frequency.

In the lexical decision task, high frequency words were correctly identified more often than low frequency words. The observation is consistent with prior studies where a decrease in lexical frequency was associated with increased error rates in healthy participants (Ratcliff et al., 2004; Stone and Van Orden, 1993) and in patients suffering from svPPA (Jefferies et al., 2009). In addition, pseudowords were more often misjudged than high frequency words, which is in line with previous reports (Ratcliff et al., 2004). The increased error rate for pseudowords probably emerged from word-likeness of the pseudowords. Word-likeness is a factor describing the relation between pseudowords and real words; high word-likeness of pseudowords reduces the amount of correct answers in lexical decision because differentiation of pseudowords and real words becomes harder (Lupker and Pexman, 2010). In this experiment, the high word-likeness of pseudowords was a consequence of the fact that pseudowords were constructed by exchanging the second syllable of words from both real word conditions. Therefore, high word-likeness is created by first syllables of pseudowords (e.g. *Farbden, Eislien*), which are identical to first syllables of real words. The perception of different lexical frequencies is a prerequisite for the elicitation of a

frequency effect in ERP signatures. Increased error rates of low frequency and pseudowords reveal that the different frequency bands of the word categories were perceived by healthy participants and PPA patients. In summary, the behavioural data prove the recognition of lexicality and its influence on the error rates of the lexical decision task.

5.4.2 The Temporal Dimension of ERP Signatures/Global Field Power Analysis

In the GFP analysis, ERP signatures' temporal dimension was investigated by elucidating time ranges of maximum spatial variance. Here, reference data was obtained from the control group. Three characteristic peaks emerged in the latency ranges 110 to 127 ms, 169 to 200 ms, and 251 to 348 ms; labelled as TOI 1, TOI2, and TOI3, respectively. SNR and RMS peaks at similar time ranges have been reported in earlier EEG and MEG studies of language processing (Chen et al., 2013; Hauk and Pulvermüller, 2004a, 2004b). SNR and RMS peaks are the same concept as GFP peaks (see Chapter 2.3.2 for a detailed discussion). Discrepancy between the expansion of time ranges in the present experiment and in previous studies is best explained by different analysis procedures. While the present analysis applied a FWQM approach, other publications used time ranges with identical topographies (Hauk and Pulvermüller, 2004a) or did not mention the criterion for time-range-definition (Chen et al., 2013; Hauk and Pulvermüller, 2004b). In addition, all publications applied different combinations of sensors/electrodes and different measures of global activation to retrieve signatures of global activation. The GFP data prove that the passive reading paradigm triggered cortical activation as expected from prior studies in healthy participants. As shown in Figure 5.3 and Table 5.4, all groups

presented with similar peak area latencies. Data from TOI 1 revealed alteration of language processing in both PPA groups, while in TOI 2 the signal decrease manifested solely in the AD-PPA group. In summary, GFP signatures in PPA patients with underlying AD pathology and with underlying FTLD-spectrum pathology were not identical and both were different from the GFP signature of the control group. This is the first electrophysiological study, revealing alteration of language processing in pathological subgroups of PPA.

When comparing GFP signatures of the svPPA and the nfvPPA subgroups to the FTLD-PPA group, which is a composite of both subgroups, diverging pattern appeared (Fig. 5.5). While nfvPPA had increased GFP amplitudes in the early GFP signature, svPPA had increased signal in later GFP signature. Although the subgroups were too small to enter statistical analysis, one can assume that the early effects are driven by the nfvPPA subgroup and the later effects are driven by the svPPA group. This expands the observation that differences occurred, depending on pathological substrates, by the hypothesis that ERP differences between clinical subtypes (svPPA, nfvPPA and lvPPA) are likely to occur. However, because of the low number of PPA patients no analysis of clinical subtypes was possible and must be undertaken in future experiments.

Although differences between experimental groups were present in GFP data, no difference between experimental conditions occurred. Given the fact that passive reading has very low task demands compared to other experimental paradigms it is arguably unsurprising that no task effect appeared (Chen et al., 2013). However, identification of three major peaks in time ranges that were described in previous studies of language processing proves feasibility of a passive reading paradigm in PPA patients (Chen et al., 2013; Hauk et al., 2009). One cannot infer the spatial locations

of signal change from GFP data. To further elucidate electrophysiology in PPA patients, spatial properties of ERP data were analysed.

5.4.3 The Spatial Dimension of ERP Signatures/ Topographical Analysis

After identification of relevant time ranges in the GFP analysis, spatial distribution of voltages in the three identified TOIs was analysed. This topographical analysis revealed occipital positivity in TOI 1, occipital negativity in TOI 2 and occipito-parietal positivity in TOI 3. These voltage distributions correspond to previously reported components P1 (Di Russo et al., 2002; Sereno et al., 1998), N1 (Simon et al., 2007), and P3 (Mecklinger et al., 1992) in language processing. Topography of P1 in both patient groups resembled decreased signal in the whole set of electrodes (Fig 5.6), while N1 topography was similar in all three groups but the AD-PPA group presented a global signal attenuation. This finding resonates with GFP data, where TOI 1 activity decreased in both patient groups while TOI 2 was decreased only in the AD-PPA group. If cortical reorganisation or atrophy of cortical signal generators would be causative for the signal attenuation in the AD-PPA groups N1, the source of the signal would have changed its place on the cortex, leading to an adaptation of current flows and an altered topography. Combining the identical timing of GFP peaks and the similarity of topographical patterns of the groups, one can derive that the signal decrease is a global effect and not a result of cortical reorganisation or atrophy. All groups revealed bilateral occipito-parietal positivity in P3 topographies. In addition, a left frontal positivity was present in the control group, absent in the AD-PPA group and amplified in the FTLD-PPA group. The increased left frontal activation in FTLD-PPA is interpreted as compensatory over-activation due to atrophy in language areas. The

whole brain MRI analysis in Chapter 3 revealed that both FTLD-associated PPA subtypes (svPPA and nfvPPA) presented with frontotemporal atrophy. The focal atrophy correlates with selective loss of language function in both clinical subtypes (Mion et al., 2010; Wilson et al., 2010). Tractography of the language network established the arcuate fasciculus with a long segment, connecting inferior frontal with superior temporal cortices directly, an anterior segment, connecting inferior frontal with inferior parietal cortices, and a posterior segment, connecting superior temporal with inferior parietal cortices (Catani et al., 2005). The central connection point of all arcuate fasciculus' segments, is located in the left temporoparietal junction, which is one of the most atrophic regions in the AD-PPA group (Fig. 3.2 & 3.3c) and the peak atrophy site in AD-positive PPA patients and lvPPA patients (Gorno-Tempini et al., 2011; Sajjadi et al., 2014). In FTLD-spectrum PPA, peak atrophy sites are in inferior frontal and temporal cortices (Gorno-Tempini et al., 2004, 2011; Rogalski et al., 2011), which resemble the endpoints of the arcuate fasciculus. In Chapter 3, the svPPA group and nfvPPA group both presented with atrophy in inferior frontal and superior temporal cortices (Fig. 3.2) and the FTLD-PPA group in Chapter 5 is a composite of both clinical groups. The different topographic alterations in both patient groups suggest two different patterns of cortical damage. In AD-PPA, where temporoparietal junction atrophy is most prominent, white matter damage affects all three segments of the arcuate fasciculus at inferior parietal cortices. In the FTLD-PPA group, atrophy surrounding inferior frontal and superior temporal cortices, both are endpoints of the arcuate fasciculus, is most prominent. This brings in the idea that transmission of information is damaged in the AD-PPA group since all arcuate fasciculus tracts surpass the inferior parietal lobe, while in the FTLD-PPA, processing of information is deficient in the atrophic endpoints of the arcuate fasciculus, namely inferior frontal and superior temporal cortices.

5.4.4 The Combination of Spatial and Temporal Information/ Electrode Space Analysis

The conclusion drawn from topographical analysis is underpinned by results from electrode space analysis. In the last step, the three TOIs were analysed in electrode space to integrate spatial and temporal information. Maximum amplitudes were observed below occipital electrodes in P1 and N1, and below occipito-parietal electrodes in P3 (Table 5.7). Besides the dominant occipito-parietal positivity in the P3 time range, left frontotemporal positivity was identified in that TOI. In the P1 time range, both patient groups presented reduced amplitudes compared to the control group. In that time range, an effect of orthographic structure of words was previously described, where longer word produced stronger signal than shorter words (Assadollahi and Pulvermüller, 2003; Hauk and Pulvermüller, 2004a). Since, in this experiment, no word-frequency effect and no lexicality effect emerged and word categories were matched for orthographic properties (word length, number of syllables, initial N-gram frequencies) any effect in the P1 time range cannot be explained by those orthographic properties or word-frequency and lexicality effects. In addition, lower amplitudes in PPA patients' P1 cannot be simply explained by atrophy in primary visual and extrastriate cortex because major atrophy was not observed there in the present patient cohort (Fig. 3.2 and Chapter 3 for details) and is not an imaging hallmark of any PPA subtype (Gorno-Tempini et al., 2011) and . However, previous DTI studies in PPA patients have shown microstructural alterations in white matter pathways connecting the occipital lobe to frontal and temporal cortices (Botha et al., 2015; Mahoney et al., 2013; Powers et al., 2013) and before 100 ms signal from the visual system already travelled from occipital cortex to frontal cortex and back to occipital cortex where the P1 is generated (Foxe and Simpson, 2002). One possible explanation for the signal

attenuation in the P1 time range is deficient signal propagation prior to 100 ms in the long white matter tracts, namely inferior longitudinal fasciculus, superior longitudinal fasciculus, and arcuate fasciculus. The other possible explanation is degeneration of grey matter that occurs before atrophy becomes measurable in PPA. This explanation emerges from the observation that all PPA subtypes develop measurable atrophy outside their respective peak atrophy sites while disease progresses (Rogalski et al., 2014, 2011). To reveal the correct explanation, future studies most use a combination of multimodal imaging and EEG/MEG source estimation to in-depth analyse possible deficiencies in very early signal propagation in PPA patients.

In the N1 time range, a frequency effect was described before where high frequency words produced lower amplitudes than low frequency words in healthy participants (Assadollahi and Pulvermüller, 2003; Hauk and Pulvermüller, 2004a). Here, the AD-PPA group presented with decreased amplitudes but those were not affected by word categories (Table 5.5). As discussed previously for the P1, (a) orthographic properties and (b) major atrophy in visual and extrastriate cortex are unlikely to explain the amplitude reduction in the AD-PPA group. Amongst diffuse left hemispheric atrophy, anterior occipital lobe atrophy but no posterior occipital lobe atrophy, where extrastriate cortex is localized, is present in the AD-PPA group (Fig. 3.2). The N1 amplitude reduction in the AD-PPA group might relate to the diffuse left-hemispheric atrophy which is maximal around the angular gyrus. Frontal, temporal and parietal cortices are involved in the processing of language and the diffuse atrophy in those cortices and around the angular gyrus might affect information flow in different parts of the ventral and the dorsal language processing stream. Both streams are known to be affected on PPA variants, where the dorsal stream is more affected in nfvPPA and associated to grammatical deficits and the ventral stream is more affected in svPPA and associated

with semantic deficits (Agosta et al., 2013). However, the recent experiment was not intended to address this issue and cannot add insights relating to this issue. Future studies must specifically investigate the role of ventral and dorsal stream processing of language and the presence of white matter tract abnormalities in AD-PPA patients.

The behaviour in later components, namely P3 and N400, differed from the reduced amplitudes in P1 and N1. Left frontal over-activation in the P3 and centro-parietal overactivation in the N400 emerged in the FTLD-PPA group, whereas the AD-PPA group did not present with such a behaviour. Two interpretations for this behaviour are possible. First, the over-activation in late components in the FTLD-PPA group is a compensatory mechanism for inefficient processing in earlier components. This interpretation seems unlikely, given the fact that the FTLD-PPA group had amplitude reduction solely in the P1, while in the AD-PPA group P1 and N1 amplitudes were reduced. According to this 'compensatory' interpretation, one would expect more over-activation in the AD-PPA group than in the FTLD-PPA group. However, the AD-PPA group did not present with over-activation in P3 and N400 (Table 5.9). The second interpretation relates to the fact that early components are associated with lexical processing while later components are associated with post-lexical processing of words (Garman, 1990). In FTLD-PPA, left inferior frontal cortex and anterior temporal cortex, which as key atrophy sites of svPPA and nfvPPA are highly associated with language disturbance in both PPA subtypes (Gorno-Tempini et al., 2011), are atrophic and likely to explain the overactivation in the FTLD-PPA groups' P3 and N400 (Fig 5.9). Even though, those areas are affected by the diffuse atrophy in AD-PPA, the atrophy in FTLD-PPA is more severe in those locations (Figure 3.3). The N400 has been increased in a previous EEG study with PPA patients (Hurley et al., 2009). However, that study investigated a group of non-subtyped PPA patients, therefore, the

comparison of FTLD-PPA and AD-PPA was not possible in that study and time ranges other than the N400 were not investigated, making it impossible to compare the N400 to other time ranges.

Unfortunately, for the lexicality and frequency effects, as seen in the behavioural data an electrophysiological correlate on a global scale (GFP analysis) and on a local scale (electrode space analysis) did not emerge. Based on previous studies of language processing, one might have expected a frequency effect in the N1 time range (Assadollahi and Pulvermüller, 2003; Pulvermüller et al., 2001). However, one study compared the effect of different language tasks on ERP signatures (Chen et al., 2013) and amplitudes of ERP peaks increased with increasing complexity of the language task. Passive reading, as the most simplistic language task, did produce lowest N1 amplitudes while lexical and semantic decision tasks, which emphasize higher-level language processing, produced increased N1 amplitudes. Based on those previous results, a low task demand is likely to not produce a strong lexicality effect. However, a low demand task was a deliberate strategy in the recent experiment to ensure that aphasic patients could engage in the paradigm. The benefit of the passive reading task was the ease of administration and, as a consequence, the low drop-out rate and high quality of EEG recordings. Moreover, the design of the task seemed beneficial for patients because there were no signs of not-attending the task present, e.g. increased alpha waves, which occur when participants' attention decreases (Luck, 2014). The combination of short blocks followed by breaks helped patients maintaining focus. Unfortunately, metal artefacts, which led to insufficient quality of most MEG datasets, could not be prevented by the recent experimental design.

5.5 Conclusion

This is, to the author's knowledge, the first study investigating language processing in a cohort of pathologically defined PPA patients. Basic language processing was investigated with a passive reading paradigm, which, in comparison to other linguistic paradigms, is closest to natural reading and has very low task demands. The presented data reveal diverging ERP signatures of language processing in PPA patients. Different ERP signatures appeared between patient groups and the control group, as well as, between both patient groups and in all analysed metrics. The low task demands extinguished a detectable lexicality effect in ERP and GFP signatures but led to maximum data quality. The data from this experiment favour different causes for deficits in the PPA groups. Diffuse atrophy in the AD-PPA group that is present in frontal, temporal, parietal and anterior-occipital cortices resulted in a reduction of early components of the ERP signature, while atrophy that is specific to frontal and temporal language areas in the FTLD-PPA group resulted in over-activation of later components. The results build a solid base for further electrophysiological experiments in PPA patients, revealing relevant time ranges and spatial locations of activation. The results produce a starting point for electrophysiological biomarkers of PPA, which ultimately can be used to track cognitive decline and to modify non-invasive intervention protocols to increase efficiency of the intervention, e.g. transcranial magnetic stimulation.

The first limitation of this study was the very low number of available PPA patients. This limitation led to the issue of creating an FTLD-PPA group, which was composed of svPPA and nfvPPA patients. For future studies, more patients must be recruited to obtain separate groups of svPPA and nfvPPA patients. The second limitation was the

unsatisfying MEG data quality and the rejection of all MEG data. MEG, as an electrophysiological recording technique, was not an ideal measurement of cortical activity because of its susceptibility for artefacts from metal implants and movement. Given the general low number of available PPA patients and the number of artefacts, MEG is unlikely to become the ideal technique for investigations in PPA. EEG, however is suited for investigations in PPA patients because artefacts related to implants and other metallic objects are not detected by it.

Chapter 6 Detecting the Influence of Language on Visual Processing in PPA

6.1 Introduction

This chapter will extend the findings from the passive reading experiment in Chapter 5. That experiment revealed decreased mean amplitudes in the early P1 and N1 components of AD-PPA patients, while FTLD-PPA patients showed over-activation of the later P3 and N400 components. Results were obtained with a passive reading task, which is a low-demanding task. Passive reading, which is similar to natural reading of single words, elicited automaticity of reading (Flaudias and Llorca, 2014). This automatic process does not depend on post-lexical processes, e.g. accessing lexicality of words. As shown in Chapter 5, lexicality, as the difference between real words and pseudowords, was recognised by the participants but did not influence ERP signatures in the passive reading task. After investigating the automatic reading of words in Chapter 5, post-lexical processing and the resulting effect in ERP signatures will be investigated in this chapter. Post-lexical processes are interesting in the sense that clinical PPA subtypes lack specific post-lexical processes, e.g. svPPA patients present with deficits in semantic access while nfvPPA patients present with impaired syntactic processing (Gorno-Tempini et al., 2011).

For Chapter 6, two oddball experiments were performed while EEG and MEG were recorded. Oddball experiments yield the demand to focus participants' attention selectively on properties of words, e.g. lexicality and semantic category of a word. In general, an oddball experiment is defined as a sequence of frequent stimuli [standard] interrupted by infrequent stimuli [oddball] (Huettel and McCarthy, 2004). The idea for Chapter 6 was to use one experimental design in two experiments, where one

experiment incorporates words and the other experiment incorporates other stimuli. By comparing both experiments, one might elucidate differences in processing of simple visual stimuli and visually-presented words in PPA patients and the influence on response times and ERP signatures. This approach taps into the fundamental idea that in PPA the language domain is initially degraded and remains the primary deficit in the course of the disease while other cognitive domains are relatively preserved.

Chapter 5 focused solely on electrophysiological markers. Besides those biomarkers, response times can elucidate deficits in processing and effects of stimulus manipulations. In the PPA literature, response time data are rarely reported and no previous study directly compared response times to linguistic and non-linguistic stimuli. The only study reporting response times in PPA patients is an early fMRI study where participants performed a synonym/homonym judgement tasks (Sonty et al., 2003). Results were increased response times in PPA patients, whereas accuracy was comparable to the control group. This finding is interesting, given the fact that accuracy was unchanged and response times, as a proxy measure for processing time, were increased. Another study simulated the typical lesion in svPPA, namely a lesion in the anterior temporal lobe, with inhibitory repetitive transcranial magnetic stimulation (rTMS) in healthy participants (Pobric et al., 2007). The virtual lesion in ATL resulted in increased response times for specific-level naming (high task demands) but not for basic-level-naming, number-naming and semantic judgement (low task demands). To rephrase, the high-demanding naming was impaired by the virtual lesion, while low-demanding naming was unimpaired. The influence of high task demands in PPA was shown by another group, when svPPA patients were not able to produce response time data in a lexical decision task (Pulvermüller et al., 2010). Participants had to use two buttons, one button for words and the other button for non-words. The patients

were not able to perform the dual-task of attending stimuli and using a button box and, consequently, experimenters had to push the buttons, resulting in the fact that authors had to discard response time data. Based on these results, the authors did not attempt to record response times in a later experiment with svPPA patients (Shebani et al., 2017). Both described scenarios (Pobric et al., 2007; Pulvermüller et al., 2010) are proof of concept for the influence of task demands on performance in PPA patients. Therefore, Chapter 5 started with a low-demand task and Chapter 6 will extend these findings by investigating the effect of higher task demands in PPA patients.

As demonstrated in the passive reading experiment, there are two early and essential ERP components known as P1 and N1. In addition to early components, the P3 component is commonly elicited in oddball paradigms. The P3 was proposed an endogenous component because it reflects the physiological reaction to the content of a stimulus rather than its physical characteristics (Sutton et al., 1965). P1 an N1 are exogeneous components because both are associated with processing of external stimuli prior to a reaction (Luck, 2014). The first description of the P3 component in an oddball paradigm found a peak latency at 300 ms with a parietocentral scalp topography (Vaughan and Ritter, 1970). However, the motor artefact from button presses overlaps with the P3 component, making the interpretation of P3 components difficult (Salisbury et al., 2001). In general, oddball paradigms are a set of experimental paradigms that share the common design of two stimulus categories. The two categories being standard stimuli and infrequent oddball stimuli (Picton, 1992). Two options are possible for circumnavigating a motor artefact that might overlap with the P3 component. First, two different buttons are used to distinguish standard stimuli from oddball stimuli. Second, the experimental design contains two sets of oddballs; one set will be attended and requests a button press/silent counting (target stimuli), while the

other oddball set will be perceived unattended and no button press is needed (oddball stimuli). From the two designs, the first design applies the motor artefact to both conditions (standard and oddball), while the second design applies the motor artefact to the target condition, therefore, the standard condition and the oddball condition are, theoretically, free of button-press-induced motor artefacts. Electrophysiological studies in PPA patients are rare. However, electrophysiological studies with oddball paradigms in other neurodegenerative diseases have been conducted. Oddball experiments with simple visual stimuli (Irimajiri et al., 2007) and more complex visual stimuli (Saavedra et al., 2012) produced interesting results in patients suffering from Alzheimer's dementia (AD). P1 and N1 amplitudes were unaffected in AD patients when processing simple visual stimuli but decreased when processing complex visual stimuli. The decrease of amplitudes in AD patients' P1 and N1 was compared with patients with amnestic mild cognitive impairment [aMCI] (Stothart et al., 2015). When processing complex visual stimuli, aMCI patients had no amplitude reduction in the P1 component but in the N1 component, while AD patients had reduced amplitudes in both, P1 and N1, components. The authors claimed the reduction of amplitudes reflects the degree of cognitive impairment, where increased cognitive impairment affects P1 and N1 while mild cognitive impairment spares the P1 component. Increasing disease progression is likely to correlate with increasing reduction of ERP components. Analogue behaviour was described before in a single PPA patient (Giaquinto and Ranghi, 2009). The N400 component decreased as disease progressed until the point where no N400 was detectable.

In view of the prior knowledge from these previous studies, this chapter addresses four questions:

1. Will response times of a control group and a group of PPA patients be different from each other?
2. Will the difference in response times be language-specific or of general nature?
3. Will ERP signatures of a control group and a group of PPA patients be different?
4. Will ERP differences be language-specific or of general nature?

6.2 Methods

6.2.1 Participants

Twelve patients with the core diagnosis PPA and sixteen healthy age-matched elderly people participated in both oddball experiments. All participants had normal or corrected-to-normal vision and were recruited from a pool of volunteers for MRI research. In the visual oddball, three patients were removed from analysis; two patients constantly moved their eyes and one patient was moving throughout the experiment. The nine remaining patients syndromically consisted of five svPPA, three nfvPPA and one AD-PPA patient. The semantic oddball experiment was completed by twelve PPA patients and sixteen healthy age-matched elderly people. Two patients were removed from the analysis due to substantial movement artefacts and two patients' EEG and behavioural responses were not recorded due to technical problems. The remaining patients were four svPPA, three nfvPPA and one AD-PPA patient. The Amyloid-PET status of all FTLD-PPA patients (clinically svPPA and nfvPPA patients) was amyloid-negative and it was amyloid-positive in all AD-PPA patients. The control group was

identical in both experiments. AD-PPA patients were excluded from further analyses because a single patient remained in both oddball experiments. Neuropsychological data for both experiments is presented in Table 6.1.

Table 6.1 Normative neuropsychological data and neuropsychological results of both oddball experiments

Neuropsychological test	Normative data	Visual Oddball			Semantic Oddball		
		FTLD-PPA (N = 7)	svPPA (N = 4)	nfvPPA (N = 3)	FTLD-PPA (N = 8)	svPPA (N = 5)	nfvPPA (N = 3)
MMSE /30	29.1 (0.8)	21.4 (5.3)	24.3 (1.3)	17.7 (6.1)	23.4 (2.4)	23.8 (1.5)	22.7 (3.3)
GDS /15	0.6 (0.8)	3.4 (3.6)	2.0 (0.7)	5.3 (4.8)	3.0 (3.5)	2.0 (0.6)	4.7 (5.2)
Digit Symbol Substitution	11.3 (1.8)	14.0* (12.6)	10.8 (0.8)	18.3* (18.4)	13.9 (11.5)	9.8 (2.0	20.7* (16.5)
Rey copy /36	32.3 (2.7)	32.1 (2.9)	33.8 (1.5)	30.0 (2.9)	33.1 (1.7)	34.0 (1.4)	31.7 (0.9)
Rey immediate recall /36	18.5 (5.8)	15.2 (3.4)	13.4 (3.0)	17.7 (2.1)	15.9 (3.5)	13.9 (2.9)	19.3 (0.9)
Rey delayed recall /36	17.8 (5.0)	13.9 (3.8)	11.4 (2.1)	17.3 (2.6)	14.9 (4.2)	12.3 (2.6)	19.3 (2.4)
Letter Fluency	12.8 (2.3)	4.6 (3.2)	6.8 (2.3)	1.7 (1.2)	4.6 (2.7)	6.0 (2.5)	2.3 (0.5)
Category Fluency	18.2 (4.1)	8.1 (3.3)	8.8 (2.2)	7.3 (4.2)	8.5 (2.5)	8.6 (2.0)	8.3 (3.3)
Boston Naming /30	27.4 (2.4)	12.6 (6.7)	7.3 (2.7)	19.7 (2.6)	13.1 (6.8)	8.2 (3.1)	21.3 (0.5)
Kaffee & Kuchen /30	27.8 (1.6)	23.0 (3.8)	21.8 (3.8)	25.5 (2.5)	23.3 (4.2)	21.4 (3.4)	28.0 (0.0)
Digit Span forward /8	6.2 (1.0)	4.6 (1.5)	5.8 (0.4)	3.0 (0.8)	4.8 (1.2)	5.6 (0.5)	3.3 (0.5)
Digit Span backward /7	4.4 (0.7)	3.0 (1.7)	4.3 (0.4)	1.3 (1.2)	3.6 (1.2)	4.4 (0.5)	2.3 (0.9)
Sentence Repetition /5	4.9 (0.3)	3.3 (2.1)	4.5 (0.5)	1.7 (2.4)	3.5 (2.1)	4.6 (0.5)	1.7 (2.4)
Repeat & Point (Repeat) /10	9.9 (0.4)	7.1 (3.9)	9.5 (0.9)	4.0 (4.2	7.5 (3.8)	9.6 (0.8)	4.0 (4.2)
Repeat & Point (Point) /10	9.8 (0.4)	7.7 (1.7)	7.3 (0.4)	8.3 (2.4)	8.5 (1.3)	7.6 (0.8)	10.0 (0.0)
SECT-V /48	45.2 (2.2)	41.0 (6.9)	44.3 (2.6	28.0* (0.0)	40.1 (8.0)	45.0 (2.8)	28.0* (0.0)

* =only one patient was able to perform the task

6.2.2 Stimuli of Both Oddball Experiments

Visual Oddball

In this experiment, simple geographic shapes were presented to participants. Stimuli are depicted together with the experimental setup in Figure 6.1.

Semantic Oddball

In this experiment, words were presented to participants. All words belonged to the category animals or the category plants. The animal category contained 10 words and the plants category contained 100 words. Stimulus parameters were obtained from the dlexDB database (http://www.dlexdb.de/), a German corpus of literature developed by the Berlin-Brandenburgische Akademie der Wissenchaften. The retrieved parameters were lemma frequency (normalised, logarithmised), word length, initial bigram frequency and neighbourhood density. Lemma frequency is a measure of the relative occurrence of a lemma in a given corpus of written words. The lemma frequency counts all inflections of a word that share the word stem and the semantic content. The lemma frequency was logarithmised to obtain linearity of the variable to behavioural responses (Whaley, 1978). Word length is the number of letters and initial bigram frequency is the relative frequency of the initial combination of two letters in the corpus. Neighbourhood density is a measure of similarity of words and defined as the number of words that can be created by exchanging, deleting or adding one letter to a word (Coltheart, 1977). For example, the word *lack* has, amongst others, the neighbours *lock lick, ack, black and slack*. Table 6.2 contains the properties for both categories of words.

Table 6.2 Descriptive data of stimulus sets for both semantic categories in the semantic oddball paradigm; freq = logarithm of lexical frequency, length = number of letters, initial bigram frequency, neigh = neighbourhood density

	Plants			
	Lexical Frequency	**Word Length**	**Initial Bigram Frequency**	**Neighbourhood density**
total	0.46 (0.55)	6.3 (1.6)	2109 (1754)	5.0 (5.6)
setA	0.46 (0.56)	6.3 (1.6)	2114 (1678)	5.1 (5.7)
setB	0.46 (0.54)	6.2 (1.6)	2105 (1843)	4.9 (5.4)
	Animals			
total	1.27 (0.33)	5.0 (0.9)	1516 (1653)	8.1 (4.6)
setA	1.28 (0.37)	5.0 (0.7)	1277 (865)	6.3 (2.8)
setB	1.26 (0.33)	5.0 (1.2)	1754 (2293)	9.9 (5.6)

6.2.3 Experimental Designs of Both Oddball Experiments

Both oddball paradigms consist of a training phase and a main experiment. All trainings were performed outside the scanner to familiarise participants with the task. If participants did not manage to understand instructions in the training phase or could not perform the task within experimental timing they were excluded from the main experiment. Main experiments took place in a MEG chamber, where all participants were seated comfortably. Experiments were presented on a screen placed one meter in front of the participants while EEG and MEG were recorded simultaneously. All participants had one button and were instructed to press that button with the right index finger.

6.2.3.1 Visual Oddball

A summary of the experimental design is depicted in Figure 6.1.

Training phase

The task instruction stated that triangles will be presented sequentially. The orientation of presented triangles' tip can be upward or downward. Participants were asked to press the button if the triangle was oriented with the tip pointing downward. One training block consisted of ten trials with eight standard stimuli (triangle tip upwards) and two oddball stimuli (triangle tip downwards). The training was counted as passed after participants responded to both oddball trials in one training block. All participants mastered the training phase in the first or second training block and entered the main experiment.

Main Experiment

The main experiment included triangles and squares. Now, oddballs [squares] and targets [triangle with the tip pointing downwards] were different stimulus categories. Instructions were identical to training instructions and the task was presented before every experimental block. Between blocks, participants had breaks to relax their eyes. Participants initiated all experimental blocks by pressing the button. The experiment consisted of 12 blocks, each containing 50 trials. A total of 600 stimuli was presented, where 500 standard stimuli, along with 50 targets and 50 oddballs, were randomly presented. Therefore, the probability of occurrence was 8.3% for both, oddballs and targets. Each stimulus was presented for 500 milliseconds. Between stimuli, participants saw an empty screen for 600 +/- 100 milliseconds. Because of geometric shapes as stimuli and fast presentation time, an empty screen was chosen for the inter-stimulus interval to erase afterimages from fixation crosses.

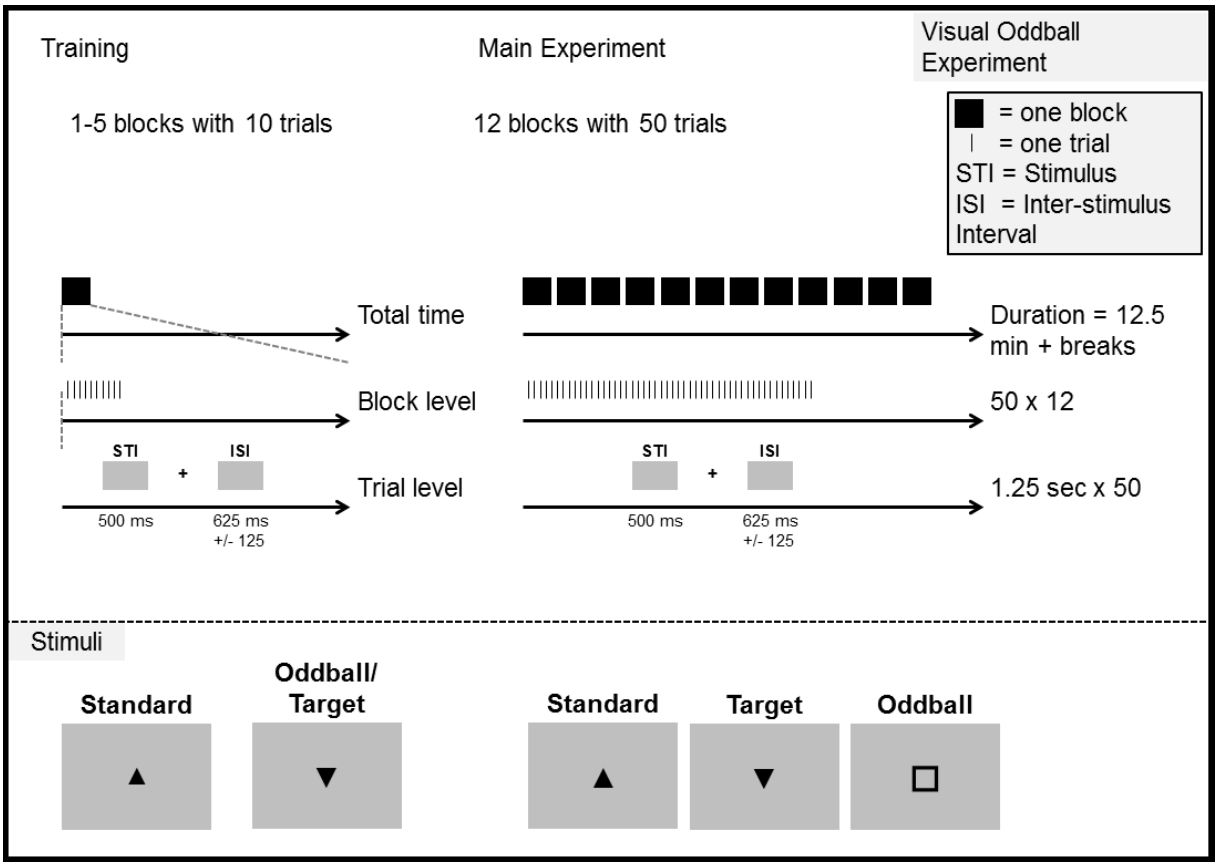

Figure 6.1 Experimental design of the visual oddball paradigm

6.2.3.2 Semantic Oddball

A summary of the experimental design is depicted in Figure 6.2.

Training Phase

The semantic oddball experiment included two training phases. The first phase was a forced-choice, two-alternative semantic decision task. 20 words, consisting of ten animals and ten plants, were presented to participants. The words were randomly chosen from the main experiment's word sets. Participants had to decide whether words were animals or plants and had to signal that decision by pressing a button first and, subsequently, verbalising their decision. The aim of this training phase was to familiarise participants with pressing one button while making a semantic decision and not verbalising the answer immediately. The experimenter corrected participants (a) if

they gave an answer parallel to pressing the button or (b) first gave an answer and subsequently pressed the button or (c) gave an answer without pressing the button. If participants classified more than two animals incorrect it was assumed they would not produce a sufficient amount of trials in the main experiment, subsequently, those participants were rejected from analysis. Fortunately, no patient was rejected from the main experiment for this reason. The second phase of this training was one block from the main experiment that was presented outside the MEG setup. The instruction started with the explanation that nouns will be presented and will be either animals or plants. Following this explanation, the task was introduced; stating to press the button, as fast as possible, if the word was an animal. The training block was presented to familiarise participants with the restrictions of experimental timing. If participants were able to identify oddballs and pressed the button appropriately, they entered the main experiment. All participants were able to identify oddballs and pressed the button appropriately.

Main Experiment

Task instructions were identical to instructions from the second training phase. The experiment was composed of ten blocks, each containing 55 stimuli. Stimuli were presented in random order and each block contained five animals and 50 plants, thus the probability of occurrence for animals was 9.1 %. The total stimulus set was comprised of ten different animals and 100 different plants and was split into two subsets of stimuli, with five animals and 50 plants each. The subsets are referred to as block A and block B. The stimulus sets were presented in alternating order (A-B-A-B-A-B-A-B-A-B). Between blocks participants had a short break to relax eyes and signalled the experimenter when they were ready for the next block. Every trial consisted of a stimulus followed by an inter-stimulus interval. Every stimulus was

presented for 500 milliseconds on the screen. Between stimuli, participants saw an empty screen for 500 - 700 ms.

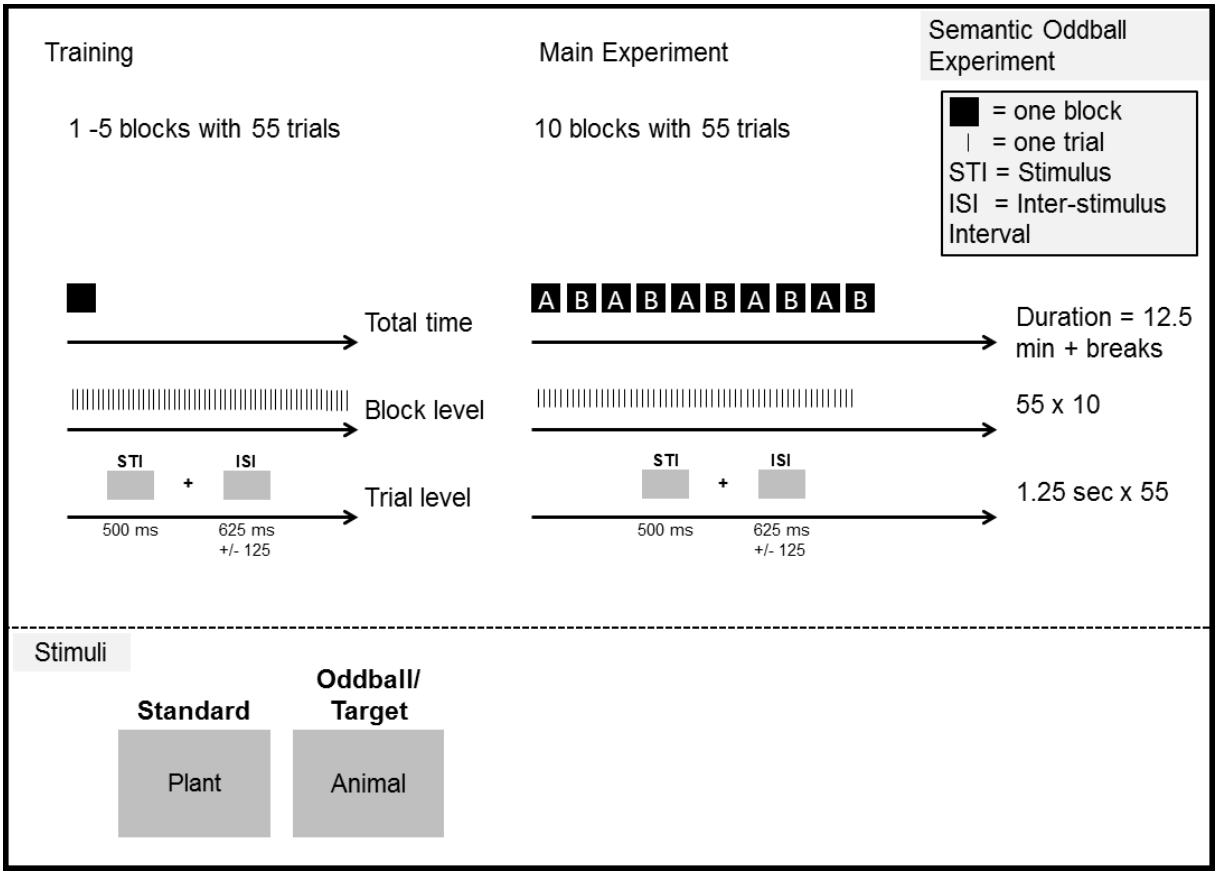

Figure 6.2 Experimental design of the semantic oddball experiment

6.2.4 EEG Post-Processing

Details of EEG and MEG pre-processing are described in Chapter 2.4.2 and processing of GFP data in Chapter 2.4.3. MEG data were heavily distorted by movement and metal artefact. Further details on insufficient MEG data quality are described and discussed in Chapter 4. Only one MEG dataset had sufficient quality for post-processing and as in the passive reading experiment (Chapter 5), MEG data were discarded from both oddball experiments.

After pre-processing, trials were defined with a pre-stimulus interval of 200 milliseconds and a post-stimulus interval of 500 milliseconds around each stimulus. The 200 ms pre-stimulus interval was used as baseline interval. Trials containing eyeblinks or incorrect behavioural responses ([a] a button press to a foil or [b] lack of a button press to a target) were rejected from averaging (those trials were rejected in all subsequent analyses). GFP signatures were generated as described in chapter 2.4.3. An FWQM analysis was performed around all peak amplitudes to create mean amplitude ranges for later analysis steps. As a next step, the topography of voltages in the mean amplitude ranges was investigated to select electrodes with maximum signal and identify EEG components. Subsequently, mean amplitudes of maximum electrodes were pooled and compared to elucidate processing differences between the control group and the FTLD-PPA group.

6.2.5 Response Time Analysis

Response times were modelled with a three-parameter model. The parameters represent the peak (μ), the left tail (σ) and the right tail (τ) of a response time distribution. This approach overcomes the problem of modelling normal-distribution parameters (mean and standard deviation) on non-normal distributed data (response times). A detailed discussion of response time analysis is to be found in chapter 2.4.4 and a visual reminder of the three-parameter model is predicted in Figure 6.3.

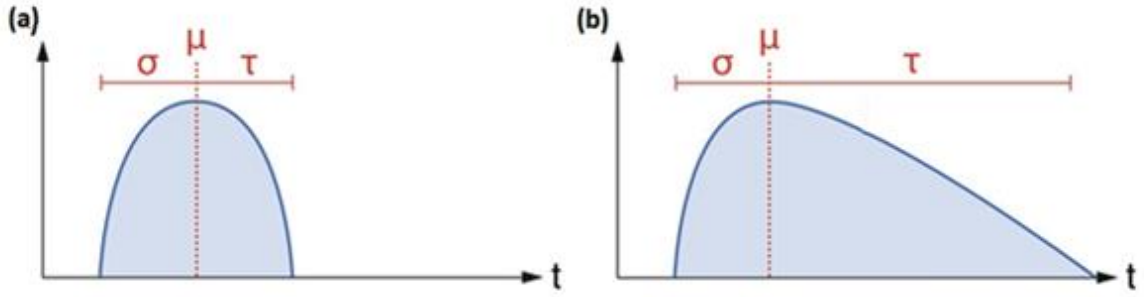

Figure 6.3 Response time parameters μ, σ and τ are plotted on two distribution; (a) plotted on a normal distribution, (b) plotted on a non-normal distribution (further details on response time parameters can be found in Chapter 2.4.4)

6.2.6 Statistical Consideration

Response time data were fitted on a three-parameter model (see Chapter 2.4.4. for details)The three parameters were analysed separately in both experiments with two-tailed t-tests to find statistically significant differences between groups. All tests were performed with a significance level of alpha = 0.05. Electrode space data were analysed with Levene test for homoscedasticity. Two-way ANOVAs with the factors group and condition were performed if homoscedasticity was not violated. If homoscedasticity was violated, non-parametric alternatives were applied. For variables with two levels, Mann-Whitney-U test with Bonferroni correction was applied. For variables with three levels, Friedman Test with Dunn-Bonferroni correction was applied. All tests were performed with a significance level of alpha = 0.05.

6.3 Results

6.3.1 Results from the Visual Oddball Experiment

6.3.1.1 Response Time Analysis

Response time data were compared with a three-parameter model, where μ resembles the peak, σ the left tail and τ the right tail of the RT distribution. Parameter estimates are depicted in Figure 6.4 and Table 6.3. No statistically significant differences between the control group and the FTLD-PPA group were present.

Table 6.3 Descriptive data and statistical values for all parameters of response time data from the visual oddball experiment

Parameter	Control Group M/SD	FTLD-PPA Group M/SD	Statistical Values
μ	431/40	410/70	t(23) = 0.948, p = 0.353
σ	32/12	33/24	t(23) =-0.186, p = 0.854
τ	66/16	74/30	t(23) =-0.962, p = 0.346

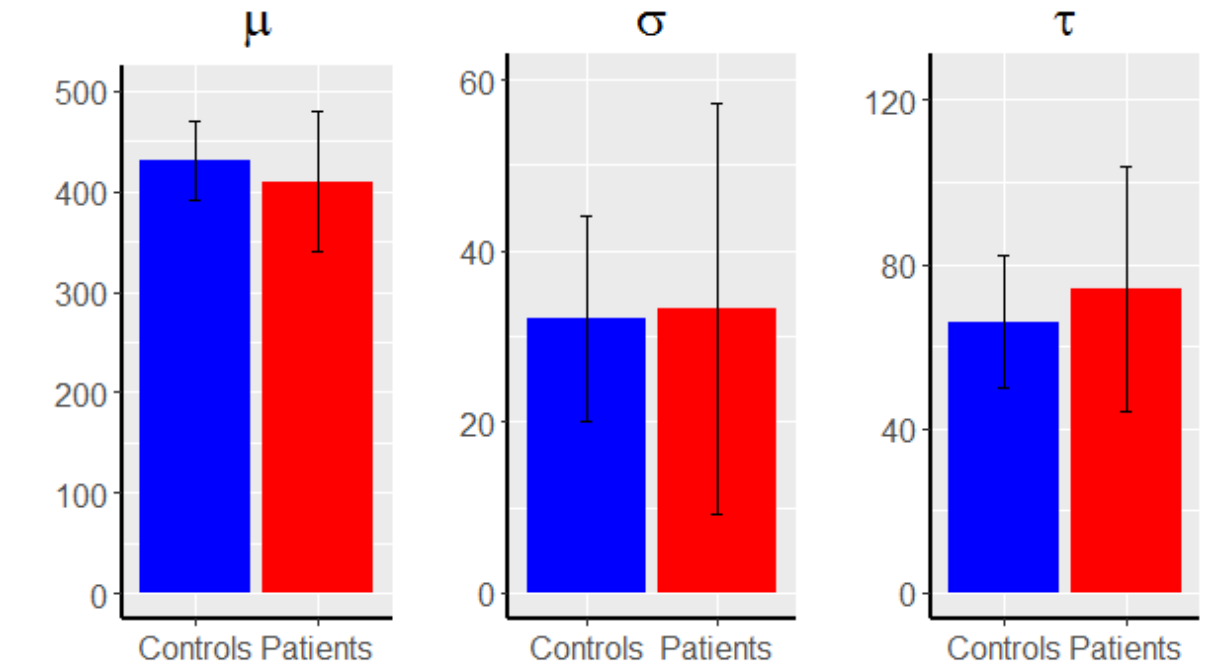

Figure 6.4 Bar Plots of the response time parameters of the visual oddball experiment

6.3.1.2 GFP Analysis

The GFP analysis was performed for the control group and the FTLD-PPA group separately. GFP signatures are visualised in Figure 6.5. The 1st peak emerged in both groups in all conditions at approximately 130 ms and FWQM analysis defined a TOI from ~115 ms to ~150 ms. The 2nd peak emerged between 150 ms and 200 ms in all conditions except the standard condition in the FTLD-PPA group. Here, no visibly detectable peak was present in the GFP signature. A 3rd GFP peak was detected in all conditions, with the peak amplitude at ~ 250 ms in standard and oddball condition and ~ 340 ms in the target condition in both groups. All peak latencies and resulting TOIs are collected in Table 6.4.

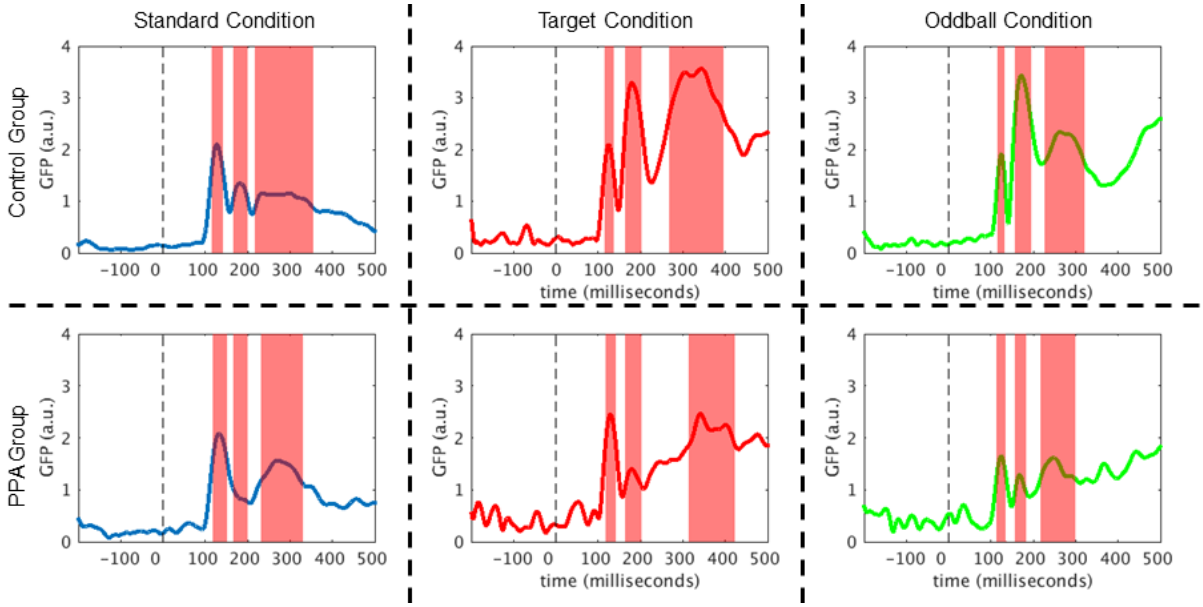

Figure 6.5 GFP signatures of the visual oddball experiment with TOIs shaded in red; upper row = Control Group, lower row = PPA Group, first column = Standard condition, second column = target condition, third column = oddball condition

As to be seen in Figure 6.5, the FTLD-PPA group did not present a GFP peak between 150 to 200 milliseconds in the standard condition. For consistency, the control group's mean amplitude range (166 - 201 ms) was used for subsequent analysis steps.

Table 6.4 Peak latencies and resulting TOIs of the visual oddball experiment; all values are in milliseconds

condition	peak latency	Mean amplitude range	peak latency	Mean amplitude range
	Control Group		FTLD-PPA Group	
standard	128	116 - 142	130	115 - 149
	183	166 - 201	no peak detectable	
	236	219 - 356	265	228 - 316
target	126	116 - 137	128	116 - 141
	180	165 - 203	176	160 - 202
	345	270 - 396	341	311 - 411
oddball	125	117 - 133	122	112 – 133
	173	157 - 195	165	155 - 179
	264	228 - 321	255	219 - 315

The GFP curves of the FTLD-group and its subgroups, namely svPPA and nfvPPA, were compared to investigate the overlap of signal from subgroups and the influence on the FTLD-PPA group's GFP signature (Fig. 6.6). Prior to 170 ms, the nfvPPA subgroup's GFP signature had highest amplitudes, whereas the svPPA subgroup had the lowest GFP amplitudes. The opposite pattern is observable after 170 ms, where the svPPA subgroup produced strongest amplitudes and the nfvPPA subgroup produced the lowest amplitudes.

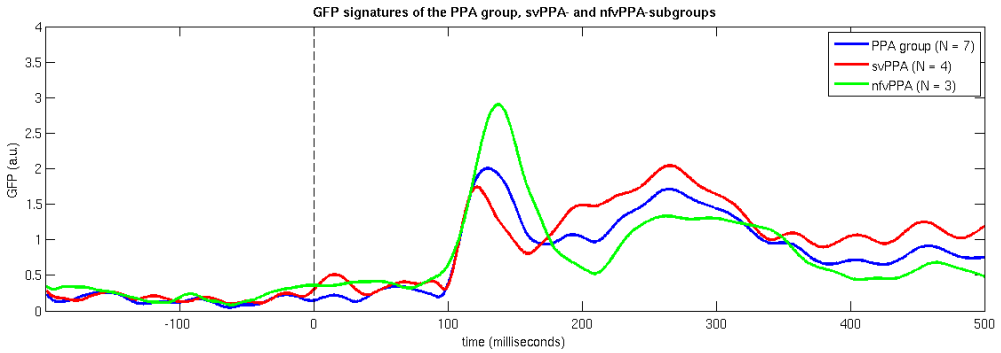

Figure 6.6 A comparison of GFP signatures of FTLD-subgroups in the visual oddball experiment

6.3.1.3 Topographical Analysis

Control Group

In TOI 1, all three conditions had identical topographies, presenting with occipital positivity. In TOI 2, the pattern of activation was dominated by occipital negativity in all three conditions with global signal reduction in the standard condition compared to oddball and target conditions. In TOI 3, the standard condition presented with centro-parietal positivity, the target condition presented with extreme frontal positivity and the oddball condition with fronto-central positivity. Topographical voltage distributions for the control group are visualized in Figure 6.7(A). Maximum electrodes for the TOIs were positive in TOI 1 and TOI 3 and negative in TOI 2 (Table 6.5).

Table 6.5 Maximum electrodes in all TOIs of the control group in the visual oddball experiment

	TOI 1	TOI 2	TOI 3
Standard	PO7,PO8,O2,Oz	P7,P8,PO7,PO8	Cp1,Cp2,PO7,PO8
Target	P8,PO7,PO8,O1	P7,PO7,PO8,O1	Fp1,Fp2,F3,F4
Oddball	P8,PO7,PO8,O2	PO7,PO8,O1,O2	F3,Fz,FC1,Cz

Taking previous literature and the identified time ranges into account, TOI 1, 2 and 3 were identified as components P1 & N1 (Bruyns-Haylett et al., 2017; Di Russo et al., 2002) and P3 (Herrmann and Knight, 2001; Polich, 2007), respectively.

FTLD-PPA Group

Topographical voltage distributions for the FTLD-PPA group are visualized in Figure 6.7(B). In TOI 1, voltage distributions in all three conditions were dominated by occipital positivity. In TOI 2, general activity was weaker than in the other TOIs. Posterior temporal and occipital negativity were dominant in oddball and target conditions. In the standard condition was the dominant negativity shifted anteriorly to temporal and

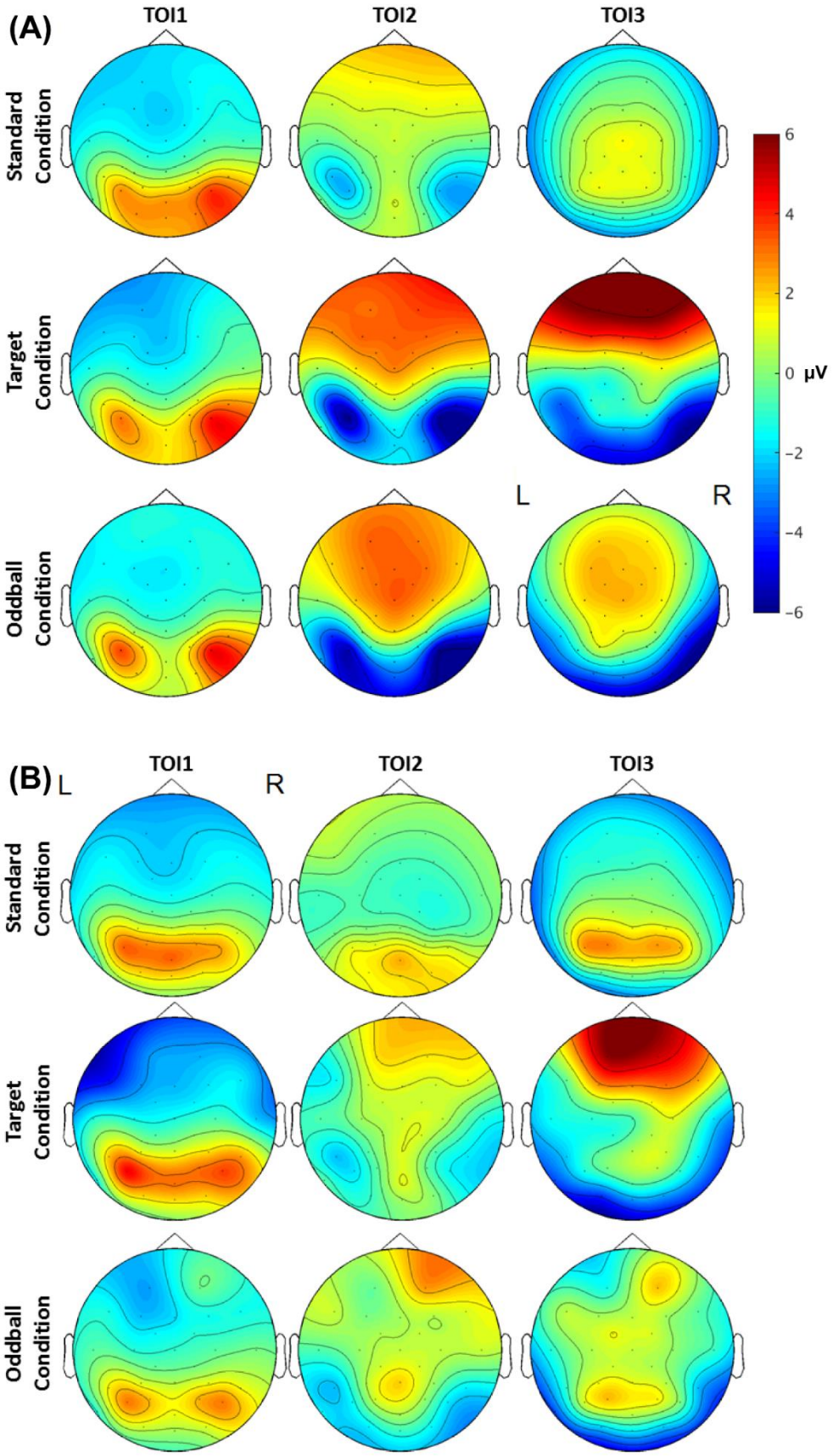

Figure 6.7 Topographical voltage distributions of (A) the control group and (B) the FTLD-PPA group in TOIs of the visual oddball experiment

central areas. In TOI 3, the standard condition presented with occipital positivity, the target condition with extreme frontal positivity and the oddball condition with smaller patches of positivity in frontal, central and parietal areas. As in the control group, maximum electrodes for the TOIs were positive in TOI 1 and TOI 3 and negative in TOI 2 (Table 6.6). Based on similarity with topographies of the control group, the TOIs were identified as components P1, N1 and P3.

Table 6.6 Maximum electrodes in all TOIs of the FTLD-PPA group in the visual oddball experiment

	TOI 1	TOI 2	TOI 3
Standard	P3,PO7,PO4,Oz	CP2,Cz,CP2,T4	P8,PO3,PO4,PO7
Target	PO4,PO7,PO8,Oz	P7,P8,PO7,PO8	Fp1,Fp2,F4,Fz
Oddball	PO3,PO4,PO7,PO8	P8,P7,PO8,O1	Fp2,P3,PO3,PO4

6.3.1.4 Electrode Space Analysis

Mean voltages for electrode clusters from the topographical analysis entered statistical analysis separately for every TOI. All values are collapsed in Table 6.7 and data are visualised in Figures 6.8, 6.9 and 6.10.

Table 6.7 Descriptive data from electrode space analysis in the visual oddball experiment

	P1	N1	P3
Control Group	3.129 µV ± 2.152	-4.198 µV ± 2.905	2.931 µV ± 2.960
FTLD-PPA Group	3.058 µV ± 1.393	-1.627 µV ± 1.927	2.834 µV ± 2.022
Standard Condition	3.046 µV ± 2.232	-1.997 µV ± 2.102	1.597 µV ± 1.359
Target Condition	3.297 µV ± 1.813	-4.029 µV ± 2.856	4.500 µV ± 3.299
Oddball Condition	2.979 µV ± 1.825	-4.220 µV ± 3.169	2.108 µV ± 1.637

P1

A Levene-Test ($F_{(5,63)}$=0.487, p = 0.784) stratified the use of a parametric test. A two-way ANOVA was performed to compare amplitudes of groups and conditions, as well as the interaction of both factors. No significant effect of the factor group ($F_{(1,63)}$ = 0.018,

p = 0.893), factor condition ($F_{(2,63)}$ = 0.337, p = 0.715), and the interaction of both factors ($F_{(2,63)}$ = 0.304, p = 0.739) was present.

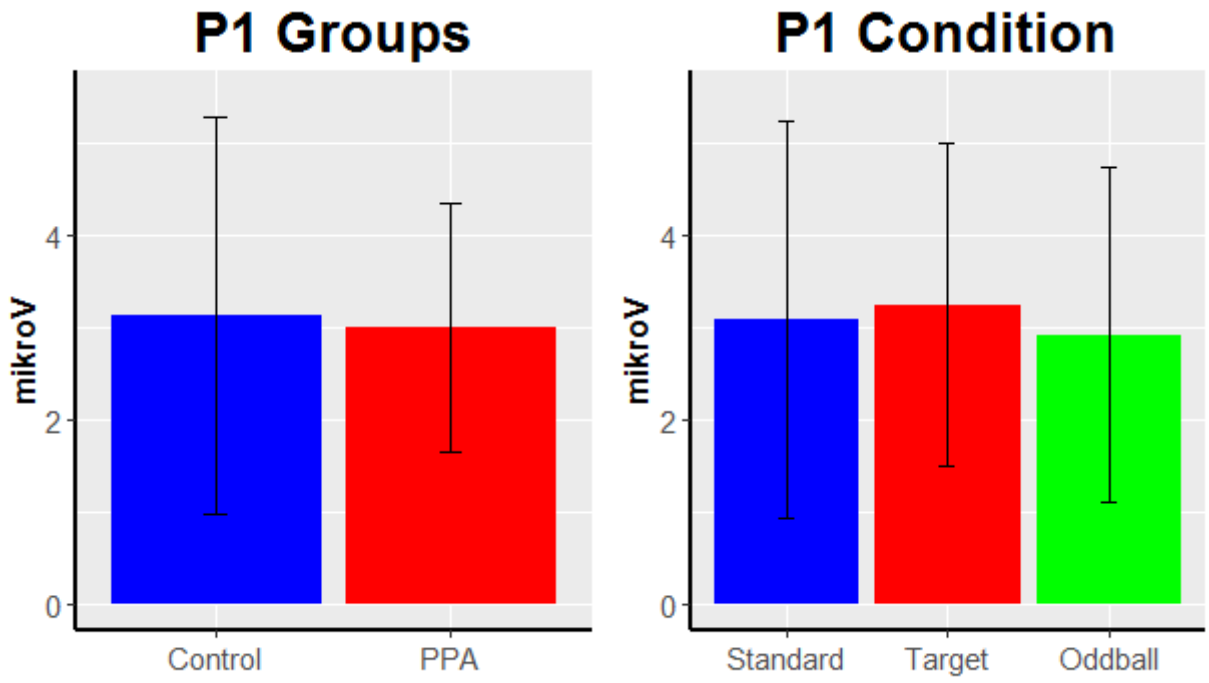

Figure 6.8 Mean amplitudes in the P1 time range (visual oddball)

N1

Levene-test ($F_{(5,63)}$=0.777, p = 0.570) stratified the use of a parametric test. A two-way ANOVA was carried out to compare amplitudes for the factors group and condition and the interaction of both factors. A statistically significant effect of the factor condition was present ($F_{(1,63)}$ = 15.564, p < 0.001) and pairwise comparison revealed a significant difference between standard condition (M = -1.997, STD = 2.101) and target condition (M = -4.029, STD = 2.856, p = 0.022), as well as between standard condition and oddball condition (M = -4.220, STD = 3.169, p = 0.011). A significant effect of the factor group ($F_{(2,63)}$ = 3.323, p = 0.042) was present, where the control group (M = -4.198, STD = 2.905) presented with more negative amplitudes than the FTLD-PPA group (M = -1.627, STD =1.927). No statistically significant interaction ($F_{(2,63)}$ = 0.850, p = 0.432) was present.

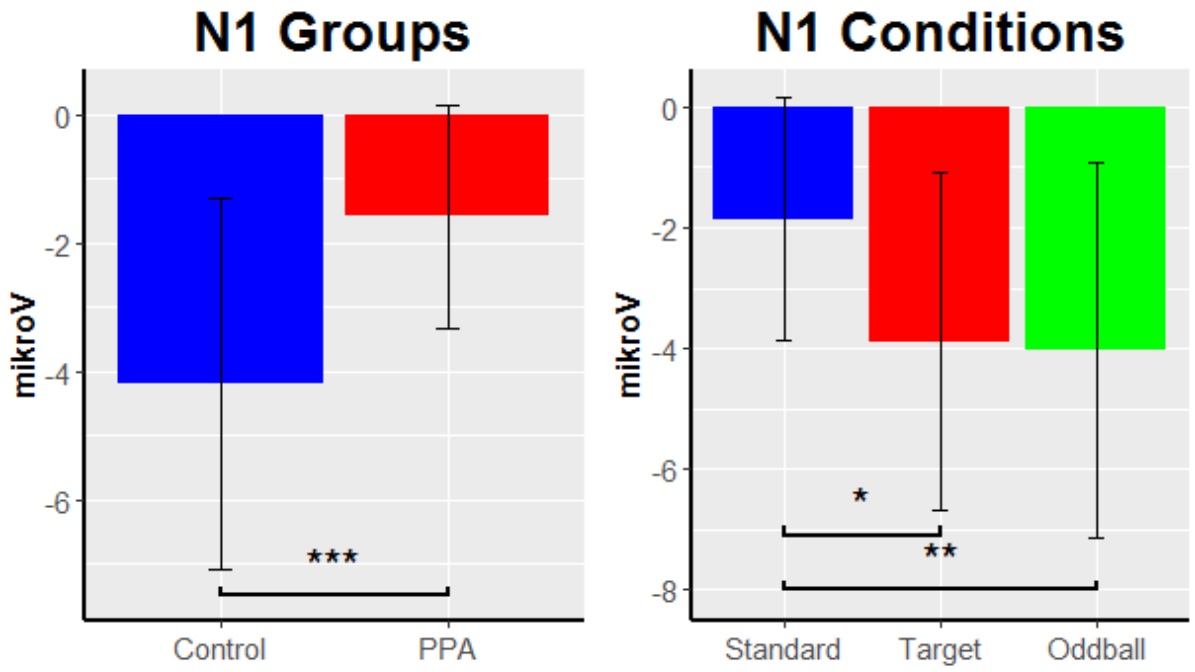

Figure 6.9 Mean amplitudes in the N1 time range (visual oddball); * p < 0.05, ** p < 0.01

P3

Levene-test ($F_{(5,63)}$=5.268, p < 0.001) did not stratify the use of a parametric test. A Friedman-test was carried out to compare the amplitudes for the three conditions (X^2(2) = 12.840, p = 0.002). Dunn-Bonferroni tests were carried out for multiple comparisons. Amplitudes of the target condition (M = 4.500 µV, SD = 3.299) were significantly more positive than amplitudes of the standard condition (M = 1.597 µV, SD = 1.359, p < 0.001) and the oddball condition (M = 2.108 µV, SD = 1.637, p = 0.003). Mann-Whitney-U test was carried out to compare amplitudes for the groups. No statistically significant difference (U = 470, p = 0.657) was present between the control group and the FTLD-PPA group. Although homoscedasticity was violated, a two-way ANOVA was performed to compare parametric and non-parametric results. The significant result from the two-way ANOVA was an effect in the factor condition ($F_{(5,63)}$=5.268, p < 0.001), where amplitudes of the target condition were higher than in the other conditions. No effect in the factor group ($F_{(1,63)}$=5.268, p < 0.001) and no interaction between factors

group and condition ($F_{(2,63)}$=5.268, p < 0.001) emerged. In summary, parametric and non-parametric statistical procedures produced similar results.

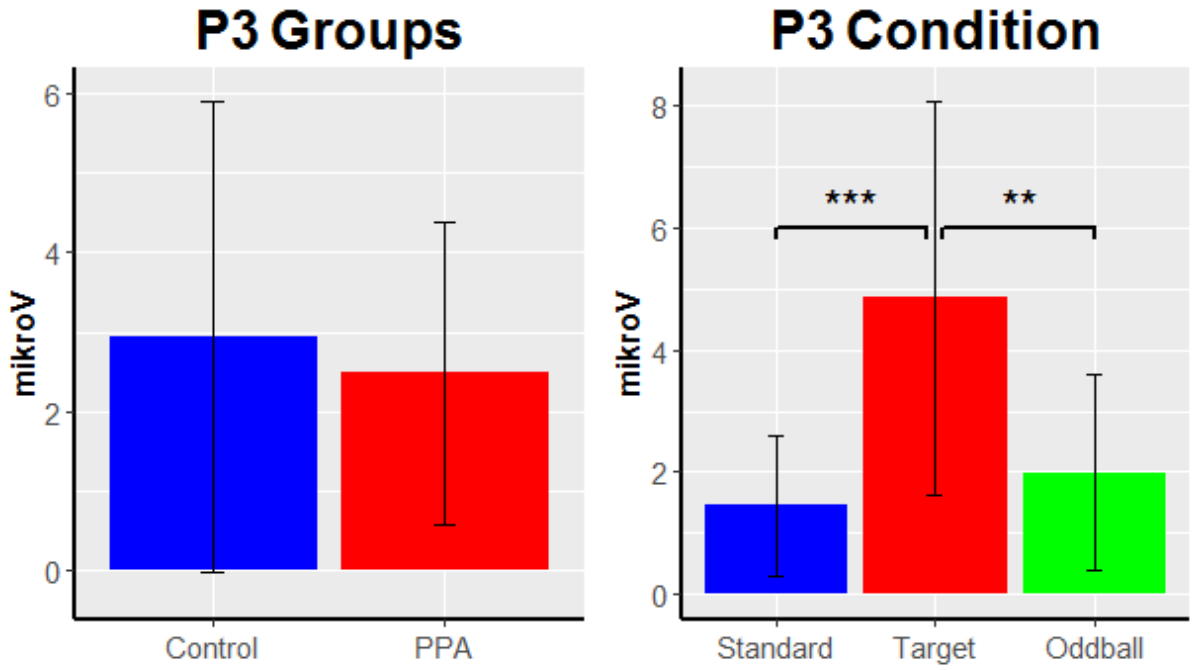

Figure 6.10 Mean amplitudes in the P3 time range (visual oddball); ** p < 0.01, *** p < 0.001

6.3.2 Results from the Semantic Oddball Experiment

6.3.2.1 Response Time Analysis

As for the visual oddball, response time parameters entered two-tailed t-tests. In the three-parameter model, the parameter τ (t(22) = -4.599, p < 0.001) was significantly increased in the FTLD-PPA group (Fig. 6.11). No significant difference between groups was observed for parameters σ and τ (Table 6.8).

Table 6.8 Descriptive data and statistical values of all parameters for response time data of the semantic oddball experiment

Parameter	Control Group (M/SD)	FTLD-PPA Group (M/SD)	Statistical Values
μ	530/36	555/110	t(22) = -0.837, p = 0.411
σ	42/19	60/43	t(22) = -1.442, p = 0.163
τ	59/30	117/28	t(22) = -4.599, p < 0.001

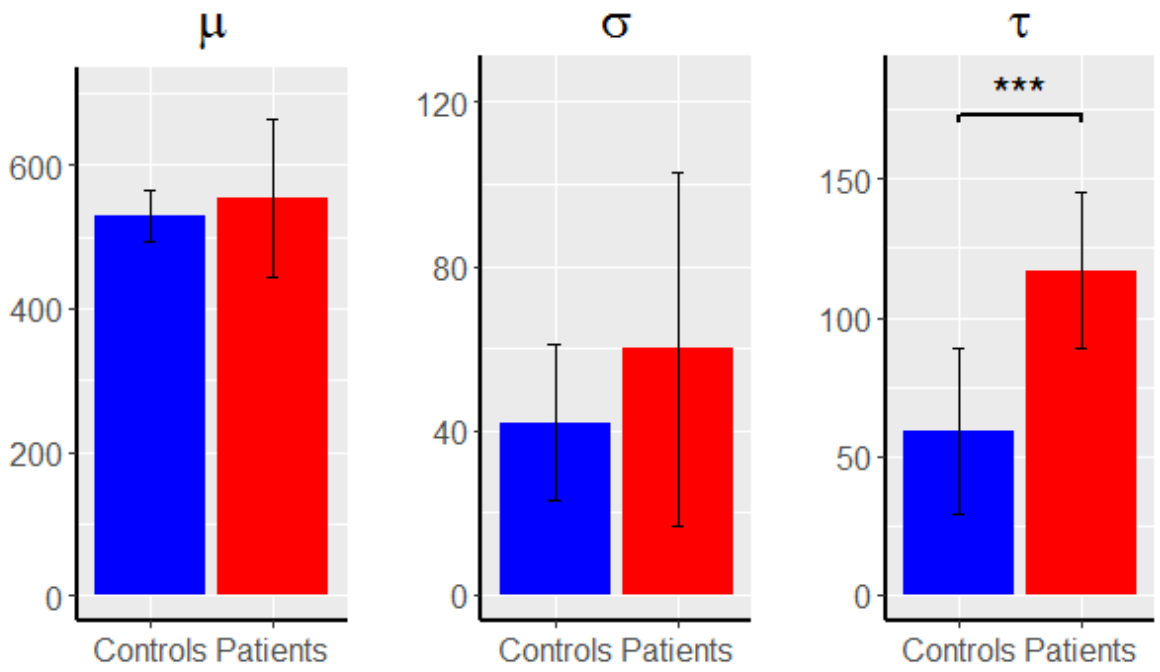

Figure 6.11 Bar Plots of the response time parameters of the semantic oddball experiment; *** p < 0.001

6.3.2.2 GFP Analysis

GFP analysis was performed for both groups separately and GFP signatures are visualised in Figure 6.12. GFP peaks were present in all conditions. The 1st peak emerged at approximately 120 ms in all conditions of both groups and FWQM analysis defined TOIs from ~110 ms to ~130 ms. The 2nd peak emerged between 150 ms to 200 ms in all conditions. A 3rd peak in the range from 200 ms to 500 ms was detectable in both conditions of the control group and in the oddball condition of the FTLD-PPA group. All peak latencies and resulting TOIs are collected in Table 6.9.

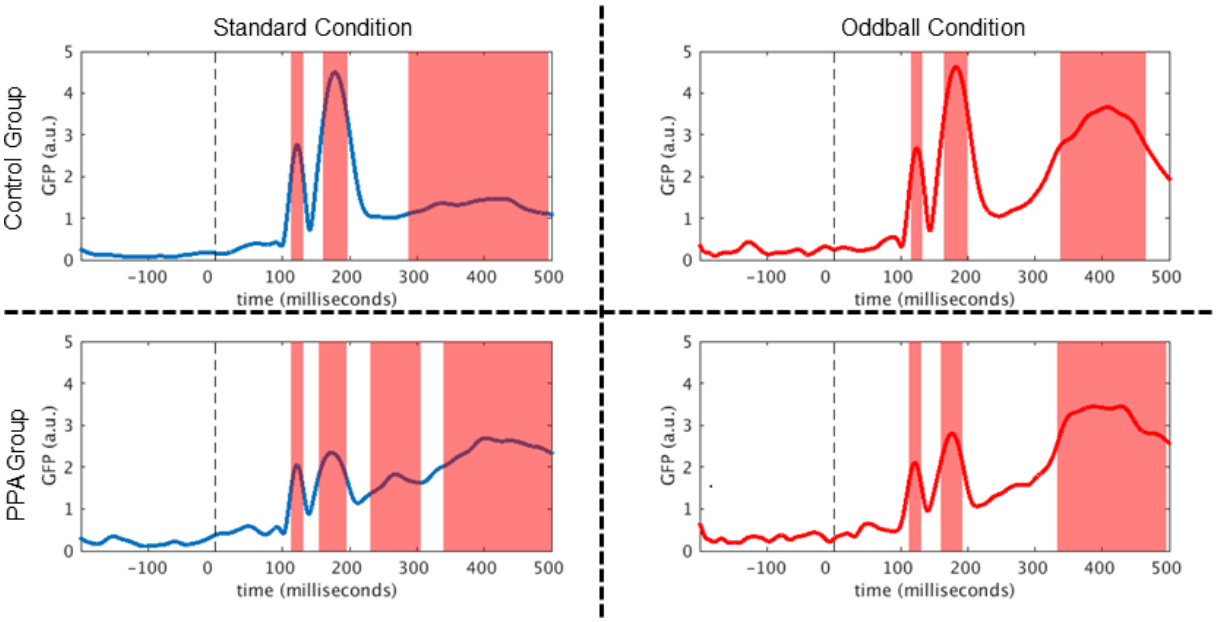

Figure 6.12 GFP signatures of the semantic oddball experiment with TOIs shaded in red; upper row = Control Group, lower row = FTLD-PPA Group, first column = Standard condition, second column = oddball condition

Table 6.9 Peak latencies and resulting TOIs of the semantic oddball experiment; values are in milliseconds

condition	peak latency	Mean amplitude range	peak latency	Mean amplitude range
	Control group		FTLD-PPA group	
standard	122	113 - 130	121	113 - 129
	178	160 - 197	167	149 - 191
	427	287 - 496	404	344 - 500
oddball	123	115 - 132	120	110 – 129
	182	165 - 199	174	156 - 189
	408	338 - 464	386	335 - 499

Figure 6.13 visualises the GFP signature of the FTLD-PPA group and its clinical subgroups. No major difference between the GFP signatures occurred prior to 200 ms, however, between 200 to 300 ms, the nfvPPA group presented an extreme peak that is absent in the svPPA group. After 300 ms the peak diminishes in the nfvPPA subgroup, while the svPPA subgroup has a slowly increase GFP peak.

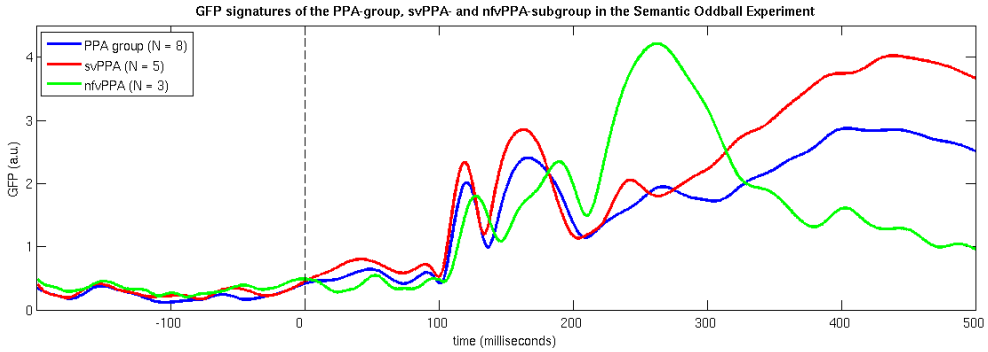

Figure 6.13 GFP signatures of FTLD-subgroups in the semantic oddball experiment

6.3.2.3 Topographical Analysis

In the topographical analysis, all TOIs topographical voltage distributions were visualized for the control group and the FTLD-PPA group (Fig. 6.14).

Control Group

In TOI 1, both conditions presented with occipital positivity. In TOI 2, the pattern of activation was identical in both conditions with occipital negativity. In TOI 3, the standard condition presented with fronto-central positivity and the target condition with extreme frontal positivity. Maximum electrodes for the TOIs were positive in TOI 1 and TOI3 and negative in TOI 2. The maximum electrodes are listed in Table 6.10 and topographic voltage distributions in TOI 1 and TOI 2 were identified as P1, N1. The topography in the standard condition's TOI 3 resembles an anterior P3 (Polich, 2007). The voltage distribution in the oddball condition in TOI 3 did not resemble a known component for that time range.

Table 6.10 Maximum electrodes in all TOIs of the control group in the semantic oddball experiment

	TOI1	TOI2	TOI3
Standard	P7,PO7,PO8,PO4	PO7,P7,O1,Iz2	Fp1,Fp2,F4,F3
Oddball/Target	P7,PO7,PO8,PO3	PO7,P7,O1,O2	Fp1,Fp2,F4,F3

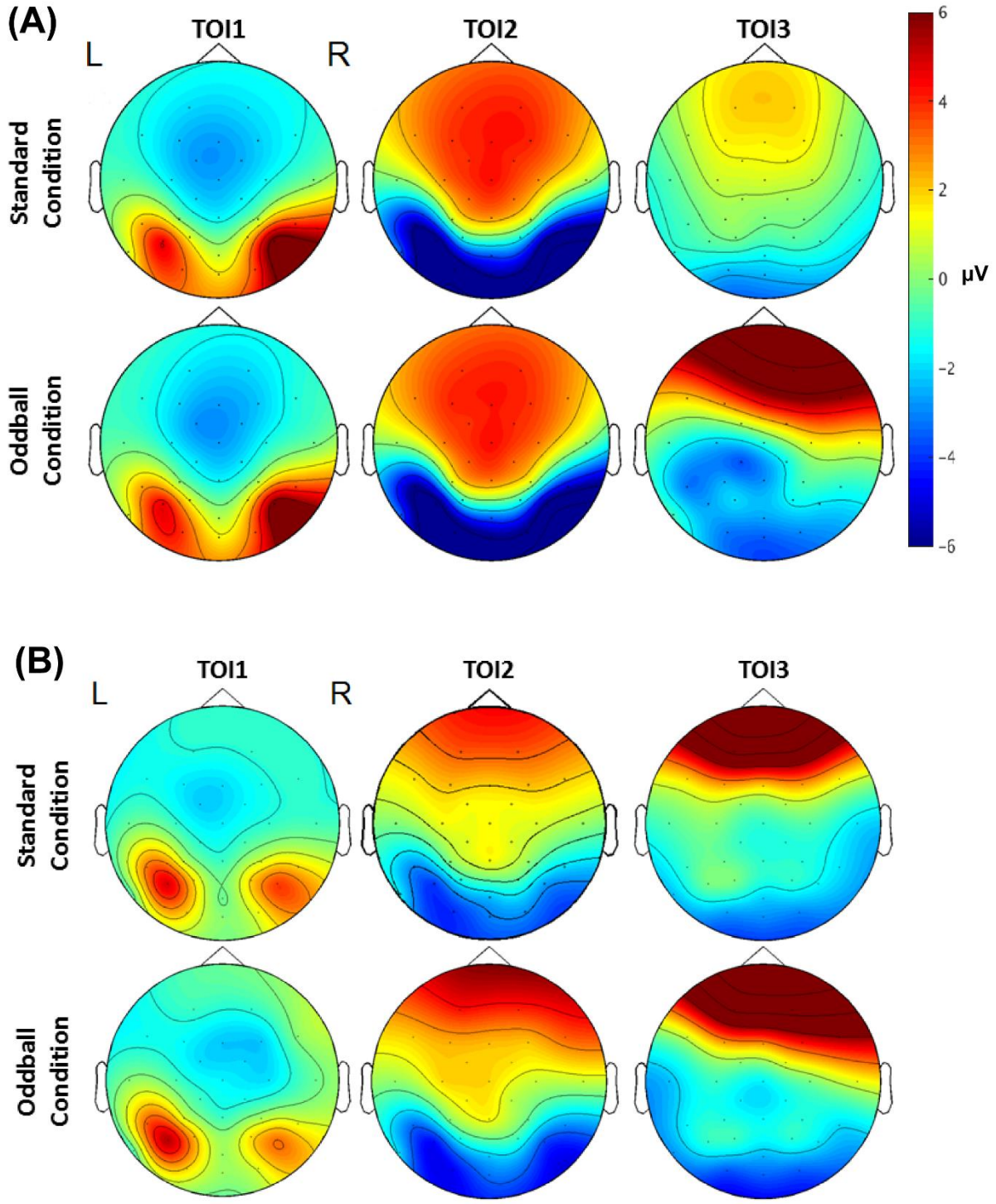

Figure 6.14 Topographical voltage distributions of (A) the control group and (B) the FTLD-PPA group in TOIs of the semantic oddball experiment

FTLD-PPA Group

In TOI 1, both conditions were identical, presenting with occipital positivity. For TOI 2, the pattern of activation was occipital negativity in both conditions. In TOI 3, both conditions presented with extreme frontal positivity. Maximum electrodes for the TOIs

were positive in TOI 1 and TOI 3 and negative in TOI 2. The maximum electrodes are listed in Table 6.11. Topographic voltage distributions in TOI 1 and TOI 2 were identified as P1 and N1. The voltage distribution in TOI 3 did not resemble a known component in that time range.

Table 6.11 Maximum electrodes in all TOIs of the FTLD-PPA group in the semantic oddball experiment

	TOI1	TOI2	TOI3
Standard	P7,P8,PO7,PO8	P7,PO7,O1,Iz	Fp1,Fp2,F3,F4
Oddball	Pz,PO3,PO7,PO8	Pz,PO7,PO8,O1	Fp1,Fp2,F4,F8

6.3.2.4 Electrode Space Analysis

Mean voltages for electrode clusters from the topographical analysis entered statistical analysis separately for every TOI. Data are collapsed in Table 6.12 and visualised in Figures 6.15, 6.16, and 6.17.

Table 6.12 Descriptive data from electrode space analysis in the semantic oddball experiment

	P1	N1	P3
Control Group	4.666 µV ± 3.559	-7.015 µV ± 3.340	4.134 µV ± 3.353
PPA Group	3.515 µV ± 2.188	-3.748 µV ± 1.349	5.808 µV ± 4.982
Standard	4.322 µV ± 3.343	-5.708 µV ± 3.241	2.944 µV ± 3.753
Oddball/Target	4.242 µV ± 3.103	-6.144 µV ± 3.251	6.441 µV ± 3.490

P1

The Levene-Test ($F_{(3,44)} = 0.484$, $p = 0.695$) stratified the use of a parametric test. A two-way ANOVA was performed to compare amplitudes of groups and conditions, as well as the interaction of both factors (Fig. 6.15). No significant effect was present in the factors group ($F_{(1,44)} = 1.339$, $p = 0.253$) and condition ($F_{(1,44)} = 0.002$, $p = 0.962$), as well as in the interaction of both factors ($F_{(1,44)} = 0.010$, $p = 0.921$).

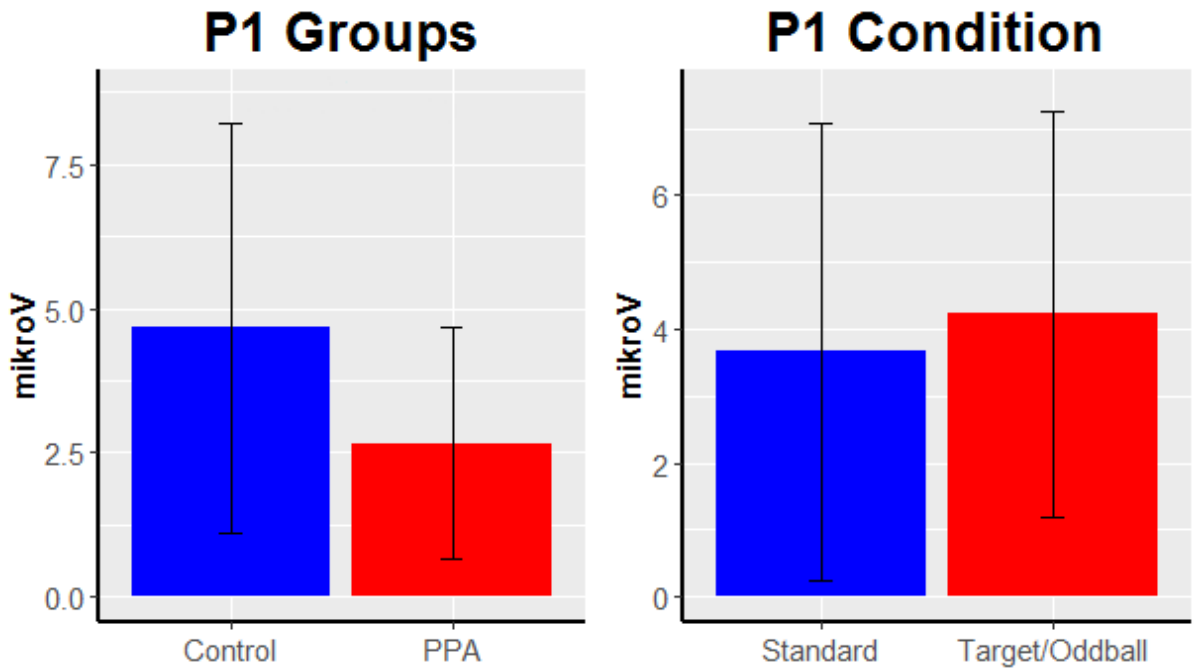

Figure 6.15 Mean amplitudes in the P1 time range (semantic oddball); * p < 0.05

N1

The Levene-Test ($F_{(3,44)}$ = 2.631, p = 0.062) stratified the use of a parametric test, therefore, a two-way ANOVA was performed. A significant effect of the factor group ($F_{(1,44)}$ = 13.515, p < 0.001) emerged, where the control group had higher amplitudes than the FTLD-PPA group (Fig. 6.16). No statistically significant effect was present for the factor condition ($F_{(1,44)}$ = 0.267, p = 0.608) and the interaction of both factors ($F_{(1,44)}$ = 0.006, p = 0.937).

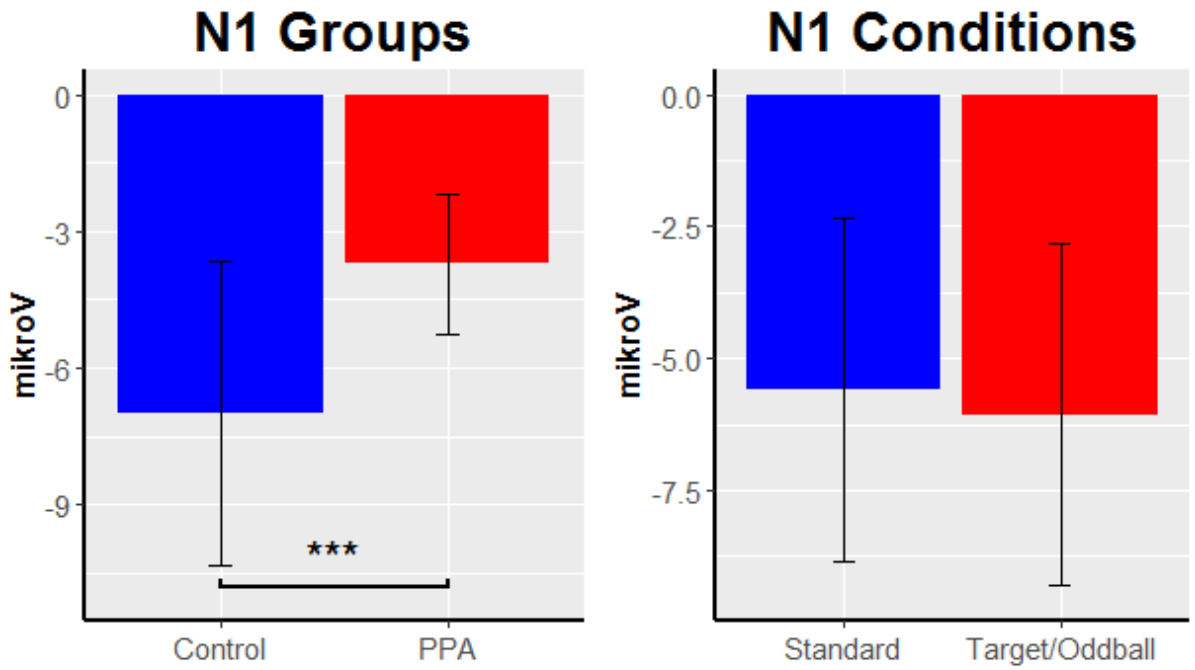

Figure 6.16 Mean amplitudes in the N1 time range (semantic oddball); *** p < 0.001

P3

Levene-test ($F_{(3,44)}$=7.278, p < 0.001) did not stratify the use of a parametric test. A Wilcoxon signed-rank test was applied to compare mean amplitudes between the standard condition and the oddball condition (Fig. 6.17). The test showed that mean amplitudes were higher in the oddball condition (z = -3.969, p < 0.001). A Mann-Whitney-U test was carried out to compare the mean amplitudes of the control group and the FTLD-PPA group. No statistically significant difference was present between mean amplitudes of the control group and the FTLD-PPA group (U = 223, p = 0.189).

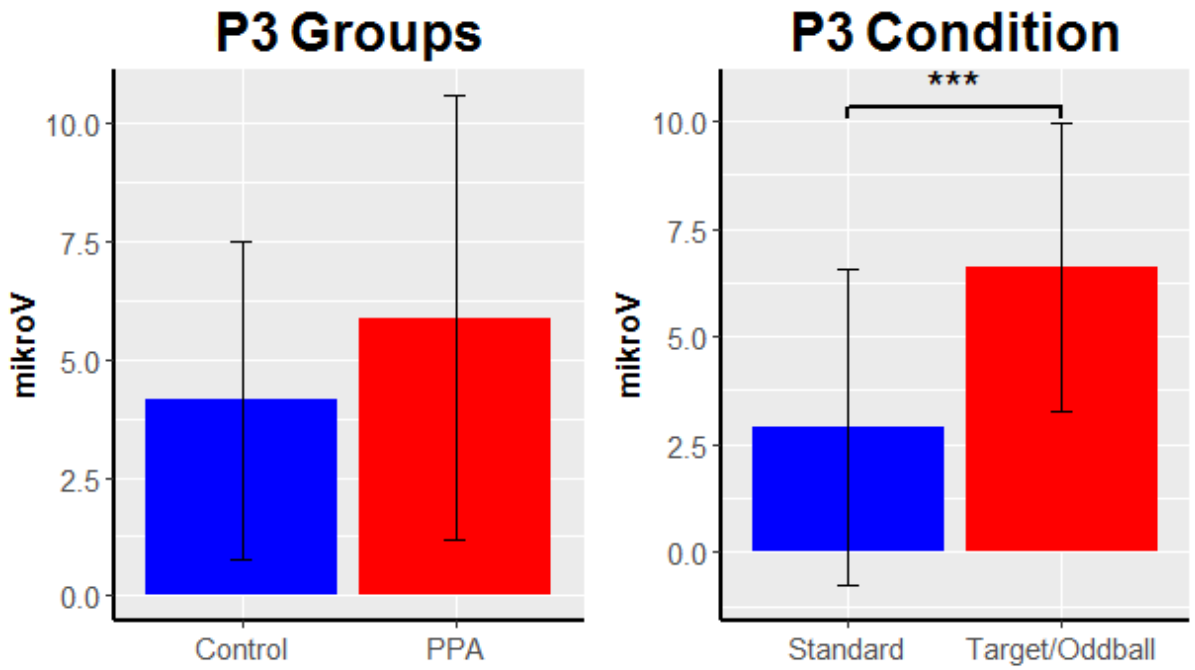

Figure 6.17 Mean amplitudes in the P3 time range (semantic oddball); *** p < 0.001

6.4 Discussion

The purpose of the two oddball experiments was to expand the insights from Chapter 5. Therefore, in Chapter 6, questions were defined that were unanswered before hands. Unfortunately, those questions will remain unanswered for AD-PPA because only one AD-PPA patient was eligible for the analysis (three AD-PPA patients were recruited but two had insufficient data quality) and comparing this individual to a group is critical. However, critical knowledge was generated for the FTLD-PPA group by comparing both oddball experiments. The first two questions regarded the lack of response time data in the PPA literature. The finding is that response times of the FTLD-PPA group are increased in the linguistic oddball and not increased in the non-linguistic oddball. This (a) proves the sensitivity of RT measures in FTLD-PPA patients and (b) underpins the specificity of language deficits in FTLD-PPA by adding RT data to existing knowledge (Gorno-Tempini et al., 2004). The third and fourth question were

related to ERP signatures of the FTLD-PPA group. ERP signatures of the FTLD-PPA group and the control group diverged from each other in several aspects and observable differences were more pronounced in the linguistic task. The difference in ERP signatures adds critical knowledge about timing and location of language processing in PPA patients and, thus, for non-invasive interventions, e.g. transcranial magnetic stimulation.

6.4.1 Relevance and Specificity of Response Time Data in PPA Patients

The response time analysis revealed differences that are specific for impaired language processing in FTLD-PPA patients. In the visual oddball experiment, simple geometric shapes were presented (Fig. 6.1) and the FTLD-PPA group did not present with increased response time latencies. However, in the semantic oddball experiment, where words were presented, increased response time latencies occurred in the FTLD-PPA group. This is a proof-of-concept for the specificity of language impairment in FTLD-PPA patients. The observation that response times are increased when PPA patients perform a language task was made before by others (Sonty et al., 2003). However, this is the first study in the PPA spectrum comparing RTs of two experiments with similar designs, where one experiment did present words and the other one presented non-language stimuli. The results indicate that the increased RTs of the FTLD-PPA group are specific for processing of linguistic but not for processing of non-linguistic stimuli. A three-parameter model, which models RT data to an ex-gaussian function, was used to analyse response time data. The increased τ reveals elongation of the right tail of the RT distribution while the mean and the left tail of the RT distribution, modelled by parameters μ and σ, were not altered (Table 6.8). This implies

no general increase of response latency because the mean and the left tail of the RT distribution remained comparable to the healthy group. The elevation of only the right tail of the RT distribution implies that a subset of stimuli increased processing efforts, which led to increased response times. Whether this observation is associated with frequency-related deterioration of the semantic memory system (see Chapter 1.2.2 for details) cannot be answered from the present stimulus set. Future studies must incorporate stimuli with more variance in lexical frequency to answer this question. If this frequency hypothesis would hold true, the decreased performance of FTLD-PPA patients in the pointing condition of the Repeat & Point test (Table 6.1), a measure for the degradation of the semantic memory system or a graded naming task could be correlated and, subsequently, become the behavioural equivalent of increased RT latencies in semantic tasks. Degradation of the semantic memory system is one of the hallmarks of svPPA (Hodges et al., 2008). Unfortunately, the low number of eligible patients disabled the analysis of clinical subtypes. In summary, the well-known specificity of language deficits in PPA patients, while other cognitive domains (in this experiment perception of visual stimuli) are preserved, is now underpinned by RT data. Based on the results one must assume that in PPA patients, reaction times will increase with increasing task demands. Whether this hypothetical relation is linear or differently shaped cannot be answered from the results and must be subject to future studies.

6.4.2 Differences in ERP Signatures

The ERP signatures of the FTLD-PPA group and the control group diverged in several aspects from each other. In summary, main differences between groups

occurred in the topographic voltage distributions of N1 and P3 time ranges, as well as in the mean amplitudes of the N1 time ranges in both experiments.

In the visual oddball experiment, posterior negativity in the N1 time range was easily identifiable in the control group (Fig. 6.7(A)). Mean amplitudes were weakest in the standard condition, revealing that processing efforts were increased in the other, oddball and target, conditions. This topographical pattern was less consistent in the FTLD-PPA group (Fig. 6.7(B)). In the P3 time range, a topographical pattern of central activity appeared in the control group and the FTLD-PPA group presented a more diffuse voltage distribution. Massive frontal positivity, which seemed to have derived from the button press, appeared in both groups' target condition but not in standard and oddball conditions. The pattern of N1 topography was similar in both oddball experiments (Fig. 6.14), where posterior negativity was less consistent in the FTLD-PPA group. The voltage distribution in the healthy control group's P3 was frontocentral activity in the standard condition and massive frontal positivity in the oddball condition; the voltage distribution in both conditions of the FTLD-PPA group was corrupted by massive frontal positivity. In contrast to the visual oddball experiment, the diverging pattern of both groups' P3 time ranges cannot be simply explained by the button press. The overall findings will be discussed in detail in the following paragraphs.

6.4.2.1 N1 Amplitude Differences

In the N1 time range, the first divergence between conditions was present with increased mean amplitudes in target and oddball conditions of the visual oddball experiment. This difference between oddball stimuli and standard stimuli proves the perception of oddball stimuli. In addition to the task-induced effect, reduced GFP peaks and mean amplitudes emerged in the FTLD-PPA and co-exist with alterations in topographical voltage distribution. A previous meta-analysis of localisation studies of

the N170 highlighted the fusiform gyrus to be its major signal generator (Gao et al., 2019). The FTLD-PPA group contained above 50% svPPA patients that presented with major atrophy in the fusiform gyrus (Fig. 3.2). The strong anterior temporal lobe atrophy in svPPA, including anterior fusiform gyri, can explain alteration in the three analysed metrics because re-localisation of the signal generator or its surrounding tissue alters the spread of voltages. The additional atrophy in frontal and parietal cortices in the FTLD-PPA group (Fig. 3.2) amplified the alteration of voltages and changes the appearance of topographical voltage distributions, as well as, GFP and electrode amplitudes. Structural changes are best detectable in the spatial dimension; therefore, future studies must extend the analysis of topographical properties of ERP signatures by simultaneously applying imaging techniques with superior spatial resolution. With MEG, cortical source estimation would have been possible but MEG quality was insufficient, making the use of MEG data impossible in both oddball experiments. Future studies with combined EEG & MEG and an artefact-reducing design might enable identification of cortical generators. Another approach might be the combination of EEG and MR imaging to increase spatial information for the ERP signature.

No GFP peak was detectable in the N1 time range of the FTLD-PPA group's standard condition (Fig. 6.5) and, subsequently, no mean amplitude range could be calculated. The mean amplitude range of the control group's GFP analysis was used for subsequent analysis steps in the FTLD-PPA group. One might speculate about this decision because of introduced bias. Two arguments enforced the decision. First, the temporal resolution of P1 and N1 components is very stable across different experiments (Chen et al., 2013; Hagoort et al., 2004; Hauk and Pulvermüller, 2004a, 2004b; Hopf et al., 2002) and, second, N1 topographies and time ranges were similar across conditions in the control group, favouring that this is the normative behaviour of

the N1 peak. The general reduction of N1 peaks proves alteration of stimulus processing in the FTLD-PPA group. This electrophysiological finding might become a novel biomarker because it is an easily identifiable difference between FTLD-PPA patients and healthy participants. Future studies might focus on the N1 range and in depth analyse its use as a biomarker for PPA.

6.4.2.2 P3 Topography Differences

Topographic voltage distributions of the control group were similar in all conditions of P1 and N1 time ranges (Fig. 6.7). However, major distortions were present in topographical voltage distributions of the P3 time range. The distortion was also present in the FTLD-PPA group and included both conditions of the semantic oddball. The massive prefrontal positivity was not consistent with previously reported P3 topographies (Knight et al., 1989; Yamaguchi and Knight, 1991). Even though, trials containing eye blinks were removed, it seems that some behavioural response was not detected by the eye blink detection algorithm and, in addition, was not visible in the continuous EEG signal while pre-processing. Therefore, the source of the artefact is not known at the moment. Potentially, stressing of jaw muscles or frowning was the source of the artefact. Further studies with advanced experimental control systems (e.g. eye tracking) might elucidate details of this artefact and can lead to the development of superior experimental designs which will overcome this artefact. For now, interpretation of the P3 is highly susceptible to the artefact and ultimately meaningless. This is, on the one hand, a big problem of this experimental design because P3 data, which have been studied intensively with oddball paradigms (Polich, 2007), cannot be interpreted in this chapter. However, strong differences between svPPA and nfvPPA subgroups emerged (Fig. 6.13). Future studies with improved design will, hopefully, gain access to time ranges beyond 300 ms and are, based on

the preliminary analysis of FTLD subgroups, likely to find subtype-specific adaptations of processing. Nevertheless, on the other hand, one aim of this thesis was to test the feasibility of high demanding language tasks in PPA patients. Based on the results, feasibility of high demand task is limited to time ranges prior to the occurrence of artefacts at the P3 time range. Regarding the artefact, the PPA group, in comparison to the control group, had increased physiological reactions to the high demanding task (Figs. 6.7 & 6.14). Therefore, future electrophysiological studies must focus on low demanding tasks to gain interpretable EEG data from PPA patients. Even though, the experimental design led to artefacts in the P3 range, important information was generated with the oddball experiments. The response times were generated for the price of losing information on the P3 component.

6.4.2.3 Missing P1 Differences

Even though a statistically significant difference was absent in the semantic oddball's P1 time range, a visible difference in mean amplitudes appeared (Fig. 6.15), where the FTLD-PPA group (3.5 µV ± 2.2) had less positive signal than the control group (4.7 µV ± 3.6). This group difference might reflect the impact of language on processing of visual stimuli in PPA and is absent when simple geographic shapes are processed by both groups (Fig. 6.8). The observation resonates with the FTLD-PPA group's P1 amplitude reduction in the passive reading experiment (Fig. 5.10). The behaviour in the P1 time range is an analogy to P1 reduction in the AD spectrum, where AD patients present with P1 reduction when confronted with complex visual stimuli (Saavedra et al., 2012) but not when confronted with simple visual stimuli in an oddball paradigm (Irimajiri et al., 2007). ERP component reduction was proposed a marker for cognitive decline in the AD spectrum, where increased cognitive decline was proposed to translate into increased distortion of ERP components (Stothart et al., 2015). The

cognitive decline in PPA patients is strongest in the language domain (Gorno-Tempini et al., 2011) and, therefore, P1 reduction is present in semantic oddball and passive reading experiments but not in the visual oddball experiment. The lack of statistical significance in the P1 time range of the semantic oddball experiment is attributed to the very low number of patients and an increase in the number of patients is likely to increase the statistical power of this result. In summary, the comparison of both oddball experiments revealed the effect of linguistic task demands on ERP signatures of a group of FTLD-PPA patients. Higher task demands translated into more distortions of early ERP components and major distortion of later ERP components.

When comparing both oddball experiments, an obvious discrepancy exists between ERP data and RT data. While RT data provide differences between the control group and the PPA group solely in the semantic oddball experiment, ERP signatures diverged in both experiments. Again, results from the AD spectrum can be utilised to explain this discrepancy. ERP components in the AD spectrum become increasingly distorted with increasing cognitive decline (Stothart et al., 2015). In PPA patients, cognitive decline is related primarily to the language domain. However, subtle decline of other cognitive domains may occur even in early stages and might affect ERP signatures. This view is supported by neuropsychological data (Table 3.2), where impairment was present in the Rey complex figure test, although that test does not include a language component. Based on the results, ERP signatures seem more susceptible than response times to subliminal cognitive decline. This notion strengthens the proposed use of ERPs as a biomarker for disease progression in dementia (Stothart et al., 2015). It is a known fact that language-specificity of symptoms in PPA decreases with increasing disease duration and cognitive domains other than language can become affected (Mesulam, 2001). A longitudinal study with EEG in PPA patients might be able

to verify this hypothesis and to elucidate electrophysiological markers of cognitive decline in PPA or in individual subtypes of PPA.

6.4.3 Feasibility of Oddball Experiments in PPA Patients

To the author's knowledge, this is the first electrophysiological investigation in PPA patients with oddball tasks. In the visual oddball experiment, a task effect appeared in N1 and P3 time ranges. In the N1 time range, target and oddball stimuli resulted in higher amplitudes than standard stimuli and, in the P3 time range, targets resulted in higher amplitudes than standard stimuli and oddball stimuli. The effect in the P3 time range must be attributed to the button press, while the N1 effect must result from the recognition of oddballs. In the semantic oddball experiment, a task effect appeared solely in the P3 time range, were targets/oddballs elicited stronger responses than standards. Here, the lack of an effect in the N1 time range probably relates to the nature of stimuli. While in the visual oddball experiment, the shape, as a visual detail of the stimulus was the difference between oddballs and standards, the defining property in the semantic oddball was semantic integration, a post-lexical process. Since the post-lexical process happens later than the pre-lexical visual analysis (Coltheart et al., 2001) the oddball effect in the semantic oddball experiment is expected to be hidden later in the ERP signature than in the visual oddball experiment. Unfortunately, the later part of the ERP signature is corrupted by massive frontal positivity, which seems to be an artefact.

Besides those task-specific effects, data show that the applicability of oddball experiments in PPA patients is generally given. Patients did not respond badly to the task or were unable to perform the task. However, the task demands were too high for

PPA patients which led to more physiological reactions, as to be seen in the strong artefact in the P3 time range. This makes oddballs with linguistic stimuli a non-ideal paradigm for electrophysiological investigations in PPA patients. However, the applicability of oddball paradigms in PPA patients is given for neuropsychological assessment and imaging techniques that are less susceptible to minor movement of facial muscles, e.g. MR imaging.

6.5 Conclusion

Both oddball experiments were able to shed light on previously unknown facts about language processing in FTLD-PPA patients. First, response times in FTLD-PPA patients were recorded and proved the specificity of language impairment while sparing of other cognitive domains. The PPA patients performed similar to healthy participants in the non-linguistic task but had increased response times when performing the identical task with words. Second, ERP signatures of the linguistic and non-linguistic oddball diverged from each other, where more alterations appeared in the linguistic oddball; the more tasks tap on language, the worse are results and the more alterations occur in ERP signatures. Future EEG studies must include more patients to enable the correlation of neuropsychological testing and electrophysiological markers to find electrophysiological correlates for symptoms and/or syndromes. Similar correlations have been done with imaging results and electrophysiologic correlates yield the potential to become markers for disease progression.

Besides the new insights in electrophysiology in PPA, the experiments had two major limitations. First, the FTLD-PPA group was very small. Therefore, future experiments

must incorporate more PPA patients, ultimately leading to patient groups that represent clinical subtypes of PPA rather than pathology-defined subtypes. This would probably reveal diverging ERP signatures for clinical subtypes. The second limitation was the design of the sematic oddball experiment. The utilised design resulted in motor artefacts which overlapped with relevant time ranges (P3 in the oddball experiments). In the visual oddball, three conditions (standard, target, oddball) were applied and standard and oddball stimuli could be investigated directly, without the influence of button presses. The problem in the semantic oddball experiment was separating oddball stimuli from button presses. In theory, semantic decision is a binominal decision where a stimulus does belong to the oddball category or does not. This process creates the problem of constructing two semantic oddball categories, where one is attended and the other one is not attended. This problem was impossible to solve for the semantic oddball experiment. Future studies must design tasks that overcome the need of physical responses, which potential corrupt ERP signatures.

Despite the two limitations, the presented data have generated important spatial and temporal information for future electrophysiological and interventional studies in PPA patients. TMS, a non-invasive stimulation technique, can be used to enhance cortical activity and to increase the efficiency of training interventions. The definition of relevant time ranges for stimulation with TMS can help increasing the effect of TMS interventions. Future studies with advanced EEG paradigms can potentially elucidate later components of the ERP signature and add more spatial and temporal information for TMS treatment in the PPA spectrum.

Chapter 7 Concluding Remarks

7.1 Main Findings of the Thesis

PPA is an umbrella term for neurodegenerative diseases that share deterioration of language abilities in the context of dementia. The PPA spectrum and its subtypes are very well described in terms of neuropsychology, neuroimaging and pathological substrates. This thesis aimed to build a basis for further electrophysiological investigations in the PPA spectrum. A cohort of PPA patients was recruited and described in terms of neuropsychological hallmarks and imaging abnormalities. In addition, the pathological status of patients was identified by amyloid PET scan. The cohort consisted clinically of svPPA, nfvPPA and mixed PPA patients. All svPPA patients and nfvPPA patients had a negative result in the amyloid PET scan, while all mixed PPA patients had a positive amyloid PET scan. By comparing cortical thickness, it was shown that in AD-PPA detectable atrophy was present in the peak atrophy sites of all PPA subtypes, whereas FTLD-associated subtypes presented atrophy primarily in the subtype-specific peak atrophy sites, namely anterior fusiform gyrus in svPPA and inferior frontal gyrus in nfvPPA. The left-hemisphere encompassing atrophy in AD-PPA is a possible explanation for why AD-PPA patients present with semantic and agrammatic deficits. In addition to the MR imaging part of this thesis, three electrophysiological experiments were administered. First, a passive reading experiment was performed to elucidate the automated processing of language while single word reading. The task itself has the lowest possible task demands and is very close to natural reading. The outcome of that experiment was diverging ERP signatures, where PPA patients were clearly different from the control group and, in addition, PPA subtypes were different from each other. This basic electrophysiological

study proved the detection of deficits in PPA patients by using EEG. The advantage of EEG is the high temporal resolution of the technique, which is superior to other imaging techniques and neuropsychology in elucidating the processing of words on a millisecond-to-millisecond scale.

Building on the findings that PPA patients processed words differently than healthy participants, and, on now available temporal and spatial information from the first experiment, the other two experiments very administered jointly. Two oddball experiments with similar design were constructed, where one experiment presented geometric shapes while the other one presented single words. Here, the aim was to detect the influence of language on visual processing and the influence of increased task demands on ERP signatures of PPA patients. In addition to EEG and MEG data, response times were recorded to add a behavioural measure to the experiment. The outcome is that increased task demands lead to increased distortion of ERP signatures. Electrophysiological data were found to be superior to response time data in the way that several spatial and temporal differences are described, whereas response time data are only a single temporal data point. However, this thesis can prove the selective impairment of language in PPA by comparing response time data from both oddball experiments. Patients' response times were increased when processing words but comparable to the control group when processing geometric shapes.

Keeping in mind the data of all experiments, one can state the feasibility of EEG in the PPA spectrum is given but increased task demands come with the price of decreased EEG quality. As being obvious from the loss of information for the P3 time range in the semantic oddball experiment, increased task demands can lead to the loss of complete sections of the ERP signature due to emerging artefacts. MEG, however, was shown

not to produce sufficient data quality, which resulted in the rejection of MEG data in all experiment. Based on the results from this thesis, MEG might not become the primary tool for neurophysiological investigations in PPA. For future studies and clinical application, EEG seems to be the more efficient tool for such investigations because of its reduced susceptibility to artefacts, induced by physiological reactions.

Taken together, this thesis can provide a solid basis of electrophysiological data for future studies in the PPA spectrum. First, spatial and temporal information about word processing was generated, which can be used to generate electrophysiological correlates for neuropsychological and imaging findings in PPA. Due to the high temporal precision, electrophysiological markers might be superior to other techniques in detecting disease progress and subtle changes in prodromal phases of PPA. Second, the electrophysiological properties might be future tools to evaluate the efficiency of interventional and drug trials.

7.2 Future Directions

The results of this thesis, hopefully, can pave the way for future investigations and the development of interventional trials in PPA. Relevant time ranges for language processing and potential spatial loci in these rime ranges were identified in a PPA cohort. A subsequent step must be the identification of definite spatial loci by the help of source localisation. Ultimately, this knowledge creates a solid basis for therapeutic intervention with brain stimulation techniques, such as transcranial magnetic stimulation. Besides this clinical application, the emerging knowledge about electrophysiology in the PPA spectrum can help understanding the basis of symptoms in PPA. Future studies must overcome the problem of small sample sizes to produce

stable results. In addition, data from a prospective cohort of PPA patients would open the stage for longitudinal analysis of electrophysiological data, thus producing an evolution of ERP malformation with increasing disease severity.

A methodological aim for the future is the improvement of task design. First, this would enlighten later segments of the ERP signature, which have been overshadowed by task-induced artefacts in this thesis. Second, it would enable the investigation of more complex language processes and post-lexical properties of language processing. Insights into more complex language processes and EEG markers for these processes can become biomarkers for the identification of PPA subtypes or the degradation of the language system. This might become a tool to track changes after interventional trials and to objectify the efficiency of such trials.

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Appendix

List of all words from the passive reading experiment in Chapter 5

Words from the High Frequency Condition			Words from the Low Frequency Condition			Words from the Pseudoword Condition		
Äffchen	Genre	Penis	Ablass	Hingang	Recke	Äffber	Pegler	Jamtung
Ärmel	Gespür	Pfeiler	Abstoß	Hölle	Relikt	Alsing	Piltur	Köpton
Abbruch	Gewürz	Pille	Adept	Hortung	Respekt	Annung	Pular	Kaftung
Alarm	Gibbon	Polster	Ahnung	Hunde	Rohling	Anlen	Quotik	Kardeen
Amsel	Glasur	Porträt	Aktien	Hünen	Rotklee	Argchen	Ratron	Kenpot
Andacht	Glorie	Pulver	Anmerk	Ideen	Runde	Atbruch	Reler	Kirzer
Anmut	Gotik	Quoten	Anteil	Instanz	Sachen	Ausarm	Roträt	Klache
Anstand	Grüße	Rüstung	Aufruf	Jackpot	Salzsee	Bädacht	Rolver	Knülnal
Antritt	Greise	Rachen	Ausbau	Jambus	Schabe	Bärmut	Roträt	Konos
Argwohn	Grippe	Rathaus	Auswahl	Juchzer	Schwere	Bagwohn	Semkord	Kranfer
Ascher	Gurken	Rekord	Bahnung	Kaffee	Seeberg	Baumung	Seufner	Kurgen
Atmung	Härte	Renner	Barfrau	Kanal	Seegrün	Beistoß	Sochen	Löler
Auslauf	Höhle	Riese	B-Dur	Karbid	Seesack	Bildel	Spadel	Lafer
Ausstoß	Hübsche	Rochen	Bedarf	Karos	Sepsis	Bissten	Sprüuhr	Lente
Bäche	Hürde	Roller	Bergsee	Kennung	Sigma	Blobus	Stütmel	Liptik
Büffel	Habicht	Rudel	Beweis	Kiffer	Sinne	Briwerk	Stoldal	Malsaal
Bündel	Hallo	Söldner	Bezirk	Kiste	Sitte	Coggen	Töpgel	Mastwen
Bürsten	Halter	Sanduhr	Bilanz	Klagen	Soldat	Düfden	Tenzies	Meltex
Bagger	Hauben	Schräge	Blutrot	Klärung	Spagat	Dahsen	Tortder	Mecin
Bambus	Hebel	Semmel	Borte	Klaue	Spasmen	Dikxen	Trile	Moven
Bauhaus	Heimweg	Seufzer	Brücke	Knüller	Speisen	Drüden	Tunphe	Muser
Bauwerk	Hergang	Skandal	Bücher	Koffer	Spinett	Echnac	Unbak	Nesdien
Beifuß	Hinweg	Solist	Buchse	Kontakt	Staden	Eislien	Vekgel	Ordthol
Bestie	Honig	Spargel	Bußgeld	Köpfe	Stigmen	Entkan	Vergik	Pasra
Beugen	Hospiz	Spaten	Butter	Kräfte	Student	Fauzug	Vornel	Pepphin
Bilden	Idylle	Spezies	Casus	Kranich	Summe	Encken	Würsatz	Plötzis
Blässe	Ingwer	Sprüche	Chancen	Kritik	Tante	Füband	Weitier	Plussel
Blende	Jauche	Ständer	Chorist	Kuppler	Tatar	Farbden	Wirmerk	Präei
Bluse	Käfig	Stütze	Combo	Kursaal	Techno	Fegut	Wodcher	Quagel
Boxen	Köder	Staude	Cytosin	Küste	Themen	Finhalt	Zilauf	Rasne
Brisanz	Küken	Stolle	Dampfer	Lager	Thorax	Foyter	Abden	Repol
Buden	Kadett	Strophe	D-Dur	Lärchen	Torwart	Freizig	Ahkür	Reweg
Bunker	Kanten	Töpfe	Deppen	Leere	Treffen	Gäßna	Akbel	Rotxis
Chirurg	Kegel	Tabak	Distanz	Lende	Trine	Gatrien	Ancher	Saler
Düfte	Ketten	Tennis	Dohle	Leucin	Trödel	Gehder	Üschuß	Schaon
Dahlien	Klöppel	Tiegel	Dreirad	Linie	Tundra	Gensen	Austoß	Seelikt
Decken	Klausel	Tortur	Drohne	Löwen	Übung	Gerie	Ausnung	Seeling
Dekan	Klinge	Tragik	Echse	Machart	Umland	Glater	Barmerk	Shide
Diktat	Klippe	Triumph	Eckzahn	Malven	Umtrunk	Gofecht	Bebung	Sitsee
Domherr	Knüppel	Tunnel	Eiben	Maser	Urteil	Greinot	Beichen	Solbe
Drüse	Kolben	Umsatz	Ekzem	Mastkur	Urtypus	Gurspür	Bebau	Spisack
Droge	Konsum	Unmut	Ersatz	Medien	Valenz	Höhbon	Bicher	Stigno
Echter	Korken	Untier	Fachamt	Melder	Verlauf	Hürrie	Borfrau	Stunal

Words from the High Frequency Condition			Words from the Low Frequency Condition			Words from the Pseudoword Condition		
Einband	Krücken	Vektor	Fäden	Menthol	Verse	Halße	Bußdarf	Tandat
Eiszeit	Krempe	Verfall	Fahrer	Meter	Vetter	Haupe	Butsee	Techmen
Enden	Kundin	Vermerk	Fatzke	Mitra	Vordach	Heimte	Caweis	Thonett
Entzug	Kutte	Viecher	Fenster	Monat	Vorjahr	Hinsche	Comrot	Trömen
Erbgut	Lüfter	Vollbad	Fernruf	Morphin	Wachtel	Hobicht	Dampcke	Trime
Erbteil	Lanzen	Vorlauf	Firma	Museum	Wähler	Ingge	Depse	Urrax
Erhalt	Lenkrad	Würfel	Fladen	Nazis	Walfang	Käbel	Dolsus	Urmen
Essenz	Linse	Waden	Flosse	Nessel	Wangen	Kügang	Drohist	Vawart
Euter	Lotto	Weihe	Fragen	Neutrum	Weber	Kannig	Echsin	Verfen
Fügung	Lunte	Weltall	Füchsin	Ölpreis	Weingut	Ketle	Ekphin	Vordra
Fünfzig	Mörser	Willkür	Fußspur	Onkel	Werke	Klauche	Fästanz	Vetne
Farbton	Mahnmal	Wirbel	Gabel	Örtchen	Wirsing	Klipder	Fachrad	Wanlenz
Fauna	Mandel	Wodka	Gamma	Partei	Witwe	Koldett	Fense	Welauf
Ferien	Masken	Wucher	Gärten	Passung	Yoghurt	Korgel	Fernben	Werter
Fette	Metall	Zitat	Gattung	Pegel	Zahlen	Kunsel	Flasatz	Witjahr
Finte	Mokka	Zirkel	Geburt	Pepsin	Zinsen	Kutge	Frasin	Zahtel
Flieder	Moslem		Gefühl	Pinne		Lanpel	Gärrer	
Foyer	Mumie		Geisha	Plötze		Linsum	Garster	
Fransen	Nörgler		Gemme	Pluspol		Luncken	Gema	
Freimut	Nager		Gesicht	Polynom		Mahndin	Geisse	
Furie	Narbe		Gesöff	Postweg		Mezen	Gepur	
Gäßchen	Neumond		Glieder	Präsent		Mokrad	Gutung	
Gatter	Nische		Gruppe	Praxis		Musto	Hüfühl	
Gebüsch	Notar		Gucker	Quader		Naser	Hefme	
Gefecht	Optik		Haltung	Radler		Neudel	Horwehr	
Gehrock	Pärchen		Hefter	Rasse		Nottall	Hunguß	
Geldnot	Patron		Heulton	Raubzug		Pärlem	Insle	

Appendix

List of all words from the semantic oddball experiment in Chapter 6

Set A			
Stimulus	**Category**	**Stimulus**	**Category**
Alraune	Plant	Linse	Plant
Ananas	Plant	Lotus	Plant
Apfelbaum	Plant	Majoran	Plant
Baldrian	Plant	Melone	Plant
Bambus	Plant	Moos	Plant
Banane	Plant	Nelke	Plant
Baum	Plant	Orange	Plant
Birne	Plant	Orchidee	Plant
Blatt	Plant	Pappel	Plant
Blume	Plant	Paprika	Plant
Dill	Plant	Porree	Plant
Efeu	Plant	Reis	Plant
Fenchel	Plant	Roggen	Plant
Frucht	Plant	Rosmarin	Plant
Getreide	Plant	Salat	Plant
Gras	Plant	Sauerkraut	Plant
Gurke	Plant	Schilf	Plant
Hafer	Plant	Tanne	Plant
Heidekraut	Plant	Thymian	Plant
Holunder	Plant	Wacholder	Plant
Kamille	Plant	Weizen	Plant
Kastanie	Plant	Zwiebel	Plant
Kirsche	Plant	Adler	Animal
Knoblauch	Plant	Esel	Animal
Krokus	Plant	Hirsch	Animal
Lavendel	Plant	Katze	Animal
Lilie	Plant	Pferd	Animal
Linde	Plant		

Set B			
Stimulus	**Category**	**Stimulus**	**Category**
Apfel	Plant	Mohn	Plant
Balsam	Plant	Möhre	Plant
Bohne	Plant	Palme	Plant
Buche	Plant	Petersilie	Plant
Busch	Plant	Pfirsich	Plant
Eiche	Plant	Pflaume	Plant
Enzian	Plant	Pilz	Plant
Erbse	Plant	Radieschen	Plant
Esche	Plant	Rhabarber	Plant
Feige	Plant	Rose	Plant
Fichte	Plant	Rosenkohl	Plant
Fingerhut	Plant	Seerose	Plant
Flieder	Plant	Spargel	Plant
Gerste	Plant	Spinat	Plant
Hirse	Plant	Staude	Plant
Ingwer	Plant	Strauch	Plant
Kaffee	Plant	Tomate	Plant
Kakao	Plant	Traube	Plant
Kirsche	Plant	Veilchen	Plant
Klee	Plant	Wurzel	Plant
Kohl	Plant	Zitrone	Plant
Kohlrabi	Plant	Zuckerrohr	Plant
Kokos	Plant	Fuchs	Animal
Kraut	Plant	Hund	Animal
Kürbis	Plant	Schwein	Animal
Mandel	Plant	Tiger	Animal
Mangold	Plant	Wolf	Animal
Minze	Plant		

Declaration of Honour

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Ulm, August 23rd, 2021

Daniel Preiß