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Longitudinal changes in brains of patients with fluent primary progressive aphasia

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ABSTRACT

Primary progressive aphasia (PPA) is a rare clinical dementia syndrome with predominant, progressive language impairment. Clinical symptoms, linguistic impairment and the course of the disease may vary considerably between patients. In order to capture these aspects, longitudinal assessments of neurofunctional changes in PPA including their relationship to behaviour and clinical symptoms are mandatory, ideally at intervals shorter than 1 year. Here, we report a longitudinal fMRI study investigating the development of lexical processing and their neural basis in PPA patients over 1 year. Four logopenic PPA patients and four matched controls were scanned 3 times (T1, T2, T3, at 6 months intervals) while performing a visual lexical decision task on German words and pseudowords. Group differences for the lexicality effect (pseudowords > words) were assessed at time point T1 and its longitudinal changes in the BOLD signal associated with the lexicality effect were analysed. Brain atrophy was assessed with a high-resolution MPRAGE sequence and analysed using deformation based morphometry (DBM). From the very beginning of the study, PPA patients showed reduced left-hemispheric and increased right-hemispheric activations compared to controls. During the progression of the disease, activation increased predominantly in left posterior middle temporal gyrus (pMTG) and inferior frontal junction area, whereas the same regions decreased in activity in control brains. Interestingly, DBM data showed that this increase in activation in PPA patients was accompanied by progressing atrophy in the same regions. At a behavioural level, the accuracy in the lexical decision task was comparably high for both groups during the whole period of examination, despite some large variability between patients. To conclude, the dissociation between (i) maintained high performance, (ii) increased activity in regions involved in lexical access such as pMTG, and (iii) progressive atrophy of the very same regions supports the notion of a compensatory mechanism in brains of PPA patients for maintaining language while brain atrophy is progressing. The activity increase within a left-lateralised fronto-temporal network seems vital for high-level performance, whereas initial right-hemispheric recruitment of homologue language regions, which is reminiscent of that in vascular aphasics, has no continuous impact on lexical performance.

1. Introduction

Primary progressive aphasia (PPA) is a rare type of dementia, belonging to neurodegenerative disorders with an onset between 60 and 70 years of age. It was first described by Mesulam (1982). The predominant impairment is in the language domain. During the course of PPA, other cognitive deficits can emerge after about 2 years, but aphasia remains the most severe impairment (Mesulam, 2001) and finally results in mutism (Gorno-Tempini et al., 2004). Because of its circumscribed deficit with relative slow progression of linguistic symptoms, PPA may reveal especially in its early phase, compensatory mechanisms of structure–function interrelation. Detecting the relationship between cognitive, neurofunctional, and neuroanatomical parameters in PPA may thus improve our understanding of the plasticity of the brain under

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pathological conditions. Consequently, this knowledge may help formulate a more general model which extends to other degenerative diseases and which may be the ground to understand the role of neurofunctional changes e.g. in other types of dementia.

In the literature, several attempts have been made to classify subtypes of PPA according to their predominant aphasic symptoms, e.g. syntactic/agrammatic deficits vs. semantic or phonological retrieval problems (e.g. Sonty et al., 2003). The most widely agreed-upon distinction pertains to (at least) one non-fluent/agrammatic type and one fluent type with word finding difficulties. Some authors (e.g. Snowden, Neary, & Mann, 1996; Neary et al., 1998; Hodges, Patterson, Oxbury, & Funnell, 1992) further distinguish between this fluent PPA variant and semantic dementia (SD): Whereas in SD, semantic memory loss is generally evident in verbal as well as non-verbal tasks, patients with fluent PPA only have circumscribed deficits in lexical semantics but are unimpaired in non-verbal semantic tasks. The distinct symptoms in subtypes of PPA are associated with different patterns of atrophy in frontal (non-fluent PPA) vs. temporal (fluent PPA) cortices (e.g. Mesulam et al., 2009). Often atrophy emerges in parallel with hypoperfusion (Perneczky, Diehl-Schmid, Pohl, Drzezga, & Kurz, 2007). Gorno-Tempini et al. (2011) have recently published a new guideline for the classification of PPA in non-fluent/agrammatic, semantic, and logopenic PPA.

The underlying neurofunctional mechanism of progression of aphasic symptoms in PPA remains largely unknown. Cross-sectional studies of cerebral blood flow showed differences between PPA patients in different stages of progression; however, these differences intermingled with regional perfusion changes in healthy aging subjects (Meinzer et al., 2009). Evidence for a reduced structural and functional connectivity in brains of PPA patients likewise rely on cross-sectional rather than longitudinal data (Oliveira et al., 2011; Sonty et al., 2007). In order to distinguish pathological changes from normal age-related changes, longitudinal examinations are mandatory (e.g. Rogalski et al., 2011), which should cover short time intervals. In addition, such studies are capable of disclosing the course of pathological changes in the individual patient, a necessary prerequisite towards personalised therapy (e.g. Dressel et al., 2010).

The present study was designed to address longitudinal changes in language performance and underlying neurofunctional changes in PPA. Over the course of 1 year, fluent (logopenic) PPA patients and matched controls were repeatedly examined at intervals of 6 months (time point T1: 0 months; time point T2: 6 months; time point T3: 12 months). In this study, we employed a lexical decision task including a battery of words and pseudowords. This lexical decision task, which was performed during fMRI scanning, tested for skills of receptive language processing, and avoided problems with expressive language in later stages of the disease. The "lexicality effect" (pseudowords vs. words), a well-established indicator of visual-lexical processing (Binder, Medler, Desai, Conant, & Liebenthal, 2005; Carreiras, Mechelli, Estévez, & Price, 2007) was used to investigate lexical processing in fluent PPA. Based on findings in the literature, the following hypotheses were tested: (1) Considering that atrophy is often associated with hypoperfusion (Acosta-Cabronero et al., 2011; Perneczky et al., 2007) indicating reduced neuronal activity (Hughes, Nestor, Hodges, & Rowe, 2011), we tested the hypothesis that brains of PPA patients show hypoperfusion (and hence, reduced BOLD signal) relative to controls, which becomes more pronounced over time. (2) During aging (Meinzer et al., 2009) as well as in aphasic patients after stroke (e.g. Saur et al., 2006), an additional recruitment of right-hemispheric regions was observed for language processing. In this context we asked the question about comparable effects during disease progression. (3) Finally, we examined whether the differences in functional activations found in the aforementioned experiments were associated with local structural changes. To this end, relative changes of the activation clusters found in the fMRI experiments were computed by means of longitudinal deformation field morphometry (Pieperhoff et al., 2008).

2. Materials and methods

2.1. Participants

Four fluent logopenic PPA patients[1] (mean age ± SD: 65.8 ± 7.0 years; 2 women; all right-handed according to the Edinburgh Inventory by Oldfield, 1971) and four matched control subjects (66.5 ± 6.5 years; 2 women) were examined repeatedly on three occasions over the course of 1 year. The details about the individual patients and control subjects are provided in Table 1. The intelligence of the participants was in the average range.[2] All PPA patients reported increasing word finding problems when first seeking clinical consultation, which had been 1–4 years before inclusion in the present study, and consequently received speech-language therapy.[3] The controls were matched with respect to age, gender, and education (Table 1).

Behavioural examination of patients and controls involved the *Aachener Aphasie Test* (AAT; Huber, Poeck, Weniger, & Willmes, 1983), a standard German aphasia test, and the Birmingham Object Recognition Battery (BORB; Riddoch & Humphreys, 1983). The AAT includes the assessment of spontaneous speech samples with respect to communication (COM), articulation (ART), and speech automatism (AUT), as well as semantic (SEM), syntactic (SYN), and phonological (PHO) symptoms, which are scored by the investigator. Furthermore, seven standardised subtests are available: Token Test (TT), Repetition (REP), Literary Language (LL), Picture Naming (NAM), Auditory Comprehension (AC), Auditory Sentence Comprehension (ASC), and Reading Comprehension (RC). The BORB assesses non-verbal semantic processing and can thus be used to determine the presence or absence of semantic dementia in patients with language impairment.

The results are given in Table 1. According to the AAT, significant language impairment in the PPA group was observed for Picture Naming (Mann–Whitney $U = 0.5$; $p = 0.029$) and Repetition (Mann–Whitney $U = 0.0$; $p = 0.029$), but not for the Token Test (Mann–Whitney $U = 4.0$; $p = 0.343$). Expressive language showed predominantly semantic speech errors. These were restricted to the verbal domain: Semantic dementia was excluded with the BORB, in which all patients showed no impairments.

2.2. Study design

Patients with fluent PPA and matched control subjects were tested three times over the course of 1 year. Each subject was scanned 3 times, once initially (T1) and then again after approximately 6 (T2) and 12 months (T3). At each time point, all subjects performed a visual lexical decision task on 48 German words and 48 pseudowords. This test requires deciding whether the stimulus was a real German word (e.g. KATZE – cat) or a pronounceable German pseudoword (e.g. KURAL) with no meaning in German. Stimuli were presented visually using *Presentation*® software (Neurobehavioral Systems, Albany, CA). Button-press responses

[1] For a multivariate description of the cognitive development of three of the PPA patients please see Etcheverry et al. (2012).

[2] T scores in the LPS 50 + (Sturm, Willmes & Horn, 1993) between 40 and 60, except patient CC with $T = 38$, and remained stable throughout the study (score of patient CC at T3: $T = 41$, i.e. average).

[3] Speech therapy may be conceived as slowing down the progression of the linguistic effects of PPA, i.e. reducing the size of longitudinal effects. Additionally, speech therapy may provide the patient with particular cognitive strategies to compensate his/her deficits, which, in turn, may reduce existing variability between patients. Future studies will have to elucidate in more detail the role of, possibly different types of, speech therapy in different subtypes of PPA.