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Decreased hemodynamic response in inferior frontotemporal regions in elderly with mild cognitive impairment

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ABSTRACT

The verbal fluency task (VFT) is a well-established cognitive marker for mild cognitive impairment (MCI) in the prodromal stage of Alzheimer´s dementia (AD). The behavioral VFT performance of patients allows the prediction of dementia two years later. But effective compensatory mechanism might cover or reduce the predictive value of the VFT. Therefore the aim of this study is to measure the hemodynamic response during VFT in patients with mild cognitive impairment (MCI) to establish the hemodynamic response during the VFT as a screening instrument for the prediction of dementia. One method which allows measuring the hemodynamic response during speech production without severe problems with moving artifacts like in functional magnetic resonance imaging (fMRI) is the functional near-infrared spectroscopy (fNIRS). It is optimal as a screening instrument, as it is easy to apply and without any contraindications. In this study we assessed the hemodynamic response in prefrontal and temporal regions in patients with MCI as well as matched healthy controls with fNIRS. We found a decreased hemodynamic response in the inferior frontotemporal cortex for the MCI group. Our results indicate that a frontotemporal decreased hemodynamic response could serve as a diagnostic biomarker for dementia.

1. Introduction

Alzheimer´s disease (AD), a progressive neurodegenerative brain disease, is of growing importance for the society (Alzheimer's Association, 2015). The prevalence of AD is estimated to increase dramatically because of a shift of the population to older ages (Prince et al., 2013). As a result, total costs of care for Americans with AD and other dementias aged 65 and older will increase from $226 billion in 2015 to $1101 billion in 2050 (Alzheimer's Association, 2015). Although effective medications have not been found to date (Langbaum et al., 2013), a reduction of risk factors like obesity, smoking, hypertension for 10–25% over a time period of 10 years would prevent 1.1–3 million cases of dementia worldwide (Barnes and Yaffe, 2011).

With regard to biomarkers for an early diagnosis of AD, a MEDLINE survey of all publications concerning biomarkers in AD resulted in 142 longitudinal studies, with the highest number of studies (n = 70) related to structural magnetic resonance imaging (MRI; Noel-Storr et al., 2013). Other recent studies investigated α-Amyloid imaging (Saidlitz et al., 2014), cerebrospinal fluid (CSF; Rosén et al., 2013) and blood biomarkers (Lambert et al., 2013) including genetic (Moulder et al., 2013), proteomic (Ghidoni et al., 2013) and inflammatory biomarkers (Bettcher and Kramer, 2014) as well as vascular (Cooper et al., 2015) and other risk factors (Di Marco et al., 2014; Ellis et al., 2013). The largest longitudinal study up-to-date is the Alzheimer´s Disease Neuroimaging Initiative (ADNI; Hendrix et al., 2015), a non-treatment naturalistic multi-site study with the goal to develop and validate imaging (Jagust et al., 2015), cognitive and laboratory biomarkers (Saykin et al., 2015). This study included structural brain imaging as well as positron emission tomography (PET) scan, but functional brain imaging data are missing. As we know that functional brain imaging data can show changes in functional brain activity in participants without behavioral deficits (for example by compensatory brain activity) we expect that functional brain activity during cognitive tasks would increase the predictive power of this assessment.

Prior studies showed the predictive validity of different cognitive measures for the development of AD dementia such as associative learning and verbal fluency (Ahmed et al., 2008; Clark et al., 2009; Hamel et al., 2014). As such, verbal and non-verbal memory, visual-spatial and executive functions and verbal fluency seem to be suited for the investigation of the time-course of cognitive deterioration

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(Reischies and Buerker, 2005). Individuals developing AD were shown to perform worse on tests of episodic memory and semantic verbal fluency compared to persons not developing AD dementia (Clark et al., 2009; Guarch et al., 2008).

Thus, measuring functional brain activity has the potential to detect early changes in brain function, before neuropsychological deficits can be detected. In this study we will focus on the functional brain activity, more specifically hemodynamic response, during the verbal fluency task (VFT). To further understand the neurocognitive function in patients with dementia and to evaluate the predictive power of the hemodynamic response during the VFT as a screening instrument we investigated patients with mild cognitive impairment (MCI; Petersen, 2004) in this study, which is thought to be a transitional stage which starts approximately five years before the onset of AD (Frigerio and Strooper, 2016).

Previous studies investigating the neural correlates of the VFT have shown that patients with AD exhibit a decreased hemodynamic response mostly in prefrontal and parietal areas compared to healthy controls (Arai et al., 2006; Herrmann et al., 2008; Hock et al., 1997; Metzger et al., 2016; Richter et al., 2007). For patients with MCI the results are less clear. Arai et al. (2006) for example found that patients with MCI have a decreased hemodynamic response in the right parietal area, but not in prefrontal regions during a VFT. In contrast, Yeung et al. (2016) described a missing left lateralization over the prefrontal cortex in the MCI group. Therefore there is a need for more studies investigating the hemodynamic response pattern during the VFT in a large sample of MCI patients.

Based on recent findings of a vascular dysfunction as a hallmark in AD (Nelson et al., 2016) and a decreased hemodynamic response in the comparison between healthy controls and AD patients, we hypothesized a decreased hemodynamic response over the frontotemporal cortex for the MCI participants.

2. Methods

2.1. Subjects

604 participants (age: 70–77 years) participated in the first data acquisition of the "Vogel-Studie" (Katzorke et al., 2017; Polak et al., 2017). The "Vogel-Studie" was approved by the local ethics committee and complied with the declaration of Helsinki in its latest version (World Medical Association, 2013). A written informed consent was signed by each participant after a full briefing. MCI was defined according to the criteria of Portet et al. (2006). Subjects were classified as *MCI* if they had a subjective as well as objective cognitive impairment, no impairment of daily activities and inconspicuous scores in the dementia and depression screenings (see Table 1 for details). *Healthy* was defined as not fulfilling our criteria for MCI and having inconspicuous scores in the dementia and depression screenings (see Fig. 1 for Flow Chart). We excluded subjects with any severe psychiatric, neurological or internal disease for the last 12 months and subjects suffering from severe and uncorrected impaired vision or hearing on the first day of examination. Furthermore, for data analysis subjects were excluded if they had a history of a central nervous system disease (multiple sclerosis, epilepsy, pain syndrome, restless legs syndrome, stroke, head injury, traumatic brain injury, cerebral bleeding, transient ischemic attack, basal skull fracture), were not right-handed, were not German native speakers, had severe problems during the VFT, and if no fNIRS or APOE data were available (see Fig. 1). We applied a statistical matching by using propensity scores as described by Bacher (2002). We chose the following risk factors for developing AD as matching control variables: Apolipoprotein-E (*APOE*), family history of dementia, years of education, sex, age, BMI and depression screening scores (see Fig. 1; Gao et al., 2013; Reitz and Mayeux, 2014; Riedel et al., 2016). This procedure resulted in a sample of 110 subjects. 55 (34 female, 21 male) of these were classified as healthy and 55 (25 female, 30 male) as MCI.

Table 1
Criteria for classification as mild cognitive impairment based on Portet et al. (2006).

Criteria that must be fulfilled	
Subjective cognitive impairment	At least one of the following have to be answered in the affirmative: ■ "Did you ever notice memory impairment?" ■ "Do you frequently have complaints about forgetting names of acquaintance, forgetting telephone numbers, losing your glasses, purse, wallet or keys?" ■ "Did your relatives ever approach you regarding cognitive problems?"
Objective cognitive impairment (clinical examination)	At least one pathological finding in clinical examination regarding ■ State of awareness ■ Orientation ■ Alertness ■ Perception ■ Concentration ■ Short and long term memory
Objective cognitive impairment (neuropsychological examination)	Cognitive impairment in at least one of the following tests ■ MMST < 27 ■ DemTect < 13 ■ Deficient results (*T*-value < 37.1) in cognitive domains of ○ Memory (VLMT, WMS-R, CFT) ○ Attention (TAP: Alertness and Divided Attention) ○ Executive functioning (CFT; TAP: Incompatibility and GoNoGo) ○ Speech (RWT)
No impairment of daily activities	All of the following have be answered in the affirmative: ■ "Do you cope with everyday life?" ■ "Do you take care of yourself regarding personal hygiene?" And the following must be true ■ B-ADL < 2.1
Inconspicuous Dementia Screening	Both of the following have to be true ■ MMST > 23 ■ DemTect > 8
Inconspicuous depression screening	Both of the following have to be true ■ BDI-II < 20 ■ GDS < 6

Note: Tests used for classification a) Mini-Mental-Status-Test (MMST; Folstein et al., 1975), b) DemTect (Kalbe et al., 2004), c) Verbal learning and memory test (VLMT; Helmstaedter et al., 2001), d) Wechsler memory scale-revised (WMS-R; Härting et al., 2000), e) Rey Complex Figure Test (CFT; Meyers and Meyers, 1996), f) Testbatterie zur Aufmerksamkeitsprüfung [battery of tests for attentional performance] (TAP; Zimmermann and Fimm, 2009), g) Regensburger Wortflüssigkeits-Test [Regensburger verbal fluency test] (RWT; Aschenbrenner et al., 2000), h) Bayer-Activities of Daily Living Scale (B-ADL; Hindmarch et al., 1998), Beck Depression Inventory-II (BDI-II; Beck et al., 1996), i) geriatric depression screening scale (GDS; Yesavage et al., 1982).

There was no difference in sex, *APOE* or family history of dementia between healthy subjects and subjects with MCI (sex: $Chi^2_{(1,\ N\ =\ 110)} = 2.96$, $p = .126$; *APOE*: Fisher´s exact test, $p = .219$, family history of dementia: Fisher´s exact test, $p = 1.000$). The groups did not differ regarding age and years of education (see Table 2). The participants of the MCI group performed worse in the dementia screening test DemTect but not in the MMST, four of the six tests of the memory domain (VLMT immediate recall, VLMT delayed recall, VLMT recognition, CFT memory) and one of the two tests of the speech domain (RWT category change; see Table 2).

2.2. Neuropsychological tests

For the diagnostic classification and characterization the participants were assessed by different additional neuropsychological tests beside the verbal fluency task (see Tables 1 and 2). These tests assessed the following domains: a) *dementia* by using the DemTect (Kalbe et al.,