Neuropsychologia 119 (2018) 145–156

Contents lists available at ScienceDirect

Neuropsychologia

journal homepage: www.elsevier.com/locate/neuropsychologia

Basal forebrain cholinergic system volume is associated with general cognitive ability in the elderly

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A B S T R A C T

Objective: At the present, it is unclear whether association of basal forebrain cholinergic system (BFCS) volume with cognitive performance exists in healthy as well as in cognitively impaired elderly subjects. Whereas one small study reported an association of BFCS volume with general cognitive ability 'g' in healthy ageing, effects on specific cognitive domains have only been found in subjects with cognitive decline. Here we aim to clarify whether an association of BFCS volume and 'g' is present in a larger sample of elderly subjects without obvious symptoms of dementia and whether similar associations can also be observed in specific cognitive domains.

Methods: 282 pre-surgical patients from the BioCog study (aged 72.7 ± 4.9 years with a range of 65–87 years, 110 women) with a median MMSE score of 29 points (range 24–30) were investigated. BFCS and brain volume as well as brain parenchymal fraction were assessed in T1-weighted MR images using SPM12 and a probabilistic map of the BFCS. Neuropsychological assessment comprised the CANTAB cognitive battery and paper-and-pencil based tests. For data analysis, generalised linear models and quantile regression were applied.

Results: Significant associations of BFCS volume with 'g' and several cognitive domains were found, with the strongest association found for 'g'. BFCS volume explained less variance in cognitive performance than brain volume. The association was not confounded by brain parenchymal fraction. Furthermore, the association of BFCS volume and 'g' was similar in high- and low-performers.

Conclusion: Our results extend previous study findings on BFCS volume associations with cognition in elderly subjects. Despite the observed associations of BFCS volume and cognitive performance, this association seems to reflect a more general association of brain volume and cognition. Accordingly, a specific association of BFCS volume and cognition in non-demented elderly subjects is questionable.

1. Introduction

The basal forebrain is the main source of acetylcholine (ACh) for hippocampal and neocortical structures. The basal forebrain cholinergic system (BFCS) comprises the medial septum nuclei (Ch1), Broca's diagonal (Ch2) and horizontal nuclei (Ch3) as well as the Nucleus basalis of Meynert (Ch4) and the Nucleus subputaminalis of Ayala (Mesulam et al., 1983; Simić et al., 1999). Its main neurotransmitter acetylcholine is well known to play a role in cognition which has been shown in several neurophysiological experiments and lesion studies of the BFCS (Parikh et al., 2007; Harati et al., 2008; Cai et al., 2012).

In patients with Alzheimer's Dementia (AD), the number of cholinergic neurons in the human brain is diminished (White et al., 1977; Kilimann et al., 2014). Furthermore, MRI studies have shown that cholinergic atrophy parallels cognitive decline as the disease process is progressing (Grothe et al., 2013). Current treatment strategies of Alzheimer's dementia aim at compensation for the cholinergic deficit by administration of ACh-esterase inhibitors (Birks 2006; Winblad et al., 2001). These drugs increase neurotransmitter persistence in the synaptic cleft by pharmacological inhibition of its degradation,

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https://doi.org/10.1016/j.neuropsychologia.2018.08.005
Received 28 April 2018; Received in revised form 2 August 2018; Accepted 6 August 2018
Available online 07 August 2018

ameliorating cognitive symptoms (Anand and Singh, 2013).

Atrophy of cholinergic cells in the basal forebrain is also seen in healthy elderly subjects without clinical evidence of dementia (Grothe et al., 2012, 2013; Teipel et al., 2015). Post mortem studies reported a decrease of histological markers of ACh-synthesis and cholinergic synapses during normal ageing which is accelerated in AD patients (Sparks et al., 1992; Perry et al., 1992). However, it is still controversial whether cholinergic deficits are also associated with age-associated cognitive decline in subjects without evidence of dementia development. Wolf et al. (2014) recently reported an association of BFCS volume with cognitive performance in a small group of healthy elderly subjects without evidence of dementia. On the other hand, ACh-esterase-inhibitors have not been proven effective in elderly patients with memory complaints without dementia (mild cognitive impairment) and cholinergic cell loss seems to occur at advanced stages of AD (Russ and Morling, 2012; Gilmor et al., 1999). Furthermore, histological studies suggested that 30% of cholinergic neurons in the basal forebrain need to be lost until relevant cognitive deficits manifest (Mini-Mental State Examination/MMSE < 24) which is questioning an association of cognition and basal forebrain volume in healthy ageing (Schliebs and Arendt, 2006).

Associations of BFCS subregion volumes and cognitive domains (episodic memory, executive functions) were reported for patients with mild cognitive impairment (MCI). This association was not observed in the healthy control group (Grothe et al., 2010, 2016). Since these studies were designed to investigate differences between healthy elderly and patients with mild cognitive impairment, one needs to take into account that the control group was strictly defined as a highly functional ("hypernormal") control group without the slightest suspicion for cognitive impairment. Thus, Grothe et al. (2016) used a control group from the Alzheimer's Disease Neuroimaging Initiative (ADNI-2) comprising individuals without any memory complaints, normal memory function according to the Wechsler Memory Scale-R and a Clinical Dementia Rating Scale (CDR) score of 0. In addition, subjects with significant systemic illness or unstable medical condition were not included in the control group. Since multimorbidity has been shown to be associated with age and cognitive impairment, exclusion of participants due to non-neurocognitive medical conditions affects the prevalence of age-associated cognitive decline in the sample (Barnett et al., 2012; Vassilaki et al., 2015).

The aim of the present study is the analysis of BFCS volume associations with cognitive performance in a natural rather than a "hypernormal" cohort of elderly pre-surgical patients (≥ 65 years) without obvious symptoms of clinical dementia (MMSE score median 29 points, range 24–30, Folstein et al., 1975).

2. Methods

2.1. Participants

Participants were recruited as part of the BioCog project (Biomarker Development for Postoperative Cognitive Impairment in the Elderly study, www.biocog.eu), which is a prospective multicentre cohort study with the aim to develop a biomarker-based algorithm for risk prediction of post-operative cognitive disorders. Only patients ≥ 65 years of age presenting for an elective major surgery were recruited (for further inclusion and exclusion criteria see Table 1).

All patients gave written informed consent to participate in the study. The study protocol was approved by the local ethics committees and conducted in accordance with the declaration of Helsinki. The study was registered at clinicaltrials.gov (NCT02832193).

In line with the study protocol, the first 400 out of 1033 participants recruited at two study centres in Berlin, Germany (N = 291) and Utrecht, Netherlands (N = 109) were selected for this interim analysis. In total, 2733 patients were screened for inclusion in the interim sample in both study centres. 297 out of 400 patients underwent anatomical neuroimaging. Two patients were excluded due to brain pathology interfering with the segmentation procedure. Thirteen datasets were incomplete with regard to demographic data or patients did not perform cognitive testing at all. Finally, data from 282 participants are included in the analysis (N = 204 from Berlin, N = 78 from Utrecht). Neuropsychological data were incomplete for several participants reducing the final sample size for test analysis.

2.2. Neuropsychological assessments

One day before surgery, all participants underwent a comprehensive computerised neuropsychological test battery (CANTAB, Cambridge Cognition Ltd., UK), comprising the Paired Associate Learning (PAL), Verbal Recognition Memory (VRM), Spatial Span Length (SSP) and Simple Reaction Time (SRT). Additionally, pen-and-paper versions of the Trail-Making-Test (TMT, Parts A and B) and a manual dexterity test called the Grooved Pegboard Task (GPT) were conducted. Testing was performed by trained doctoral students and study nurses based on a standard operating procedure which was consented with two neuropsychologists.

PAL: The participant is shown different patterns in fixed locations on a screen in a randomised order. Subsequently, the patterns are obscured and the participant is asked to indicate the location where a particular pattern has been shown previously. In case of an error, the participant is asked to repeat the task for a maximum of ten trials. The task is then repeated on another stage with increased difficulty level. The first trial memory score is calculated as the number of patterns correctly allocated at first attempt for all completed stages. The PAL memory score assesses explicit visuospatial memory and has been found to indicate dementia, especially of Alzheimer's type (Lee et al., 2003).

VRM: The participant is shown a list of twelve words and asked to recall freely as many items as possible. Subsequently, the participant is shown a second list including the previously presented words as well as distractors and is asked to choose the items he or she recognises. The recognition procedure is repeated after twenty minutes. The number of items recognised after delay is analysed, since recognition memory has been shown to be associated with medial septal volume in the BFCS in younger participants (Butler et al., 2012). Furthermore, two studies suggest associations of BFCS volume with delayed recall in memory tasks (Grothe et al., 2010, 2016).

SSP: The participant is shown colour changing boxes on a screen. He or she is then asked to indicate the correct sequence by which the boxes have changed colours. The parameter of interest analysed is the longest sequence of boxes recalled (span length), which is thought to represent visual working memory (Monaco et al., 2013).

SRT: The participant is shown a square on a computer screen. He or she is asked to respond to this stimulus by selecting a button as fast as possible. Mean response latency (reaction time) is the parameter of interest. Reaction time is considered to be a marker of fluid intelligence and age-associated decline in cognitive ability (Der and Deary, 2018).

TMT: The participant is asked to connect dots marked with ascending numbers in Part A or alternating numbers and letters (e.g. 1-A-2-B-3…) in Part B. When a mistake is made, the participant is asked to correct it. Time for completion of both parts is the parameter of interest. Values above commonly used cut-off thresholds (180s for TMT-A, 300s for TMT-B) were excluded during a plausibility check before data analysis. Part A is considered to be a measure of visual search and motor speed, whereas part B measures executive functions including cognitive alternation, working memory and attention (Bowie and Harvey, 2006; Crowe, 1998).

GPT: The participant is asked to insert 25 pegs with a key alongside into wholes in a board. The key slots are rotated randomly, demanding visual-motor coordination skills and manual dexterity (Otten et al., 2012). Test parameter of interest is the time for completion with the dominant hand. Data from participants who exceeded a limit of 300 s for this task were excluded during the plausibility check.