Neuropsychologia 53 (2014) 54–63

Contents lists available at ScienceDirect

Neuropsychologia

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

Association of basal forebrain volumes and cognition in normal aging

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ARTICLE INFO

Article history:
Received 23 July 2013
Received in revised form
29 October 2013
Accepted 8 November 2013
Available online 21 November 2013

Keywords:
Basal forebrain cholinergic system
Brain resilience
Cognition
General intelligence
Normal aging
Nucleus basalis of Meynert

ABSTRACT

The basal forebrain cholinergic system (BFCS) is known to undergo moderate neurodegenerative alterations during normal aging and severe atrophy in Alzheimer's disease (AD). It has been suggested that functional and structural alterations of the BFCS mediate cognitive performance in normal aging and AD. But, it is still unclear to what extend age-associated cognitive decline can be related to BFCS in normal aging. We analyzed the relationship between BFCS volume and cognition using MRI and a comprehensive neuropsychological test battery in a cohort of 43 healthy elderly subjects spanning the age range from 60 to 85 years.

Most notably, we found significant associations between general intelligence and BFCS volumes, specifically within areas corresponding to posterior nuclei of the nucleus basalis of Meynert (Ch4p) and the nucleus subputaminalis (NSP). Associations between specific cognitive domains and BFCS volumes were less pronounced. Supplementary analyses demonstrated that especially the volume of NSP but also the volume of Ch4p was related to the volume of widespread temporal, frontal, and parietal gray and white matter regions. Volumes of these gray and white matter regions were also related to general intelligence. Higher volumes of Ch4p and NSP may enhance the effectiveness of acetylcholine supply in related gray and white matter regions underlying general intelligence and hence explain the observed association between the volume of Ch4p as well as NSP and general intelligence. Since general intelligence is known to attenuate the degree of age-associated cognitive decline and the risk of developing late-onset AD, the BFCS might, besides the specific contribution to the pathophysiology in AD, constitute a mechanism of brain resilience in normal aging.

1. Introduction

The basal forebrain cholinergic system (BFCS) provides the major cholinergic projections to cortical and limbic structures (Mesulam, 1996). The cholinergic neurons of this complex have been shown to be selectively vulnerable to degeneration in Alzheimer's disease (AD). Several postmortem studies of AD patients demonstrated severe neurofibrillary degeneration and cell loss within the BFCS, most pronounced in the nucleus basalis of Meynert (NBM) (Arendt, Bigl, Tennstedt, & Arendt, 1985; McGeer, McGeer, Suzuki, Dolman, & Nagai, 1984; Sassin et al., 2000; Vogels et al., 1990; Whitehouse, Price, Clark, Coyle, & DeLong, 1981). Moreover, first MRI-based in vivo studies in AD patients revealed severe atrophy of the BFCS (Grothe, Heinsen, & Teipel, 2012a, 2012b; Hanyu et al., 2002; Muth et al., 2010; Teipel et al., 2005, 2010). Atrophic and neurodegenerative changes of the BFCS have also been reported in normal aging (Grothe et al., 2012a, 2012b; Lowes-Hummel, Gertz, Ferszt, & Cervos-Navarro, 1989; Mann, Yates, & Marcyniuk, 1984; McGeer et al., 1984). However, atrophic alterations were less pronounced than in AD (Grothe et al., 2012a, 2012b).

About 30 years ago, Bartus (2000) suggested that functional disturbances in cholinergic activity may contribute to memory dysfunction and related cognitive impairments in normal aging and AD—a theory known as the “cholinergic hypothesis”. Up to now, several lines of evidence support this theory. In AD patients it has been shown that the extent of cholinergic dysfunction is associated with dementia severity, suggesting that cholinergic degeneration is at least in part responsible for cognitive impairments in AD (Baskin et al., 1999; Pappas, Bayley, Bui, Hansen, & Thal, 2000). Further studies demonstrated that cholinergic lesions in AD are related to specific cognitive impairments in memory and attention (Bartus, 2000; Muir, 1997; Sarter, Bruno, & Givens, 2003). Pharmacological investigations revealed that the application of acetylcholinesterase (AChE) inhibitors enhanced cognitive function

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http://dx.doi.org/10.1016/j.neuropsychologia.2013.11.002

in AD patients (Birks, 2012). In normal aging, comparable results have been reported (Dumas & Newhouse, 2011). The cholinergic system has been implicated in several aspects of cognition, including attention, working memory, inhibition of irrelevant information, and improved performance on effortful tasks.

However, despite this large number of studies supporting the cholinergic hypothesis, the data on the relationship between the cholinergic system and cognitive function in normal aging and AD are not as homogeneous as these studies might implicate. In AD patients, evidence of only modest improvements of cognitive symptoms after the application of AChE inhibitors, as well as evidence of the existence of nonresponders, cast doubts on the cholinergic hypothesis (Dumas & Newhouse, 2011). Some results of pharmacological interventions in healthy elderly also stand in contrast to the hypothesis by reporting that AChE inhibitors have not been successful in reversing cognitive deficits related to normal aging (Drachman, Glosser, Fleming, & Longenecker, 1982). Apart from pharmacological interventions, animal studies demonstrated limited or a complete lack of effects of selective cholinergic lesions on memory functions (e.g. (Baxter, Bucci, Gorman, Wiley, & Gallagher, 1995; Wenk, Stoehr, Quintana, Mobley, & Wiley, 1994)). Since the most robust association between the cholinergic system and a specific cognitive domain was reported for attentional processes, several authors hypothesized that the effect of the cholinergic system on other cognitive domains may be mediated by its effects on attentional capacity (Bartus, 2000; Sarter et al., 2003).

The recent introduction of stereotaxic cytoarchitectonic maps of the basal forebrain cholinergic nuclei, based on magnetic resonance imaging (MRI) and histological sections of postmortem brains (Teipel et al., 2005; Zaborszky et al., 2008), provides new possibilities for in vivo automated morphometric analyses of the BFCS and for the study of the BFCS and cognitive performance in healthy and pathological aging. The current study was conducted to analyze the relationship between the volume of the BFCS, as measured by automated morphometry techniques based on high-dimensional image warping and a cytoarchitectonic map of basal forebrain cholinergic nuclei, and cognition, including general intelligence and a broad range of specific cognitive domains (attention, memory, processing speed, executive function, and logical reasoning), in healthy elderly. Furthermore, in order to gain deeper insights in the underlying mechanism of associations between BFCS volumes and cognition, we subsequently investigated the role of regional cerebral gray and white matter (GM, WM) volumes in the relationship between BFCS volumes and cognition.

2. Materials and methods

2.1. Subjects

Participants were recruited by advertisements posted in the University Medical Center of the Johannes Gutenberg University Mainz, several public institutions, and via newspaper announcement. Interested subjects underwent a psychiatric screening interview (Diagnostic expert system for psychiatric disorders—Stamm Screening Questionnaire; DIA-SSQ (Wittchen & Pfister, 1997)) in combination with IDCL (International Diagnostic Checklists for ICD-10 and DSM-IV) (Hiller, Zaudig, & Mombour, 1997). Subjects were excluded if they had a history of psychiatric, neurologic or cognitive disease or if they were taking medications that could alter cognitive performance. The study group finally included 43 healthy elderly subjects (age range 60–85 years). Sample characteristics are shown in Table 1. The study has been approved by the local Ethics Committee and all subjects provided written informed consent.

2.2. MRI acquisition

MRI images of the brain were acquired on a 3-Tesla Siemens TrioTim scanner (Siemens, Erlangen, Germany) using a high-resolution T1-weighted magnetization prepared rapid gradient echo sequence (MP-RAGE; matrix dimensions: 256 × 256 mm; spatial resolution: 0.8 × 0.8 × 0.8; repetition-time: 1.770 ms; echo time: 2.38 ms; inversion time: 900 ms; flip angle: 15°; number of slices: 224). Apart from the high resolution MPRAGE sequence, PD/T2 weighted, fluid attenuated inversion recovery (FLAIR) weighted, and Time-of-Flight (TOF) sequences were applied to identify currently existing brain pathology, including brain tumors and lacunar or silent infarcts. None of the included subjects had to be excluded based on this screening. Furthermore, in order to assure that white matter hyperintensities are independent of the volume of the BFCS, we calculated correlation coefficients between individual total white matter hyperintensitiy volumes and volumes of the BFCS sub-ROIs. None of the volumes of the BFCS sub-ROIs were significantly related to the total volume of white matter hyperintensities.

Table 1
Demographic, neuropsychological, and ROI-based characteristics of the study group ($N=43$).

	Mean (SD)
Demographic characteristics	
Age	70.02 (7.75)
Education years	12.23 (3.21)
Gender	
Male	18 (42%)
Female	25 (58%)
Neuropsychological characteristics	
WAIS-R IQ	138 (15.62)
VLMT 1–5 (number of correct responses)	51.19 (9.48)
VLMT recognition (number of correct responses)	10.09 (2.85)
WMS-R digit span (number of correct responses)	14.40 (3.13)
WMS-R block span (number of correct responses)	14.56 (2.77)
LPS4 (number of correct responses)	24.09 (3.93)
TV-L (number of correct responses)	15.21 (2.48)
TMT-B (seconds)	91.05 (32.75)
TAP—tonic alertness (milliseconds)	284.54 (89.04)
TAP—phasic alertness (milliseconds)	0.07 (0.08)
TAP—divided attention (milliseconds)	739.54 (93.02)
TMT-A (seconds)	36.62 (11.57)
BFCS volumes (TIV corrected)	
Total BFCS volume (mm^3)	336.18 (22.61)
BFCS sub-volumes	
Ch2 volume (mm^3)	46.14 (3.55)
Ch3 volume (mm^3)	91.15 (7.51)
Ch4p volume (mm^3)	58.17 (4.43)
Ch4a_i volume (mm^3)	70.36 (6.05)
NSP volume (mm^3)	63.43 (5.64)

Continuous variables are represented as mean (SD) and categorical variables as number (%).
Abbreviations: WAIS-R IQ=intelligence scores of Wechsler-adult-intelligence-scale-revised; VLMT=German version of the auditory verbal learning test; WMS-R=Wechsler-memory-scale-revised; LPS4=subtest for nonverbal reasoning of a German standardized intelligence scale; TV-L=Tower of London; TMT-B=trail-making-test-B; TAP=test battery for attention performance; TMT-A=trail-making-test-A; TIV=total intracranial volume; BFCS=basal forebrain cholinergic system; Ch2 (nucleus of the vertical limb of the diagonal band), Ch3 (nucleus of the horizontal limb of the diagonal band), Ch4p (posterior part of the nucleus basalis Meynert), Ch4a_i (anterior and intermediate parts of the nucleus basalis of Meynert), NSP (nucleus subputaminalis)=sub-regions of basal forebrain cholinergic system.

2.3. MRI processing

MPRAGE scans were processed using Statistical Parametric Mapping toolboxes (SPM8, Wellcome Trust Centre for Neuroimaging, University College London, England) running on Matlab R2010b (The MathWorks Inc., Natick, Massachusetts). First, images were segmented into different tissue classes using the revised unified segmentation routine of SPM8 (Ashburner & Friston, 2005). The resulting tissue probability maps included GM, WM, cerebrospinal fluid (CSF), and three sets of non-brain partitions. Based on the resulting GM partitions, a GM template was generated through a high-dimensional iteratively non-linear registration using Differomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL (Ashburner, 2007a, 2007b)). The GM template was normalized to MNI space and the resulting deformations were applied to the individual GM segments of each participant. Voxel values were modulated to preserve the original amount of GM volume present before normalization and images were smoothed with a 4 mm FWHM Gaussian filter.