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Research Report

Basal forebrain integrity and cognitive memory profile in healthy aging

Sandra Düzel[a], *Thomas F. Münte*[d], *Ulman Lindenberger*[e], *Nico Bunzeck*[c], *Hartmut Schütze*[b], *Hans-Jochen Heinze*[a], *Emrah Düzel*[b,c,f,*]

[a]*Department of Neurology, Otto-von-Guericke University, Leipziger Str. 44, 39120 Magdeburg, Germany*
[b]*Institute of Cognitive Neurology and Dementia Research, Otto-von-Guericke University, Leipziger Str. 44, 39120 Magdeburg, Germany*
[c]*Institute of Cognitive Neuroscience, University College London, 17 Queen Square, London, WC1N 3AR, UK*
[d]*Department of Psychology II, Neuropsychology Unit, Otto-von-Guericke University Magdeburg, Germany*
[e]*Center for Lifespan Psychology, Max Planck Institute for Human Development, Lentzeallée 94, D-14195 Berlin, Germany*
[f]*German Centre for Neurodegenerative Disorders Magdeburg, Otto-von-Guericke University Magdeburg, Germany*

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ABSTRACT

Age-related dysfunctions in cholinergic and dopaminergic neuromodulation are assumed to contribute to age-associated impairment of explicit memory. Both neurotransmitters also modulate attention, working memory, and processing speed. To date, in vivo evidence linking structural age-related changes in these neuromodulatory systems to dysfunction within or across these cognitive domains remains scarce. Using a factor analytical approach in a cross-sectional study including 86 healthy older (aged 55 to 83 years) and 24 young (aged 18 to 30 years) adults, we assessed the relationship between structural integrity—as measured by magnetization transfer ratio (MTR)—of the substantia nigra/ventral tegmental area (SN/VTA), main origin of dopaminergic projections, basal forebrain (major origin of cortical cholinergic projections), frontal white matter (FWM), and hippocampus to neuropsychological and psychosocial scores. Basal forebrain MTR and FWM changes correlated with a factor combining verbal learning and memory and working memory and, as indicated by measures of diffusion, were most likely due to vascular pathology. These findings suggest that frontal white matter integrity and cholinergic neuromodulation provide clues as to why age-related cognitive decline is often correlated across cognitive domains.

1. Introduction

Age-related decline in learning and memory, often termed age-associated memory impairment (AAMI) (Crook et al., 1986), is a well-documented finding in healthy older adults (Balota et al., 2000; Cabeza et al., 2000; Craik, 1994; Salthouse, 2003), but the neurobiological correlates of this decline are still under debate. A consistent pattern of AAMI is a decrement in declarative memory (Tulving, 1985) most clearly apparent in impaired free recall and recollection (Buckner, 2004; Craik, 2006; Hedden and Gabrieli, 2004; Nilsson, 2003). Evidence from lesion studies in humans and animals indicates that

* *Corresponding author*. Institute of Cognitive Neuroscience, University College London, 17 Queen Square, London WC1N 3AR, UK. Fax: + 44 (0)20 79168517.
E-mail address: e.duzel@ucl.ac.uk (E. Düzel).

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declarative memory is critically dependent on the integrity of the medial temporal lobe (MTL) structures, including the hippocampus and adjacent rhinal cortex (Abe et al., 2004; Mishkin et al., 1997) and the prefrontal cortex (Stuss and Levine, 2002). Therefore, recent studies have sought to investigate the relationship between structural age-related degeneration of gray and white matter in these regions and learning and recall (Brickman et al., 2007; Buckner, 2004; Craik, 2006; Mungas et al., 2005; Schiltz et al., 2006). However, it has also been pointed out that AAMI is not only a result of degeneration of prefrontal and MTL regions but also a result of age-related dysfunction in cholinergic (Mesulam, 2004b) and dopaminergic (DA) (Backman et al., 2006) neuromodulation. The focus of the present study is on these neuromodulatory influences.

An important issue in this context is the observation that, aside from declarative memory, other cognitive faculties also show age-related decline and have been shown to be correlated with learning and memory performance in aging, in particular measures of executive functions (Kray and Lindenberger, 2000; Parkin and Java, 1999), working memory (Baddeley et al., 1999), and processing speed (Salthouse, 2000). A correlated dysfunction across different cognitive domains could indicate distributed structural degeneration such that the different brain regions mediating different cognitive functions undergo correlated age-related degeneration. Another possibility that could act either in isolation or in addition to a distributed pathology could be dysfunction in neuromodulation. Major cholinergic and dopaminergic projections originate in circumscribed brain regions of the basal forebrain and the midbrain but critically modulate function in distributed brain regions and across several cognitive domains. Relatively localized structural changes in the origins of cholinergic and dopaminergic neuromodulation could thus have widespread and relatively unspecific cognitive consequences.

Both dopaminergic and cholinergic neuromodulation play a critical role in learning and recall. There is converging evidence that dopamine plays a role not only in reinforcement learning but also in hippocampus-dependent declarative memory formation (Adcock et al., 2006; Lisman and Grace, 2005; Schott et al., 2006; Wittmann et al., 2005). As in animals (Lisman and Grace, 2005), also the human SN/VTA responds to stimulus novelty even in the absence of reward (Bunzeck and Duzel, 2006). These data provide evidence in favor of a recent model suggesting a functional hippocampal–SN/VTA loop of novelty processing and encoding (Lisman and Grace, 2005). Prefrontal dopaminergic neuromodulation is also held to be critical for attention (Robbins and Roberts, 2007) and for the ability to maintain and manipulate stimulus information online in working memory (Wang et al., 2004; Williams and Goldman-Rakic, 1995). Cortical and hippocampal cholinergic innervation derives almost exclusively from the basal forebrain (medial septal nucleus, diagonal Band of Broca and Nucl. Basalis of Meynert, NBM) (Mesulam, 2004a). A number of pharmacological and lesion studies in humans and animals show that cholinergic neuromodulation is critical for learning and memory (Chudasama et al., 2004; Drachman and Leavitt, 1974; Sarter et al., 2005; Tang et al., 1997; Turchi et al., 2005; Warburton et al., 2003) and for regulating and maintaining attention possibly by enhancing the response to sensory input (Hasselmo and Giocomo, 2006; Mesulam, 2004a). Also, cholinergic neuromodulation is implicated in the ability to maintain stimulus information online in working memory (Hasselmo and Stern, 2006). Both dopaminergic and cholinergic neuromodulation undergo age-related degeneration (for reviews, see Backman et al. (2006)). Human autopsy data indicate a 3% age-related decrease in dopamine D1 (Cortes et al., 1989; Rinne et al., 1990; Seeman et al., 1987) and D2 receptors (Seeman et al., 1987) per decade. There is a 2% to 6% loss of dopaminergic neurons in the SN/VTA per decade (Fearnley and Lees, 1991), and this loss is correlated with the decrease in striatal dopamine availability (Snow et al., 1993). In older adults, behavioral deficits in episodic memory are better accounted for by D2 receptor binding than by age (Backman et al., 2000). Recently, Bunzeck et al. (2007) quantified age-related structural degeneration of the mesolimbic system in healthy elderly using magnetization transfer ratio (MTR) and correlated it with mesolimbic hemodynamic responses (HRs) to stimulus novelty. Their findings support the model of a hippocampal–SN/VTA loop of mesolimbic novelty processing by showing that the hemodynamic activation in SN/VTA and hippocampus for novelty is selectively affected by age-related degeneration of these structures. In the cholinergic system, neurons in the NBM are very prone to accumulate neurofibrillary tangles (Mesulam, 2004a,b), such that tangles in this region are also observed in healthy elderly people (Mesulam, 2004b; Sassin et al., 2000). Even in the absence of neuronal loss, the accumulation of such tangles in the NBM can be associated with a decrease in cholinergic neurotransmission as revealed by postmortem counts of cholinergic axons (Geula and Mesulam, 1989) and by in vivo SPECT mapping of cholinergic terminals (Kuhl et al., 1996). In animal studies (e.g., Weible et al., 2004; Woodruff-Pak et al., 2001) and in patients with Alzheimer's disease cognitive improvement can be achieved by nicotinergic as well as muscarinic receptor action (Oh et al., 2005; Raskind et al., 2000; Tariot et al., 2000).

To our knowledge, it is so far unclear whether in vivo age-related structural changes of cholinergic and dopaminergic projection systems provide an explanation for the unspecific nature of age-related cognitive impairment in aging. To address this issue, we investigated to what extent degeneration of SN/VTA and basal forebrain as quantified using MTR (Bunzeck et al., 2007) is related to age-associated decline in list learning and recall, working memory span, processing speed, and attention.

Another important aspect in studying the relationship between cognitive performance and brain structure is to control for non-cognitive variables related to health and lifestyle. It is possible that cognitive function and brain structure are cumulatively affected by individual health behavior, years of education, wealth, the ability to cope with stress, personality traits, and indicators of physical health such as body mass index (BMI) (Backman et al., 2006; Colcombe et al., 2003; Craik, 2006; Lindenberger and Baltes, 1997; Salthouse, 2003; Singh-Manoux et al., 2004; Smith, 2003; Springer et al., 2005). Therefore, we also examined the influence of psychosocial and physical health factors on cognitive and structural variables. We used a factor analytical approach to determine which cognitive and psychosocial functions undergo correlated changes in a group of healthy