Neuropsychologia 46 (2008) 3042–3052

Contents lists available at ScienceDirect

Neuropsychologia

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

A close relationship between verbal memory and SN/VTA integrity in young and older adults

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ARTICLE INFO

Article history:
Received 24 January 2008
Received in revised form 2 June 2008
Accepted 8 June 2008
Available online 12 June 2008

Keywords:
Substantia nigra/VTA
Hippocampus
White matter integrity
Diffusion
Anisotropy
Verbal memory
CVLT

ABSTRACT

Age-related dysfunction in dopaminergic neuromodulation is assumed to contribute to age-associated memory impairment. However, to date there are no in vivo data on how structural parameters of the substantia nigra/ventral tegmental area (SN/VTA), the main origin of dopaminergic projections, relate to memory performance in healthy young and older adults. We investigated this relationship in a cross-sectional study including data from the hippocampus and frontal white matter (FWM) and also assessing working memory span and attention. In groups of young and older adults matched for the variance of their age distribution, gender and body mass index, we observed a robust positive correlation between Magnetization Transfer Ratio (MTR) – a measure of structural integrity – of the SN/VTA and FWM with verbal learning and memory performance among older adults, while there was a negative correlation in the young. Two additional imaging parameters, anisotropy of diffusion and diffusion coefficient, suggested that in older adults FWM changes reflected vascular pathology while SN/VTA changes pointed towards neuronal loss and loss of water content. The negative correlation in the young possibly reflected maturational changes. Multiple regression analyses indicated that in both young and older adults, SN/VTA MTR explained more variance of verbal learning and memory than FWM MTR or hippocampal MTR, and contributed less to explaining variance of working memory span. Together these findings indicate that structural integrity in the SN/VTA has a relatively selective impact on verbal learning and memory and undergoes specific changes from young adulthood to older age that qualitatively differ from changes in the FWM and hippocampus.

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 old adults (Balota, Dolan, & Duchek, 2000; Craik, 1994; Grady & Craik, 2000; Salthouse, 2003) but the neurobiological underpinnings of this decline are still under debate. A consistent pattern of AAMI is a decrement in episodic memory (Tulving, 1985) apparent in impaired free recall and recollection (Buckner, 2004; Craik, 2006; Hedden & Gabrieli, 2004; Nilsson, 2003). Evidence from lesion studies in humans and animals indicate that episodic memory is critically dependent on the integrity of the medial temporal lobes (MTL) (Mishkin, Suzuki, Gadian, & Vargha-Khadem, 1997; Squire, Stark, & Clark, 2004) and the prefrontal cortex (Stuss & Levine, 2002). Therefore, recent studies have sought to investigate the relationship between structural age-related degeneration of grey and white matter in these regions and learning and recall (Brickman, Habeck, Zarahn, Flynn, & Stern, 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 medial temporal brain regions, but also a result of age-related dysfunction in their dopaminergic (DA) (Backman, Nyberg, Lindenberger, Li, & Farde, 2006) neuromodulation, a finding that can potentially motivate

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doi:10.1016/j.neuropsychologia.2008.06.001

new pharmacological treatment strategies for age-related memory dysfunction. The focus of the present study is on these neuromodulatory influences.

Investigations into the relationship between dopamine and AAMI have been fuelled recently by improved understanding of the role that dopamine plays in memory formation (Lisman & Otmakhova, 2001) and the age-related degeneration of dopaminergic circuitry (Backman et al., 2000; Backman et al., 2006). There is converging evidence that dopamine is not only critically involved in reinforcement learning but also in hippocampus-dependent episodic memory formation (Lisman & Grace, 2005). Functional anatomical evidence for the role of dopaminergic midbrain in episodic encoding comes from recent studies using functional magnetic resonance imaging (fMRI). Reward-related activation of the substantia nigra/ventral tegmental area (SN/VTA), the origin of dopaminergic neuromodulation, is associated with improved hippocampus-dependent long-term memory formation and possibly consolidation (Adcock, Thangavel, Whitfield-Gabrieli, Knutson, & Gabrieli, 2006; Wittmann et al., 2005). Encoding-related midbrain activation also occurs independently of reward (Schott et al., 2006). Indeed, as in animals (Lisman & Grace, 2005), also the human SN/VTA responds to stimulus-novelty in the absence of reward (Bunzeck & Duzel, 2006). These data provide evidence in favour of a recent model suggesting a functional hippocampal-SN/VTA loop of novelty-processing and encoding (Lisman & Grace, 2005). Furthermore, dopamine plays a critical role in regulating the subcortical flow of information between medial temporal structures such as the hippocampus and prefrontal cortex (Grace, Floresco, Goto, & Lodge, 2007). Hence, dopaminergic dysfunction in aging should impact on novelty processing, long-term consolidation as well as on learning tasks that depend on the functional interplay between prefrontal and medial temporal brain regions.

What makes this functional relationship between SN/VTA activity and memory formation particularly relevant for aging research is that dopaminergic neuromodulation undergoes age-related degeneration (for a review see Backman et al., 2006). Human autopsy data indicate a 3% age-related decrease in dopamine D1 (Cortes, Gueye, Pazos, Probst, & Palacios, 1989; Rinne, Lonnberg, & Marjamaki, 1990; Seeman et al., 1987) and D2 receptors (Seeman et al., 1987) per decade. There is a 2–6% loss of dopaminergic neurons in the SN per decade (Fearnley & Lees, 1991a) and this loss is correlated with the decrease in striatal dopamine availability (Snow et al., 1993). In older adults, behavioural 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.

Magnetization transfer in tissue relates to the exchange of proton magnetization between mobile water protons and protons that are immobilized by macromolecules (Wolff & Balaban, 1989). MTR reductions have been observed in the SN in patients with Parkinson's disease (PD) (Eckert et al., 2004; Seppi & Schocke, 2005). PD is characterized by a selective depletion of dopaminergic, neuromelanin-containing neurones of the SN (pars compacta). Neuromelanin is the dark insoluble macromolecule that confers the black colour to the SN. Neuronal loss as well as degradation of the neuromelanin macromolecule scaffolding (Fasano, Bergamasco, & Lopiano, 2006) could lead to a reduction of MTR and it is conceivable that both mechanisms could also lead to some reduction in MTR in apparently healthy older adults who do not have PD. Together with our recent observation that SN/VTA MTR is correlated with the magnitude of hemodynamic novelty responses in the mesolimbic system (Bunzeck et al., 2007), these properties make MTR an interesting imaging modality for studying the relationship between structural SN/VTA integrity and memory in aging.

In the present study we investigated whether degeneration of components of the mesolimbic system (SN/VTA and hippocampus) as quantified by MTR is related to age-associated decline in list learning and recall. To that end, we matched a group of 21 older adults (mean age of 65 years) and 21 younger adults with respect to the variance of their age distribution, their gender, and, to minimize differences in health status also body mass index (Table 1). Given that SN/VTA and the hippocampus although being grey matter structures also contain white matter, we used frontal white matter as a 'reference' region for the structural integrity of white matter tracts. We hypothesized that integrity of the SN/VTA is correlated positively with verbal learning because dopaminergic dysfunction should impact on novelty processing – an early stage of declarative long-term memory encoding (Tulving, Markowitsch, Craik, Habib, & Houle, 1996) – as well as the functional interplay between prefrontal and medial temporal brain regions. A widely used example of a verbal learning and memory task, the California verbal Learning and Memory task (Delis, Kramer, Kaplan, & Ober, 1987), was used here. Alternatively, degeneration in this region might have a less selective impact and might also impair working memory and attention. The issue of specificity is of general importance as it is still unclear to what extent certain neurobiological changes in aging specifically influence learning and memory in comparison to other cognitive faculties that 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 & Lindenberger, 2000; Lindenberger, Marsiske, & Baltes, 2000; Parkin & Java, 1999), working memory (Baddeley, Cocchini, Della Sala, Logie, & Spinnler, 1999) and processing speed (Salthouse, 2000).

2. Methods

2.1. Participants

86 older adults aged above 55 (mean age = 65 years, age range = 55–82 years, S.D. = 5.6 years, 36 males) and 21 young adults aged between 18 and 30 (mean age = 23 years, age range = 21–30 years, S.D. = 2.2 years, 8 males) participated in the study. All participants were native speakers of German. Exclusion criteria for both groups were a history of neurological and psychiatric disorders, cerebral vascular disease, drug addiction, metabolic diseases like diabetes mellitus, metallic implants, tinnitus, obesity, a Geriatric Depression Scale with a depression score of more the five points (GDS ranges from 0 to 15; scores of higher than 11 indicate depression), a Mini-Mental State lower than 27 (MMSE ranges from 0 to 30; scores of lower than 25 are taken as indicators of pathology), and severe untreated hypertonia. Individuals with mild hypertonia according to the World Health Organization (WHO) and International Society of Hypertonia (ISH) classification (WHO & ISH, 1999) of hypertonia who were treated with one antihypertensive medication were eligible for participation in the study. The Local Ethics Committee of the University of Magdeburg (Germany) approved the study. All participants gave written informed consent.

2.2. Procedure

Participants were recruited using local newspaper announcements. Initial screening for exclusion or inclusion criteria was done using a structured phone interview with around 120 volunteers. 100 eligible volunteers were invited for neuropsychological and psychosocial assessment. After neuropsychological testing (duration of 90 min) participants completed psychosocial interviews and questionnaires (duration of 40 min) the results of which will be reported elsewhere. Immediately after neuropsychological and psychosocial testing all participants underwent Doppler-sonography of the extra- and intracranial vessels by a trained neurologist. Blood pressure was measured bilaterally, and a blood sample was taken for genetic studies (results are not reported here). If none of the exclusion criteria was met and audition and corrected vision was sufficient to allow neuropsychological testing, MR imaging was conducted within a week after neuropsychological and psychosocial assessment. After inspecting proton-density and T2 weighted MR