NeuroImage 153 (2017) 211–220

Contents lists available at ScienceDirect

NeuroImage

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

Dopamine and memory dedifferentiation in aging

Hunar Abdulrahman [a,*], Paul C. Fletcher [b,c], Edward Bullmore [b,c,d], Alexa M. Morcom [e]

[a] MRC Cognition & Brain Sciences Unit, University of Cambridge, Cambridge, CB2 7EF, UK
[b] Brain Mapping Unit, Department of Psychiatry, Behavioural and Clinical Neuroscience Institute, University of Cambridge, Robinson Way, Cambridge CB2 0SZ, UK
[c] Cambridge and Peterborough Foundation trust, Fulbourn Hospital, Cambridge CB21 5EF, UK
[d] GlaxoSmithKline, ImmunoPsychiatry, Alternative Discovery & Development, Stevenage SG1 2NY, UK
[e] Centre for Cognitive Ageing and Cognitive Epidemiology, Psychology, University of Edinburgh, Edinburgh EH8 9JZ, UK

ARTICLE INFO

Article history:
Received 19 December 2014
Accepted 14 March 2015
Available online 21 March 2015

Keywords:
Aging
Dedifferentiation
Episodic memory
Hippocampus
Prefrontal cortex
Dopamine

ABSTRACT

The dedifferentiation theory of aging proposes that a reduction in the specificity of neural representations causes declines in complex cognition as people get older, and may reflect a reduction in dopaminergic signaling. The present pharmacological fMRI study investigated episodic memory-related dedifferentiation in young and older adults, and its relation to dopaminergic function, using a randomized placebo-controlled double-blind crossover design with the agonist Bromocriptine (1.25 mg) and the antagonist Sulpiride (400 mg). We used multi-voxel pattern analysis to measure memory specificity: the degree to which distributed patterns of activity distinguishing two different task contexts during an encoding phase are reinstated during memory retrieval. As predicted, memory specificity was reduced in older adults in prefrontal cortex and in hippocampus, consistent with an impact of neural dedifferentiation on episodic memory representations. There was also a linear age-dependent dopaminergic modulation of memory specificity in hippocampus reflecting a relative boost to memory specificity on Bromocriptine in older adults whose memory was poorer at baseline, and a relative boost on Sulpiride in older better performers, compared to the young. This differed from generalized effects of both agents on task specificity in the encoding phase. The results demonstrate a link between aging, dopaminergic function and dedifferentiation in the hippocampus.

Introduction

The dedifferentiation theory of cognitive aging proposes that there is a loss of specificity of neural representations as people become older. These pervasive changes are assumed to impact predominantly on the complex cognitive functions which decline the most (Baltes and Lindenberger, 1997; Li et al., 2001). Functional magnetic resonance imaging (fMRI) studies have revealed widespread age-related reductions in the specificity of distributed cortical patterns of activity elicited by different categories of visual stimuli (Carp et al., 2010b; Goh et al., 2010; Park et al., 2004) and different actions (Carp et al., 2011). Preliminary evidence also supports the prediction that dedifferentiation impacts on functions and regions which decline prominently in old age: the visual category-specificity of cortical activity patterns correlates with older adults' fluid processing ability, and varies with working memory load in frontal and parietal cortex (Carp et al., 2010a; Park et al., 2010; Payer et al., 2006). However, little is currently known about the mechanisms of dedifferentiation, nor its impact on episodic memory, one of the cognitive functions most affected by aging. We investigated whether memory representations are less specific in older adults and explored the modulation of memory specificity by dopaminergic drugs.

Normal aging is accompanied by a marked decline in detailed recollection of events, and an increase in false memory (Schacter et al., 1997; Spencer and Raz, 1995). These episodic memory difficulties are typically attributed to declines in the integrity of the prefrontal cortex (PFC) and the hippocampus (e.g., Head et al., 2008; Yonelinas et al., 2007). However, regional age-related changes may be secondary to generalized neural changes such as dedifferentiation. The first aim of the present study was to examine whether the specificity of episodic reinstatement differs according to age. Episodic recollection is thought to involve hippocampal reactivation of stored memory traces which represent events' particular sensory and cognitive properties (Alvarez and Squire, 1994; McClelland et al., 1995). Consistent with this, functional imaging studies show that successful episodic memory retrieval is accompanied by reinstatement of cortical activity associated with the original events (Danker and Anderson, 2010). Studies using multi-voxel pattern analysis (MVPA) have further shown that the specificity of this episodic reinstatement for particular tasks and categories of stimuli varies with strategic

* Corresponding author at: MRC Cognition & Brain Sciences Unit, 15 Chaucer Road, Cambridge, CB2 7EF, UK.
E-mail address: hunar.abdulrahman@mrc-cbu.cam.ac.uk (H. Abdulrahman).

http://dx.doi.org/10.1016/j.neuroimage.2015.03.031
1053-8119/

memory search and with competition between relevant and irrelevant memories, suggesting that it reflects the specificity of recollection (Kuhl et al., 2011; McDuff et al., 2009). Using MVPA, St-Laurent et al. (2014) recently showed less distinctive cortical reinstatement in older adults for individual items. We examined the specificity of distributed patterns of reinstatement for two different encoding task contexts involving semantic and phonological processing (Johnson et al., 2009; Polyn et al., 2005). We then determined the degree to which distinct task-related activity patterns present during encoding were reinstated during subsequent retrieval, predicting that this measure of memory specificity would be reduced in older relative to younger adults.

According to computational models, age-related dedifferentiation may reflect a reduction in dopamine signaling and neural signal-to-noise in prefrontal cortex (PFC; Li et al., 2001), and potentially elsewhere. Modeling dedifferentiation in this way reproduces disruption of episodic binding functions found in older adults (Li et al., 2005). This is in line with wider evidence of a 'correlative triad' between aging, cognition and dopamine function (Bäckman et al., 2006). The second aim of the present study was to extend the findings of our previous report, which examined dopaminergic modulations of brain activity associated with successful episodic encoding across the two encoding tasks (Morcom et al., 2010). The study had a cross-over placebo-controlled design, in which we administered a dopamine agonist (Bromocriptine) and an antagonist (Sulpiride) to manipulate dopamine signaling. Morcom et al. (2010) found age-related differences in dopaminergic effects on activity associated with successful episodic encoding in PFC and hippocampus. This dopaminergic sensitivity was most pronounced in the older adults with poorer memory, consistent with the notion that dopaminergic decline impairs the ability to encode new memories. Specifically, there were reversed subsequent memory (subsequent forgetting) effects within MTL in the older group: i.e., encoding phase activity predicted later forgetting rather than remembering (Morcom et al., 2010). We proposed then that older adults may encode less distinctive memory representations which do not support specific recollection (Morcom et al., 2010; Wagner and Davachi, 2001).

This novel joint analysis of task-specific activity at encoding and its reinstatement at retrieval allowed us directly to test the link between dopamine, aging and dedifferentiation of episodic memory. We predicted that the expected age-related reduction in memory specificity would vary with changes in dopamine signaling. If dopaminergic decline causes dedifferentiation, loss of memory specificity should be dopamine-sensitive. Predictions about the nature of this sensitivity were derived from the results of the successful encoding study (Morcom et al., 2010) and the dopamine aging hypothesis. First, we expected that dopaminergic modulation of memory specificity would track individual differences in memory ability in the older group, and that poorer older performers would show greater dopamine sensitivity, distinguishing them from the young. Second, we predicted that the dopaminergic effect on memory specificity would parallel that previously reported for the univariate memory encoding (subsequent memory) effects. In addition, if the reversed, subsequent forgetting, effects in the older group reflected impaired memory specificity as proposed by Morcom et al. (2010), then Bromocriptine should reduce memory specificity in poorer older performers just as it enhanced subsequent forgetting effects.

Methods

Subjects

Sixteen younger (7 female, mean age = 24.9, SD = 4.7 years) and sixteen older adults (9 female, mean age = 66.9, SD = 3.3 years) contributed data. These comprised all subjects from the previous report on the encoding data, as well as 1 young and 3 older subjects who had not provided sufficient data for that event-related analysis, and 1 older participant who contributed data only for the Placebo session. An additional 3 older subjects and 1 young were excluded due to missing Placebo session data (3 with data acquisition or storage issues, 1 withdrew). Therefore, the Placebo condition analyses included 16 young and 16 older subjects, and the drug analyses included samples of 16 and 15. A further older subject was also excluded from analyses of covariance due to an outlier value for the performance covariate, yielding sample sizes of 16 and 14 (see Results: Task specificity and Feature selection). Volunteers were screened on initial telephone contact using a standard questionnaire. The exclusion criteria were a history of any significant psychiatric or physical condition which was likely to affect the brain or cerebral vasculature, current vasoactive or neurotropic medication, and contraindications to the study drugs or to MRI. Each subject also had an electrocardiogram prior to taking part in functional MRI scanning, reviewed by a physician, as well as a structural scan. The groups were matched on years of education (in young, mean = 4.6, SD = 2.6; in old, mean = 4.0, SD = 3.0; $t < 1$). Estimated verbal IQ using the National Adult Reading Test (Nelson, 1982) was slightly higher in the older group as expected (Backman and Nilsson, 1996); for young, mean = 112, SD = 6.0; for old, mean = 118, SD = 6.5, $t(34) = 2.96$, $p = .006$; for details see Morcom et al. (2010).

Experimental design and task

Subjects took part in 3 experimental sessions in which they received Sulpiride 400 mg, Bromocriptine 1.25 mg, or a Placebo orally, in a randomized double-blind crossover design. The scanned episodic memory task commenced after 3 h, and comprised a study (encoding) phase, followed by 2 test (retrieval) phase blocks. To avoid nausea within the double-blind procedure, the study drug was given with 10 mg of the peripheral dopamine antagonist Domperidone (Reddymasu et al., 2007). Subjects were also asked to eat beforehand. For Sulpiride the mean time to maximal plasma concentration is about 3 h, and it has a plasma half-life of around 12 h, and oral bioavailability of about 35%. Plasma prolactin concentration is maximal after about 1 h, then declines slowly (Wiesel et al., 1982; von Bahr et al., 1991; Caley and Weber, 1995). Bromocriptine's central effects are also long lasting, though somewhat slower to onset than those of Sulpiride, with measurable effects from as early as 1 1/2 h post-dose which maximal after 3 h and persist for some time (Luciana et al., 1998; Müller et al., 1998; Oranje et al., 2004). fMRI data acquisition began at about 3-h post-dose and the sessions were separated by a minimum washout period of a week. Subjects were randomly allocated to each of 6 possible counterbalanced session orders. After exclusions, there were minor imbalances in session ordering between and across age groups. The main analyses are reported with the full N, but we conducted check analyses to rule out possible confounds of session effects: none were found, and effects were if anything more robust once session ordering was balanced. Details of these check analyses are given in the Supplementary material.

Study and test stimuli were 4–9 letter nouns of 1–3 syllables from the CELEX database (http://www.ru.nl/celex/; for details see Morcom et al., 2010). The paradigm is illustrated in Fig. 1. The study phase consisted of 16 "mini-blocks" of 15 trials each. Subjects performed two different orienting tasks, one involving a semantic and one a phonological judgment. Semantic and phonological mini-blocks alternated and each pair was followed by 21 s fixation. This task ordering was counterbalanced across subjects. Semantic mini-blocks were preceded by the cue "Living?" and subjects judged whether each word referred to a living or a non-living