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Research report

Compensation or inhibitory failure? Testing hypotheses of age-related right frontal lobe involvement in verbal memory ability using structural and diffusion MRI

Simon R. Cox [a,b,c,*], Mark E. Bastin [a,b,d], Karen J. Ferguson [b,e], Mike Allerhand [b,c], Natalie A. Royle [a,b,d], Susanna Muñoz Maniega [a,b,d], John M. Starr [b,e,f], Alasdair M.J. MacLullich [b,e,g], Joanna M. Wardlaw [a,b,d], Ian J. Deary [b,c] and Sarah E. MacPherson [b,c]

[a] Brain Research Imaging Centre, University of Edinburgh, Edinburgh, UK
[b] Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh, Edinburgh, UK
[c] Department of Psychology, University of Edinburgh, Edinburgh, UK
[d] Scottish Imaging Network: A Platform for Scientific Excellence (SINAPSE) Collaboration, UK
[e] Geriatric Medicine, University of Edinburgh, Edinburgh, UK
[f] Alzheimer Scotland Dementia Research Centre, University of Edinburgh, Edinburgh, UK
[g] Endocrinology Unit, University of Edinburgh, Edinburgh, UK

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ABSTRACT

Functional neuroimaging studies report increased right prefrontal cortex (PFC) involvement during verbal memory tasks amongst low-scoring older individuals, compared to younger controls and their higher-scoring contemporaries. Some propose that this reflects inefficient use of neural resources through failure of the left PFC to inhibit non-task-related right PFC activity, via the anterior corpus callosum (CC). For others, it indicates partial compensation – that is, the right PFC cannot completely supplement the failing neural network, but contributes positively to performance. We propose that combining structural and diffusion brain MRI can be used to test predictions from these theories which have arisen from fMRI studies. We test these hypotheses in immediate and delayed verbal memory ability amongst 90 healthy older adults of mean age 73 years. Right hippocampus and left dorsolateral prefrontal cortex (DLPFC) volumes, and fractional anisotropy (FA) in the splenium made unique contributions to verbal memory ability in the whole group. There was no significant effect of anterior callosal white matter integrity on performance. Rather, segmented linear regression indicated that right DLPFC volume was a significantly stronger positive predictor of verbal memory for lower-scorers than higher-scorers, supporting a compensatory explanation for the differential involvement of the right frontal lobe in verbal memory tasks in older age.
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* *Corresponding author*. Department of Psychology, University of Edinburgh, 7 George Square, Edinburgh EH8 9JZ, UK.
E-mail address: simon.cox@ed.ac.uk (S.R. Cox).
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1. Introduction

Some aspects of memory functioning decline with age (Craik & Rose, 2012). Functional imaging studies of verbal memory tasks that compare activation patterns between young and older people show that older age is accompanied by "over-recruitment"; that is, greater cortical activation both in the brain regions engaged by young subjects, and also in a more distributed network that has additional regions (reviewed in Craik & Rose, 2012; Goh, 2011; Park & Reuter-Lorenz, 2009). What this over-recruitment might represent is a matter of debate. Some authors have posited that it reflects an attempt to supplement the functioning of a failing network and thus makes a positive compensatory contribution to memory performance (Cabeza, Anderson, Locantore, & McIntosh, 2002; Park & Reuter-Lorenz, 2009). Others propose that such differences could reflect changes that are potentially detrimental to cognitive performance, either through general breakdown in the functional specialization of the cortex (Li, Brehmer, Shing, Werkle-Bergner, & Lindenberger, 2006) or an inability to shut down activity not related to the cognitive task being performed (Logan, Sanders, Snyder, Morris, & Buckner, 2002). However, a breakdown in functional specialisation could also be compatible with a compensatory interpretation of over-recruitment, and as such these cannot be treated as mutually exclusive accounts. In the current study, we propose that the use of structural MRI data can provide an alternative perspective for testing hypotheses on this phenomenon that have arisen from the functional neuroimaging literature.

One brain region that has been shown to exhibit age-related over-recruitment during verbal memory encoding is the right prefrontal cortex (PFC). Activation of the right PFC has been reported in older, but not younger participants, in addition to the expected blood oxygen level dependent (BOLD) response found in the left lateral PFC and bilateral medial temporal lobe in young participants during verbal memory recall tasks (de Chastelaine, Wang, Minton, Muftuler, & Rugg, 2011; Duverne, Motamedinia, & Rugg, 2009; Logan et al., 2002; Morcom & Friston, 2012; Morcom, Good, Frackowiak, & Rugg, 2003; Reuter-Lorenz et al., 2000). Moreover, these additional rightward-frontal activations are not necessarily present in every individual within the older group, but are associated with poorer memory performance (de Chastelaine et al., 2011; Duverne et al., 2009; Persson et al., 2006). In other words, the older individuals who tend to perform more poorly on memory encoding tasks tend also to be the members of their age group who exhibit the greatest additional right PFC activity.

This link between *increased* right frontal BOLD activity and *poorer* memory performance is intuitively more consistent with an inability to direct neural resources to the task being performed than with the view that right PFC makes positive contributions to performance. Some authors have argued that, during verbal memory tasks which are usually supported by strongly lateralised neural activity, reduced callosal integrity facilitates coactivation of homotopic cortex that is detrimental to performance (Buckner & Logan, 2002; Logan et al., 2002). Thus, increased BOLD activity in poorer performers might arise due to an inability of the left frontal lobe to inhibit the right via the anterior corpus callosum (CC). Presumably then, lower volume of the left PFC and integrity of the CC leads to impaired trans-callosal inhibition and additional recruitment of the right PFC found in functional MRI (fMRI) studies. We shall refer to this as the *inhibitory hypothesis*. However, another possible interpretation is that of partial compensation (Duverne et al., 2009; Rossi et al., 2004), which suggests that whatever auxiliary processing is facilitated by the additional activation found in some older people is not sufficient to fully replicate a normally-functioning network, but would lead to much poorer performance if this alternative cognitive route were not available. We shall refer to this as the *partial compensation hypothesis*.

Predictions from these two hypotheses can be formalised and usefully tested by examining the neurostructural correlates of verbal memory performance in older age. We address this question from the following viewpoint: Disruption to one or more components of the large-scale brain network involved in memory may disrupt the state of normal parallel processing necessary to support unhindered performance (Bressler & Menon, 2010; Mesulam, 1990). Accumulated brain insults over the life course may well be such a mechanism of disruption. For each component of the large-scale memory network, such insults can be broadly indexed by individual differences in diffusion and structural MRI measures (white matter tract integrity parameters and regional brain volumes controlled for intracranial volume). We shall therefore use structural brain measures of an *a priori* selection of memory network components (hippocampus, CC and lateral frontal lobe) to test competing accounts of frontal lobe involvement in verbal memory performance among a group of healthy older adults in their early 70s.

We first aim to verify that left frontal lobe, hippocampus and CC constitute parts of a memory network and that each contributes unique variance to memory performance (Bressler & Menon, 2010; Mesulam, 1990). The inhibitory hypothesis would predict positive associations between memory ability and indices of left lateral frontal lobe and anterior CC (genu; Buckner & Logan, 2002; Logan et al., 2002; Persson et al., 2006; Sullivan & Pfefferbaum, 2007). Furthermore, a significant positive relationship between right frontal volume and memory ability would be incompatible with the inhibitory hypothesis, which suggests no benefit to verbal memory performance from a larger right frontal lobe. Conversely, the partial compensation hypothesis (Duverne et al., 2009; Rossi et al., 2004) would assert that larger volume of the area providing auxiliary processing (in this case, the right frontal lobe) would positively associate with memory score, but only for poorer performers, who putatively rely on its compensatory function. Thus, the association between right frontal lobe volume and verbal memory score should be 1) significantly positive in lower, but of no significant benefit to higher performers, and, 2) of a significantly different magnitude between lower and higher performers.

However, using structural MRI variables and cognitive scores does not allow us to parse apart the contributions that brain regions might differentially make to encoding and retrieval phases of a memory task (an undeniable advantage of fMRI). The right frontal lobe has been implicated in monitoring/checking processes during retrieval of some types of

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