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Mnemonic function in small vessel disease and associations with white matter tract microstructure☆

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ABSTRACT

Cerebral small vessel disease (SVD) is associated with deficits in working memory, with a relative sparing of long-term memory; function may be influenced by white matter microstructure. Working and long-term memory were examined in 106 patients with SVD and 35 healthy controls. Microstructure was measured in the uncinate fasciculi and cingula. Working memory was more impaired than long-term memory in SVD, but both abilities were reduced compared to controls. Regression analyses found that having SVD explained the variance in memory functions, with additional variance explained by the cingula (working memory) and uncinate (long-term memory). Performance can be explained in terms of integrity loss in specific white matter tract associated with mnemonic functions.

1. Introduction

Cerebral small vessel disease (SVD) refers to pathological processes that affect the cerebral arterioles, venules, and capillaries resulting in damage to the deep grey matter and white matter tissue (Wardlaw et al., 2013). In SVD, white matter damage reduces the efficiency of grey matter connections, disrupting the neural networks that support cognitive abilities (Lawrence et al., 2014; Shim et al., 2015). Particularly affected in SVD is executive function ability which includes mental flexibility and the ability to monitor performance. There is also impairment in working memory and this contrasts with relative sparing of long-term memory abilities (Brookes et al., 2012). (Please note we are using the definition of episodic long-term memory as described by Tulving, and distinct from working memory (Tulving, 1983)). These mnemonic functions rely on networks across the brain with strong connections to frontal regions (Metzler-Baddeley et al., 2011; Zahr et al., 2009). This paper will focus on white matter tracts that connect frontal to other brain areas and examine whether the relatively spared mnemonic function of long-term memory is associated with the uncinate fasciculi (white matter tracts connecting frontal and temporal lobes). The temporal lobes are often spared white matter damage in spontaneous SVD. This will be contrasted with the mnemonic function of working memory which relies on fronto-parietal connections often disrupted by white matter damage in the centrum semiovale, and often impaired in SVD.

Previous studies in neurotypical adults have demonstrated that working and long-term memory have both shared and unique cognitive features (Moscovitch et al., 2005). Working memory combines both executive and mnemonic function, the cognitive operations associated with it requiring maintenance of information, simultaneous processing and updating (Baddeley, 2012). Long-term memory involves memory for personally experienced events, remembered over a longer period (Kramer et al., 2003). Both abilities require information to be maintained in memory but working memory is more reliant on executive processes, particularly abilities that coordinate central processing resources to manipulate information or maintain it in an active state (Baddeley, 2012). In keeping with these shared and unique cognitive systems, brain networks also demonstrate shared and unique white matter involvement (Charlton et al., 2013). In a tract-based spatial statistic (TBSS) study in typical ageing, the white matter microstructure of the genu of the corpus callosum was associated with both mnemonic abilities, whereas working memory was additionally supported by the cingula and long-term memory by the uncinate fasciculi (Charlton et al., 2013).

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Damage in SVD is focused on the white matter particularly in the centrum semiovale and deep grey matter nuclei, with relative sparing of white matter in the temporal lobes and cortical grey matter (Wardlaw et al., 2013; Shim et al., 2015). The location of such damage is likely to disrupt direct communication pathways between distinct brain regions, and thus be vital to information transfer (Reijmer et al., 2016). Working memory may be particularly affected in SVD due to both the location of damage in the brain, and because performance requires reiterative integration of information across multiple brain regions (Wardlaw et al., 2013; Charlton et al., 2008; O'Sullivan et al., 2004). While executive functions are generally considered to rely more on the prefrontal cortex, working memory has been shown to be supported by fronto-parietal interactions (Ranganath et al., 2003). Thus small amounts of damage to these regions and disruption of important white matter tracts (i.e. the cingula) that support working memory networks may have a disproportionate effect on cognition (Charlton et al., 2010a). Executive function impairments have been frequently described in SVD (Brookes et al., 2012, 2015; Prins et al., 2005), although working memory has not been examined as regularly, poorer performance has been demonstrated (O'Sullivan et al., 2005). Although other studies have examined brain connectivity in SVD (Reijmer et al., 2016), to our knowledge no previous study has directly compared working and long-term memory in SVD with tracts of hypothesised importance.

Whilst long-term memory is generally thought to be relatively spared in the earlier stages of cognitive impairment associated with SVD (O'Sullivan et al., 2005; Schmidtke and Hüll, 2002), studies have demonstrated impairments in performance in sporadic (Prins et al., 2005; Cummings, 1994) and genetic forms of the disease (Buffon et al., 2006). In a population study with follow-up over five years, performance on a list-learning task declined but was not associated with change in white matter hyperintensities or cortical/subcortical atrophy (Prins et al., 2005). Long-term memory has been shown to rely on integration of information across multiple brain regions, including the prefrontal cortex and temporal lobe (Moscovitch et al., 2005; Daselaar et al., 2003). Previous studies have demonstrated that the microstructure of the uncinate fasciculi (connecting frontal and temporal lobes) is associated with long-term memory performance among health older adults and in disease states such as Alzheimer's disease (Bucur et al., 2008; Charlton et al., 2010b; Yasmin et al., 2008). The location of the uncinate fasciculi may mean that it is relatively spared in SVD, as damage in the temporal lobe is not common in spontaneous SVD (although such damage may occur in a genetic form of SVD, namely Cerebral Autosomal-Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy). In contrast, the cingula are located in the sensitive centrum semiovale region (Wardlaw et al., 2013; Charlton et al., 2010a). As yet it is unclear whether long-term memory ability (which is relatively spared in SVD), is associated with the microstructure of the uncinate fasciculi.

Previous studies have demonstrated strong associations between multiple areas of white matter and white matter tracts, with both working and long-term memory (Metzler-Baddeley et al., 2011; Zahr et al., 2009). Two tracts were selected for examination in this study based on their involvement in mnemonic functions and location in areas either typically affected (cingulum) or spared (uncinate) in spontaneous SVD (Wardlaw et al., 2013; Shim et al., 2015; Reijmer et al., 2016). Tracts were selected to be associated with hypothesised functions (see Hypotheses below), and to act as “control” tracts for the alternative function. Working memory relies on fronto-parietal connections and has been associated with the cingulum (Zahr et al., 2009; Charlton et al., 2013, 2010a) which passes through the centrum semiovale. Long-term memory function is associated with microstructure of the uncinate connecting frontal and temporal regions with temporal regions generally being spared in sporadic SVD (Metzler-Baddeley et al., 2011; Charlton et al., 2014). Although the fornix is strongly associated with mnemonic function in both healthy ageing and disease (Metzler-Baddeley et al., 2011; Zahr et al., 2009), it is unclear if this tract is spared or damaged in SVD and does not connect directly to the frontal lobes, therefore was not considered in this analysis.

In this study we examine the associations between the specific mnemonic functions of working and long-term memory and the microstructure of the two white matter tracts (the cingula and uncinate fasciculi) hypothesised to support these functions, in a group of patients with SVD and healthy older adults. We hypothesise that 1) working memory ability will be lower in SVD compared to healthy older adults, whereas long-term memory will be relatively spared, 2) working memory performance will be associated with the microstructure of the cingula, whereas long-term memory performance will be associated with the microstructure of the uncinate fasciculi. Thus in Hypothesis 2, long-term memory will act as a “control” function for the working memory analysis and vice versa, and the uncinate will act as a “control” tract for the cingulum and vice versa.

2. Materials and methods

Ethical approval for this study was obtained from the Wandsworth REC and St George's local research ethics committee. All participants gave informed, written consent.

2.1. Participants

2.1.1. SVD patients

A sample of 121 patients with SVD were recruited to the St George's Cognition and Neuroimaging in Stroke (SCANS) study from stroke services at three South London hospitals (St George's Hospital, St Thomas's Hospital, and King's College Hospital). SVD was defined as a clinical lacunar stroke syndrome (Bamford et al., 1991), with confluent leukoaraiosis (Fazekas Scale, grade 2 or more) on MRI (Fazekas et al., 1987), and with an anatomically appropriate lacunar infarct on MRI. SCANS is a longitudinal study assessing both cognition and brain changes using MRI. Data presented in this paper utilise only baseline data. Baseline MRI scanning and cognitive testing was performed at least three months after any stroke to avoid the influence of acute ischaemia on cognition or MRI. All participating patients were fluent in English. Exclusion criteria in the SCANS study were: any cause of stroke or leukoaraiosis other than SVD, cortical infarcts of any size, sub-cortical infarcts $>$ 1.5 cm, evidence of large artery disease (vertebral, carotid, or intracranial stenosis), any other source of cardiac embolism, major psychiatric disorders (with the exception of depression which was not an exclusion variable), and any other major central neurological system disorders. Participants with contraindications to MRI scanning, including claustrophobia, were also excluded. From the sample of 121 participants, a further 15 were excluded (3 due to missing cognitive measures; 12 due to poor quality images in the DTI sequence and inability to extract one or more white matter tract). The final sample population used for this study was 106 SVD patients.

2.1.2. Healthy older adults

A stroke-free control group was used for comparison with the SVD MRI data. Forty healthy older adults (HOA) were recruited from the four-year follow-up of the longitudinal GENIE (St George's Neuropsychology and Imaging in the Elderly) study (Charlton et al., 2006). GENIE includes neuropsychological assessments and MRI completed at baseline and repeated after 2 and 4 years. Data from the participants at the 4 year follow-up are included in this analysis as MRI acquisition used the same MR scanner as the SCANS project. For full details of the study see (Charlton et al., 2006). In brief, participants were recruited through family doctor lists, were aged 50–90 at baseline, had English as a first language, and were free from any neurological or psychiatric problems. All participants included in this analysis remained cognitively intact with abilities within the normal range and had no evidence of neurological problems. Of the 40 participants, five had incomplete MRI, so the final sample was 35 HOA. The final sample