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Neuroanatomical correlates of verbal fluency in early Alzheimer's disease and normal aging

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ABSTRACT

Verbal fluency (VF) impairments occur early in Alzheimer's disease (AD) and to a lesser extent also in normal aging. However, the neural underpinnings of these impairments are not fully understood. The present study evaluated whether VF impairments in early AD and normal aging rely upon common or different neuroanatomical correlates. We examined the association between VF performance and brain structure in 18 mild AD patients and 24 healthy elderly. Linear regressions were performed between accuracy and time intervals in VF scores and structural measurements of cerebral gray matter (GM) and white matter (WM) using MRI. Results showed that semantic VF correlated exclusively with GM in cerebellum, left temporal fusiform cortex, and WM in uncinate fasciculus, inferior fronto-occipital fasciculus and corpus callosum. Phonemic VF showed unique associations between intervals and WM in left-hemisphere tracts. The association between GM in hippocampus, subcortical structures and semantic accuracy differentiated patients from controls. Results showed that VF impairments are primarily associated with same structural brain changes in AD as in healthy elderly but at exaggerated levels. However, specific VF deficiencies and their underlying neural correlates exist and these clearly differentiate the initial stages of AD.

1. Introduction

Impaired word finding is a cognitive deficit occurring early in Alzheimer's disease (AD). It is usually assessed by verbal fluency (VF) performance, which measures the speed and accuracy of produced words according to phonemic or semantic cues. In the phonemic variant, individuals must generate words starting with a designated letter, while the semantic variant requires generating exemplars from a certain category. All verbal fluency tests (VFT) are time limited to usually 1 min (Benton, 1967). Despite comparable demands on both VFTs, such as sustained attention, strategic search and articulation, each variant also assess exclusive cognitive capacities. Semantic VF better evaluates semantic memory as it relies upon the integrity of conceptual knowledge storage (Henry, Crawford, & Phillips, 2004). In turn, phonemic VF demands higher executive functioning (Bryan & Luszcz, 2000) due to more engagement of working memory processes in the selection and matching of words based on orthographic cues and of inhibitory processes suppressing semantic associations (Shao, Janse, Visser, & Meyer, 2014). Performance across both types of VFTs is significantly impaired early in AD (Laws, Duncan, & Gale, 2010), but semantic VF appears to be particularly affected due to the breakdown of semantic memory (Henry et al., 2004). A decline in VF is also associated with normal aging, but to a lesser degree than in AD (Clark et al., 2009; Kozora & Cullum, 1995). Currently, it is not known whether there is a common cause for the VF impairments in AD and normal aging or if there are different underlying mechanisms.

Functional studies on healthy subjects have shown that VF relies on a network of regions, primarily in the left hemisphere, including the inferior frontal gyrus, fusiform gyrus, caudate, middle frontal gyrus and superior parietal lobe (Birn et al., 2010). There

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is also evidence that the phonemic and semantic fluency utilize slightly different functional networks. Lesion studies have shown that lesions in the temporal lobe affect mainly semantic fluency (Henry & Crawford, 2004; Monsch et al., 1994) while lesions in the frontal lobe tend to affect phonemic fluency more than semantic fluency (Baldo, Shimamura, Delis, Kramer, & Kaplan, 2001; Henry & Crawford, 2004). This is generally supported by fMRI studies contrasting the two types of verbal fluency tasks. Birn et al. (2010) found larger activation for phonemic fluency in the left precentral and inferior frontal gyrus, ventral occipitotemporal cortex bilaterally and superior parietal cortex bilaterally. Whereas semantic fluency had greater activation in occipital cortex, fusiform gyrus bilaterally and left middle frontal gyrus compared to phonemic fluency (Birn et al., 2010). Although VF tends to activate regions primarily in the left hemisphere, healthy older people have a more bilateral activation pattern compared to younger people (Meinzer et al., 2009). To our knowledge, there are no fMRI studies of VF in AD or in the preclinical stage of mild cognitive impairment (MCI).

There are however, crucial differences between the VF tasks used in fMRI studies and the standard VF tasks, which makes a direct comparison problematic. VFTs for fMRI studies need to be adapted for their assessment in scanner conditions. For instance, it could be required that responses are given after a cue, or within short intervals (e.g., 5 s). An alternative approach is therefore, to study neuroanatomical correlates to VF in order to understand the brain networks involved during performance of these tasks. This issue is especially relevant in conditions like AD, where massive brain degeneration exists. For instance, it is known that semantic fluency impairments in AD are related to reduced gray matter (GM) volume in the medial temporal lobes including the hippocampus and left fronto-temporal regions (Dos Santos et al., 2011; Serra et al., 2010; Venneri et al., 2008). Moreover, it has been demonstrated that phonemic fluency impairments are associated with GM volume reduction in the orbitofrontal cortex (Serra et al., 2010), left middle and superior frontal gyri, right inferior frontal gyrus and several regions on the temporal and occipital lobes (Venneri et al., 2008). In early AD, the greater impairment in semantic fluency versus phonemic fluency has been explained by the disproportionate degeneration of temporal lobe structures in relationship to frontal lobe regions (Haugrud, Crossley, & Vrbancic, 2011).

VF performance has also been associated with white matter (WM) integrity. However, the findings are divergent. Some investigators have found among AD and MCI patients an association between semantic fluency and FA in the genu and splenium of corpus callosum as well as with the posterior periventricular WM (Chen et al., 2009; Kavcic, Ni, Zhu, Zhong, & Duffy, 2008). However, others have failed to find any significant association (Serra et al., 2010).

Divergent findings regarding the brain networks involved during VF performance might be explained, to some extent, by the great variation among studies on type of verbal fluency examined and type of parameter employed to assess VF performance. For example, some studies only assess semantic VF (Chen et al., 2009; Kavcic et al., 2008), while other address phonemic VF (Sjobeck et al., 2010) or both (Charlton et al., 2006; Serra et al., 2010).

To understand the neural substrates of VF performance, proper measurements of word generation are required. Usually, most studies only register accuracy scores (correct words) which are then correlated with neuroanatomical parameters. In spite of been a customary procedure, this approach might not be optimal. Sailor and coworkers (Sailor, Antoine, Diaz, Kuslansky, & Kluger, 2004) suggested a detailed analysis comprising intervals (between word latencies) and accuracy data for understanding word retrieval impairments in AD. So far, only accuracy data have been used to correlate with brain neuroanatomy and therefore, we propose that the addition of in-between word intervals is a relevant measure to apprise the common element of processing speed in both VF tests.

Another source of discrepancy regarding the brain-behavior associations of VF performance is the focus on either GM or WM status separately. Although, AD is regarded primarily as a disease affecting cerebral gray matter, white matter degeneration also occurs at preclinical stages (Kehoe, McNulty, Mullins, & Bokde, 2014). In the initial phases, GM loss is restricted to the hippocampus and entorhinal cortex, while WM degeneration occurs in parahippocampal regions as well as in areas connecting directly to medial temporal lobe structures (Salat et al., 2010). Thus, to understand the anatomical correlates contributing to VF impairments in early AD, an evaluation of GM and WM degeneration is necessary. To our knowledge, there are no studies examining the parallel contribution of GM and WM degeneration on altered verbal production in aging and dementia. Therefore, in this study we aimed to better understand the neural correlates of VF tasks among elderly patients at the early stages of AD and a group of healthy older adults. We hypothesize that the involvement of reduced GM volume and WM degeneration will differ between VF tasks due to specific cognitive requirements of each task and between groups due to the brain degeneration in AD.

(1) For semantic VF, we expect a significant association between impaired performance and subcortical GM loss in medial temporal structures in AD patients. We furthermore hypothesize that WM integrity in networks connecting the parahippocampal regions will also be associated with semantic VF impairments. As a whole, we expect that semantic VF correlates positively with a broad network of brain regions reported in previous studies that include bilateral GM and WM in inferior and middle frontal gyri, superior temporal gyri, cerebellum and supplementary motor areas (Meinzer et al., 2009; Nagels et al., 2012).
(2) For the phonemic VF we hypothesize that possible group differences may exist in the degree of association and not in different brain networks associated. Although, frontal areas have been often associated with phonemic VF, we cannot be certain to expect a special correlation between phonemic outcomes and frontal lobe regions as no functional study has yet tested the type of networks underlying phonemic VF in AD or MCI subjects. Nonetheless, based on the literature, elderly samples are expected to show significant correlations between phonemic VF scores and a diffuse network comprising frontal, temporal and parietal regions as well as the cerebellum (Melrose et al., 2009; Zhang et al., 2013).

2. Materials and methods

2.1. Study participants

Participants were recruited for a larger aging study at the University of Tromsø, Norway. Originally 53 individuals were recruited; however seven patients and one control were excluded due to movement artifacts or an incomplete scanning session. Additionally, three more did not complete neuropsychological testing. The final sample included 42 participants; 18 AD patients and 24 healthy elderly controls. The patient group was recruited at the University Hospital of North-Norway from the Neurology and Geriatrics departments. Only mild AD patients with a Mini Mental Score Examination (MMSE) (Folstein, Folstein, & McHugh, 1975) greater than 20 were included in the study. Each patient underwent clinical and neurological examinations including standard check of CSF concentrations of tau, phosphorylated tau and