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Phonemic word fluency is related to temporal and striatal gray matter volume in healthy older adults

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ABSTRACT

Word fluency (WF) tasks that tap verbal and executive function show deteriorating performance by advancing age. To address the scarcely studied age-related brain correlates of WF, we employed whole-brain voxel-based morphometry to examine gray matter (GM) correlates of semantic and phonemic WF in 46 healthy older adults. Lower phonemic WF score was related to smaller anterior medial temporal GM volume as well as smaller GM volume in the putamen bilaterally. A disproportionally weak score on phonemic WF in relation to semantic WF was associated with smaller GM volume in the left inferior frontal cortex, the right anterior medial temporal lobe, and the right striatum. There were no significant associations for semantic WF. The fact that our temporal and subcortical findings were bilateral and right-lateralized, may reflect age-related compensation by these brain areas.

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Voxel-based morphometry; verbal fluency; phonemic word fluency; semantic word fluency; normal aging

Introduction

Age-related cognitive decline varies between different domains: while executive functions (EF; higher-order control processes needed for goal-directed behavior), learning, and processing speed decline with age (for reviews see e.g., Glisky, 2007; Prinicotta et al., 2014), for example, vocabulary has been considered to remain largely intact in healthy older adults or even peak at older age (Hartshorne & Germine, 2015). In research on age-related cognitive changes and their neural correlates, the widely used word fluency (WF) tasks have been of importance. These tasks require fast, time-limited production of words by preset criteria (e.g., animal names in semantic WF; words beginning with a certain letter in phonemic WF). Successful performance on WF tasks calls for verbal skills, EF, and processing speed, but results have been somewhat contradictory concerning the role of these cognitive domains in semantic vs. phonemic WF tasks (Aita et al., 2019; Whiteside

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et al., 2016). The cognitive correlates of WF performance can also differ between younger and older adults (Stolwyk et al., 2015), indicating age-related differences in the neural substrates of WF performance as well. As the available evidence on the neural underpinnings of WF performance in the elderly is limited, we examined the structural brain correlates of semantic vs. phonemic WF performance in healthy older adults.

As noted above, the contributions of different cognitive mechanisms on semantic vs. phonemic WF tasks remain somewhat unclear. A long-held assumption has been that the more difficult phonemic WF tasks engage particularly EF, whereas semantic WF task performance, in addition to EF, relies on semantic memory (Henry & Crawford, 2004). However, more recent behavioral studies paint a more complex picture. For example, Kraan et al. (2013) reported that in younger healthy adults, phonemic WF was linked to verbal intellectual function and processing speed, while semantic WF was associated with working memory and semantic word retrieval. In turn, research by Amunts et al. (2020, 2021) related semantic WF especially to EF (cognitive flexibility, inhibition) and processing speed, in line with the factor analytic findings of Aita et al. (2019). Furthermore, Whiteside et al. (2016) concluded in their study that language processing rather than EF is a key component for both phonemic and semantic WF. The pattern of results is further complicated by differences in associated background cognitive factors between age groups: Stolwyk et al. (2015) found that while in younger adults verbal intelligence and processing speed predicted phonemic WF and semantic retrieval semantic WF, for older adults the only observed association was between verbal intelligence and phonemic WF. In another study focusing on determinants of WF performance in older adults, phonemic WF was related to vocabulary knowledge, while semantic WF performance was best predicted by lexical retrieval speed and the use of visualization strategies (Gordon et al., 2018).

The shift in cognitive predictors of WF with advancing age is particularly interesting when considering the actual pattern of performance on phonemic vs. semantic WF tasks in younger vs. older adults. Phonemic WF is a more demanding task, which is reflected in a lower performance in absolute terms compared to semantic WF in different age groups (St-Hilaire et al., 2016; Vaughan et al., 2016). At the same time, many studies have found that semantic WF performance is relatively more affected by advancing age than phonemic WF performance (e.g., Gordon et al., 2018). This pattern does not fit in the original view of semantic WF tapping semantic memory (well preserved in aging) and phonemic WF reflecting EF (impaired in aging)(e.g., Lezak et al., 2012). However, the findings by, e.g., Gordon et al. (2018) do concur with the pattern of age-related impairment of semantic WF: vocabulary knowledge associated with phonemic WF is well preserved in the elderly, while processing speed and EF-dependent strategy use associated with semantic WF become impaired by advancing age.

Based on *focal cortical lesion studies*, the general finding is that the integrity of left-hemispheric fronto-temporal structures is critical for both types of WF performances, but that phonemic WF relies more on left frontal regions and semantic WF on left temporal regions (e.g., Baldo et al., 2001, 2006; Schwartz & Baldo, 2001; Thye et al., 2021, see Table 1). More recent studies have given a more versatile picture. For example, two large-scale lesion-symptom mapping studies by Biesbroek et al. (2016, 2021) took into account lesions in all brain areas and found partially shared and partially fluency-type specific correlates in several brain areas (see Table 1), indicating the recruitment of multiple cognitive processes. Chouiter et al. (2016) reported a somewhat different pattern of results in their lesion study. They found that both phonemic and semantic WF performance correlated with areas on the left basal ganglia, whereas phonemic WF was specifically related to superior temporal regions and semantic WF to middle temporal regions (see Table 1). Although not directly related to the present study, it is also interesting to note that white matter damage was seen as the primary correlate especially for semantic WF in the lesion study by Thye et al. (2021). Also, *functional magnetic resonance imaging (MRI) studies* on WF performance in healthy adults have highlighted especially the role of left frontal function (Wagner et al., 2014, for more details, see Table 1), and this pattern of activation is seen in older adults as well (Meinzer et al., 2009, 2012). In addition, Mohanty et al. (2021) found in their functional neuroimaging study that better phonemic WF performance in elderly adults was related to stronger functional connectivity in distinct brain areas (see Table 1). Furthermore, cognitive reserve mediated this finding in older adults, but not in younger participants. These results would suggest that high-performing older adults recruit compensatory mechanisms that are reflected in higher functional connectivity in some brain areas. Also, La et al. (2016) found a recruitment of additional brain areas during a phonemic WF task in older adults (see Table 1), supporting the view that compensatory processes are needed for healthy elderly participants.

Relating more closely to the present study, the number of *structural MRI studies* on the neural correlates of WF performance is more limited. These studies have mainly been conducted with either children, young adults, study groups with a wide age range, or with patient groups (Ellfolk et al., 2014; Gonzalez et al., 2021; Grogan et al., 2009; Jones et al., 2019; Newman et al., 2007; Pereira et al., 2009; Peter et al., 2016; Rodríguez-Aranda et al., 2016; Roerich-Gascon et al., 2015; Thames et al., 2012). A study closely related to the present one was published by Vonk et al. (2019) who examined cortical thickness in relation to WF in whole-brain analyses in healthy older adults. They found that both semantic and phonemic WF performance correlated with thickness measures in several brain areas (Table 1). Interestingly, the results were nearly symmetrical in the right hemisphere, and also some distinct correlates for semantic and phonemic WF were found. Newman et al. (2007), who used a mixed group of healthy young and older adults, found that phonemic WF performance was positively related to gray matter (GM) in the left inferior and middle frontal gyri across the group. Grogan et al. (2009) also used a mixed group, and they found that the GM volume of the left inferior temporal cortex correlated positively with semantic relative to phonemic WF, and that phonemic WF relative to semantic WF was positively associated with caudate volume. In the study by Thames et al. (2012), associations between semantic and phonemic WF and the basal ganglia were studied in HIV-infected adults. They found an association between phonemic WF and left caudate volume, as well as between phonemic switching and left putamen volume, whereas semantic WF did not show any significant associations with the basal ganglia. Rodríguez-Aranda et al. (2016) studied the correlations of WF and GM as well as white matter in healthy elderly and patients with Alzheimer's disease. Their results showed that both phonemic and semantic WF accuracy was positively correlated with GM volume in the left inferior frontal gyrus, left insular cortex and bilaterally in the hippocampus and parahippocampal gyrus across groups. Additionally, semantic WF accuracy showed associations with in a more extensive region of GM. The fact that the associations between phonemic WF accuracy and GM as well as white matter were mainly left-lateralized, made

Table 1. Summary of earlier lesion studies, as well as structural and functional MRI studies in relation to WF.

Study	Participants	Type of WF measured	Shared neural correlates for semantic and phonemic WF	Distinct neural correlates for semantic WF	Distinct neural correlates for phonemic WF
Lesion studies					
Baldo et al. (2001)	11 patients with focal frontal lobe lesions and 11 healthy controls	Semantic and phonemic	Frontal lobe patients were impaired both on semantic and phonemic fluency. Patients with left frontal lesions were more impaired on WF than right frontal lesion patients	–	–
Schwartz and Baldo (2001)	13 patients with focal frontal lobe lesions and 11 healthy controls	Semantic	–	Left frontal lesion patients differ from right frontal lesion patients in how they qualitatively generate words from a semantic category, indicating that left and right frontal areas differ with regard to semantic networks	–
Baldo et al. (2006)	48 left-hemisphere stroke patients	Semantic and phonemic	Left parietal cortex, insula and putamen, areas in post-central gyrus	Primarily left temporal cortex lesion loci	Primarily left frontal cortex lesion loci
Biesbroek et al. (2016)	93 stroke patients (both left and right)	Semantic and phonemic	Voxel-based lesion-symptom mapping: left frontal lobe (inferior and medial frontal and precentral gyri, as well as rolandic operculum, insula and putamen), region of interest based analyses: left inferior frontal and left insula	Voxel-based lesion-symptom mapping: left medial temporal lobe (hippocampus, and perihippocampal, inferior temporal, lingual, and fusiform gyri), as well as right frontal lobe (inferior frontal gyrus and periventricular white matter); region of interest based analyses: left putamen	Voxel-based lesion-symptom mapping: left middle frontal gyrus; region of interest based analyses: left rolandic operculum, left medial frontal gyrus
Chouiter et al. (2016)	191 stroke patients (both left and right)	Semantic and phonemic	Left cortical areas including putamen, caudate nucleus, pallidum, left cortical areas including superior and middle temporal gyri, angular gyri, insula, parts of the supramarginal gyri	Posterior middle temporal gyrus, pallidum	Anterior middle temporal and superior temporal areas, mostly rolandic operculum and supra-marginal gyrus
Biesbroek et al. (2021)	1231 stroke patients (both left and right)	Semantic and phonemic	Mostly left hemisphere, including mainly left frontotemporal regions, to lesser degree parietal and occipital areas, the left thalamus, basal ganglia and surrounding white matter	Left temporo-occipital part of middle and inferior temporal gyri, entire fusiform cortex, parahippocampal gyrus (posterior part), triangular part of the inferior frontal gyrus, orbital frontal cortex, corpus callosum (splenium)	Left middle and inferior temporal gyri (anterior divisions)

(*Continued*)

Table 1. (Continued).

Study	Participants	Type of WF measured	Shared neural correlates for semantic and phonemic WF	Distinct neural correlates for semantic WF	Distinct neural correlates for phonemic WF
Thye et al. (2021)	55 left-hemisphere stroke patients	Semantic and phonemic	Left frontal and temporal regions	Larger network of regions, including additional left temporal regions (more posterior), as well as a part of the left temporal pole, and a left frontal cluster extending into the supplementary motor area	An area stretching from left inferior frontal gyrus to the left insula was seen for the phonemic WF network.
fMRI studies					
Meinzer et al. (2009)	16 older and 16 younger healthy adults	Semantic and phonemic	The younger group: strongly left lateralized frontal pattern	The older group: more bilateral pattern, in addition weaker performance related to greater activity mainly in the right inferior and middle frontal regions compared to younger group	Left frontal activity in both groups, for the young adults activation was larger in anterior ventral (BA 45) and posterior dorsal (BA 44/9) regions of the inferior frontal gyrus
Meinzer et al. (2012)	14 older and 14 younger healthy adults	Semantic and phonemic	The younger group: strongest activity bilaterally in the medial superior frontal area and the anterior rostral cingulate zone. Lateral frontal activity was strongly left-lateralized The older group: Very similar activity pattern during both fluency tasks compared to younger group, except for more extensive clusters in frontal areas, bilaterally	The older group: more pronounced right frontal activity in relation to weaker performance (negative correlation with performance)	The younger group showed a larger difference in the degree of negative task-induced activity (larger clusters and more clusters in the younger group) compared to the older group in the phonemic WF vs. semantic WF task, suggesting that negative activity became more negative with increasing task demands for younger adults, whereas it is less modulated in older adults.
Wagner et al. (2014)	28 studies included	Semantic and/or phonemic	Most prominent results in left inferior/ middle frontal gyrus and anterior cingulate cortex, but results also found in left parietal precuneus, left and right insula, left thalamus and putamen, and right claustrum and caudate head, and cerebellum	–	Posterior-dorsal left inferior frontal gyrus (BA 44)

(*Continued*)

Table 1. (Continued).

Study	Participants	Type of WF measured	Shared neural correlates for semantic and phonemic WF	Distinct neural correlates for semantic WF	Distinct neural correlates for phonemic WF
La et al. (2016)	19 older, 18 middle-aged and 20 young adults	Phonemic	–	–	Activation in left inferior frontal gyrus, left middle frontal gyrus, and supplementary motor area, and the right cerebellum was seen in all age groups, and older adults showed a more bilateral activation pattern, as well as larger areas of the left hemisphere showing activation compared to younger participants, suggesting a compensatory mechanism. The expansion of activated areas in the oldest group was not limited to the prefrontal homologs, but also included posterior regions. In the middle-aged group, an activation decrease was seen, possibly reflecting compensatory activation due to an initial cognitive decline.
Mohanty et al. (2021)	73 older and 60 younger adults	Phonemic	–	–	Better performance was significantly associated with stronger functional connectivity in of Wernicke's area with ipsilateral and contralateral cuneus, precuneus, calcarine cortex and lingual gyrus across age groups. Older adults with weaker functional connectivity performed more poorly compared to younger adults, suggesting that greater functional connectivity in older age reflects compensatory mechanisms
Structural MRI studies					
Newman et al. (2007)	221 healthy adults (mixed group with large age range)	Phonemic	–	–	Positive correlation with left inferior and middle frontal gyri, indicating that primarily frontal areas are important in relation to the task

(*Continued*)

Table 1. (Continued).

Study	Participants	Type of WF measured	Shared neural correlates for semantic and phonemic WF	Distinct neural correlates for semantic WF	Distinct neural correlates for phonemic WF
Grogan et al. (2009)	59 healthy adults (mixed group with large age range)	Semantic and phonemic	Higher gray matter density in both left and right cerebellum in relation to better performance	No significant results across the whole brain, but ROI analysis showed a significant positive correlation with inferior temporal lobe, bilaterally	Significant positive correlation to head of caudate, bilaterally, as well as in the pre-supplementary motor area in the whole brain analysis. No significant results were found in the ROI analysis (let inferior frontal and premotor region).
Pereira et al. (2009)	32 Parkinson's disease patients	Semantic and phonemic	–	Significant positive correlation to GM density in temporal, frontal and cerebellar areas	No GM correlations
Thames et al. (2012)	20 hIV+ adults	Semantic and phonemic	–	No significant results	ROI analysis (basal ganglia) showed a significant positive correlation to left caudate volume (word generation) and left putamen volume (task switches).
D. G. Clark et al. (2014)	10 mild Alzheimer's disease patients, 22 Mild Cognitive Impairment patients, and 22 healthy controls	Semantic and phonemic	–	Significant positive correlation to left inferior frontal and lower temporal, as well as subcortical areas	Significant positive correlation to dorsal frontal regions, left subcortical nuclei, right inferior frontal gyrus, lower temporal and inferior parietal/ superior temporal region
Ellfolk et al. (2014)	28 Parkinson's disease patients and 28 healthy controls	Semantic and phonemic	–	Association between poorer performance and smaller GM volume in the left parietal cortex for the pooled group	Association between poorer performance and smaller GM volume in the right caudate (PD patients only)
Roerich-Gascon et al. (2015)	21 young adults	Semantic	–	Mainly areas in the left inferior frontal cortex and bilateral insula (both positive and negative correlations found)	–
Peter et al. (2016)	20 amnestic mild cognitive impairment patients and 30 healthy controls	Semantic	–	Healthy controls: Left superior frontal gyrus predicted performance, patients with aMCI: Left inferior frontal gyrus, right superior frontal gyrus predicted performance	–

(*Continued*)

Table 1. (Continued).

Study	Participants	Type of WF measured	Shared neural correlates for semantic and phonemic WF	Distinct neural correlates for semantic WF	Distinct neural correlates for phonemic WF
Rodríguez-Aranda et al. (2016)	18 Alzheimer's disease patients and 24 healthy controls	Semantic and phonemic	Positive association with GM density in left inferior frontal gyrus, left insular cortex and bilaterally in the hippocampus and parahippocampal gyrus (across groups, WF accuracy)	In addition to shared areas with phonemic WF: more extensive region of cingulate gyrus, caudate, and cerebellum (WF accuracy) positively associated with performance	–
Jones et al. (2019)	590 participants including patients with AD, MCI, Lewy body disease, vascular dementia and frontotemporal dementia	Semantic and phonemic	Highest correlation in the temporal lobe, lower but significant in the frontal lobe, parietal lobe, and occipital lobe	The temporal correlation was strongest for semantic WF, and on the left side of the brain. Semantic WF also showed an association with left frontal lobe and precuneus (bilateral). Bilateral parietal lobes more important semantic WF compared to phonemic WF.	Left frontal lobe more important for phonemic WF. The association with precuneus was prominent for the right side in phonemic WF
Vonk et al. (2019)	505 older participants (that were not diagnosed with dementia)	Semantic and phonemic	Positive correlation with cortical thickness in left frontal lobe, parietal lobe, temporal lobe and occipital lobe. The pattern in the right hemisphere was almost symmetrical to that in the left	The positive correlation with cortical thickness was stronger compared to phonemic WF in certain areas in the pars opercularis, precentral gyrus, middle frontal gyrus, medial orbitofrontal cortex, caudal middle frontal gyrus, postcentral gyrus, insula, transverse temporal gyrus, superior temporal gyrus, supramarginal gyrus, angular gyrus, and lateral occipital gyrus.	The positive correlation with cortical thickness was stronger in the fusiform gyrus, compared to semantic WF
Gonzalez et al. (2021)	73 typically-developing children	Semantic and phonemic	Better WF performance was associated with higher right superior longitudinal fasciculus/arcuate fasciculus fractional anisotropy	Explorative analyses suggested positive associations with fractional anisotropy in corpus callosum, and right inferior fronto-occipital fasciculus	Modest association with lower left superior longitudinal fasciculus/ arcuate fasciculus fractional anisotropy

the authors to suggest that phonemic WF represents a language task that is less dependent on brain regions associated with semantic processing. Ellfolk et al. (2014), who studied the relationship between GM volume and both semantic and phonemic WF in Parkinson patients and healthy older control subjects found no significant associations within their controls, possibly due to the fact that the control group was rather small (n = 27). In a more recent study by Jones et al. (2019), both semantic and phonemic WF were found to be positively correlated with cortical thickness in all lobes in a memory disorders clinic population, with the strongest relationships in the temporal lobe. Furthermore, the left frontal lobe was of greater importance in phonemic WF compared with semantic WF. Peter et al. (2016) did not include phonemic WF in their study, and the semantic WF task was somewhat different from the one used in the present study. The relationship between semantic WF (and non-verbal design fluency) and pre-determined regions limited to the superior frontal gyrus, the inferior frontal gyrus and the temporal pole, was studied in healthy elderly controls and patients with amnestic mild cognitive impairment. For the healthy elderly controls, the left superior frontal gyrus was associated with semantic WF, whereas associations between the semantic WF task and GM volume were found in both hemispheres in the patient group, encompassing the right superior frontal gyrus and the left inferior frontal gyrus. Finally, it is also interesting to note that Gonzalez et al. (2021), who studied both GM thickness and white matter connections in relation to WF in children, found right-lateralized results, showing that WF in children depends also on the right hemisphere, which could indicate that some linguistic functions related to WF are right-lateralized, or the right hemisphere may play a larger role due to the executive demands set by WF tasks.

The review above indicates that WF tasks are multifactorial, tapping on various aspects of verbal skills, EF, and processing speed. This means that WF performance depends on the concerted action of multiple brain regions (e.g., Aita et al., 2019). Across studies, the most consistently observed brain correlates for word fluency tasks have been located in the frontal and temporal cortex, albeit parietal as well as subcortical medial temporal and basal ganglia foci have also been reported. These brain correlates have been predominantly left-lateralized, but bilateral findings have not been uncommon. More bilateral findings in the elderly are in line with the HAROLD model, which stipulates that prefrontal activity during cognitive tasks is less lateralized in older adults vs. younger adults (Cabeza, 2002). There could be different underlying reasons for this age-related laterality difference (Cabeza, 2002), such as dedifferentiation of cognitive abilities or compensation in the elderly. Cabeza et al. (2018) define compensation as “cognition-enhancing recruitment of neural resources in response to relatively high cognitive demand” (p.7),” and compensation can occur by upregulation, selection, or by reorganization. As aging affects certain cognitive domains more than others and may lead to various ways to compensate for these changes in performances, the findings on shifting neurocognition of WF are not surprising as such. However, what these changes are is not yet fully clear. Some of the earlier studies have also involved mixed groups or groups spanning an age over the entire range of adulthood, obscuring possible differences in the neural substrates of WF related to age or brain pathology. As there is very little research on GM volume and WF in healthy older adults, we examined the relationships between brain GM and semantic and phonemic WF, respectively, in 46 healthy older adults using Voxel-Based

Morphometry (VBM). In the light of the existing lesion and structural MRI studies on WF, we expected to find GM volume associations with both semantic and phonemic WF, and we expected the brain correlates to be located in frontal, temporal, and subcortical areas. Structural MRI studies allow investigating the relationships between individual variability in brain structure and inter-individual differences in behavior (Kanai & Rees, 2011). In comparison to functional neuroimaging studies where the task of interest has to be adapted to scanner conditions, structural methods allow for the investigation of neural correlates of tasks that have been performed in a less constrained setting.

Methods

Participants

Altogether 49 Finnish-speaking healthy older adults took part in this study. The present sample is the same as in Saarela et al. (2017), and detailed exclusion criteria are described in their study. Besides age, native tongue, corrected-to-normal vision and normal hearing, and normal health, a further inclusion criterion was normal cognitive functioning, defined as a Clinical Dementia Rating memory box score of 0 (CDR; Morris, 1993), a Mini-Mental State Examination (MMSE; Folstein et al., 1975) score of at least 25/30, and performance equal to or less than one standard deviation below the age-appropriate norms within a cognitive domain[1] for a battery of standardized neuropsychological tests. For more information about the neuropsychological test battery, see Saarela et al. (2017), and for neuropsychological test scores, see Table 2. A decline in an individual subtest was allowed as a sign of intraindividual variation, as long as performance within that cognitive domain as a whole fulfilled the criterion (Brooks et al., 2011). Three participants were excluded from the study after failing to meet these criteria. The remaining 46 participants were included (29 women/17 men).

The age range of the 46 participants was 50–79 years, and the mean years of education was 13.55 years (*SD* = 2.79 years) (Table 3). All participants, but one, reported being dominantly right-handed, as determined by a cutoff score of at least 87 on a modified version of the Edinburgh Handedness Inventory (Cohen, 2008). The ethical committee of Turku University Central Hospital approved the study in 15 April 2008 (ETMK 36/180/2008, protocol 4/2008, §127, with an extension dated 18 October 2011, §309). All participants gave written informed consent for participation in keeping with the Declaration of Helsinki and its later amendments. None of the participants received monetary compensation. This study was part of a larger research project, and all participants underwent an electroencephalogram (EEG) experiment in addition to the MRI scan.

Word fluency measures

In order to assess phonemic WF, the participants generated words beginning with the letter S during 60 s, excluding proper nouns and different inflectional forms of the same word. After that, semantic WF was assessed with the generation of animal names during 60 s, acceptable responses including also male/female

Table 2. Means and standard deviations of neuropsychological test scores.

	Mean (SD) ($n = 46$)
MMSE	28.61 (1.15)
WAIS-III (raw scores)	
Similarities	23.83 (3.69)
Block design	39.83 (10.53)
Digit span forward sum score	9.07 (1.76)
Digit span forward max span	5.96 (1.01)
Digit span backward sum score	7.00 (1.51)
Digit span backward max span	4.85 (0.87)
Digit symbol	60.54 (12.70)
Object memory test[2]	
Immediate free recall	13.41 (2.15)
Delayed free recall	12.11 (2.18)
WMS-R (selected subtests, raw scores)	
Logical memory I	26.26 (5.30)
Logical memory II	23.15 (6.10)
Verbal paired associates (easy, immediate)	10.37 (1.48)
Verbal paired associates (difficult, immediate)	7.11 (3.12)
Verbal paired associates (easy, delayed)	3.63 (0.53)
Verbal paired associates (difficult, delayed)	3.04 (1.26)
Boston Naming Test[3]	
Correct 0–31 (max. 31), including semantic cues correct	27.85 (2.45)
Trail Making	
A (numbers), duration in seconds	42.22 (12.72)
B (numbers+letters), duration in seconds	80.18 (24.61)
Stroop	
Colour, duration in seconds	70.35 (13.13)
Word-color conflict, duration in seconds	131.32 (27.45)
Rey-Osterrieth Complex Figure Test	
Copy score	34.04 (1.86)
CERAD	
Clock drawing	5.48 (0.78)

Table 3. Means, standard deviations, and ranges for demographic characteristics and WF scores.

	Women ($n = 29$)	Men ($n = 17$)	All ($n = 46$)
Age *M (SD)/range*	62.79 (8.08)/50–79	62.12 (8.50)/50–77	62.54 (8.15)/50–79
Education, years *M (SD)/range*	12.95 (3.02)/6–17	14.59 (2.00)/12–17	13.55 (2.79)/6–17
Semantic WF *M (SD)/range*	23.69 (7.04)/12–37	22.94 (5.79)/10–31	23.41 (6.55)/10–37
Phonemic WF *M (SD)/range*	17.03 (5.65)/6–28	12.59 (5.27)/3–23	15.39 (5.87)/3–28
Fluency ratio *M (SD)/range*	0.42 (0.08)/0.27–0.60	0.35 (0.11)/0.22–0.56	0.39 (0.01)/0.22–0.60

terms, terms referring to animals representing different age groups, different breeds of a species, and synonyms. In addition to total scores (i.e., number of correct words), the fluency ratio was calculated (see, e.g., Robinson et al., 2012) as follows: phonemic WF/(phonemic + semantic WF). A low ratio score thus indicates low performance and a high ratio score high performance on the phonemic relative to the semantic task. Total correct raw scores of the two separate fluency measures as well as the fluency ratio score were examined in relation to regional brain GM volume using VBM.

Correlational analyses were used to examine associations between word fluency, age, and years of education. Independent samples t-tests were conducted to study sex differences in verbal fluency performance. Linear regression analyses were conducted in order to find out whether age, sex, education, or white matter (WM) hyperintensities predicted WF performance. All statistical analyses of the behavioral data were performed with SPSS version 28 (SPSS Inc. IBM Company, 2016).

MRI acquisition

MRI scanning was conducted within 22 weeks of the neuropsychological assessment ($M = 14.5$, $SD = 5.8$ weeks). The MRI was conducted with a 3T scanner (Verio, Siemens Medical Imaging, Erlangen, Germany) at the Department of Radiology, Turku University Hospital. The parallel acquisition technique (GRAPPA) was used in all sequences. A routine 12-channel head coil was used. For VBM, 3DT1 sequence with TR of 2300 ms, TI of 900 ms, TE of 3 ms, FOV of 256 mm × 240 mm, and (FA) Flip Angle of 9 degrees was obtained. In addition, to exclude brain abnormalities, we obtained T2-weighted and FLAIR images. T2-weighted images had TR (Repetition Time) of 5210 ms, TE (Echo Time) of 96 ms, FOV (Field-Of-View) 220 mm × 165 mm, 4 mm slice thickness, and a 30% gap between images. FLAIR sequence had TR of 5000 ms, TI (Inversion Time) of 1800 ms, TE of 395 ms, FOV 250 mm × 250 mm, voxel size 1 mm × 1 mm × 1 mm, and 160 slices in total with no gap between slices.

Visual MRI ratings

Age-related white matter changes were visually rated using the Wahlund scale (Wahlund et al., 2001). General atrophy (Victoroff et al., 1994), hippocampal atrophy (Scheltens et al., 1992), and frontal atrophy (Jokinen et al., 2009) were also rated. All white matter changes and atrophy findings were regarded to be within the limits of normal aging: 39.1% of the participants did not have focal white matter lesions, 52.1% exhibited focal lesions, and 8.7% showed beginning confluence of lesions. More detailed information regarding the age-related white matter changes and degrees of atrophy can be found in a recent study (Saarela et al., 2017) that included the same participants as the present one.

VBM

The analyses were conducted using VBM toolbox (VBM8, Christian Gaser, University of Jena, Jena, Germany; http://dbm.neuro.uni-jena.de/vbm/) implemented in Statistical Parametric Mapping software (SPM8, Wellcome Department of Cognitive Neurology, London, UK) and run in Matlab 2011 (Mathworks Inc., Natick, MA) (Ashburner, 2007; Ashburner & Friston, 2000; Ashburner & Segmentation, 2005; Cuadra et al., 2005). The T1-weighted images were bias-corrected, segmented, and warped to Montreal Neurological Institute (MNI) space using high-dimensional spatial normalization (DARTEL). The GM images were modulated using Jacobian determinants derived from the warping procedure to control the effects of non-linear warping procedure. Finally, the images were smoothed using an 8 mm Full-width-at-half-maximum (FWHM) isotropic Gaussian kernel to improve the signal-to-noise ratio. Total intracranial volumes were calculated from the native space images. The associations between word fluency (semantic WF, phonemic WF, fluency ratio) and whole brain volume were tested using the general linear model (GLM) with age, sex, and total intracranial volume as nuisance covariates. An absolute voxel value threshold was set to 0.1 to exclude non-GM regions from the analyses. Family-wise error (FWE) at cluster level was applied to correct for multiple comparisons. *P* values less than 0.05 were considered significant. Anatomical regions included in clusters were defined using the Automated Anatomical Labeling (AAL) toolbox (http://ww.gin.cnrs.fr/AAL) (Tzourio-Mazoyer et al., 2002). The peak coordinates are presented in MNI standard space. The results were visualized using Mango software (version 4.0.1; Lancaster, Martinez, http://rii.uthscsa.edu/mango/).

Results

The means, standard deviations, and ranges for the different word fluency measures are shown in Table 3. As shown by a paired-samples t-test, the number of words produced in the semantic WF task was significantly higher compared to the phonemic WF task $t(45) = 7.87$, $p = <.001$, bootstrap 95% CI [−10.07, −5.97]. Independent samples t-tests showed that women significantly outperformed men, on phonemic WF, $t(44) = 2.64$, $p = .011$, $d = 0.51$, bootstrap 95% CI [1.12, 7.58] and the fluency ratio; $t(44) = 2.41$, $p = .020$, $d = 0.73$, bootstrap 95% CI [0.01, 0.12]. There were no significant sex-related differences in semantic WF; $t(44) = 0.37$, $p = .713$, $d = 0.12$, bootstrap 95% CI [−3.12, 4.69]. The Pearson correlations did not reveal any associations between any of the word fluency measures and age or years of education. Semantic and phonemic WF were positively correlated, $r = .385$, bootstrap 95% CI [0.10, 0.63], $p = .008$. Semantic WF and fluency ratio were expectedly negatively correlated, $r = -.302$, bootstrap 95% CI [−0.57, 0.01], $p = .041$, and phonemic WF and fluency ratio were expectedly positively correlated, $r = .736$, bootstrap 95% CI [0.00, 0.06], $p < .001$.

In order to investigate whether white matter (WM) visual rating scores, as well education (years), age, and sex had an impact on performance, we conducted three linear regression analyses, with semantic WF, phonemic WF, and fluency ratio as dependent variables, respectively. The predictors in all three analyses were education (years), age, sex, and white matter (WM) (no hyperintensities vs. visible hyperintensities with all participants having either focal lesions or beginning confluence pooled together). The regression model was non-significant for semantic WF ($F(4,41) = 1.19$, $p = .330$). Neither education ($\beta = .26$, $p = .107$), age ($\beta = -.19$, $p = .258$), sex ($\beta = -.14$, $p = .383$), nor WM hyperintensities ($\beta = -.003$, $p = .984$) significantly predicted semantic WF performance. For phonemic WF, the model reached statistical significance ($F(4,41) = 3.58$, $p = .015$, $R^2 = .26$). Of the individual predictors, education ($\beta = .29$, $p = .044$) and sex ($\beta = -.48$ $p = .002$) significantly predicted phonemic WF performance, whereas age ($\beta = .15$, $p = .315$) and WM hyperintensities ($\beta = -.27$, $p = .090$) did not. With regard to fluency ratio, the model was significant ($F(4,41) = 2.81$, $p = .038$, $R^2 = .22$). Sex significantly predicted fluency ratio ($\beta = -\ .40$, $p = .009$), but education ($\beta = .12$, $p = .407$), age ($\beta = .30$, $p = .062$), and WM hyperintensities ($\beta = -.29$, $p = .076$) did not.

Semantic WF and GM volume did not show any significant associations. However, lower scores on the phonemic WF task were associated with smaller GM volumes bilaterally in the anterior medial temporal lobe (MTL) and putamen [cluster size 2875 voxels, peak MNI coordinates (mm) xyz = −33, −10, 0 (left), Pfwe = 0.03; cluster size 4641, peak MNI coordinates (mm) xyz = 34, −4, 1 (right), Pfwe = 0.002] (Figure 1a). Also, lower scores on the fluency ratio (reflecting a disproportionally weak performance in the phonemic WF task compared to the semantic WF task) were associated with smaller GM volumes in the left inferior frontal cortex [cluster size k = 1605 voxels, peak MNI coordinates (mm) xyz = −51, 17, 3, Pfwe = 0.04], as well as the right anterior MTL and the right caudatus/putamen/pallidus area [cluster size k = 1782 voxels, peak MNI coordinates (mm) xyz = 22, −1, −15, Pfwe = 0.02] (Figure 1b).

Discussion

We set out to examine the structural GM correlates of two types of word fluency performance, semantic and phonemic, in healthy older adults. These two widely used cognitive-linguistic tasks make for an interesting comparison, and previous related research focusing specifically on healthy older adults is very limited. In line with the previous literature, word fluency performance was lower in the phonemic than in the semantic task. Regarding the structural brain correlates, we found that phonemic WF performance was associated with GM volume in the anterior medial temporal lobe and in the putamen bilaterally. Moreover, a phonemic/semantic word fluency ratio correlated with GM volume in the left inferior frontal cortex, the right anterior medial temporal lobe, and the right caudatus/putamen/pallidus area. In contrast, no significant associations

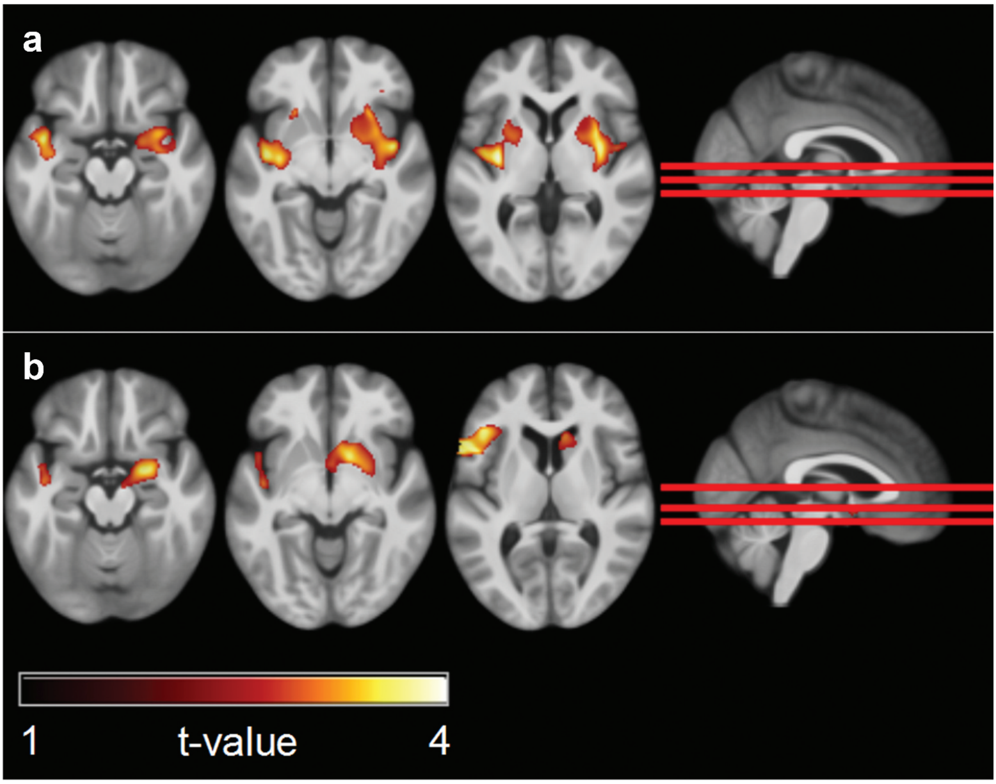

Figure 1. Association between regional GM volumes, and phonemic fluency (a) and fluency ratio (b). Only significant clusters (Pfwe <0.05) are shown overlaid on the average normalized T1-weighted image of the studied sample ($n = 46$).

between regional GM volume and semantic WF were observed. Below we discuss these findings in detail.

Our results, obtained with healthy older individuals free from cognitive decline or significant GM atrophy, link phonemic WF performance to the structural integrity of anatomically widespread areas encompassing cortical fronto-temporal as well as subcortical medial temporal and striatal regions in both hemispheres. The reason for phonemic WF being highlighted here is most probably related to heavier cognitive demands posed by that task. As expected, our participants' performance was clearly lower on the phonemic than on the semantic WF task. This finding supports the fact that while a semantic WF task follows the semantically based organizational principles of the mental lexicon (see, e.g., Aitchison, 1989), phonemic WF calls for a fast implementation of non-semantic strategies, which makes the task more demanding (e.g., Lezak et al., 2012). In other words, the phonemic WF task called for EF and fast implementation of self-generated effective strategies of our participants, as non-semantic word retrieval strategies do not come naturally from the way the mental lexicon is organized (Henry & Crawford, 2004; Koziol & Budding, 2009).

Regarding the specific structural brain correlates of phonemic WF, the association with GM volume in the bilateral anterior MTL is in line with some previous studies showing that phonemic WF is mediated by several brain areas, including medial temporal regions (Rodríguez-Aranda et al., 2016; Vonk et al., 2019). In the phonemic WF task, the participants must remember the words they have already mentioned while applying their search strategy. This may very well recruit MTL, which is important for immediate memory and working memory, in addition to the formation of long-term memory (for a review, see Jeneson & Squire, 2011). Moreover, working memory and language processing are known to be closely linked (Martins et al., 2015). It could be that elderly participants with lower GM volume in the MTL area cannot efficiently maintain this information in working memory. In addition, it is possible that our participants could not employ EF-related switching in an effective way, as associations between switching and GM volume in the MTL in patients with mild cognitive impairment (MCI) have been found previously (Zheng et al., 2014). This is plausible also because there are connections between MTL areas and the prefrontal cortex which are important for EF (Takahashi et al., 2007). We can thus speculate that a smaller GM volume in the MTL attenuates the functional efficacy of the prefrontal-MTL network needed for phonemic WF performance in our elderly participants.

Concerning the striatum that is closely linked to the prefrontal cortex, we found that lower phonemic WF performance was also associated with smaller GM volume in the bilateral putamen area. This finding was not unexpected, as previous studies have found similar associations (Baldo et al., 2006; Ellfolk et al., 2014; Grogan et al., 2009; Thames et al., 2012). However, Ellfolk et al. (2014) found that lower scores on phonemic WF were associated with smaller right striatal volume in patients with Parkinson's disease only, but not in the healthy control group. This could be due to their control group being smaller and somewhat younger than ours. In other words, it is possible that our larger sample showed more heterogeneity, leading to better chances for finding an association. Also, we used a higher resolution 3T scanner as opposed to a 1.5T scanner employed in the Ellfolk et al. (2014) study. There are dense reciprocal connections between the frontal lobe and the basal ganglia, and these pathways are thought to be important for response inhibition, working memory updating, as well as task switching (for review, see Neubert &

Mars, 2013), all of which are required in the phonemic WF task. It has also been suggested that the left basal ganglia may be involved in linguistic processes, such as morphological structure building and lexical-semantic selection (for reviews, Rodríguez-Fornells et al., 2009; Ullman, 2001). In sum, we suggest that the present association between phonemic WF and putaminal GM may reflect the role of the striatum as an important component of the frontostriatal system that subserves executive functioning, a cognitive domain that is particularly sensitive to age-related changes.

Regarding the fluency ratio, we found that a lower ratio that reflects a disproportionally weak performance on phonemic vs. semantic performance was associated with smaller left inferior frontal GM volume. This is in line with some previous findings on phonemic WF and structural MRI correlates (Jones et al., 2019; Newman et al., 2007). The left inferior frontal cortex is a crucial area for both phonological and semantic processing, and it has been proposed that this area is also engaged when information among competing alternatives is chosen (Bookheimer, 2002; Thompson-Shill et al., 1997). As a low fluency ratio entails weaker performance on phonemic compared to semantic WF, our finding may reflect the fact that phonemic WF places greater demands on brain areas that are responsible for phonological processing and word selection, compared with semantic WF that taps more on semantic networks. The left-lateralization was expected, and lesion data shows that patients with left frontal lesions are more impaired on phonemic WF and have a lower fluency ratio compared with right frontal lesion patients (Robinson et al., 2012). Our results are also in line with functional neuroimaging studies that have linked the left inferior cortex to phonemic WF (e.g., Wagner et al., 2014), a finding which is also seen in older adults (Meinzer et al., 2009, 2012). In sum, we surmise that the present association between fluency ratio and left inferior frontal GM volume reflects demands on phonological processing and lexical selection among competing alternatives that are inherent to phonemic WF.

A lower fluency ratio score was also associated with smaller GM volume in the right anterior MTL and the right caudatus/putamen/pallidus area, i.e., roughly within the same areas as for the phonemic WF score. The right lateralization of our finding is somewhat surprising, as previous lesion mapping studies with stroke patients have usually found associations between WF and right hemisphere regions to a limited extent (see, e.g., Biesbroek et al., 2021). However, a structural MRI study that relates more closely to the present one, found that phonemic WF performance was associated with clusters in the right hemisphere as well (Vonk et al., 2019). Furthermore, response inhibition, which is needed in phonemic WF, has often been linked with the right hemisphere (e.g., Neubert & Mars, 2013). The right lateralization related to response inhibition is usually seen in the frontal cortex, but there are dense connections between the frontal and striatal areas as well as the MTL (Neubert & Mars, 2013; Takahashi et al., 2007). It is also possible that the left and right hemispheres are involved in different kinds of lexical-semantic processes that complement each other (Schwartz & Baldo, 2001). More specifically, Schwartz and Baldo (2001) argued that the right hemisphere may be important for more indirect, category-independent associations, as opposed to context-based semantic associations in word fluency tasks. Although Schwartz and Baldo (2001) based these conclusions on results on patients with frontal lesions, and their findings are not directly comparable with ours, we may speculate whether the right-lateralization of our results reflects the task demands of the phonemic WF task. Another interesting possibility is that the right-lateralization of our results partly reflects age-related compensatory processes. For example, La et al. (2016) who studied phonemic WF with fMRI in young, middle-aged, and older adults found that the older adults recruited additional right-sided frontal, temporal, and cerebellar brain regions during the phonemic WF task compared to young and middle-aged subjects. They concluded that their findings reflected compensatory processes that are needed in maintaining task performance, as age-related neural atrophy is starting to occur. In addition, D. G. Clark et al. (2014) who studied word fluency and GM volumes on a cognitively intact-Alzheimer's disease continuum found that the right hemisphere, including certain temporal areas, was associated with phonemic WF. At a more general level, structural MRI findings have shown that older adults with better naming skills can rely on several right hemisphere regions and pathways in order to perform successfully in naming tasks (Obler et al., 2010). Furthermore, functional neuroimaging studies have also indicated that bilateral activation patterns may reflect compensatory processes in older adults (see, e.g., Cabeza, 2002; Reuter-Lorenz et al., 2000). This type of age-related compensatory neural reorganization has been found in VF tasks (La et al., 2016; Meinzer et al., 2012), as well as other types of cognitive tasks (Park et al., 2004: Wierenga et al., 2008; Carp et al., 2011). We welcome further studies using a young adult comparison group to clarify this issue.

No significant associations were found between semantic WF and GM volume. This is not fully unexpected, since, for example, Ellfolk et al. (2014) also failed to find significant relationships between semantic WF and GM volume in either patients with early-stage Parkinson's disease ($n = 28$) or healthy control subjects ($n = 27$). However, when Ellfolk et al. (2014) pooled the groups together ($n = 55$), significant associations were found. This is likely due to a combined effect of higher statistical power with a larger sample size and a higher degree of variability in both volumetric and behavioral measures when mixing healthy controls and participants with brain pathology. Also, Grogan et al. (2009) did not find significant results for semantic fluency relative to phonemic fluency at the whole brain level, although an effect was found when the search volume was restricted. It is thus plausible that still a larger sample size, or a more restricted ROI analysis would have revealed significant associations in the present study, as the variability in the measures is more subtle in healthy individuals. Semantic WF performance is often found to be negatively affected by age (Tomer & Levin, 1993; Kozora & Cullum, 1995; Bolla et al., 1998; Loonstra et al. 2001; Brickman et al., 2005; L. J. Clark et al., 2009), so concurrent age-related brain changes should also be present. In the present sample, the variation regarding the semantic and phonemic WF performance was quite similar. Hence, the lack of associations between GM volume and semantic WF was not due to this factor. Our study has certain limitations that affect the generalizability of the results. First, our participants consisted of a convenience sample and no young adults were included. However, in terms of sex and education, the group was quite representative of its age segment in Finland (Statistics Finland, 2016). Second, the sample size was not very large, but still comparable to sample sizes in earlier studies in the field. Third, there was quite a long time-lapse between the behavioral tasks and the MRI scan, 13.4 weeks on average. Research has shown that when constructing age-appropriate norms, there can be a risk for inclusion of people with subclinical cognitive dysfunction in the normative sample, which lessens the sensitivity and specificity of the norms in differentiating between healthy and pathological aging (Sliwinski et al., 1996). As our sample consisted of older participants and their performance on the neuropsychological tests was compared to age-appropriate norms constructed in accordance with the standards at the time of data collection, it is possible that some of the participants might actually have had a subclinical mild cognitive impairment. This, in turn, might have affected our results.

In conclusion, we found that phonemic WF and fluency ratio (phonemic WF relative to semantic WF) were related to regional GM volume in certain brain areas in healthy older adults. In line with the limited number of related earlier studies, our results indicate that structural MRI in healthy elderly may paint a broader picture of the brain areas related to WF when compared to traditional lesion studies. The present brain-behavior associations were bilateral and right-lateralized, which may reflect age-related compensation by these brain areas against contralateral age-related neural decline. We only found associations between phonemic WF and certain brain areas, but not regarding semantic WF, which could be due to several factors. In order to draw conclusions about the specific impact of aging on verbal fluency and GM volume, future studies should include a young subject group as well. It would also be of interest to include large enough young-old and old-old groups in future studies to explore possible changes in brain-behavior correlates within the elderly.

Notes

1. Auditive short-term memory and working memory, episodic memory (immediate and delayed recall), verbal learning, naming, visuoconstructive abilities, visuomotor speed, verbal reasoning, and attention.
2. Portin et al. (1995).
3. Karrasch et al. (2010).

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Disclosure statement

Juho Joutsa has received a lecturer honoraria from Lundbeck, Novartis, Addiktum and Nordic Infucare, and travel support from Insightec, Abbvie and Abbot, and consulting fees from Teva Finland, Summaryx and Adamant Health; advisory board membership with Teva Finland; stocks of Neurologic Finland and Suomen Neurolaboratorio. Juha O. Rinne serves as a neurology consultant for CRST Oy. None of the aforementioned had any role in the present study, including data collection, preparation or analysis. None of the other authors have any commercial or financial relationships to declare that could be construed as a potential conflict of interest.

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Consent to participate

All participants gave written informed consent for participation in keeping with the Declaration of Helsinki and its later amendments. None of the participants received monetary compensation.

Data availability statement

The GDPR legislation requires us to protect the identity of participants and conform to the permissions they have given, and due to these policies and legislation, the present data cannot be shared. Regarding the MRI data, the raw MRI images that we used in the analyses cannot be publicly shared, as they contain personally identifiable information. Personal identifiers in the MRI data are linked to the pseudonymised behavioral data that cannot be published either, because we do not have the participants' consent for sharing their pseudonymised behavioral data.

Ethics approval

The ethical committee of Turku University Central Hospital approved the study on 15 April, 2008 (ETMK 36/180/2008, protocol 4/2008, §127, with an extension dated 18 October 2011, §309).

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