

Regional Atrophy and Nonverbal Semantic Memory in Behavioral Variant Frontotemporal Dementia and Alzheimer's Disease

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Introduction

Neurocognitive measures have demonstrated mixed utility in the diagnostic assessment of behavioral variant frontotemporal dementia (bvFTD) (McGeown, Shanks, Forbes-McKay, & Venneri, 2009). Semantic memory is necessary to identify analogies that conceptually link two visually, and functionally distinct entities. Nonverbal semantic memory is associated with the bilateral anterior temporal regions, which are areas of involvement in bvFTD, typically characterized by a right-hemisphere prominence (Borroni et al., 2012). A measure of nonverbal semantic memory, Pyramids and Palm Trees (PPT; Howard and Patterson, 1992), has demonstrated utility in distinguishing semantic dementia (an alternate frontotemporal dementia) from Alzheimer's disease and typically corresponds with left hemispheric degeneration (Hutchinson & Mathias, 2007). However, the neural correlates of a nonverbal version of this task have not been identified in bvFTD or contrasted with early-onset Alzheimer's disease (EOAD).

Method

Participants: Sixteen patients with bvFTD and 20 with EOAD, diagnosed according to established consensus criteria (Rascovsky et al., 2011; McKhann et al., 1984) were matched in age and cognitive severity and characterized with baseline neuropsychological and neuroimaging measures.

Procedures: Participants received neuropsychological tasks including verbal fluency tasks (COWAT FAS/Animals), WMS-III Logical Memory, and the Boston Naming Test (BNT), as well as the Pyramids and Palms Trees Test (PPTT). The PPTT task is a 52-item, nonverbal measure of semantic knowledge. The picture version of the PPTT was utilized which consists of two pictures presented below a target picture and requires the subject to identify the picture that conceptually best matches the target.

Table 1. Patient Demographics – Independent Samples T-Test

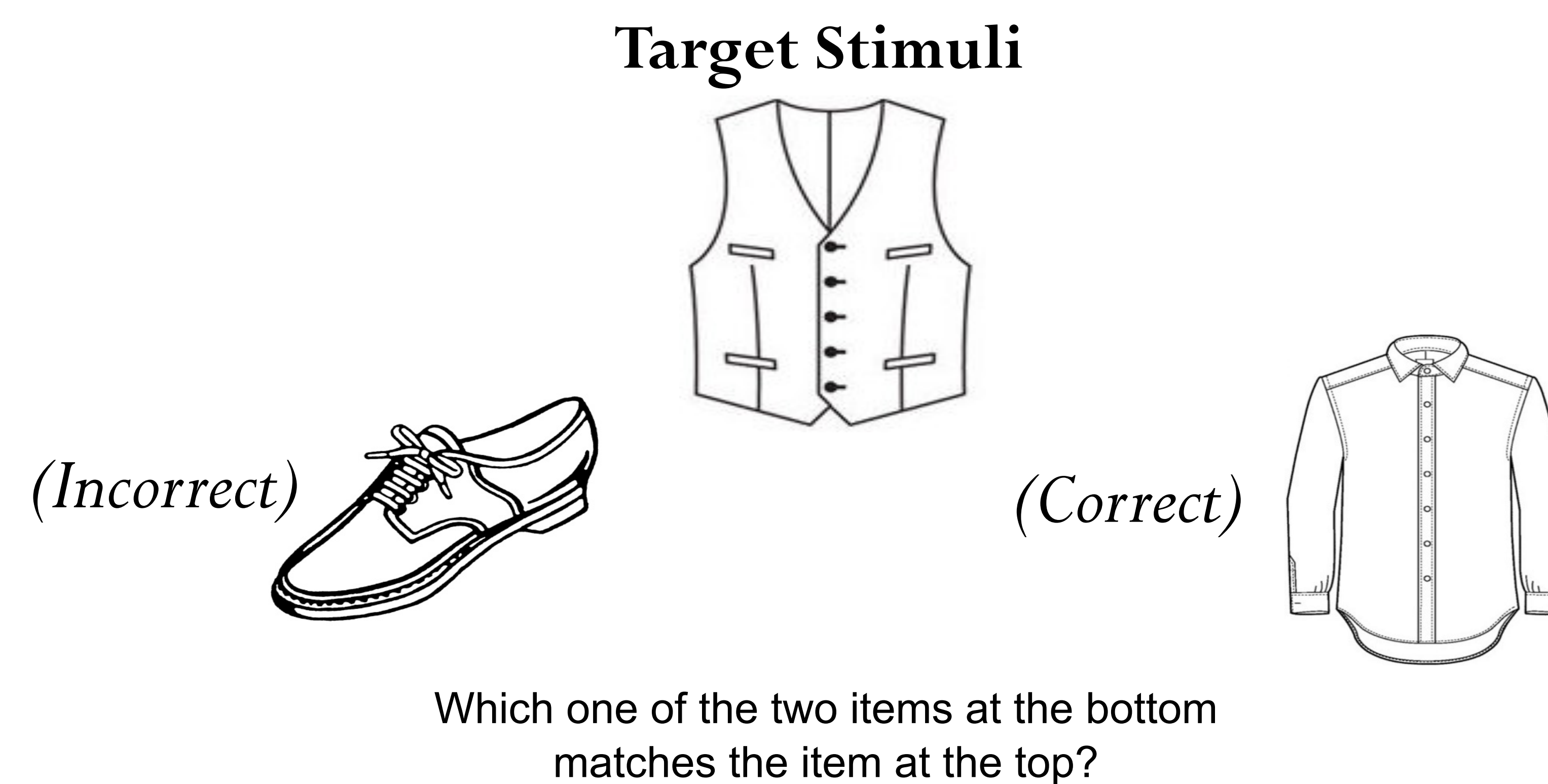
| | BvFTD (n=16) M (SD) | EOAD (n=20) M (SD) | p value |
|----------------------------------|---------------------------|--------------------------|---------|
| Age (years) | 58.7 (±10.6) | 59.5 (±5.3) | .78 |
| Gender (males/females)* | 8M / 8F | 7M / 13F | .36 |
| Est. age of onset (years) | 54.9 (± 9.9) | 55.6 (± 6.3) | .79 |
| Education (years) | 15.3 (±2.5) | 16.8 (±1.8) | .05 |
| Wechsler WTAR Verbal IQ (VIQ) | 104.5 (±11.5) | 110.3 (±7.9) | .19 |
| MMSE (raw) | 23.8 (±5.3) | 25.1 (±3.9) | .41 |
| Boston Naming Test (60-item) | 47.1 (±10.8) | 48.8 (±12.4) | .73 |
| COWAT FAS Fluency (raw) | 16.4 (±13.8) | 36.8 (±18.9) | .01 |
| COWAT Animals fluency (raw) | 11.2 (±7.3) | 14.2 (±5.1) | .28 |
| WMS-III Logical Memory I (%ile) | 13.69 (±17.8) | 7.6 (15.6) | .40 |
| WMS-III Logical Memory II (%ile) | 17.2 (±23.5) | 10.9 (17.6) | .49 |

* Chi-square used for gender

MRI Protocol: A portion of the participants ($n = 22$, 11 bvFTD, 14 EOAD) underwent MRI with standardized protocol on the same 1.5T Siemens Avanto MRI scanner. High-resolution T1-weighted 3D MRI scans were acquired in the coronal plane using an MPRAGE sequence with the following acquisition parameters: TR=2000 ms, TE=2.49 ms, TI = 900ms, flip angle = 8°, slice thickness = 1mm, 25.6 cm field of view, and final voxel size of 1.0 mm³. An automated Brain Surface Algorithm (BSE) was applied, with manual editing to generate a de-skulled brain volume with the scalp, dura, and meninges removed. To adjust for global differences in brain positioning and scale across individuals, all scans were linearly registered to the stereotaxic space defined by the International Consortium for Brain Mapping (ICBM) with a 9-parameter transformation. Globally aligned images were resampled in an isotropic space of 230 voxels for each axis (x, y, and z) with a final voxel size of 1 mm³. To quantify 3D patterns of volumetric brain differences for each subject, an individual change map, or Jacobian map, was computed by non-linearly registering each individual scan to a template brain.

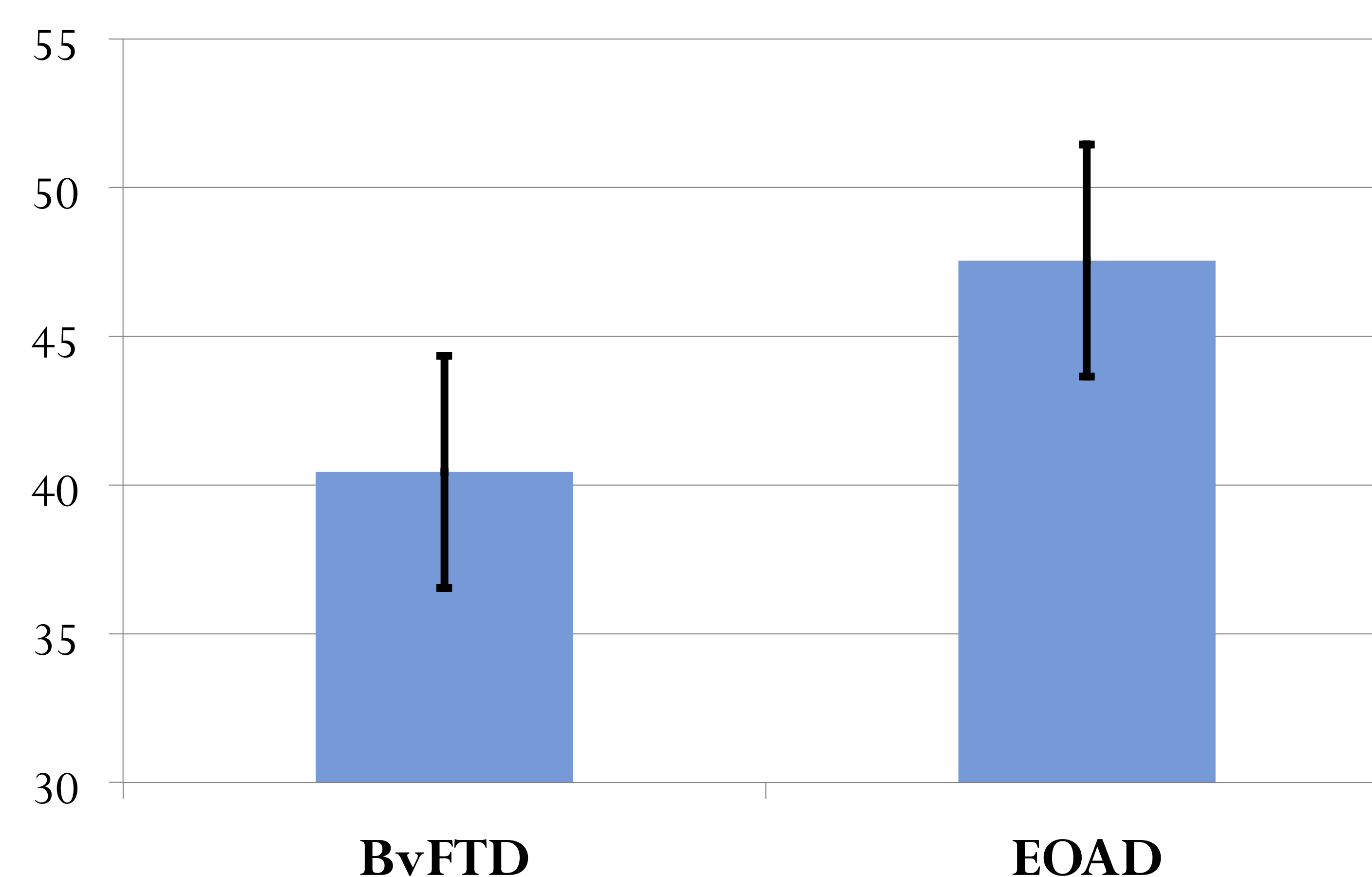
Results

Figure 1. Sample Analog Pyramids and Palm Trees Item



PPTT score was not significantly correlated with age, gender, education, or estimated premorbid verbal intelligence in the total sample (all p 's > .19). On cognitive measures, PPTT score was correlated with the MMSE ($r = .38$, $p = .02$) and the BNT ($r = .44$, $p = .04$); however, not with the COWAT FAS and Animals or Logical Memory I or II (p 's > .13).

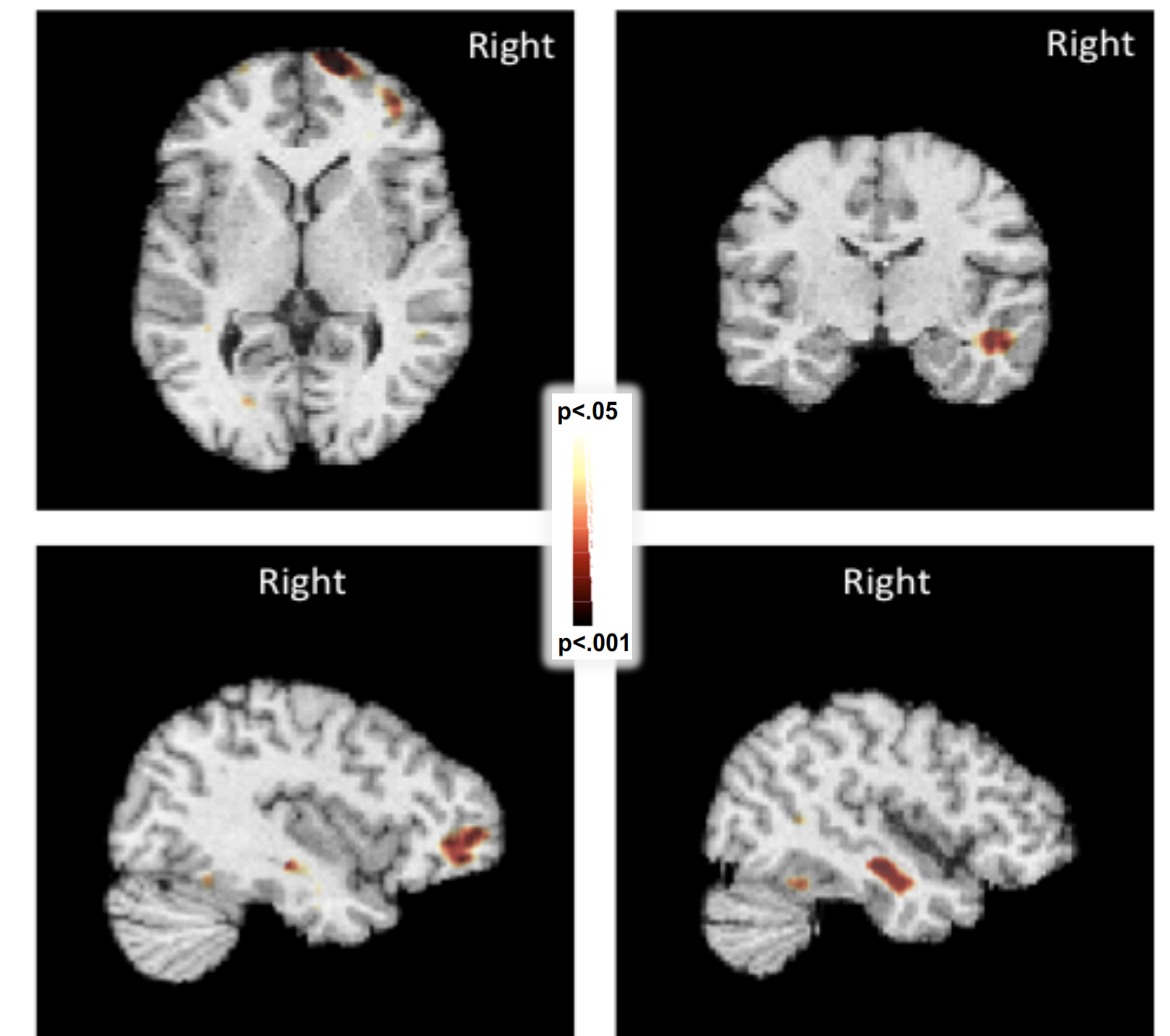
Figure 2. Pyramids and Palm Tree Test Performance



Note. Out of 52 items the bvFTD group performed worse (lower) than the EOAD group, $t(34) = -2.28$, $p = .03$. Bars are one \pm SD.

In a partial correlation lower PPTT score was significantly correlated with lower regional brain volume in the right frontal, $r(20) = .41$, $p = .03$) and the right temporal lobes ($r = .46$, $p = .02$), after controlling for age, education, and diagnosis. A trend was noted with the right orbitofrontal lobe ($r = .30$, $p = .09$).

Figure 2. TBM Voxel-wise partial correlation reveals the right frontal and right temporal regions are associated with lower PPTT scores.



Conclusions

Patients with bvFTD exhibit comparatively poorer nonverbal semantic memory (PPTT) than patients with EOAD which was associated with right frontotemporal atrophy in the total sample. While impaired semantic knowledge as assessed by the PPTT is associated with greater left-hemispheric involvement in the literature, decline in nonverbal semantic memory appears associated with right frontotemporal atrophy. While both bvFTD and EOAD patients exhibit semantic decline, bvFTD being a predominant right-sided frontotemporal disorder, may be particularly distinguished by nonverbal tests of semantic knowledge. The identification of degradation in nonverbal semantics in bvFTD warrants further exploration.

References

- Borroni, B., Grassi, M., Premi, E., Gazzina, S., Alberici, A., Cosseddu, M.,... Padovani, A. (2012). Neuroanatomical correlates of behavioural phenotypes in behavioural variant of frontotemporal dementia. *Behav Brain Res*, 235(2), 124-129. doi: 10.1016/j.bbr.2012.08.003
- Hutchinson, A.D., & Mathias, J. L. (2007). Neuropsychological deficits in frontotemporal dementia and Alzheimer's Disease: a meta-analytic review. *J Neurol Neurosurg Psychiatry*, 78(9), 917-928. doi: 10.1136/jnnp.2006.100669
- McGeown, W. J., Shanks, M. F., Forbes-McKay, K. E., & Venneri, A. (2009). Patterns of brain activity during a semantic task differentiate normal aging from early Alzheimer's disease. *Psychiatry Res*, 173(3), 218-227. doi: 10.1016/j.psychres.2008.10.005

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