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Distinct neuroanatomical substrates and cognitive mechanisms of figure copy performance in Alzheimer's disease and behavioral variant frontotemporal dementia

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ABSTRACT

Figure copy is the most common method of visual spatial assessment in dementia evaluations, but performance on this test may be multifactorial. We examined the neuroanatomical substrates of figure copy performance in 46 patients with Alzheimer's disease (AD) and 48 patients with the behavioral variant of Frontotemporal dementia (bvFTD). A group of 94 neurologically healthy controls were studied for comparison. In AD, poor figure copy correlated significantly with right parietal cortex volumes but not with right dorsolateral prefrontal cortex volumes, whereas in bvFTD, figure copy performance correlated significantly with right dorsolateral prefrontal cortex volumes and there was only a trend with right parietal cortex volumes. The cognitive processes associated with figure copy performance also differed by diagnostic group such that figure copy was associated with spatial perception and attention in AD and with spatial planning and working memory in bvFTD. Spatial planning accounted for unique variance in the figure copy performance of bvFTD even after accounting for spatial perception, attention, and working memory. These results suggest that figure copy performance in AD and bvFTD is not anatomically specific and is differentially impacted by bottom-up and top-down aspects of visual spatial processing. Alternative methods of visual spatial assessment for dementia evaluations are proposed.

Visual spatial impairments are often among the first symptoms of neurodegenerative disease. Patients in the early stages of Alzheimer's disease (AD) often get lost, forget where they placed their belongings, and have trouble driving or parking their car (delpolyi, Rankin, Mucke, Miller, & Gorno-Tempini, 2007; Hamilton, Fay, & Rockwood, 2009; Monacelli, Cushman, Kavcic, & Duffy, 2003; Pai & Jacobs, 2004). AD can impact a wide range of visual processes including contrast sensitivity, angle discrimination, motion perception, object recognition, mental rotation, and navigation learning, consistent with the impact of the disease on critical visual spatial processing areas in the parietal and temporal lobes (Rabinovici et al., 2007). Similarly, patients with the behavioral variant of frontotemporal dementia (bvFTD) can show deficits on visual tasks, but these deficits may be due to different mechanisms. The top-down control of visual processing has been shown to be affected in early bvFTD, including visual discrimination learning and the inhibition of spatial attention (Carey et al., 2008; Krueger et al., 2009; Rahman, Sahakian, Hodges, Rogers, & Robbins, 1999), and bvFTD patients tend to make more rule violation and perseveration errors on visual tasks (Carey et al., 2008; Chester et al., 2009; Possin et al., 2009). In contrast, bottom-up aspects of visual spatial cognition such as perceptual processing are relatively preserved in bvFTD (Possin, 2010). While the driving of patients with AD is described as unsteady with poor orientation, the driving style of patients with bvFTD has been characterized as risky with increased traffic violations and collisions (de Simone, Kaplan, Patronas, Wassermann, & Grafman, 2007; Ernst et al., 2007).

The most common method for evaluating visual spatial cognition in a dementia evaluation is to ask the patient to copy a figure. BvFTD patients generally outperform AD patients on figure copy tests (Diehl and Kurz, 2002; Elfgren et al., 1994; Mendez et al., 1996; Rascovsky et al., 2002; Rascovsky, Salmon, Hansen, & Galasko, 2008), although they have been equally impaired in some studies when the figure to be copied is complex (Frisoni et al., 1995; Kramer et al., 2003; Lindau, Almkvist, Johansson, & Wahlund, 1998; Pachana, Boone, Miller, Cummings, & Berman, 1996; Perry & Hodges, 2000). On these complex figure copy tests, such as the Rey-Osterrieth Complex Figure, performance is known to be influenced not only by parietally mediated skills such as visual spatial perception and integration, but also by frontally mediated executive skills such as organization, strategic processing, and working memory (Choi et al., 2004; Freeman et al., 2000; Hernandez et al., 2003; Varma et al., 1999). This task complexity makes it possible to

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explore differential mechanisms of impairment in different disorders. AD patients, for example, may be more likely to make spatial errors on figure copy, whereas bvFTD patients may be more likely to make organizational or perseverative errors with preserved spatial configuration (Thompson, Stopford, Snowden, & Neary, 2005).

The purpose of this study was to examine whether figure copy difficulties in AD and bvFTD were associated with different anatomical substrates and cognitive mechanisms. We focused our analyses on right-sided regions of interest based on previous studies, which suggest a preeminent role of right hemisphere dysfunction in causing visual spatial processing deficits in neurodegenerative disease (Boxer, Kramer, et al., 2003; Forster et al., 2010; Haxby et al., 1990; Mega et al., 1998; Teipel et al., 2006; Whitwell et al., 2007) (but see Teipel et al., 2006), and because of the high collinearity between corresponding brain regions in two hemispheres. We hypothesized that poor figure copy in AD would correlate with right parietal atrophy, but that in bvFTD it would correlate with right dorsolateral prefrontal atrophy. The parietal and dorsolateral prefrontal cortices were chosen as our primary regions of interest because they are understood to play critical roles in dorsal stream and top-down aspects of visual spatial processing, respectively (Kastner and Ungerleider, 2000; Miller and Cohen, 2001; Robertson, 2003), which are both important for good figure copy. Further, in patients with AD who present with primary visual spatial impairment (i.e., "Posterior Cortical Atrophy" syndrome), the right parietal or parietal-occipital cortex shows prominent atrophy and selective hypometabolism, and further, dorsal stream cognitive functions (e.g., features of Balint's syndrome) are more impaired than ventral stream functions at first presentation (McMonagle, Deering, Berliner, & Kertesz, 2006; Nestor, Caine, Fryer, Clarke, & Hodges, 2003; Whitwell et al., 2007). We also included right lateral temporal cortex, which is important for ventral visual stream processing and plays a role in figure copy (Boxer, Kramer, et al., 2003; Forster et al., 2010). In addition, we hypothesized that different cognitive mechanisms underlie poor figure copy in these groups. In particular, we posited that poor figure copy would be associated with spatial perception and attention impairment in AD and spatial planning and working memory impairment in bvFTD.

1. Method

1.1. Subjects

We searched the University of California, San Francisco Memory and Aging Center (UCSF MAC) database for all patients with a diagnosis of probable AD (McKhann et al., 1984), behavioral variant FTD (Neary et al., 1998), or neurologically healthy control who received a 1.5 T high-definition MR anatomical scan within 90 days of figure copy assessment and scored at least 18 on the Mini Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975). When there was more than one visit when the patients met these criteria, the first visit was selected. Diagnoses were derived based upon a comprehensive evaluation including neurological history and examination, a caregiver interview, and a brief neuropsychological assessment that included tests of memory, executive function, language, visual spatial skills, and mood using a previously described standard protocol (Kramer et al., 2003). Exclusionary criteria included presence of another neurologic condition affecting behavior or cognition, a longstanding Axis I psychiatric disorder, a metabolic disorder or major organ dysfunction, alcohol abuse or dependence within 5 years, head trauma (with loss of consciousness greater than 30 min), deteriorating cardiovascular disease, or prominent white matter disease. Forty-six patients with AD and 48 patients with bvFTD met these criteria and were included in the sample. A sample of 94 neurologically healthy controls was selected who met these criteria and were comparable in terms of age, sex, and education to the patients. The study was approved by the UCSF committee on human research. All subjects provided written informed consent before participating. Demographic and clinical variables are reported in Table 1.

1.2. Visual spatial assessment

All patients were administered the "Benson Figure," which is a simplified version of the Rey-Osterrieth figure that was developed by Frank Benson, M.D. (see Fig. 1). Patients were asked to copy the figure and no limit was placed on response time. Performance was scored on a scale from 0 to 17 that emphasized both accuracy of design elements and their placement. A subset of 22 patients with bvFTD and 16 patients with AD were administered the Visual Object and Space Perception Number-Location subtest, which is a test of spatial perception (Warrington & James, 1991); the Delis–Kaplan Executive Function System California Tower Test (Delis, Kaplan, & Kramer, 2001), which is a test of spatial planning; and the Wechsler Memory Scale – Third Edition Spatial Span Test (Wechsler, 1997), which is a test of spatial attention (forward span) and working memory (backward span). Not all patients and none of the controls were administered these tests because they have not always been part of our cognitive battery. Demographic information and clinical variables by diagnostic group are presented for the entire patient sample and for the subgroup who received the additional visual spatial assessment in Table 1.

Table 1
Demographic characteristics and figure copy scores by diagnostic group.

	N	Age	Education	Males	MMSE	Figure copy
Full sample						
bvFTD	48	61.8 (9.8)	16.6 (2.2)	33	26.0 (3.6)	14.6 (2.7)
AD	46	65.5 (9.7)	16.0 (3.1)	27	23.8 (3.1)	11.9 (5.4)
HC	94	63.7 (7.2)	16.6 (7.2)	56	29.5 (.7)	15.8 (1.0)
Visual spatial test sample						
bvFTD	22	59.7 (7.3)	17.3 (1.8)	18	26.6 (3.6)	15.6 (1.6)
AD	16	62.6 (8.2)	15.6 (3.4)	9	25.2 (2.0)	13.0 (5.0)

Values represent mean (s.d.).

1.3. Neuroimaging data

MRI scans were obtained on a 1.5-T Magnetom VISION system (Siemens, Iselin, NJ) at the San Francisco Veteran's Administration Hospital. A volumetric magnetization prepared rapid gradient-echo MRI (MPRG, TR/TE/TI = 10/4/300 milliseconds) was used to obtain T1-weighted (MP-RAGE) images of the entire brain, 15-degree flip angle, coronal orientation perpendicular to the double spin-echo sequence, 1.0 mm × 1.0 mm in-plane resolution and 1.5 mm slab thickness.

1.4. Freesurfer analyses

The T1 MPRAGE structural MR images were analyzed using Freesurfer, which is documented and freely available for download online at: http://surfer.nmr.mgh.harvard.edu/. Previous publications have detailed and validated the software (Segonne et al., 2004; Dale, Fischl, & Sereno, 1999; Fischl, Sereno, & Dale, 1999; Fischl, Liu, & Dale, 2001). Freesurfer is a surface-based structural MRI analysis tool that segments white matter and tessellates both gray and white matter surfaces. The procedure, in brief, involves the removal of non-brain tissue using a hybrid watershed/surface deformation procedure (Segonne et al., 2004) and intensity normalization (Sled et al., 1998), followed by automated Talairach transformation and volumetric segmentation of cortical and subcortical gray and white matter, subcortical limbic structures, basal ganglia and ventricles (Fischl et al., 2002; Fischl, Salat, et al., 2004). Estimated total intracranial volume (ICV) is calculated via an atlas normalization procedure (Buckner et al., 2004). The surfacing algorithm uses intensity and continuity data, and corrects topological defects to generate a continuous cortical ribbon used to calculate gray matter volume and thickness (Fischl & Dale, 2000; Fischl et al., 2001; Segonne et al., 2004; Segonne, Pacheco, & Fischl, 2007), a procedure validated against histological analysis (Rosas et al., 2002) and manual measurements (Kuperberg et al., 2003; Salat et al., 2004). This cortical surface is then inflated and registered to a spherical atlas and parcellated into regions of interest (ROI) based on gyral and sulcal structure (Fischl, Sereno, & Dale, 1999; Fischl, van der Kouwe, et al., 2004; Fischl, Sereno, Tootell, & Dale, 1999; Desikan et al., 2006). Cortical regions of interest were the right dorsolateral prefrontal cortex (rDLPFC), the right parietal cortex (rPC), the right lateral temporal cortex, the right entorhinal cortex, the right hippocampus, the right anterior cingulate, and the right orbitofrontal cortex (Desikan et al., 2006). The rDLPFC was defined as the middle frontal gyrus. The rPC did not include the postcentral gyrus because it is more important for somatosensory than visual processing and it is relatively spared in both AD and bvFTD (Rabinovici et al., 2007).

2. Results

Demographic characteristics and figure copy scores by diagnostic group are presented in Table 1. In the full sample, the diagnostic groups did not differ significantly in age, $F(2, 185) = 2.13$, $p = .12$, or in the proportion of males, $F(2, 185) = .68$, $p = .51$. MMSE scores differed between the groups, $F(2, 185) = 95.55$, $p < .001$. Tukey follow-up procedure ($p < .05$) indicated that the ADs scored lower on the MMSE than the bvFTD patients, $d = .65$, and the controls, $d = 2.54$, and the bvFTD patients scored lower than the controls, $d = 1.35$. Figure copy performance differed between the groups, $F(2,$