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The functional oculomotor network and saccadic cognitive control in healthy elders

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ABSTRACT

Decline in executive function is the most common age-associated cognitive deficit and may be a risk factor for neurodegenerative disease. The antisaccade (AS) task involves inhibition of a prepotent visuomotor response and is a well-validated executive function test in aging and neurodegeneration. We investigated the functional connectivity of the cortical oculomotor network during successful AS performance in healthy elders. Elevated BOLD activity in the right lateral frontal eye field (rlatFEF), a region linked to volume loss in individuals with impaired AS performance, was associated with worse AS performance and weaker network efficiency. In contrast, hub integrity of the right dorsolateral prefrontal cortex (rDLPFC) and anterior cingulate cortex (rACC) was associated with better AS performance. These data suggest that while several right lateral frontal regions are central nodes in the oculomotor network, the rlatFEF demonstrates early neural aberrations and the rDLPFC and rACC continue to support inhibitory cognitive control in healthy elders. We conclude that alterations in AS task functional connectivity, quantified as hub and network efficiency, may be clinically-relevant biomarkers of cognitive decline in executive functioning.

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Introduction

Aging is commonly associated with changes in cognitive function, which may reflect "normal aging" or an underlying neuropathological process. One of the earliest cognitive domains to exhibit age-related changes is executive function, which comprises higher-level cognitive control, such as planning, switching and inhibiting lower-level automatic functions (Stuss, 2007). Although age-related changes in executive function do not necessarily predict future cognitive decline, they may reflect underlying neuropathology of Alzheimer's disease or other forms of dementia (Grady, 2012). Thus, understanding the mechanisms underlying executive dysfunction in aging is critical for improving assessment of individuals at risk for future cognitive decline.

The antisaccade (AS) task has emerged as a sensitive tool for evaluating executive function and was recently validated in a multicenter study of normal elders and individuals with neurological disease (Hellmuth et al., 2012). It is a simple oculomotor paradigm that is commonly used to study basic aspects of cognitive control and inhibition, as well as cognitive changes in aging and neurological disease (Hallet, 1978; Luna et al., 2008; Munoz and Everling, 2004). The task requires individuals to inhibit a prepotent, visually-guided saccade towards a peripheral target and to generate a voluntary saccade in the opposite direction. In healthy elders, impaired AS performance is strongly correlated with executive dysfunction and frontal oculomotor network brain volume (Mirsky et al., 2011). The AS task is also highly sensitive to changes in brain structure that occur with neurodegenerative diseases of aging (Boxer et al., 2006, 2012; Garbutt et al., 2008), including the detection of presymptomatic neurodegeneration (Golding et al., 2006). Although a variety of studies have identified correlations between advancing age and declining AS performance (Klein et al., 2000; Luna et al., 2008; Olincy et al., 1997), there is considerable variability in AS performance in healthy elders. Elucidating the neural mechanisms responsible for this heterogeneous AS performance could lead to better stratification of healthy elders at risk of future cognitive decline or potentially new strategies for mitigating age-associated executive dysfunction.

Functional magnetic resonance imaging (fMRI) studies of the AS task in young adults have demonstrated greater activation of frontal and parietal lobe oculomotor control regions during AS conditions relative to reflexive, visually-guided prosaccade (PS) control conditions (Connolly et al., 2002; Curtis and D'Esposito, 2003). This is consistent with human lesion studies of AS task performance that implicated similar structures, particularly the dorsolateral prefrontal cortex (DLPFC) and anterior cingulate gyrus (ACC), as critical for correct performance (Hodgson et al., 2007; Pierrot-Deseilligny et al., 2003). In neurological diseases, such as schizophrenia, AS fMRI has elucidated neural mechanisms associated with executive dysfunction, revealing connectivity changes within the oculomotor network that correlate with impaired inhibition and error monitoring (Polli et al., 2008; Tu et al., 2010).

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To investigate the neural mechanisms of executive function in healthy elders, we conducted an fMRI study of AS task performance to measure neural integrity in the cortical oculomotor network. Based on a previous study that found a significant relationship between volume loss in the right lateral frontal eye field (rlatFEF) and impaired AS task performance in patients (Boxer et al., 2006), we hypothesized that the rlatFEF would be an early site of executive dysfunction and that other key frontal regions, such as the DLPFC, would demonstrate compensatory activity to maintain performance in healthy elders.

Methods

Participants

Forty-five healthy elders (age 70.4 ± 7.1 years; range 57–85 years; 22 females) gave written informed consent to participate in this study, which was approved by the University of California, San Francisco Committee for Human Research. Two participants were removed from the group analysis due to poor data quality from excessive head motion. Participants were recruited from the University of California, San Francisco Memory and Aging center. Each participant underwent an extensive clinical evaluation including a detailed history, physical and neurological examination, neuropsychological testing, and study partner interview. The interview with the study partner involved the Clinical Dementia Rating (CDR) to assess functional abilities and the Neuropsychiatric Inventory (NPI) to evaluate behavior (Berg, 1988; Cummings et al., 1994). Screening for depression was done using the 30-item Geriatric Depression Scale (GDS) (Yesavage et al., 1983).

Participants had to have a CDR sum of boxes score of 0, a Mini-Mental State Examination (Folstein et al., 1975) score ≥28 and score within 1 SD of normative age and education-matched values on all neuropsychological tests. Of note, the selection of healthy elders without signs of cognitive impairment on traditional neuropsychological tests fits the study goal of examining subtle neural changes associated with executive function using a sensitive and validated AS task. Participants were excluded if they met criteria for mild cognitive impairment (Petersen et al., 1999) or dementia (McKhann et al., 2011), had a neurological disorder that could affect cognition, significant psychiatric illness, head trauma with loss of consciousness greater than 10 min, severe sensory deficits, substance abuse, or were taking medications that affect cognition.

Neuropsychological testing

Individuals were administered a comprehensive battery of neuropsychological tests assessing executive function, language, visuospatial skill, and memory. Tests of executive function included a modified Trailmaking Test (time to complete), DKEFS Design Fluency Condition 1 (number of unique designs in 60 s), Stroop interference (number correct in 60 s), letter fluency (D words in 60 s), calculations (out of 5), abstractions (3 similarities, 3 proverbs), and backward digit span (longest length) (Kramer et al., 2003). Tests of language included a 15-item Boston Naming Test (number correct) (Kaplan et al., 1983) and Category fluency (number of animals in 60 s) (Goodglass and Kaplan, 1983). Tests of visuospatial function included copy of the Benson figure and Number Location subtest from The Visual Object and Space Perception Battery (VOSP) (Warrington and James, 1991). Tests of memory included 20-minute delayed recall on California Verbal Learning Test-II (Delis et al., 2000) and 10-minute recall of the Benson figure (Possin et al., 2011).

Experimental design

Participants practiced a computerized version of the task prior to the fMRI scanning session to ensure their understanding of the task. Participants viewed the stimulus presentation monitor through a mirror located in front of their eyes. Stimuli were presented using E-Prime 2.0 software (Psychology Software Tools, Inc.: Pittsburgh, PA) (see Fig. 1). Participants completed three sessions during the fMRI block-design study. Each session consisted of four randomized blocks of each condition (AS and PS). Each block consisted of 10 trials, for a total of 120 trials of each condition (3 sessions × 4 blocks × 10 trials). At the start of each block, the participant viewed instructions to "Follow the dot" (PS condition) or "Look away from the dot" (AS condition). Participants were presented with a central fixation spot containing a "+" symbol (PS condition) or "−" symbol (AS condition) for 300–500 ms. The fixation spot remained illuminated for 1300–1500 ms followed by a 200 ms gap. A target appeared 7° to the right or left of the center for 1000 ms. Participants either looked at the eccentric target (PS condition) or in the opposite direction of the eccentric target (AS condition). A 1000 ms blank screen and 2000–6000 ms fixation period followed.

fMRI eye tracking

Eye movements during the fMRI task were recorded with an MRI-compatible infrared eye tracking system (Applied Sciences Laboratory Eye-Trac 6). Eye movement data were sampled at 120 Hz. Eye movement traces were analyzed interactively offline using customized Matlab software (Mathworks, Natick, MA; release 2008b). To ensure fidelity of eye tracking data, all eye position traces were visually inspected for quality and any trials with unclear movements or missing data during the saccadic epoch were discarded. Direction was determined by marking the endpoint position of the first eye movement. Prosaccades were discarded if the eye movement was in the wrong direction. Antisaccades were considered correct if the first eye movement was in the direction opposite the target location. Self-corrected AS errors were recorded, but were not included in the AS task performance measure.

fMRI data acquisition

All fMRI data was collected on a Siemens 3T MAGNETOM Trio with stimuli presented on an LCD monitor positioned behind the head of the participants and viewed using a mirror rigidly attached to a 12-channel head coil. Echo planar imaging data were acquired (FA = 77°, TE = 28 ms, TR = 2 s) with 29 interleaved axial slices and a 1.8 × 1.8 × 3 mm voxel size (FOV = 23 cm; 128 × 128 matrix). All pre-preprocessing of the data was conducted in SPM5 (Statistical Parametric Mapping, Wellcome Department of Imaging Neuroscience, London, England). Raw blood oxygen level dependent (BOLD) data was corrected offline for slice-timing acquisition and motion-artifacts. A 5 mm isotropic Gaussian smoothing kernel was applied prior to modeling the data. To aid in anatomical localizations of BOLD activity, high-resolution T1-MPRAGE images were acquired (1 × 1 × 1 mm voxel size; FOV = 160 × 240 × 256 mm, TR = 2300 ms, TE = 3 ms, FA = 9°).

Separate regressors were used to model the entire period of each stage (preparation and response) of the trial and convolved with a canonical Gaussian hemodynamic response function using SPM5. The single instruction period at the start of each block was removed from the analysis. In addition, three translational (X, Y, Z) and three rotational (pitch, roll, yaw) motion parameters were included in the GLM to account for motion-related artifacts. The resulting regression vector yielded scalar beta weights corresponding to the relative changes in signal strength associated with a particular trial stage. Correct and incorrect trials were modeled separately and only correct trials were subjected to further analysis. The preparation stage of the trial (cue, fixation and gap) was the focus of the analysis based on previous studies that demonstrated action planning occurs just prior to the presentation of the target in frontal and parietal regions (Brown et al., 2007; Curtis and Connolly, 2008).