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Anti-saccade performance predicts executive function and brain structure in normal elders

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Abstract

Objective—To assess the neuropsychological and anatomical correlates of anti-saccade (AS) task performance in normal elders.

Background—The AS task correlates with neuropsychological measures of executive function and frontal lobe volume in neurological diseases, but has not been studied in a well-characterized normal elderly population. Because executive dysfunction can indicate an increased risk for cognitive decline in cognitively normal elders, we hypothesized that AS performance might be a sensitive test of age-related processes that impair cognition.

Method—The percentage of correct AS responses was evaluated in forty-eight normal elderly subjects and compared with neuropsychological test performance using linear regression analysis and gray matter volume measured on MRI scans using voxel-based morphometry.

Results—The percentage of correct AS responses was associated with measures of executive function, including modified trails, design fluency, Stroop inhibition, abstraction, and backward digit span, and correlated with gray matter volume in two brain regions involved in inhibitory control: the left inferior frontal junction and the right supplementary eye field. The association of AS correct responses with neuropsychological measures of executive function was strongest in individuals with fewer years of education.

Conclusions—The AS task is sensitive to executive dysfunction and frontal lobe structural alterations in normal elders.

Keywords

anti-saccade; normal aging; executive function; frontal lobe; cognitive reserve

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1. Introduction

Healthy aging is characterized by changes in brain structure and function. In normal elders, reduced gray matter volumes in the hippocampus and cerebral cortex are associated with impairment in memory and executive function, respectively. Such age-related changes in the brain are hypothesized to indicate an increased risk of cognitive decline, particularly if they are attributable to incipient neurodegenerative processes. [1, 2] Moreover, impaired performance on neuropsychological tests of executive function precedes cognitive decline in many normal elders [1, 3-5] and conversion to Alzheimer's disease in elders with mild cognitive impairment. [3] Potential mechanisms of age-related declines in executive function may include alterations in the structure of specific cortical and subcortical brain networks due to incipient neurodegenerative disease, effects of genetic risk factors such as apolipoprotein E (ApoE) 4 alleles, or reductions in cognitive reserve. [6-8] Because neuropsychological tests of executive function may have multiple cognitive components, more precise tools are needed to better understand the effects of aging on executive function and the clinical significance of executive dysfunction in normal elders.

The anti-saccade (AS) task [9] is a well-characterized measure of inhibitory control that is easily quantifiable and highly-correlated with neuropsychological tests of executive function in a variety of neurological and psychiatric disorders. [10-18] AS performance is tightly regulated by a cortical network involved in inhibition that includes the frontal, supplemental and parietal eye fields (FEF, SEF and PEF, respectively)[12, 19-21] as well as the dorsolateral prefrontal cortex (DLPFC). [22, 23] Other regions, such as the superior colliculus, striatum, cerebellum, and the inferior frontal junction (IFJ) [26] have also been implicated in successful AS performance.[12, 24, 25] The percentage of correct AS responses is sensitive to asymptomatic brain dysfunction in Huntington disease and is abnormal in first degree relatives of schizophrenics,[27, 28] suggesting that the AS task might be a candidate preclinical marker of processes that impair frontal lobe function. Although the percentage of correct AS responses declines with advancing age in normal elders, [29-32] it remains unclear whether such change is associated with altered cognitive function or brain structure, both of which are associated with age-related cognitive decline.

The goal of this study was to determine the neuropsychological and anatomical correlates of AS task performance in normal elders. We hypothesized that performance on the AS task would predict executive function and frontal lobe structure within the oculomotor network, supporting future use of the AS task to detect executive dysfunction, and potentially predict cognitive decline in normal elders.

2. Materials and Methods

2.1. Subjects

Forty-eight voluntary participants (mean age 67.1, range 48-79; 17 male and 31 female) were evaluated at the University of California, San Francisco (UCSF) Memory and Aging Center. Subjects received neurological examination, neuropsychological testing, brain MRI scans, and eye movement measurements within a three month window. All subjects had no neurological complaints, normal neurological and neuropsychological examinations [14] and clinical dementia rating (CDR) sum of boxes scores of 0. [33] ApoE4 genotypes were determined as previously described. [34] All procedures were approved by the UCSF Committee on Human Research, and written informed consent was obtained from all participants.

2.2. Eye movement recording

Eye movement recordings were obtained and analyzed using standard protocols as previously described. [14] Briefly, subjects were seated with their heads stabilized and presented with stimuli that consisted of small white targets on a dark CRT monitor located 80 cm away in a dark room. The movements of the right eye were recorded on a Generation 6.1 Dual Purkinje Image Eye Tracker (Fourward Technologies, Buena Vista, VA) at 1000 samples/s and low pass filtered at 330 Hz.

Stimuli were presented in a "block design." First, visually-guided prosaccade (PS) trials, consisting of randomly interleaved 5 and 10° targets presented up, down, left, or right of a central fixation point, were run to verify normal oculomotor responses. Each trial began with illumination of a central fixation spot for 1000 ms. When the fixation light was extinguished, targets appeared after a 200 ms gap (Figure 1A). The eccentric target remained illuminated for 1000 ms. Subjects were instructed to look at the central fixation point while it was illuminated, then to look at the eccentric target; each target was presented 10-15 times. Second, anti-saccade (AS) trials began with the illumination of the central fixation point for 1000 ms. After a 200 ms gap, targets appeared 10° to the left or right and remained illuminated for 1000 ms. Subjects were instructed to look in the opposite direction of target movement and to correct mistakes if they erroneously followed the target; at least 18 AS trials were recorded in each direction.

Horizontal 10° PS and AS eye movement data were analyzed interactively offline. [14] Briefly, saccade latencies were computed as the duration of the interval from the appearance of an eccentric target to the onset of the first eye movement. Saccade first and end gains were computed as the difference in eye position between fixation and the end of the first movement and the final eye position for the trial, respectively. The peak saccadic velocity was determined as the maximum eye velocity during the initial saccade. AS responses were considered to be correct if the first eye movement after eccentric target onset had an amplitude greater than 3° in the direction opposite the target (Figure 1C), and self-corrected AS errors were defined as antisaccades that occurred within 500 ms of the initial erroneous PS (Figure 1D).

2.3. Neuropsychological and clinical evaluation

Tests of general cognition and functional abilities included the Mini-Mental State Examination (MMSE) [35] and the clinical dementia rating (CDR), [33] and psychological status was assessed by the Geriatric Depression Scale (GDS). [36] Neuropsychological tests of executive function assessed set-shifting (time to make all correct lines in a modified trailmaking test), [37] inhibition (the Stroop interference condition), [37] generation (trial 1 of the design fluency subtest from the Delis-Kaplan Executive Function System), [38] and working memory (longest correct backward digit span), [39] as well as the ability to perform 5 arithmetic calculations and interpret 3 similarities and 3 proverbs (abstraction). Language skill was evaluated by phonemic fluency (number of D-words in 1 minute), category fluency (number of animals in 1 minute) and a 15-item Boston Naming Test (BNT). [40] Visuospatial abilities were tested by a copy of a simplified version of the Rey-Osterrieth figure and the Number Location condition from the Visual Object Spatial Perception (VOSP) battery. [41] Memory was assessed by a 10-minute recall of the same simplified version of the Rey-Osterrieth figure.

2.4. Magnetic Resonance Images

MRI scans were obtained for forty-four of the subjects on either a 1.5 Tesla Magnetom VISION system (n = 29) or a 3 Tesla TIM Trio scanner (n = 15; both Siemens Inc., Iselin, NJ). Scanning parameters for the 1.5 Tesla scanner have been previously described. [13] For

the 3 Tesla scanner, scan parameters were: TR/TE/T1, 2300/3/900 ms, flip angle 9°, 26 cm field of view (FOV), 256 × 256 in plane matrix, with a phase FOV of 0.94 and slice thickness of 1.0 mm. Three-dimensional T1-weighted scans were used for voxel-based morphometry (VBM) analysis. Images were preprocessed and statistically analyzed with the SPM5 software package (http://www.fil.ion.ucl.ac.uk/spm/), using standard procedures [42, 43] outlined previously. [13] We modeled the relationship between the percentage of correct AS responses and regional gray matter volume as an ANCOVA with age, gender, education, scanner model on which data were acquired, and total intracranial volume (TIV) as covariates of no interest. Since we had an *a priori* hypothesis about the involvement of inhibitory control network nodes, we used a region of interest (ROI) approach [13] focused on 12 mm spherical ROIs surrounding the peak associated BOLD activations from published functional MRI studies that used AS [44, 45] and task-shifting [46] paradigms to identify 5 regions: frontal eye fields (FEF), supplementary eye fields (SEF), inferior frontal junctions (IFJ), dorsolateral prefrontal cortex (DLPFC), and parietal eye fields (PEF; Figure 2; Supplementary Table 1). In the absence of published bilateral coordinates, the inverse X value (MNI coordinates) of unilateral ROIs was used to create the contralateral ROI. A statistical threshold of $p < 0.05$ corrected for multiple comparisons using family wise error (FWE) was accepted. To address whether volume changes in brain regions outside of the ROIs were related to the percentage of correct AS responses, we also analyzed all brain gray matter voxels simultaneously, at a lower statistical threshold ($p < 0.1$) to increase sensitivity.

2.5. Statistics

We calculated bivariate Pearson correlations of AS parameters (percentage of correct AS responses, percentage of correct AS responses plus self-corrected errors, and mean response latency) and PS parameters (mean response latency, peak velocity, first gain, and final gain) with age, years of education (education), GDS scores, and MMSE. We also compared each parameter using independent t-tests between groups based on gender and ApoE4 genotype. Eye movement parameters and neuropsychological scores were compared between higher and lower AS performers split by median percentage of correct AS responses (81.6%) using independent t-tests. The association of the percentage of correct AS responses and the percentage of correct AS responses plus self-corrected errors with neuropsychological performance was determined using linear regression with models including age, gender and education as independent variables and neuropsychological measures as the dependent variable. We considered the neuropsychological measurements to come from four domains (executive function, language, visuospatial, and memory) and corrected our analyses for multiple tests within each domain using false discovery rate. [47] The interaction between education and the percentage of correct AS responses and the percentage of correct AS responses plus self-corrected errors was detected by adding interaction terms to the previous models. Models of executive function performance showed an interaction between education and the percentage of correct AS responses, these analyses were repeated by removing education as a regressor and splitting subjects based on the median education (18) into lower (range 10-17; n = 20) and higher (range 18-22; n = 28) education groups. For all tests, significance was accepted at the $p < 0.05$ level. All analyses were performed using SPSS software (version 17.0, SPSS Inc., Chicago, IL).

3. Results

Subjects completed the AS task with a mean percentage of correct AS responses (± SD) of 76.0% (± 20.4), and 87.6% (± 19.9) of errors were self-corrected (Table 1; Figure 1). PS velocity decreased with age ($B = -0.351$; $p = 0.016$); otherwise, there was no relationship between PS or AS parameters and demographic variables, including age, gender, education, GDS score, MMSE, or ApoE4 genotype (Supplementary Figure 1; Supplementary Table 2).

Lower AS performers (percentage of correct AS responses below the median of 81.6%) corrected more errors compared with higher AS performers (percentage of correct AS responses above the median; $p = 0.012$, t-test) such that the aggregate measure of total correct responses (percentage of correct AS responses plus self-corrected errors) was similar between groups. There was no difference between PS characteristics in the higher and lower AS performance groups.

3.1. AS performance predicts executive function

Our analyses detected statistically significant associations of the percentage of correct AS responses with several measures of executive function in linear regression analyses, after controlling for age, gender and education: design fluency correct ($p = 0.006$), modified trails time ($p = 0.025$), Stroop inhibition correct ($p = 0.027$), and abstraction ($p = 0.020$; Table 2, Figure 3). However, only design fluency correct was statistically significant after applying the false discovery rate (FDR) correction. The percentage of correct AS responses was not associated with performance on neuropsychological tests of language, visuospatial skill or memory. Inclusion of ApoE4 genotype in the regression models did not alter the relationship between percentage of correct AS responses and executive function measures (data not shown). The percentage of correct AS responses plus self-corrected errors correlated with modified trails time ($p = 0.004$, $p < 0.05$ FDR corrected) and backward digit span ($p = 0.021$). Lower AS performers had lower design fluency, Stroop inhibition, and modified Rey recall scores than higher AS performers ($p < 0.05$; t-test), but there were no other differences between the groups' neuropsychological performance (Table 1).

There was an interaction between education and the percentage of correct AS responses in predicting modified trails time ($B = 0.107$, $p = 0.001$), which led us to explore the relationship between AS and executive function test performance in subgroups stratified by education (Figure 3A). In the lower education group (below the median of 18 years), the percentage of correct AS responses was positively associated with three executive function measures (design fluency correct, $B = 0.094$, $p < 0.001$; modified trails time, $B = -0.513$, $p = 0.005$; abstraction, $B = 0.018$, $p = 0.031$) and negatively associated with modified trails errors ($B = -0.017$, $p = 0.021$) and Stroop inhibition errors ($B = -0.009$, $p = 0.042$). Design fluency and modified trails time remained significantly associated with AS performance after FDR correction. In contrast, no measures were associated with AS performance in the higher education group (education including and above the median of 18 years).

The percentage of correct AS responses plus self-corrected errors was associated with modified trails time ($B = -2.26$, $p = 0.004$; $p < 0.05$ FDR corrected), modified trails errors ($B = -0.091$, $p = 0.002$; $p < 0.05$ FDR corrected), Stroop inhibition errors ($B = -0.046$, $p = 0.018$), and backward digit span ($B = 0.130$, $p = 0.034$) in the lower education group, but not in the higher education group. In all analyses, a higher percentage of correct AS responses predicted better neuropsychological performance.

Since it is possible that the difference in AS-neuropsychological performance correlations in the lower and higher education groups could be confounded by unequal variance in the behavioral measures (due to ceiling effects), we compared the variance of each of the neuropsychological measurements in both groups (Table 3). Variance was similar in the lower and higher education subjects for design fluency correct, Stroop inhibition correct, and abstraction, yet unequal for modified trails time ($p = 0.004$; Levene's test), modified trails errors ($p = 0.048$) and Stroop inhibition errors ($p = 0.009$).

3.2. AS performance correlates with inhibitory control network gray matter volume

To investigate whether structural differences in the inhibitory control network could account for variability in the percentage of correct AS responses in normal elders, we performed a VBM analysis that focused on regions of interest (ROIs) including the dorsolateral prefrontal cortex (DLPFC), inferior frontal junction (IFJ), frontal eye fields (FEF), supplementary eye fields (SEF), and parietal eye fields (PEF; Figure 2, Supplementary Table 1). Controlling for age, gender, education, MR scanner on which data were acquired, and TIV, we found that the percentage of correct AS responses positively correlated with gray matter volume in the right SEF (MNI coordinates [x,y,z]: 14,−6,60; $p = 0.015$, FWE corrected) and left IFJ (−34,10,34; $p = 0.013$, FWE corrected). No significant correlations were found in the other ROIs. A whole-brain analysis using a less stringent statistical threshold ($p < 0.1$, FWE corrected) identified the same SEF and IFJ regions, but failed to identify any other brain regions correlated with the percentage of correct AS responses.

4. Discussion

Here we demonstrate that the AS task is a sensitive marker of executive dysfunction and frontal lobe structure in a well-characterized group of cognitively and functionally normal elders. Even after controlling for demographic variables such as age, gender, education, and ApoE4 genotype, the percentage of correct AS responses was related to executive function, most significantly, set-shifting on the modified trails task and generation on the design fluency task (Table 2, Figure 3). The percentage of correct AS responses plus self-corrected errors also predicted modified trails time. In contrast, the percentage of correct AS responses was not associated with performance on tests of language, visuospatial skill or memory. The percentage of correct AS responses correlated with gray matter volume in two nodes of the inhibitory control network: the right supplementary eye field (SEF) and left inferior frontal junction (IFJ). These results suggest that the AS task is sensitive to subtle frontal lobe dysfunction in normal elders that might indicate an increased risk of future cognitive decline.

The strong association of the percentage of correct AS responses (with or without self-corrected errors) with a variety of measures of executive function in normal elders is consistent with work in patients with neurological disease. We have previously demonstrated that patients with neurodegenerative dementia show similar correlations between AS task and neuropsychological performance, most strongly on executive function measures, [13] and similar correlations have also been identified in schizophrenic patients. [10, 15-18] As might be expected, given the greater variability in scores in demented subjects, the correlations between AS and neuropsychological performance are stronger and more widely distributed across cognitive domains in individuals with dementia than in normal elders.

Similar to our previous work in dementia, [13] we also identified a correlation between the percentage of correct AS responses and gray matter volume in both medial and lateral frontal lobe inhibitory control regions in normal elders. Both the right SEF and left IFJ gray matter volume were correlated with the percentage of correct AS responses; however, like the neuropsychology data, the strength of the association identified in the current analysis was smaller than that previously identified in dementia patients. The right SEF region that correlated with the percentage of correct AS responses is proximal to the right premotor region previously reported to be correlated with the percentage of correct AS responses in younger normal subjects (mean age 33 years). [48] Previous lesion studies have identified the DLPFC as critical for AS performance, but our analyses did not show a direct association of AS performance with DLPFC gray matter volume using a ROI based on published fMRI-derived coordinates. However, the IFJ region where gray matter volume correlated with the

percentage of correct AS responses would have been encompassed by the lesions designated as DLPFC in a previous study that identified DLPFC as important for saccade inhibition in younger adults.[22] Thus, the IFJ area we identified may have been involved in saccade inhibition in the lesion study. Together, the SEF and IFJ findings suggest that a low percentage of correct AS responses is associated with structural alterations within the same frontal lobe inhibitory control network nodes in normal older adults**,** adults with focal cortical lesions, and adults with neurodegenerative dementia, and that differences in severity of AS impairment reflect differences in the degree of inhibitory control network structural abnormality. We speculate that these structural abnormalities in our normal elders may arise either from genetic or developmental variation in frontal lobe structure or from degeneration of this network due to aging or incipient neurodegenerative disease.

Like a previous study that focused on normal elders, [31] we found no correlation between age and performance on the AS task with a 200 ms gap prior to stimulus onset. However, other studies have identified a relationship between age and AS performance. [29-32] In addition to differences in the AS stimuli that were used, several methodological considerations could account for the disparity between our findings and those from other groups. For example, previous studies did not account for education in their models and cognitive function was not rigorously assessed. Because age is a risk factor for Alzheimer's disease, it is possible that some of the older subjects in these studies had subtle cognitive impairments that differed from the younger subjects.

Our findings support a possible role for cognitive reserve (CR) in maintaining executive function in normal elders. The CR hypothesis posits that cognitive decline resulting from brain damage can be limited by engaging other brain networks and mechanisms to compensate for a loss of function and that education is a surrogate for CR. [6, 49, 50] We found that the association of correct AS performance with executive function was most prominent in the lower education group (Table 2, Figure 3) Education did not correlate with the percentage of correct AS responses, suggesting that education alone cannot account for the observed variability in the AS performance in our subjects. The lack of association between AS and executive function in the higher education group therefore suggests that CR may play a role in mitigating the effects of inhibitory control network dysfunction to maintain executive function in normal elders. This might occur through greater compensatory activity or by recruiting of different networks in individuals with greater education and, by extension, CR.

Limitations of this analysis are the overall high levels of education in our subjects and the greater variance in performance in the lower education group for several tasks (modified trails time, modified trails errors and Stroop inhibition errors; Table 3) that demonstrated a differential effect of education on the ability of the percentage of correct AS responses to predict executive function performance, suggesting that ceiling effects in executive function performance in the higher education group could explain part of this effect. However, this would not account for the effects of education on design fluency, Stroop inhibition or abstraction. More work using executive function tasks that are less vulnerable to ceiling effects in individuals with higher levels of education, and testing of a cohort with a broader range of education, will be necessary to confirm and better understand the potential role of CR in maintaining executive function in the setting of inhibitory control network damage.

We speculate that impaired performance on the AS task could serve as a marker of elevated risk of cognitive decline in normal elders. In a number of normal aging studies, declines in executive function precede age-related memory decline, [1, 3-5] however the mechanisms and clinical significance of these findings are not known. Since a lower percentage of AS correct responses indicates increased genetic risk of schizophrenia [51] and is a preclinical marker of

Huntington disease, [27, 28] such findings in normal elders could indicate an alteration in frontal lobe structure due to a genetic risk factor or incipient neurodegenerative process, such as Alzheimer's. By analogy to amyloid positron emission tomography scans [52, 53] or cerebrospinal fluid amyloid and tau levels [54] that can identify incipient AD pathology in normal elders, the AS task may be sensitive to frontal lobe processes that increase risk of cognitive decline.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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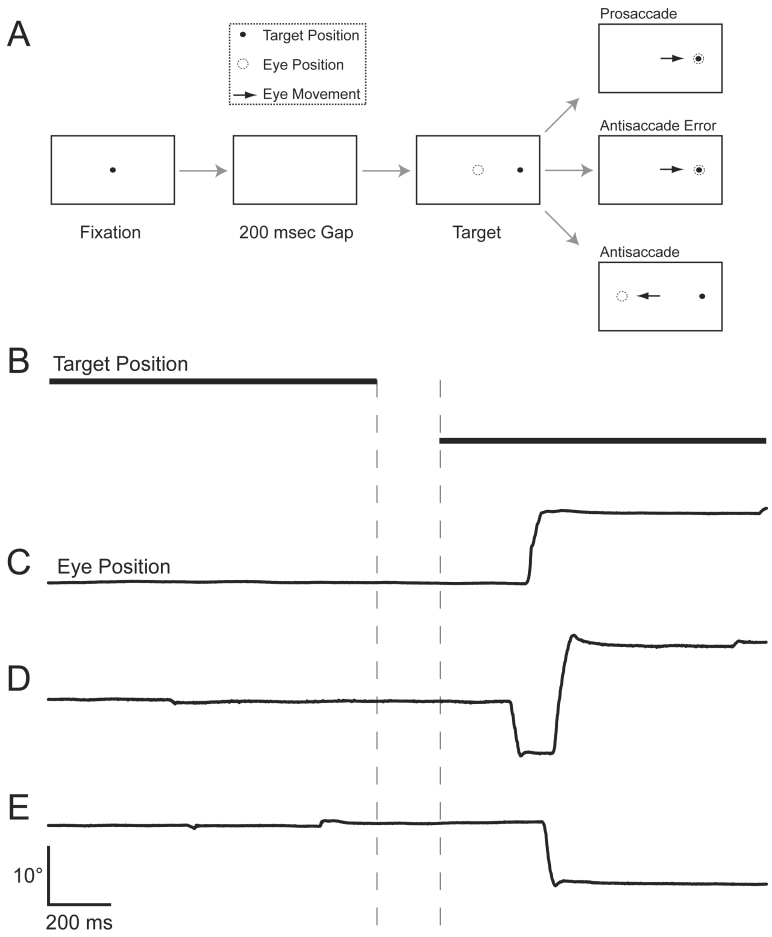

Figure 1. Eye movement paradigm and traces

The eye movement paradigm consisted of 1000 ms of central fixation followed by a 200 ms gap and an eccentric target for 1000 ms (illustrated as moving to the right) **(A)**. Relative to target position **(B)**, representative eye traces for a correct response **(C)**, a self-corrected error response **(D)** and an uncorrected error response **(E)** are shown. In **B-E**, down indicates left and up indicates right; this particular trial indicates a target to the left.

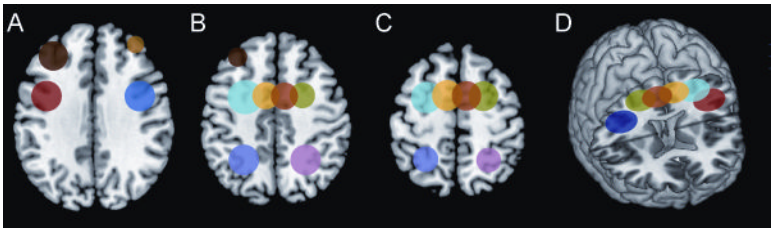

Figure 2. ROIs used in VBM analysis

Regions of interest are visualized in axial views at z values of 35 mm **(A)**, 45 mm **(B)**, 55 mm **(C)**, as well as a rendered whole brain image with a cutout at y value of 0 mm **(D)** on the CH2bet template. Brown = left DLPFC, red = left IFJ, light blue = left FEF, yellow = left SEF, orange = right SEF, green = right FEF, dark blue = right IFJ, tan = right DLPFC, purple = left PEF, pink = right PEF.

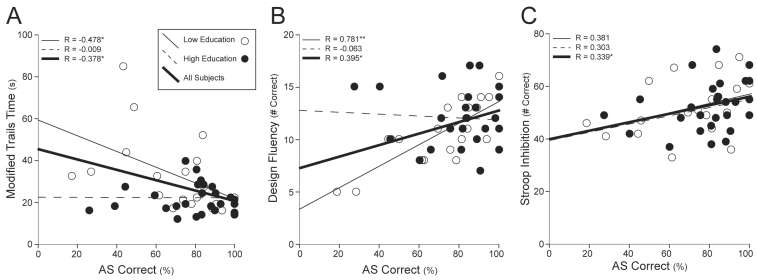

Figure 3. AS performance predicts executive function

Scatter plots demonstrate the relationship between the percentage of correct AS responses and tests of executive function: modified trails **(A)**, design fluency **(B)** and the Stroop task **(C)**. Circles indicate subjects with low education (unfilled) and high education (filled). Lines indicate the trend for all subjects (thick, solid), subjects in the low education group (thin, solid) and subjects in the high education group (dotted). * indicates $p < 0.05$; ** indicates $p < 0.001$.

Table 1

Summary of eye movements and neuropsychological performance.

		AS Percent Correct	
	Total	**Low**	**High**
Demographics			
N	48	24	24
Age	67.1 ± 7.0	67.1 ± 7.4	67.1 ± 6.4
Education	17.4 ± 2.4	17.0 ± 2.1	17.9 ± 2.7
Gender (m/f)	17/31	6/18	11/13
GDS (max 30)	3.15 ± 3.32	3.65 ± 3.80	2.65 ± 2.76
MMSE (max 30)	29.8 ± 0.4	29.8 ± 0.4	29.8 ± 0.4
Eye Movements			
AS Correct (%)	76.0 ± 20.4	61.2 ± 19.0	90.8 ± 6.3*
AS Self-Corrected Errors (%)	78.5 ± 33.0	90.5 ± 12.0	66.4 ± 42.1*
AS-Total (%)	97.3 ± 4.6	96.1 ± 5.8	98.5 ± 2.7
AS Latency (ms)	294 ± 64	278 ± 57	310 ± 69
PS Latency (ms)	217 ± 47	206 ± 39	228 ± 52
PS Velocity (deg/s)	386 ± 89	390 ± 65	383 ± 108
PS First Gain (deg)	8.40 ± 1.34	8.34 ± 1.12	8.45 ± 1.55
PS Final Gain (deg)	9.61 ± 1.11	9.70 ± 1.01	9.53 ± 1.20
Executive Function			
Modified Trails Time (s)	26.9 ± 13.5	30.2 ± 16.5	23.2 ± 8.1
Modified Trails Errors (#)	0.30 ± 0.59	0.42 ± 0.72	0.18 ± 0.40
Design Fluency Correct (#)	11.4 ± 2.9	10.3 ± 2.9	12.6 ± 2.5*
Stroop Inhibition Correct (per minute)	52.2 ± 9.8	48.4 ± 8.6	56.0 ± 9.6*
Stroop Inhibition Errors (per minute)	0.48 ± 0.97	0.42 ± 0.58	0.54 ± 1.25
Calculations (max 5)	4.81 ± 0.45	4.92 ± 0.28	4.71 ± 0.55
Abstraction (max 6)	5.21 ± 0.80	5.08 ± 0.88	5.33 ± 0.70
Backward Digit Span (max 9)	5.50 ± 1.34	5.38 ± 1.38	5.63 ± 1.31
Language			
D-Words (per min)	16.6 ± 4.3	15.9 ± 4.5	17.2 ± 4.0
Animals (per min)	24.2 ± 5.1	24.3 ± 5.1	24.1 ± 5.1
Boston Naming Test (max 15)	14.5 ± 0.7	14.5 ± 0.7	14.6 ± 0.7
Visuospatial			
Modified Rey Copy (max 16)	15.9 ± 0.9	16.0 ± 0.7	15.7 ± 1.1
VOSP (max 10)	9.19 ± 0.98	9.13 ± 0.90	9.25 ± 1.07
Memory			
Modified Rey Recall (max 16)	12.3 ± 2.8	11.3 ± 3.1	13.4 ± 2.1*

Values represent mean ± SD. All eye movement values are for the 10° horizontal condition.

*indicates $p < 0.05$ in an independent samples t-test. Low = below the median percentage of correct AS responses (81.6%); High = above the median percentage of correct AS responses (81.6%); AS-Total = percentage of correct AS responses plus self-corrected errors.

Table 2

Association of AS performance with neuropsychological performance.

	AS Correct	AS Total
Executive Function		
Modified Trails Time	−0.209 *	−1.15 *§
Modified Trails Errors	−0.005	−0.031
Design Fluency Correct	0.054 *§	0.017
Stroop Inhibition Correct	0.154 *	0.300
Stroop Inhibition Errors	−0.002	−0.028
Calculations	−0.002	0.007
Abstraction	0.012 *	0.007
Backward Digit Span	0.009	0.090 *
Language		
D-Words	−0.004	0.037
Animals Correct	0.020	0.009
Boston Naming Test	0.002	−0.020
Visuospatial		
Modified Rey Copy	−0.002	−0.003
VOSP	0.000	0.000
Memory		
Modified Rey Recall	0.022	0.004

Values represent regression coefficients (B) in a linear regression model with the percentage of correct AS responses, age, gender, and education as regressors.

*indicates $p < 0.05$;

§indicates $p < 0.05$ after controlling for multiple comparisons using a false discovery rate. AS Correct = percentage of correct AS responses; AS Total = percentage of correct AS responses plus self-corrected errors.

Table 3

Variance of eye movements and neuropsychological measures of executive function.

	Low Education	High Education	Variance difference (p value)
AS Correct	70.5 ± 22.6	79.9 ± 18.1	0.172
Modified Trails Time	33.4 ± 17.7	22.3 ± 6.8	0.004 *
Modified Trails Error	0.42 ± 0.69	0.22 ± 0.51	0.048 *
Design Fluency Correct	10.6 ± 3.0	12.1 ± 2.7	0.702
Stroop Inhibition Correct	51.9 ± 10.5	52.4 ± 9.5	0.616
Stroop Inhibition Error	0.25 ± 0.44	0.64 ± 1.19	0.009 *
Abstraction	4.95 ± 0.83	5.39 ± 0.74	0.821

Values for each education group represent mean ± SD. p values are from Levy's Test of Variance;

* indicates $p < 0.05$. AS Correct = percentage of correct AS responses.