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Neuroscience Letters 328 (2002) 225–228

Neuroscience Letters

www.elsevier.com/locate/neulet

Relationship between brain structure and saccadic eye movements in healthy humans

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Received 11 March 2002; received in revised form 6 May 2002; accepted 8 May 2002

Abstract

This study used structural magnetic resonance imaging (MRI) to investigate associations between brain structure and saccadic eye movements. Seventeen healthy subjects underwent structural MRI and infra-red oculographic assessment of a reflexive saccade task. Volumes of prefrontal, premotor, and occipitoparietal cortex, caudate, thalamus, and cerebellar vermis were used as predictors in multiple regression with prosaccade gain as a dependent variable, controlling for whole-brain volume. Using voxel-based morphometry (VBM), gain was entered into correlational analysis with grey matter density. Regression analysis indicated that vermis volumes predicted prosaccade gain. VBM replicated this finding: gain was correlated with grey matter in the left cerebellar hemisphere and vermis. These findings agree with previous studies on the role of the cerebellar vermis in saccadic gain and support the validity of structural neuroimaging methods in elucidating the neural correlates of saccadic eye movements.

Keywords: Structural magnetic resonance imaging; Voxel-based morphometry; Prosaccade (reflexive saccade); Cerebellar vermis; Human

Magnetic resonance (MR) imaging has been used to study the patterns of structural brain abnormalities in neuropsychiatric disorders as well as the relationship between volumes of brain structures and cognitive function. Brain structural volumes have been related to cognition given the hypothesis that volume is an important tissue property intimately related to function [6]. Previous research has demonstrated a relationship between total and regional brain volumes and cognitive function, indicating that larger volumes are associated with better performance [8].

No published study has examined the relationship between brain volume and saccadic eye movements in healthy humans. Saccades are rapid eye movements serving to bring the image of an object of interest onto the fovea. Cortical areas controlling reflexive saccades (prosaccades) include frontal, supplementary, and parietal eye fields. Subcortical areas include superior colliculus, thalamus, basal ganglia, and paramedian pontine reticular formation [10]. Several lines of evidence suggest a role of the cerebellar vermis in saccadic accuracy. Functional neuroimaging studies have demonstrated increased neural activity in vermis during saccades [9]. Vermis lesions have been shown to lead to both *hypo*metria (reduced amplitude) as well as *hyper*metria (increased amplitude) in humans and non-human primates [4,11,14,16].

The present study investigated the relationship between brain structure and prosaccade gain, defined as the match of eye and target amplitude. We hypothesized that saccadic gain would be associated with vermis volumes and addressed this relationship using regions of interest (ROI) analysis as well as topographically unrestricted voxel-based morphometry (VBM).

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0304-3940/02/$ - see front matter
PII: S0304-3940(02)00517-7

Seventeen subjects (11 males; age range, 19–39 years; mean = 24.65; SD = 5.15) were screened for neurological disorder, current or past DSM-IV Axis I and II diagnoses, drug or alcohol abuse, and history of psychosis in first-degree relatives. All subjects provided written informed consent. The study was approved by the Bethlem and Maudsley Ethics Committee (Research).

Subjects were scanned on a 1.5 T GE Signa Advantage (Milwaukee, WI). Three-dimensional T_1-weighted Spoiled Gradient Recalled scans were acquired in the axial plane (*TE* (*echo time*) = 2.2 ms, *TI* (*inversion recovery time*) = 300 ms, *TR* (*repetition time*) = 11.3 ms, field of view = 22 cm, flip angle = 20°, *NEX* (*number of excitations*) = 1), producing 124 1.5-mm slices of the whole brain.

ROI were selected to approximate the saccadic circuitry [10]. Cortical grey matter parcellation was based on Bilder et al. [3], using subcortical landmarks to approximate cortical cytoarchitectonic boundaries. Prefrontal cortex was defined as the area between the frontal pole and rostrum of the corpus callosum. Premotor cortex ranged between the rostrum of the corpus callosum and the most anterior appearance of the thalamus. Occipitoparietal cortex extended from the splenium of the corpus callosum to the most caudal appearance of the occipital lobe. For thalamic boundaries, see Ettinger et al. [7]. Caudate boundaries are clearly visible on MR images. Vermis measurements included lobules I–X. Total cerebrum included cortical and subcortical grey and white matter but not brainstem or cerebellum.

ROI volumes were obtained using stereological assessment software [2], superimposing a three-dimensional grid over images in three mutually orthogonal planes. Grid points falling within a ROI were marked manually. Volumes were calculated from the number of marked grid points. Inter- and intra-rater reliabilities in our laboratory are high ($r > 0.80$) [7,13].

For VBM, scans were processed using spatial normalization and segmentation algorithms in SPM99 [1]. Scans were normalized to a template approximating the standard space of Talairach and Tournoux [15] using a 12 parameter affine registration and low frequency cosine basis functions. Images were segmented into probabilistic maps of grey matter, white matter and cerebrospinal fluid by a modified mixture-model clustering algorithm. Segmented grey matter images were adjusted for effects of spatial normalization to preserve the original amount of grey matter at each voxel, and smoothed using a two-dimensional Gaussian filter with the full width at half maximum = 5 mm to reduce effects of individual variation in sulcal/gyral anatomy.

Eye movement stimuli were presented on a horizontal light-emitting diode array at a 200 cm distance from subjects. The target subtended a visual angle of approximately 0.15°. Head movements were minimized using a chinrest. Testing took place in a quiet, darkened room.

A prosaccade trial consisted of a 500 ms central target followed by a 500 ms peripheral target (±5°, ±10°, ±15°). Twelve trials were performed. Subjects were instructed to follow the target as accurately as possible. Eye movements were recorded using infra-red oculography at a sampling frequency of 500 Hz (IRIS 6500; Skalar, Delft, The Netherlands). Left eye recordings were analyzed using interactive software (EYEMAP; AMTech, Weinheim, Germany). After calibrating data, saccades (minimum velocity = 30°/s; minimum amplitude = 1.5°; minimum latency = 100 ms) were identified by the software and accepted or rejected by the rater. Saccade gain was measured as the primary saccade amplitude divided by the target amplitude multiplied by 100. A gain score of 100% therefore reflects perfect match of eye and target amplitude.

Multiple regression models were performed in SPSS 10 predicting prosaccade gain from ROI volumes. To control for individual differences in brain size, cerebral volume was entered as a covariate. Cortical regions, caudate, thalamus, and vermis were entered as predictors using the Stepwise method (probability to enter set at 0.05). For VBM, correlations between prosaccade gain and grey matter volume were calculated at each voxel. Spatial statistics and permutation testing were used for inference [5].

Means and standard deviations of prosaccade gain and ROI volumes are in Table 1. Regressing gain on total cerebral volume yielded a multiple correlation coefficient of $R = 0.001$, showing that brain volume did not predict prosaccade gain. Vermis was the only variable included in the model using stepwise regression, resulting in a 40% increase in the percentage of variance explained. After adjusting for total cerebral volume, larger vermis volumes were associated with larger gain values (Beta = 0.84; $P = 0.009$; Fig. 1).

VBM results showed a significant cluster ($P < 0.001$; less than one false positive predicted) where prosaccade gain was correlated with grey matter (Fig. 2), centred at co-ordinates $x = -19$, $y = -66$, $z = -19$ (cluster size, 1498 voxels). The cluster principally comprised the left

Table 1
Descriptive statistics of saccadic gain and regional brain volumes[a]

	Mean (SD)
Prosaccade	
Gain	95.82 (8.50)
Regional brain volumes	
Cerebrum	1060.65 (110.62)
Prefrontal cortex	85.57 (15.66)
Premotor cortex	98.27 (19.99)
Occipitoparietal cortex	188.84 (17.98)
Caudate	6.73 (0.99)
Thalamus	14.95 (1.42)
Vermis	20.57 (4.32)

[a] $N = 17$. Prosaccade gain (%) reflects saccadic amplitude divided by target amplitude multiplied by 100. Volumes are in cm^3.

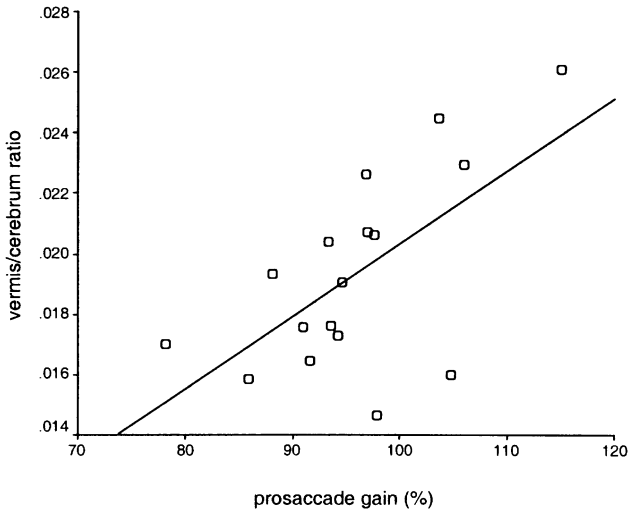

Fig. 1. Relationship between adjusted vermis volume and prosaccade gain. Vermis/cerebrum ratio is calculated as vermis volume divided by whole-brain volume.

cerebellar hemisphere and cerebellar vermis, and extended superiorly into left lingual and fusiform gyri (BA17, BA18).

The finding of a statistical relationship between prosaccade gain and vermis volume may be interpreted with reference to previous observations of a role of the vermis in saccadic eye movements. The present study contributes to this literature by demonstrating that, in addition to structural and functional integrity [4,11,14,16] and neural activation levels [9], vermis *volume* might be a crucial determinant of saccadic accuracy. Previous studies have not considered this property. Individual differences in brain structural volumes might relate to the number of neurons or glial cells, cell size, or extent of dendritic arborization.

The relationship between vermis and saccadic gain indicated that larger volumes were associated with increasing *accuracy* up until gain scores of 100%. However, this linear relationship was observed for the entire range of gain scores, i.e. including those above 100%, which may be considered slightly hypermetric. Two explanations may be offered for this observation. A first interpretation might be that vermis volume is not associated with saccadic accuracy but with amplitude. However, a second interpretation focuses on the connectivity of the vermis with other cerebellar oculomotor structures. As Takagi et al. [14] argued, the vermis regulates saccadic accuracy through its inhibitory projection to the fastigial oculomotor region (FOR), which in turn inhibits the brainstem saccade pulse generator. The FOR is believed to act as a 'brake', stopping the saccade when an accurate eye position is reached. If the inhibitory input from the vermis is reduced due to damage, the FOR may inhibit the saccade before an accurate position is reached, resulting in saccadic hypometria. Conversely, lesions of both vermis and FOR lead to hypermetric saccades [14]. Given the role of the vermis in inhibiting the FOR it is possible that larger vermis volumes may exert a stronger inhibitory influence on the FOR leading to reduced inhibition of the brainstem saccade generator, thereby resulting in hypermetric saccades.

The present finding throws open the question of why larger volumes, which may be considered functionally advantageous [8], were associated with increased saccadic error in subjects whose gain scores exceeded 100%. It is possible that these increases in volume are compensatory benefits and were achieved at the expense of other (oculomotor) structures, given that they represent vermis/cerebrum ratios, thereby compromising saccadic control. Recent studies suggest increased cerebellum/cerebrum ratios might be related to intellectual function [12].

Patients with posterior vermis lesions, arguably suffering loss of functional neural tissue, were shown to make hypometric saccades [16], consistent with the present association between reduced vermis volumes and hypometric gain. However, Bötzel et al. [4] observed hypometric as well as hypermetric saccades in patients with lesions including, but

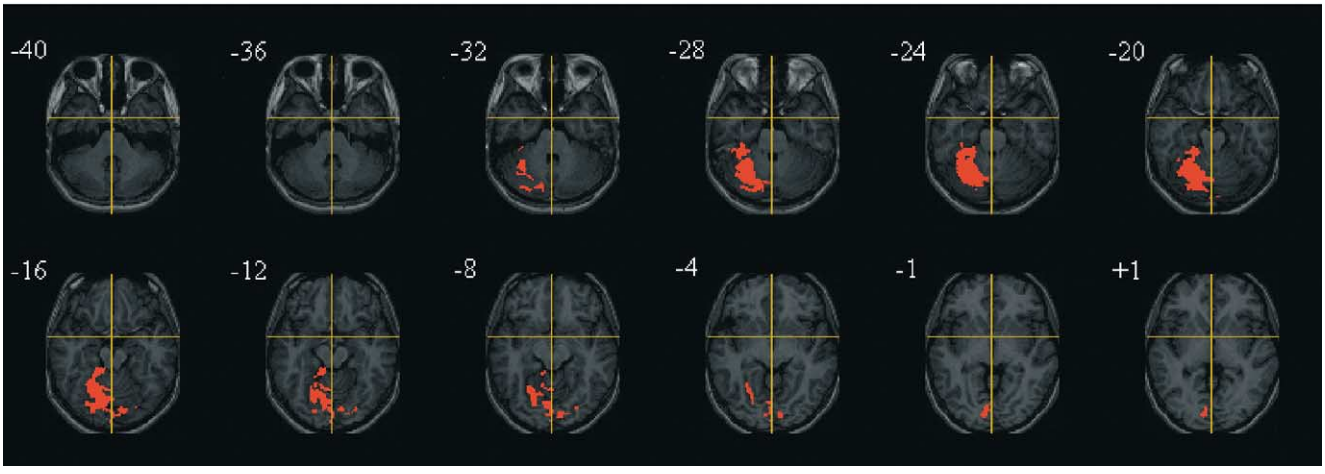

Fig. 2. VBM cluster map for prosaccade gain. Positive correlations between grey matter density and prosaccade gain are shaded in red. Numbers refer to slices in Talairach space. Images are in neurological orientation.

not restricted to, the vermis, possibly due to damage to other cerebellar structures [14].

In conclusion, our study has two implications. First, our findings point to a role of volumetric parameters in the control of saccadic gain by the cerebellar vermis. Future research is needed to explore whether vermis volume primarily influences saccadic amplitude or accuracy. Second, our study provides evidence of the usefulness of structural neuroimaging methods in elucidating the neural control of saccadic eye movements, and preliminary evidence of the concurrent validity of the ROI and VBM methods. Future structural neuroimaging studies might consider other tasks, such as the antisaccade, believed to be a measure of frontal integrity [10].

The authors wish to acknowledge the financial support of Psychmed Ltd., Cognitive Therapeutics Ltd., and Eastwood Care Homes plc. Veena Kumari holds a BEIT Memorial Fellowship.

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