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Functional anatomy of predictive vergence and saccade eye movements in humans: A functional MRI investigation

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ABSTRACT

Purpose: The purpose of this study is to investigate the functional neural anatomy that generates vergence eye movement responses from predictive versus random symmetrical vergence step stimuli in humans and compare it to a similar saccadic task via the blood oxygenation level dependent signal from functional MRI.

Methods: Eight healthy subjects participated in fMRI scans obtained from a 3 T Siemens Allegra scanner. Subjects tracked random and predictable vergent steps and then tracked random and predictable saccadic steps each within a block design. A general linear model (GLM) was used to determine significantly ($p < 0.001$) active regions of interest through a combination of correlation threshold and cluster extent. A paired t-test of the GLM beta weight coefficients was computed to determine significant spatial differences between the saccade and vergence data sets.

Results: Predictive saccadic and vergent eye movements induced many common sites of significant functional cortical activity including: the dorsolateral prefrontal cortex (DLPFC), parietal eye field (PEF), cuneus, precuneus, anterior and posterior cingulate, and the cerebellum. However, differentiation in spatial location was observed within the frontal lobe for the functional activity of the saccadic and vergent network induced while studying prediction. A paired t-test of the beta weights from the individual subjects showed that peak activity induced by predictive versus random vergent eye movements was significantly ($t > 2.7$, $p < 0.03$) more anterior within the frontal eye field (FEF) and the supplementary eye field (SEF) when compared to the functional activity from predictive saccadic eye movements.

Conclusion: This research furthers our knowledge of which cortical sites facilitate a subject's ability to predict within the vergence and saccade networks. Using a predictive versus random visual task, saccadic and vergent eye movements induced activation in many shared cortical sites and also stimulated differentiation in the FEF and SEF.

1. Introduction

There are five major types of eye movements originally described by Dodge in 1903. Three adjust the position of the eye to keep the object of interest on the fovea and two stabilize the eye during head movement (Dodge, 1903; Goldberg, Eggers, & Gouras, 2000). Saccades are fast, tandem, conjugate movements which rapidly shift the fovea to a new target. Smooth pursuit movements keep the image of a moving target on the fovea. Vergence is the inward (convergence) and outward (divergence) turning of the eyes to track targets at different depths. Numerous studies have been conducted to study saccade and vergence anatomy.

Prediction in the visual system dates to the research of Dodge in 1931 and is a strategy that the brain utilizes in oculomotor control to reduce the response latency and generate a movement with greater peak velocity (Dodge, 1931). Predictive behaviors have been reported in saccade, smooth pursuit and vergence eye movements (Barnes & Asselman, 1991; Kowler & Steinman, 1979; Kumar, Han, Garbutt, & Leigh 2002; Rashbass & Westheimer, 1961; Ron, Schmid, & Orpaz, 1989; Stark, Vossius, & Young, 1962). Studies of saccadic eye movements have reported that when prediction is utilized responses show reduced latencies, even as small as zero msec and some responses show anticipatory movements before stimulus onset (Kowler & Steinman, 1979). Rashbass and Westheimer first analyzed the use of predictable sinusoids varying in depth in 1961 and reported that predictive vergence sinusoidal responses showed a decrease in latency compared to step or pulse responses when the subject did not know when the target would change positions (Rashbass & Westheimer, 1961). A step input is an abrupt

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change in vergence disparity such as when a person fixates on a far away target then fixates to a target located at close range. They suggested that this behavior is due to the anticipation of future disparity changes. Another study showed that the latency in convergent and divergent repetitive vergence step stimuli decreased, especially when the frequency was less than 1 Hz, providing evidence of a prediction operator that was most effective at 0.5 Hz (Krishnan, Farazian, & Stark, 1973). Our group has also reported a decrease in latency, an increase in peak velocity, and anticipatory movements when comparing vergence responses from a predictable symmetrical step disparity vergence stimulus where subjects knew the timing and magnitude information of the stimulus compared to a random vergence step stimulus (Alvarez, Semmlow, Yuan, & Munoz, 2002). Furthermore, Kumar et al. (2002) showed that the anticipatory movements observed in vergence eye movements to predictable step stimuli were influenced by the previous visual stimuli suggesting that working memory is involved in anticipatory drifts (Kumar et al., 2002). These results suggest different cortical resources may be recruited when prediction is utilized resulting in reduced latency, increased peak velocity and anticipatory movements.

Cortically, investigators report that a predictive controller resides in the dorsolateral prefrontal cortex (DLPFC) (Pierrot-Deseilligny, Müri, Nyffeler, & Milea, 2005). Pierrot-Deseilligny and colleagues studied patients with a lesion limited to the DLPFC and report a significant decrease in anticipatory saccades compared to control subjects when studying predictive saccadic movements. They report that the DLPFC is involved, specifically in the timing control of predictive saccades; however, vergent eye movements were not investigated in their study.

Single cell primate studies of vergence have reported cellular activity evoked by using vergence stimuli in the primary visual cortex (Poggio, 1995), the posterior parietal area (Genovesio & Ferraina, 2004; Gnadt & Mays, 1995), the bilateral frontal eye fields (FEF) (Akao, Mustari, Fukushima, Kurkin, & Fukushima, 2005; Gamlin & Yoon, 2000), the cerebellum, (Gamlin & Clarke, 1995; Miles, Fuller, Braitman, & Dow, 1980; Nitta, Akao, Kurkin, & Fukushima, 2008; Zhang & Gamlin, 1998), and the midbrain (Judge & Cumming, 1986; Mays & Porter, 1984; Mays, Porter, Gamlin, & Tello, 1986). Several behavioral vergence eye movement studies of prediction have been conducted; yet they do not provide functional cortical insight. Prediction can easily be studied in humans via fMRI. An fMRI study using predictive versus random vergence eye movements has not been conducted previously and hence will be the focus of this study.

Numerous behavioral, animal, fMRI and clinical investigations have been reported for the saccadic system. Several review papers summarize the functional anatomy using fMRI to study cognitive control of saccades (Pierrot-Deseilligny, Milea, & Müri, 2004), its role in spatial attention (Luna & Sweeney 1999), and its role in spatial working memory (Curtis, 2006). Other reviews describe the cortical control of saccades through a detailed investigation of single cell studies, lesion or fMRI experiments in primates, as well as transcranial magnetic stimulation and case reports from humans (Gaymard, Ploner, Rivaud, Vermersch, & Pierrot-Deseilligny, 1998; Leigh & Zee, 2006; Pierrot-Deseilligny et al., 2004). Hence, the influence of prediction upon the saccadic system will be investigated to confirm our findings with those published by others. It will also be compared to how prediction influences the vergence system which has not been previously studied via fMRI investigations.

The aim of this current study is to investigate prediction in the vergence and saccade neural network in humans. Since vergent and saccadic eye movements both exhibit anticipatory movements and reduced latencies when stimuli are predictive, we hypothesize that the cortical resources for prediction will be similar for both systems. In this study, a predictive versus random symmetrical vergence step stimulus is used to obtain vergence neural activity and is compared to the saccade neural activity induced by predictive versus random saccade stimulus. Hence, this is the first paper to systematically perform a whole brain study on the anatomical network responsible for vergence predictive behavior in humans using fMRI. We hypothesize (1) functional activity will be induced in the DLPFC from prediction in both the saccade and vergence neural networks, (2) spatial differentiation between the two networks will be observed within the bilateral frontal eye fields, which has been previously reported in single cell experiments from primates and (3) similar activation sites in the sensory area, parietal lobe and cerebellum will be observed.

2. Materials and methods

2.1. Subjects

Eight subjects who did not know the hypotheses of the experiment participated in this study (5F, 3M, mean age 26 ± 4 years). All subjects had normal binocular vision assessed by the Randot Stereopsis test with a fixation disparity better than 70 s of arc and a near point of convergence less than 10 cm. Six of the subjects were emmetropes and two were corrected for normal refraction where the average prescription among the myopes was -1D. All subjects were right handed. None of the subjects had a history of brain injury or other neurological disorder. Subjects participated in an eye movement experiment prior to functional scanning. Each subject's eye movements were recorded to ensure the subject understood the task. All subjects were able to perform the task required. Subjects gave informed consent approved by the University of Medicine and Dentistry of New Jersey and the New Jersey Institute of Technology Institution Review Boards.

2.2. Materials and apparatus

Images were acquired using a 3.0 T Siemens Allegra MRI scanner with a standard head coil (Erlangen, Germany). Visual stimuli were a set of non-ferrous LED targets that formed a line 5 cm in height by 2 mm in width located at three positions. Eye movement recordings confirmed that the subject could perform both the saccadic and vergent oculomotor tasks.

Eye movements were recorded using an infrared ($\lambda = 950$ nm) limbus tracking system manufactured by Skalar Iris (model 6500, Delft, Netherlands). All of the eye movements were within the linear range of the system (±25°). The left-eye and right-eye responses were calibrated, recorded and saved separately for offline analysis. Digitization of the eye movements was performed with a 12-bit digital acquisition hardware card using a range of ±5 volts (National Instruments 6024 E series, Austin, TX, USA). A custom Matlab™ 7.0 (Waltham, MA, USA) program was used for offline eye movement data analysis and eye movement data were plotted using Axum (Cambridge, MA, USA).

2.3. Imaging instrumentation and procedure

The subject was positioned supine on the gantry of the scanner with his/her head along the midline of the coil. All participants were instructed to limit head motion. Foam padding was used to restrict additional movement and motion correction software described below was utilized to ensure head motion did not influence the results. Ear plugs which still enabled the participant to hear instructions from the operators were used to ensure communication during the scan while reducing scanner noise by up to 30 dB. In all experiments, the radio frequency power deposition