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Characterizing the Brain Dynamics and Eye Movement Behavior of Memory-Guided Saccades: a Preliminary Investigation of Distractor Influence on Memory-Guided Saccades

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CHARACTERIZING THE BRAIN DYNAMICS AND EYE MOVEMENT BEHAVIOR OF MEMORY-GUIDED SACCADES: A PRELIMINARY INVESTIGATION OF DISTRACTOR INFLUENCE ON MEMORY-GUIDED SACCADES

By

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This manuscript has been read and accepted for the Graduate Faculty in Cognitive Neuroscience for satisfaction of the thesis requirement for the degree of Master of Science.

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ABSTRACT

Characterizing the Brain Dynamics and Eye Movement Behavior of Memory-Guided Saccades: A Preliminary Investigation of Distractor Influence on Memory-Guided Saccades

by Angelo Colmenero

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Research has helped to shed light on the functional organization and neural mechanisms of distractors on memory-guided saccades. In our current study we have utilized eye tracking and EEG technology to simultaneously record the changes in saccadic eye movement (SEM) behavior and event-related potentials (ERPs) associated with performance on a memory-guided saccade task with distractor conditions. Thirteen healthy control participants (n = 13; 6 female) were tasked to complete 864 memory-guided saccade trials with both visible (white) and invisible (black) distractors presented on a black background before saccade initiation. Compared with the control (black) distractor condition, distractor presentation produced a significant change in saccade latency; whereas visible contralateral vs ipsilateral distractor presentation produced no significant change in ERP amplitude or time. The results of our study suggest that distractor presentation prior to initiating a memory-guided saccade has an observable effect on saccadic eye movement, but no effect on ERP profiles in healthy control participants. From these data we may conclude that suddenly appearing stimuli have a measurable influence on the behavior of our memory-guided eye movements.

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TABLE OF CONTENTS

Title Page	i
Copyright Statement	ii
Approval Page	iii
Abstract	iv
Acknowledgements	v
Table of Contents	vi
List of Tables and Figures	vii
Chapter 1: Introduction	1
Neuroanatomy of Eye Movements	2
Kinematics of Saccadic Eye Movements	3
Saccade Inhibition	4
Event-Related Potentials in the Memory-Guided Saccade Task	6
Blindsight	8
Chapter 2: Methods	9
Participants and Display	9
Saccadic Eye Movement Recording and Display	9
Eye Movement Recording Device, Setup, and Calibration	9
Electroencephalography Setup and Recording	11
Memory-Guided Saccade Task with Distractor Condition	11
Behavioral Saccade Data Analysis of Memory-Guided Saccade Task	14
Electroencephalography Data Analysis of Memory-Guided Saccade Task	15
Electroencephalography and Saccade Latency Data Analysis of Memory-Guided Saccade Task	16
Chapter 3: Results	17
Distractor Condition Event-Related Potentials	17
Distractor Condition Saccadic Eye Movements	19
Event-Related Potential Amplitude and Saccade Latency	22
Chapter 4: Discussion	24
Memory-Guided Saccade Event-Related Potentials	25
Eye Movement Behavior	27
Event-Related Potentials and Saccadic Eye Movement Behavior of Memory-Guided Saccades	28
Limitations	31
Future Directions	32
Conclusion	33
References	34

List of Tables and Figures

Figure 1. Visual Timeline of Experimental Set-Up 12
Figure 2. Aligned Saccade Latency Probability Density Function 19
Figure 3. Participant ERPs Under Control and Distractor Conditions. 21
Figure 4. Amplitude and Saccade Latency at Pz 23

Table 1. Statistics for the Saccade Latency Percent Reduction for Contralateral and Ipsilateral Conditions 18
Table 2. (KSD) Statistics for Saccade Probability Density Curve Difference 18
Table 3. N1 Amplitude Pairwise T-Test by Electrode Site 22
Table 4. Pz N1 Amplitude and Saccade Latency Linear Regression Analysis Tables 24

Chapter 1: Introduction

Cognitive processes such as attention and mental effort are generally private phenomenon that are difficult to investigate in real-time without experimenter-participant interaction. It has been found that cognitive effort can be quantifiably measured by proxy using pupillary dilation, whereas attention can be investigated by saccadic eye movements (Eckstein et al., 2017). Through these behaviors, researchers are able to observe and measure otherwise elusive phenomenon.

Visual attention is known to exist in two forms: overt and covert - where the former applies to instances when we move our eyes to an object of interest; in the latter form of attention we foveate on an object, yet attend elsewhere without moving our eyes. Eye movements that are made in response to changes in attention are brief and measure in tens of milliseconds (Fischer & Ramsperger, 1984) – these sensorimotor processes can be observed in experiments with suddenly appearing stimuli.

Both overt and covert forms of attention have been studied via eye movement tracking. The oculomotor system has been seen to be facilitated or inhibited by stimuli presented 80 milliseconds prior to saccadic eye movement in healthy participants (Edelman & Xu, 2009). It is unclear to what extent unconscious detection of objects can influence saccadic eye movements. For example, while much is known about the neuroanatomy, brain dynamics, and kinematics of eye movements, it is not known if blindsight patients - who are incapable of consciously perceiving visual stimuli - would be affected by visual distractors in a visual saccade task.

Neuroanatomy of Eye Movements

The function of saccadic eye movements is rapidly shift the line of gaze, generally to visual stimuli. This sensorimotor activity requires the transfer of retinotopic and craniotopic information of a stimulus's location to the motor system, from which a motor plan for a saccade is generated and then executed in the brainstem. The effector system responsible for adjusting the position of the eye involves a network of brainstem nuclei that ultimately innervate the lateral, superior, medial, and inferior rectus, and superior and inferior oblique muscles (Martin, 2012). Through the tight control of these muscles the eye is capable of both reflexive and conscious control of its position.

The superior colliculus (SC) is one such structure of the oculomotor system regulating eye movements, which, like other structures in the primate brain, appears to demonstrate an organizational motif along its dorsal-ventral axis across its seven cell layers. In its dorsal "superficial" layers, the macaque monkey SC demonstrates visual cortex characteristics - receiving direct retinal, striatal, pretectal, and lateral geniculate input and generates signals which it sends to the ventral SC (Cynader & Berman, 1972). In the ventral, "deeper", layers of the SC, neural activity related to motor output of the eye is generated. Damage to these layers can produce deficits in saccade generation and accuracy (Schiller et al., 1980). While the "deeper" SC receives input from superficial SC, the deeper layers can operate independently via direct visual cortex input (Apter, 1946). An additional axis of organization can be found in each collicular substructure along their rostral-caudal axis. Both superficial and deeper layers of the superior colliculi exhibit a map corresponding to the visual field which is logarithmically compressed such that the inner-most area, containing representation of areas at or near the fovea,

is disproportionately represented and successive concentric areas from the center are represented smaller. Deeper SC uses this map through population coding to represent a target stimulus or goal. Monkey electrophysiology experiments have revealed that when saccades are discrepant from the target stimulus, deeper SC activity maps onto the target stimulus much better than saccadic behavior toward the stimulus (Optican, 2005).

Pharmacological inhibition (via muscimol) of rostral SC GABAergic neurons decreases the latency of express saccades (saccades with a latency < 110 ms), while visual fixation is impaired; administration of a GABA antagonist (bicuculline) reverses this pattern of behavior (Hikosaka et al., 1986; Lee et al., 1988). Conversely, caudal regions of the SC exhibit an inverted relationship between GABA manipulations and behavioral output (Goffart et al., 2003).

The frontal eye fields (FEF) sends and receives input to extrastriate cortex and are hypothesized to encode task relevant stimuli, attention, and saccadic eye movements. The FEFs have been found to respond to objects relevant to task goals, and as such are believed to represent a visual priority map (Salinas & Stanford, 2018). Pharmacological inactivation of macaque FEF (via muscimol microinjection) has been found to increase saccade latency in a memory-guided saccade task compared to a visually-guided saccade task. This is presumably because FEF is involved with endogenously driven saccades, rather than exogenously driven as with visually-guided saccades.

The Kinematics of Saccadic Eye Movements

Saccadic eye movements were once thought to be ballistic in nature – that is, once in-flight, a saccade motor program is immune to revision; however, this hypothesis has been discredited with evidence to the contrary (Westheimer, 1954; Becker & Jurgens, 1979). As

implicated by saccade research, the brief temporal character of saccades is a critical property to be analyzed, since they reveal and define the temporal parameters of sensorimotor integration for one of the human body's fastest functions. Saccade motor programs can be influenced up to 70 ms prior to initiation – approximately the length of time needed for sensory information entering the retina to signal the visual and oculomotor systems. Despite this incredible speed, it has been demonstrated that saccades can be modified in-flight. In their 1994 study, Sheliga et al. found that lateralized successively presented stimuli produced a curved vertical saccade trajectory rather than step-wise movement when participants were tasked to make a saccade directly toward a target location above or below the fixation point.

Saccade Inhibition

The stimuli characteristics that influence saccade behavior are those that make stimuli more salient compared to their environment, such as a color that strongly contrasts with its background; the sudden appearance of such stimuli may temporarily inhibit the execution of a saccade as first discovered by Reingold & Stampe (2002). While this behavior has been observed under laboratory settings, it is conceivable that saccade inhibition is ecologically valid in conditions where the threat and motion of a predator interrupts and captures the eye of otherwise unsuspecting prey. This interruption can be remarkably quick, occurring in as few as 70 ms from the presentation of the stimulus and is thought to be regulated by the SC (Munoz et al., 2000), as the SC found to be involved in regulating and initiating stimulus-elicited saccades.

Collicular activity regulating eye movements is the result of orchestrated action between three cell types within the intermediate layer of the SC. These cell types are burst, buildup, and fixation neurons. Burst neurons may fire in bursts (hence their namesake) before and during a

saccade whereas buildup neurons become active and gradually increases in activity until a saccade is initiated and may also rapidly fire during saccadic eye movement (Munoz & Wurtz, 1995). Conversely, fixation neurons are silent immediately prior to and during a saccade, but are otherwise active when the eye is fixated on an object (Munoz & Wurtz, 1993). Additionally, these neurons appear to be inversely active when compared to burst and buildup neurons - that is, when fixation neurons are active burst and buildup neurons are silent and vice-versa. Together, these three types of SC neurons are thought to represent a visual response field as they demonstrate both visual field receptivity and activation with eye movement (Dorris et al., 1997).

Within the intermediate layer of the SC rostral pole, fixation neurons representing the central visual response field become active when an individual becomes foveates on an object and stimulation of this layer elicits eye fixation (Munoz & Wurtz, 1993). Caudal SC neurons on the other hand represent the peripheral visual field and both burst and build-up neurons may excite or inhibit one another if stimulated SC neurons are near or distant from one another, respectively (Munoz & Istvan, 1998). Consistent with this finding, distractor stimuli that are presented ipsilateral (near) or contralateral (far) from a target stimulus induces saccade facilitation or inhibition, respectively (Edelman & Xu, 2008).

The strength of saccade inhibition has been found to be strongest in tasks where participants were tasked to make a saccade to an empty target location while a distractor was presented contralaterally to the target location. In visually-guided saccade tasks, distractor inhibition does not appear to be as strong in the blank target location condition, and it is weakest when presented along with a suddenly appearing target (Edelman & Xu, 2008). Interestingly, when a distractor is presented ipsilateral to the target location (or target stimulus), a facilitation effect is seen and saccade latencies decreased compared with control conditions. This finding

suggested that saccades can be influenced while being executed. Additionally, both distractors ipsilateral and contralateral from the target were seen to have their largest effect when presented approximately 70-100 ms prior to saccade initiation (Reingold & Stampe, 2002). As noted by Edelman and Xu (2008), visually-guided saccades may be less influenced by distractor saccades presented distally than voluntary saccades, as the distractor may compete with the voluntary saccade program over the saccadic system thereby producing a transient disruption in it.

Event-Related Potentials and Saccadic Eye Movement in the Memory-Guided Saccade Task

Working memory (WM) allows animals to maintain sensory information after the original stimulus has already passed; this ability can allow an animal to represent information consciously or unconsciously until a task is completed (Baddeley, A.D., 1983). The memory-guided saccade task requires a participant to maintain their gaze on a fixation point while a target stimulus is flashed peripherally; after the disappearance of the fixation point the participant is then to make a saccade to the target location (Edelman & Xu, 2009). To successfully perform this task, participants must hold the spatial location of the target in working memory until they execute a saccade.

Event-related potential (ERP) studies have found that memory saccade (MS) tasks were associated with an increase in frontoparietal activity, specifically over the anterior frontal and central-parietal regions during the delay period between target offset and fixation point offset (Evdokimidis et al., 2001; Brignani et al., 2010). Using standardized low-resolution electromagnetic tomography (sLORETA) neuroimaging, Brignani et al (2010) found that the spatial location of this activity was consistent with significant activation of the frontal eye field (FEF), inferior parietal lobe (IPL), and extrastriate cortex representing stimulus location. Target

presentation to either to the left or right of the fixation point evoked lateralized ERPs observed at non-midline electrode sites which exhibit mirrored positive or negative components depending on the direction of the saccade. This pattern is inverted between left and right electrode sites (Csibra et al., 1996). Our investigation of changes in ERP activity due to distractor influence on memory-guided saccades will be directed at Fz and Pz given these previous findings.

Previous research investigating the relationship between ERP activity and saccade latency, found saccade latency to be independent of distractor-related positivity over occipital electrodes in a visually-guided saccade task (Weaver et al., 2017). Participants in this task were instructed to quickly make a saccade to a target stimulus (e.g. an angled line embedded in a line array) and ignore a distractor stimulus (e.g. a line in a different orientation), following fixation point offset. Participant ERP amplitude predicted the spatial accuracy of the visually-guided saccade, but not its latency. Based on all of these data, it is hypothesized that distractor stimuli may influence memory-guided saccades and that this influence will be might be detected in cortical ERP measures. Distractor presentation may impact P1 and N1 ERP components at Fz and Pz, which are associated with visuospatial attention capture (Fu et al., 2005; Melloni et al., 2011).

In our current study, we use the (2009) Edelman and Xu memory-guided saccade paradigm to evaluate whether the sudden appearance of distractor stimuli can influence saccadic eye movements and the event-related potentials associated with them. The literature surrounding this topic is incomplete, as studies either use memory-guided saccade paradigms or visually-guided saccade paradigms, but none featuring an ERP and behavioral analysis of memory-guided saccades with visual distractors.

Blindsight

In addition to elucidating the neural mechanisms of memory-guided saccades with the presentation of distractors, our current investigation will help to provide context for future studies exploring the role of visual awareness on saccadic eye movements in blindsight patients. Despite extensive human and animal research, it is still not clear whether blindsight is a condition where patients have visual function without phenomenal experience or just lack the capacity to recognize the contents of their vision (Overgaard & Mogensen, 2015). Currently, blindsight has been broken into two types - type I and type II. With blindsight type I, patients lack complete awareness of visual stimulus presentation yet process visual information at above-chance levels, whereas in type II blindsight, patients tend to report having a vague "feeling" that something has been visually presented to them despite not having visual awareness of the stimuli and performing at above-chance levels in tasks that require intact vision. These two variations have raised the question of what qualifies as blindsight; that is, does blindsight include introspection? If not, then Type I blindsight does not exist, as patients lack any conscious awareness of visual phenomenon ("feelings" included) in this form of blindsight. However, if blindsight does included introspection, then it isn't just a visual phenomenon and therefore may also be a disorder of *access consciousness*, such that patients are unable to semantically process or access the contents of consciousness (Block, 2007). Critically, the memory-guided saccade task may offer some perspective on what features blindsight includes as this paradigm requires participants to store a conscious representation of the stimulus over a delay period and is not just guided by visual awareness.

Chapter 2: Methods

Participants and Display

Thirteen healthy participants (N = 13; 5 female) with normal or corrected-to-normal vision participated in this study. Participants were screened for co-morbidities, such as epilepsy, schizophrenia, and any other major neurological disorder via consent form questionnaire. Data from an additional 7 participants were excluded from analysis in this study due to data artifacts or excessive difficulty with the task (i.e. failing to follow instructions after multiple training sessions).

Saccadic Eye Movement Recording and Display

Saccadic eye movement behavior was recorded with an EyeLink 1000 (SR Research Ltd.) device placed below the CRT display monitor (100 Hz refresh rate) used for psychophysical testing. The Eyelink 1000 device was connected to a personal computer used for capturing eye movement data; a different computer was used to run the memory-guided saccade paradigm via the software, Experiment Builder. All stimuli were presented against a black background. The EyeLink 1000 system sampled participant saccadic eye movement behavior at 1000 Hz. Participants sat approximately 57 cm from the display monitor with their head stabilized in a chin and forehead rest (SR Research Ltd.).

Eye Movement Recording Device, Setup, and Calibration

Participant saccadic eye movement behavior was collected in a memory-guided saccade task with and without distractor presentation; both EEG and saccadic eye movement data were

collected over 3 memory-guided saccade task testing sessions. Prior to each session, the EyeLink 1000 system was calibrated to eye position using a 3 x 3 grid. Additionally, calibration for eye tracking drift was performed before every block.

Baseline saccadic reaction time (SRT) was measured in the memory-guided saccade task without a distractor. This session consisted of 90 trials, with 18 trials per block for 5 blocks. During this no-distractor session (see Figure 1), participants completed a memory-guided saccade task in which they were instructed to foveate on a central fixation point (500-800 ms), 100 ms after the appearance of the fixation point, a green target stimulus flashed briefly (300 ms) 10° to either the left or right of the central fixation point. Once the central fixation point disappeared, participants were to make a saccade to the location of the flashed target. Immediately after the saccade a white square (1 x 1°) briefly appeared (300 ms) at the target location. If a participant failed to make a saccade within 500 ms of central fixation point offset, a notification was displayed on the screen to the participant and the trial was ended. The message "Saccade Off Target" would appear if participants made an incorrect saccade, whereas in the event that a premature (latency < 50 ms) anticipatory saccade was made, "Left Initial Fixation Point" was displayed. Error messages were displayed for 300 ms. After correctly or incorrectly completing a single trial, the central fixation point immediately reappeared. The latency required to initiate a saccade to the target location was recorded relative to central fixation point offset; these latencies were recorded and averaged over 54 trials (the first 2 blocks constituted as practice). The raw average SRT value generated from these trials was then used to create a time window in which a distractor could appear following saccade initiation.

Electroencephalography Setup and Recording

EEG activity was recorded with 18 gold electrodes using the 10-20 electrode placement system. Left and right mastoids electrodes were used as reference for F3, Fz, F4, C3, Cz, C4, P3, Pz, P4, O1, Oz, O2 scalp electrodes. To capture oculomotor activity, electrodes were placed above and below the participant's right eye (EV1 and EV2, respectively) and horizontally to the left eye (EH). A ground electrode was placed on the participant's forehead (FPz). All electrode impedances were confirmed to be below 10 kΩ prior to experimental trials; EEG signals were amplified using Grass amplifiers (Natus Medical Inc.) and sampled at 1000 Hz with a 30 Hz online low-pass filter. Continuous recording began at the start of experimental testing.

Memory-Guided Saccade Task with Distractor Condition

After the participant's scalp was fixed with EEG electrodes, the EyeLink 1000 system was recalibrated for eye position tracking with a 3 x 3 position grid to ensure that eye tracking remained consistent between training and experimental sessions. Experimental trial design was nearly identical to the SRT trial design, with a few notable exceptions. First, the experimental testing period consisted of 3 sessions with each session consisting of 288 trials (for a total of 864 trials); 144 trials presented the target stimulus on the left side and 144 presented the stimulus on the right. Of the set of 144 trials per side, 96 were distractor trials and the remaining 48 were no-distractor trials, where the distractor was black (against the black background). Participants were allowed short ad-lib breaks between blocks and sessions.

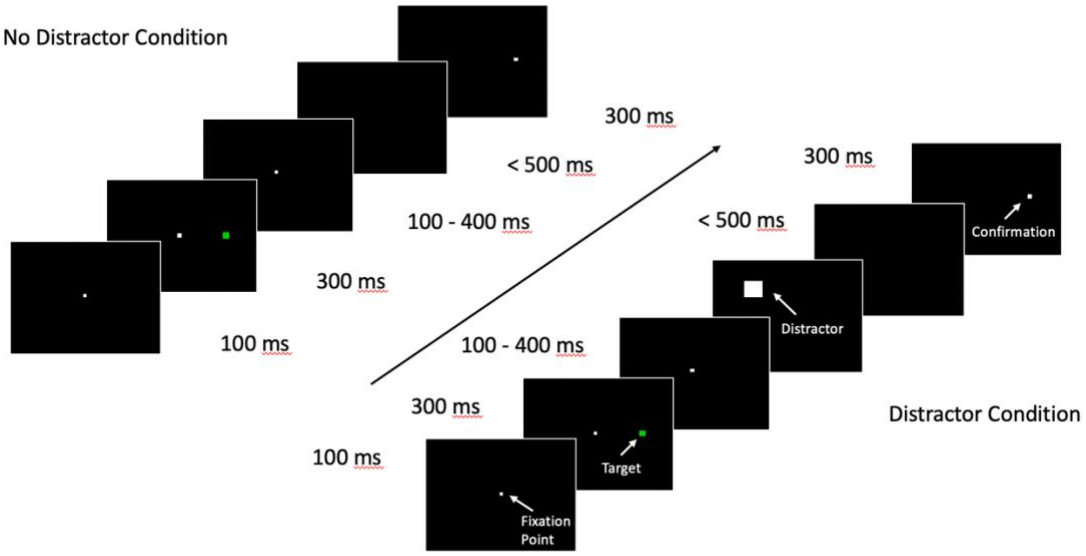

Fig 1. Visual timeline of experimental set-up. On the left side of the arrow of time, the chronology of the no-distractor trials is displayed. At the beginning of the trial, a fixation point is presented for 100 ms, then a target stimulus is presented peripherally to the left or right of the screen for 300 ms. After target offset, the fixation point remains on screen for 100-400 ms longer before disappearing and cuing the participant to saccade to the memorized target location within 500 ms. The participant is then presented with a 300 ms stimulus, which confirms that they have made a successful saccade to the target location. To the right of the arrow of time, a similar presentation pattern is presented to participants, except that after fixation point offset, a distractor stimulus appears at a time point that is randomly selected from 4 possible pre-determined times. The participant is to ignore the distractor and saccade over to the target location; successful completion of the task is confirmed with a 300 ms stimulus.

Distractors could appear at one of 6 different locations along an imaginary circle centered at the fixation point, with the polar directions – 0° (rightward), 22.5°, 135°, 180°, 225°, and 337.5°, with values indicating a counterclockwise direction. In this study we have grouped and categorized distractors as potentially belonging to 2 of 4 conditions: ipsilateral (0°, 22.5°,

337.5°), contralateral (135°, 180°, 225°), above (22.5°, 135°), and below (225°, 337.5°). Previous research has shown that distractor presentation position tends to produce saccade facilitation or inhibition, depending on whether it is presented ipsilateral or contralateral to the target stimulus, respectively (Edelman & Xu, 2009). Furthermore, distractors presented ipsilateral to the target stimulus disproportionately affect saccade amplitude over latency, whereas distractors presented contralateral from the target affect saccade latency more than amplitude (Walker et al., 1997).

Distractor appearance could occur at one of four times relative to the mean SRT value to maximize saccade inhibition; these four timepoints were calculated by taking the participant's SRT and subtracting 85 ms, then using this new value, setting interval values 30 ms apart from one another, such that the mean of these values would equal SRT – 85. As an example, consider a participant whose SRT is 160 ms - using the Edelman and Xu (2009) method for creating distractor intervals, 85 ms would be subtracted from this value to produce a 75 ms mean time for four intervals 30 ms apart (30, 60, 90, 120 ms) between when the fixation point disappears and the distractor appears. As soon as a saccade was made, following fixation point offset, the distractor would disappear. In our experiments, 105 ms instead of 85 ms was used, in order to compensate for a 20 ms system lag between stimulus presentation and EyeLink 1000 response. Due to human error, an alternative method was developed for creating distractor onset latencies which took the participant's SRT minus 20 ms (system lag correction), divided the difference in half, and subtracted 25 from this value, such that an original SRT of 160 ms would create a mean distractor interval of 90 ms (45, 75, 105, 135). This method of generating distractor onset intervals was applied to half of all participants in the study and generated differences in

distractor onset intervals no greater than 77 ms. At the end of testing, participants were given a $15 monetary compensation for each hour volunteered.

Behavioral Saccade Data Analysis of Memory-Guided Saccade Task

Behavioral data analysis of the memory-guided saccade task was primarily performed using MATLAB routines developed by one of the investigators. Additional routines were developed by the author to graph and visually examine participant saccade latencies in the distractor and no-distractor conditions.

Quantitative analysis of distractor effect was performed by creating a histogram of saccade initiation latency, with zero aligned to distractor onset. Trials with an incorrect response, anticipatory saccades, or failure to saccade were excluded from this analysis. Histograms were binned by 5 ms to adequately detail the probability distribution of saccade latencies. If saccade latencies were impacted by the presence of a distractor, a "notch" should appear in the histogram corresponding to the disruption of ongoing oculomotor processes related to saccade generation. The mean onset time of the distractor should be centered to the middle of the "notch". In order to quantitatively measure the impact of the distractor, no-distractor conditions in which an black distractor was presented, was compared. Because 1 in 3 (288 out of 864) trials presented to participants were without a distractor, correct trials of both distractor and no-distractor conditions were bootstrapped to 5000 iterations each for fair comparison. These bootstrapped samples were binned and plotted as a kernel density function to compare the frequency of saccade latencies following visible or black distractor presentation. The experimental and control curves generated by this process were then compared between the frequency of minimum latency bin of the experimental condition to the corresponding time point on the control condition curve.

A ratio between these points (experimental/control) was generated for each of the thirteen participants and then averaged to give the mean peak reduction in saccade probability. The mean peak reduction in saccade probability was then subtracted by 1 and multiplied by 100 to obtain the percentage reduction of mean peak probability, a reduction of 100% denotes complete saccade inhibition, whereas 0% means no inhibition was produced. To evaluate if a significant difference exists in mean peak reduction of saccade probability among distractor conditions, *t*-tests were performed between distractor and control conditions.

In addition to evaluating percent saccade probability reduction, a set of analyses were performed on examining whether a significant absolute difference between probability distribution curves (ipsilateral or contralateral experimental vs control conditions) existed using the Kolmogorov-Smirnov test. This test examines the maximum distance between probability distribution curves to evaluate if they differ significantly from one another in a *t*-test.

Electroencephalography Data Analysis of Memory-Guided Saccade Task

All participants completed 864 trials from the experimental testing session, with 288 no-distractor trials and 576 distractor trials. All trials were filtered offline with a 0.1-30 Hz bandpass filter; trials with blink or other motion artifacts were excluded from data analysis using visual inspection of trials epoched to -200 to 1800 ms. Additionally, incorrect trials and trials where participants took longer than 500 ms to initiate a saccade following fixation offset and received a "Failed to Leave Fixation Point" screen were excluded from analysis. Timestamps associated with eye movement and EEG data collecting devices were evaluated for consistency to ensure recorded events were properly synchronized. If timing discrepancies were found between devices, timestamp files were processed offline to restore synchrony and in the event the

discrepancies could not be eliminated, the data files were not included in the study. No-distractor and distractor trials were separated for analysis. Event-related potentials were time-locked to distractor onset with a 500 ms epoch and 200 ms baseline correction. It should be noted that while target-related ERPs may have offered useful information regarding early visual stimulus processing and memory, as well as an additional standard for comparision, they are not included in this study to keep focus on the effects of distractors on memory-guided saccades. Future directions of this study may investigate measures of this stimulus, however.

An ANOVA was performed on participant ERP data to compare the differences in ERP peak amplitude and time between distractor conditions. Peak amplitude for ERP components, P1, N1, and P2, was found by computing each participant's ERP waveform and obtaining the voltage maxima or minima between timepoints. Peak amplitude of P1 and P2 components were found by obtaining the voltage maximum voltage between 75 & 150 ms and 250 & 350 ms for P1 and P2, respectively; whereas N1 peak amplitude was collected by computing the voltage minimum between 150 and 250 ms. Participants were treated as a random effect for this analysis. For this study, just frontal (Fz) and parietal (Pz) locations were chosen a priori in order to minimize the chance of incurring type I errors (Luck & Gaspelin, 2016). Based on the results of ANOVA testing, significant differences in time or amplitude were further inspected with *t*-tests between conditions.

Electroencephalography and Saccade Latency Data Analysis of Memory-Guided Saccade Task

In order to assess the relationship between eye movement behavior and ERP activity, a linear regression analysis between saccade latency and ERP amplitude was performed. ERP waveforms selected for this analysis were chosen based on ANOVA analyses performed on ERP

peak amplitude and time from the previous section, such that only ERPs with significant differences between conditions at Pz were used for this analysis.

Chapter 3: Results

Distractor Condition Saccadic Eye Movements

Mean peak saccade probability reduction scores were captured from individual participant probability density functions, specifically between (ipsilateral or contralateral) experimental and control conditions. The averaged mean peak reduction scores were then evaluated with a two-way *t*-test, with a theoretical null mean of 1 (denoting no change between distractor and control conditions as 1.00 - 0.00 = 1, whereas a value of zero suggests maximum saccade inhibition caused by the distractor, as 1.00 - 1.00 = 0.00). The results of this *t*-test demonstrate a significant effect of contralateral distractor presentation on saccade latency, where contralateral distractors produced a mean peak probability reduction of 43.87% ($t = 5.17$, $p < 0.0002332$, *95% CI* = 25.80038 – 61.93016) compared to the theoretical null value. In the ipsilateral distractor condition, a non-significant 4.92% mean peak probability reduction was observed ($t = 0.60242$, $p < 0.5581$, *95% CI* = -9.255264 – 19.093333), suggesting that the ipsilateral distractor conditions evoked a much weaker inhibitory effect than the contralateral distractor condition (see table 1). The mean reaction time for a participant to generate a saccade after fixation point disappearance was 208.2 ms (std = 25.48068) under control conditions; visible distractors induced slightly longer mean saccade latencies following fixation point disappearance with a 241.7 ms (std = 47.91075 ms) latency, which corresponds roughly to the near end of the N1 (150 - 250 ms) ERP time window as distractor presentation was calibrated to appear approximately 85 ms prior to the estimated SRT. As discussed later, this timing correspondence may have had some impact on ERP signal quality.

With respect to the absolute differences distractors have on saccade latency probability distribution curves (experimental conditions against control), a Kolmogorov-Smirnov test was

conducted to examine whether ipsilateral vs. contralateral curves are significantly different from the control condition distribution curves. The KSD analysis revealed (KSD mean -0.93221, 95% CI = -0.04688649 - 0.01878761, p < 0.3696) that the distances between each experimental condition and the control condition curves they were compared against are not significantly different from one another (see table 2).

The two different methods used to generate the set of 4 time points for distractor presentation varied at a maximum of 77.5 ms between methods and a minimum of 2.7 ms. Because of this small time difference, both methods were treated as equivalent and not analyzed separately.

Table 1. Statistics for the Saccade Latency Percent Reduction for Contralateral and Ipsilateral Conditions

Saccade Latency Percent Reduction

Condition	t	Df	P-value	Mean of x	95-Percent Confidence Interval
Contralateral	5.17,	12	0.0002332	43.86527	25.80038 - 61.93016
Ipsilateral	0.60242	12	0.5581	4.919035	-9.255264 - 19.093333
Contralateral vs Ipsilateral	3.4004	12	0.005266	38.94623	13.99133 - 63.90114

Table 2. (KSD)Statistic for Saccade Probability Density Curve Difference.

(KSD) Saccade Probability Density Curve Difference

Condition	t	Df	P-value	Mean of x	95-Percent Confidence Interval
Contralateral vs Ipsilateral	-0.93221	12	0.3696	-0.01404944	-0.04688649 - 0.01878761

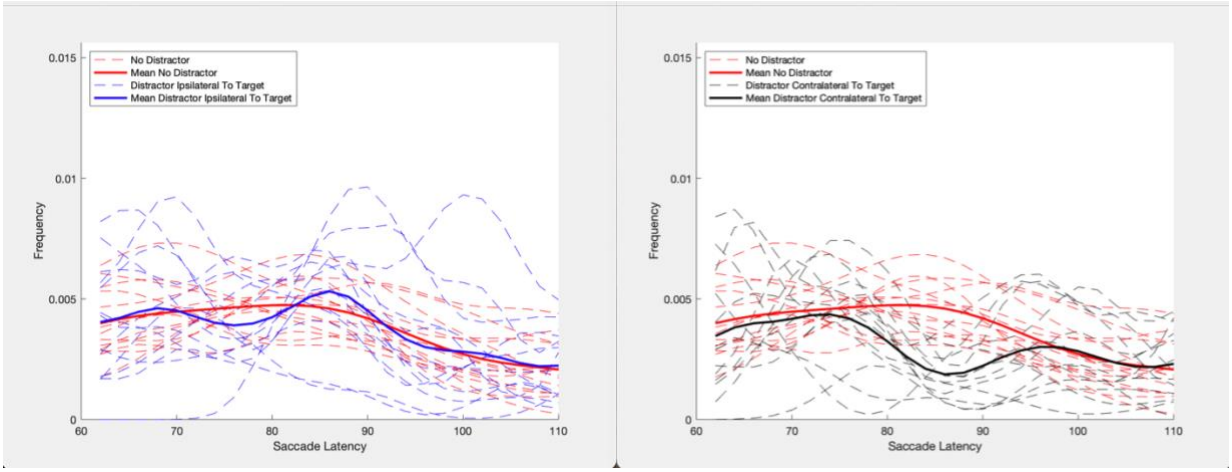

Fig 2. Aligned Saccade Latency Probability Density Function. The distractor-aligned saccade latencies from each participant were analyzed and delineated by category (distractor or control). Each plotted curve was aligned by mean peak distance from the control curve and only peaks between 60 and 110 ms (as distractor onset occurred approximately ~85 ms prior to SRT) were used for plotting distractor effects on the probability density function. When averaged together, the curves illustrate the magnitude of mean peak saccade probability reduction, which can be seen as a "notch" in conditions with distractors presented contralateral from the target location, or a "bump" for distractors presented ipsilateral to the target. This measurement of distance between curves (experimental/distractor vs control/no-distractor) is the basis for Kolmogorov-Smirnov testing.

Distractor Condition Event-Related Potentials

Following distractor presentation, participant P1, N1, and P2 ERP components were evaluated for changes in amplitude or timing from 75 to 150 ms, 150 to 250 ms, and 250 to 350 ms after distractor presentation, respectively. ERP component analysis was limited to frontal (Fz) and parietal (Pz) electrodes as discussed earlier - parietal P1 and N1 components have been associated with visuospatial attention capture and may be modulated by stimulus saliency features such as size (Fu et al., 2005). Additionally, whereas the P2 parietal component is recognized as being inversely associated with conscious perception of a stimulus, a high P2 amplitude coincides with poor stimulus visibility/non-detection, frontal P1 and N1 appear to be associated with visuospatial attention capture and orientation, respectively (Melloni et al., 2011; Natale et al., 2006). The definition of when these ERPs occur varies from paper to paper, however, they align with the time windows used here - P1: 75 - 150 ms, N1: 150-250, P2: 250-350; the N1 component in this time range is defined as a negative peak at Fz and Pz in relation to obligatory Oz measurement. In addition to the points mentioned above, our analysis was restricted to Pz and Fz electrodes as previous research conducted by Evdokimidis et al. (2001) found that during the early delay period following target offset in a memory-guided saccade task

only frontal-central electrode sites exhibited a significant increase in amplitude (this occured 500 - 1000 ms after target offset in their study - a time window of analysis that proceeds ours by 300 - 400 ms). Finally, by focusing analyses to these regions *a priori*, the probability of incurring a type I error is reduced. The ERP plots below visually demonstrate the amplitude differences found in these ERP components.

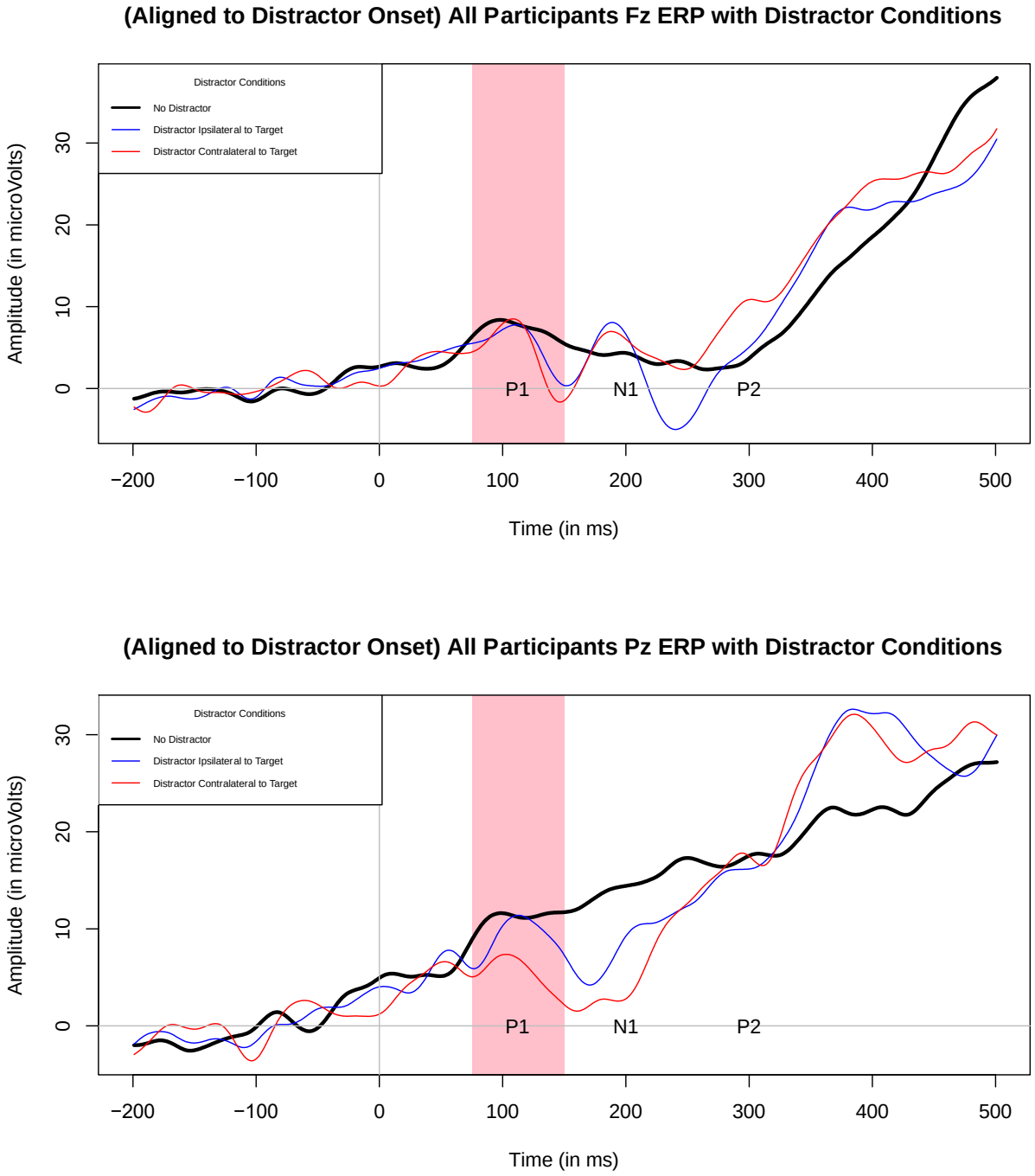

Fig 3. Participant ERPs under control and distractor conditions. Participant ERPs were analyzed from 2 of 16 recorded electrode sites, which have been found to exhibit increased activation during an early delay period (500 - 1000 ms) following target offset. A 200 ms window preceding time point 0 is used for baseline correction. ERPs are

presented in microvolts (uV) over time (ms). (Distractor Conditions Legend: (Black) No-Distractor, (Blue) Distractor Ipsilateral to Target, (Red) Distractor Contralateral From Target

Table 3: N1 Amplitude Pairwise T-Tests by Electrode Site.

N1 Amplitude Pairwise T-Tests by Electrode Site

Fz N1 Amplitude Conditions	t	Df	P-value
Ipsilateral vs Contralateral	-0.45803	12	0.6551

Pz N1 Amplitude Conditions	t	Df	P-value
Ipsilateral vs Contralateral	1.4562	12	0.171

ANOVA testing of the ERP components revealed a significant difference in N1 amplitude at Pz ($F = 7.631$, df = 2, $p < 0.00272$) and a nearly significant difference in N1 amplitude at Fz ($F= 3.239$, df = 2, $p < 0.0569$). These data are significant only for ANOVAs that include all three conditions, - no-distractor, ipsilateral, and contralateral distractor conditions.. Excluding no-distractor control conditions, ANOVA testing yields no significant findings.

Further investigation of the data using pairwise t-tests demonstrated no significant difference in N1 amplitude at Pz among ipsilateral vs contralateral conditions ($t = 1.4562$, df = 12, $p < 0.171$), nor at Fz N1 for ipsilateral vs contralateral conditions ($t = -0.45803$, df = 12, $p < 0.6551$) (see Table 3). As with the behavioral analysis of saccadic eye movement, both methods used for generating distractor onset SOAs were treated as equivalent and not analyzed separately in ERP analyses.

Event-Related Potential Amplitude and Saccade Latency

To further assess the relationship between ERP amplitude and saccadic eye movement latency, a linear regression analysis was performed between N1 amplitude and saccade latency for each distractor condition (ipsilateral and contralateral) at Pz (see Figure 5). The results from

this analysis indicate that N1 amplitude is not a significant predictor of saccade latency in ipsilateral and contralateral conditions at Pz (see Table 4).

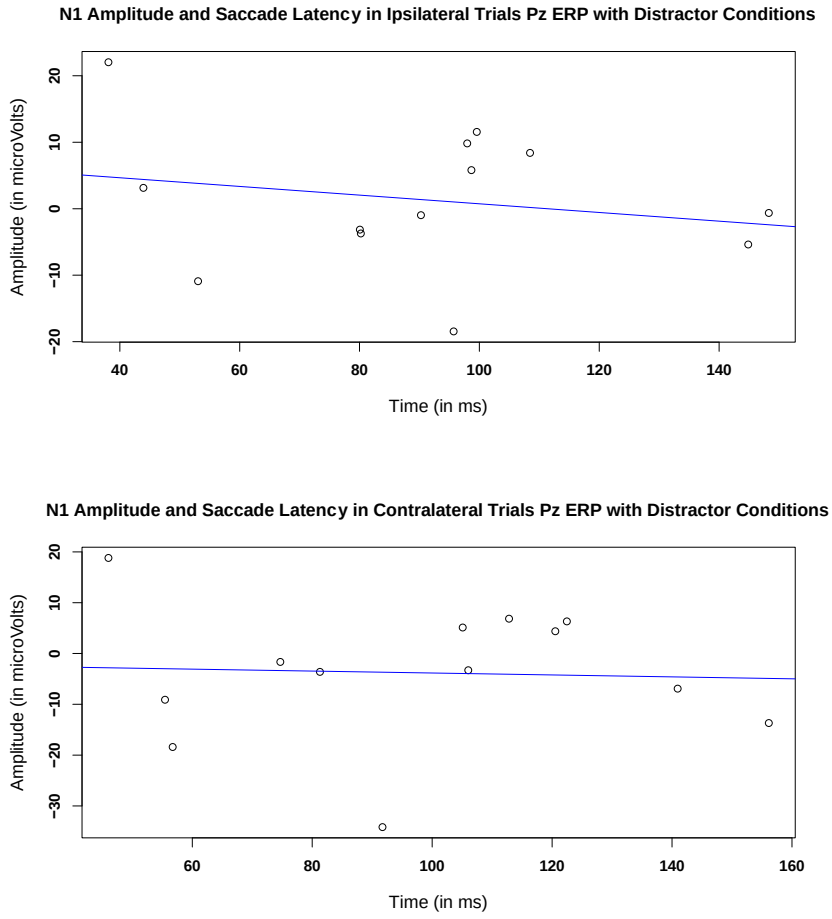

Fig 4. Amplitude and Saccade Latency at Pz. Linear regression models of N1 amplitude and saccade latency under ipsilateral (adjusted r^2 = -0.4376) and contralateral distractor (adjusted r^2 = -0.08839) conditions at Pz show non-significant linear trends between the two parameters.

Table 4. Pz N1 Amplitude and Saccade Latency Linear Regression Analysis Tables. Linear regression model analysis was performed to investigate the relationship between N1 amplitude and saccade latency under ipsilateral and contralateral distractor conditions. The results of this analysis indicate that N1 amplitude is independent of saccade latency.

Pz N1 Amplitude and Saccade Latency Linear Regression Analysis

	Estimate Std.	Error	T-value	P-value
Ipsilateral Intercept	7.27119	8.91135	0.816	0.432
Ipsilateral Latency	-0.06529	0.09263	-0.705	0.496
Contralateral Intercept	-1.94405	12.26393	-0.159	0.877
Contralateral Latency	-0.01902	0.11912	-0.160	0.876

Chapter 4: Discussion

In this study, the brain dynamics and eye movements involved in memory-guided saccades with and without distractor presentation were investigated in healthy control participants. The results of our data suggest that the appearance of distractors to ipsilateral or contralateral positions relative to the target can differentially influence memory-guided saccades and the presentation of these stimuli do not have ERP signatures that are detectable in the frontal and parietal regions of the brain, at least for the measures examined here. Future iterations of this study will explore if other electrode sites may uncover a relationship between distractor presentation and changes in ERP time and amplitude, as well as whether similar interruptions of memory-guided saccades are seen in hemianopic patients. In doing so, we may help parse the conscious and unconscious processes mediating this behavior.

Memory-Guided Saccade Event-Related Potentials

The ERP component of our investigation into memory-guided saccades with distractor presentation has yielded some surprising findings that should be taken with some degree of caution. This is because the mean saccade latency relative to distractor onset (control trials: 65.675 +/- std 33.34 ms, experimental trials: 94.19 +/- std 33.12774 ms) happened to fall within the P1, but not N1 or P2 time frame. As eye movements are notorious for introducing electrical noise into EEG signal, the nature of our study is vulnerable to movement artifacts. This makes it difficult to correctly interpret the full effect of visual distractors in the memory-guided saccades task, as despite visual rejection of EEG artifacts, it is possible that the saccade initiation event invariably injected noise into the EEG signal.

If saccade onset introduced noise to the signal then ERP waveform signatures of distractor presentation may be distorted and are not well-characterized in this preliminary study. However if this is not the case, then this suggests that distractors impact memory-guided saccades at Pz around 150-250 ms after presentation of the distractor. Interestingly, frontal and parietal regions did not appear to respond differently to the onset of distractors, regardless of where they were presented onscreen. Again, these non-significant findings may be the result of eye movement artifacts contaminating the ERG signal, since previous studies the presence of suddenly appearing stimuli have been observed to alter activity in the lateral intraparietal (LIP) sulcus, reflecting changes in visuospatial processing of attention (Danckert & Rossetti, 2005; Rossetti 1998; Grefkes & Fink, 2005).

Our findings are very much unlike he results of a previous ERP study where memory-guided saccade tasks without distractors elicited changes in parietal (and central) negativity (Evdokimidis, 2001). In their study, Evdokimidis et al. found that activity at frontal and parietal

electrodes was significantly between sites during the early and late delay periods - when participants needed to maintain the target location in working memory. In the early delay period just after the disappearance of the target stimulus, a negative ERP peaked at 150 ms and was followed by a P300 deflection; relative to all other electrode groups, the central electrode group detected larger (more positive) peak ERP amplitude ERP during this period. However in the late delay period (500 ms prior to the go signal), while frontal and parietal electrodes remained different from one another in activity, frontal electrodes relative to parietal detected a significantly smaller peak amplitude. These findings of relatively high parietal activity are different to those observed in this study, perhaps because the experimental designs differed in some notable ways, namely: 1) the late delay period in which parietal activity was relatively elevated occurred 500 ms preceeding the go signal, or 700 to 5700 ms after the start of the trial in the 2001 Evdokimidis et al. study; The time window which N1 in our study only minimally overlaps with this time window; and 2) the elevated parietal activity in our study is most likely in response to distractor presentation, rather than preparatory activity for saccade production. Furthermore, with respect saccade generation, in a 2017 study by Weaver et al., ERP signals associated with initiation of visually-guided saccades were found to exhibit an increase in (occipital) N2pc amplitude when analysis was time-locked to 50 ms prior to saccade onset. Their N2pc time window (150-200ms) that overlaps with the N1 time window (150-250 ms) in the current paper. While the Weaver et al. study (2017) evaluated ERP signals of visually-guided saccades, participants had to generate saccades in the presence of a distractor co-appearing with the target stimulus. Therefore, participants were required to covertly attend and evaluate the presented stimuli, before making a saccade to the target stimulus. The use of a distractor appearing after the target in our paper led to a different outcome.

Like the (2001) Evdokimis et al. study, the Weaver et al. findings hold limited importance for the validity of our results. The notable differences between our study and (2017) Weaver et al.'s, lie in: 1) their experimental paradigm was visually-guided, rather than memory-guided; 2) their distractor stimulus was presented jointly with the target stimulus instead of after; 3) ERP analysis was time-locked to 50 ms prior to saccade onset, instead of to distractor presentation; 4) the occipital region of the scalp was investigated instead of the frontal and parietal regions, as evaluated in our study. A future analysis can be undertaken to examine whether using the guidlines in 3) and 4) will reveal similarities to findings in their study.

Eye Movement Behavior

The results of our study indicate that memory-guided saccades are interrupted by the presentation of a distractor. As earlier mentioned, it has been found that distractors presented ipsilateral (at 0°, 22.5°, 337.5°) the target stimulus location were observed to produce a facilitation effect on saccade latencies, whereas distractors presented contralateral from the target stimulus (at 135°, 180°, 225°) exhibited a suppression effect (Walker et al., 1997; Edelman & Xu, 2009). The mean peak saccade latency probability reduction findings of our study add some convergent validity to the Edelman and Xu (2009) study, by demonstrating that distractors presented ipsilateral to the target location have almost no inhibitory effect on saccade generation, unlike distractors in the contralateral condition. Overall, the absolute differences the distractors have on saccade latency probability distribution curves (experimental conditions against control) are only minimal since their effect is so short lived in healthy participants as KSD analysis revealed.

Event-Related Potentials and Saccadic Eye Movement Behavior of Memory-Guided Saccades

In further investigating the relationship between N1 amplitude and distractor presentation at Pz, the relationship between saccade latency and neural activity present before and during saccadic eye movements was explored and appeared to be non-existent. Our linear regression analyses found no significant association between N1 amplitude and mean saccade latency, suggesting that this waveform at parietal sites is not directly involved in the timing and execution of saccadic eye movements. These findings are consistent with similar research recently conducted by Kulke, Atkinson, and Braddick (2020) where participants were asked to make a visually-guided saccade to a target object in the presence and absence of a fixation point. In that study, no significant association was found in linear regression models created for ERP amplitude (110 - 180 ms post-target onset at frontal or occipital sites, coinciding with P1 and N1 waveforms in our study) and saccade latency in either competition (fixation point presence coinciding with target onset) or non-competition conditions (fixation point disappearing with target onset); however, distractors were not used in their study.) Similarly, while ERP amplitudes were predictive of saccade accuracy, they did not predict saccade latency in the Weaver et al. (2017) study. Taken together, the findings of these visually-guided saccade studies lend limited support for the results of our study.

With these data in mind, it remains to be determined if such distractor-induced patterns of memory-guided saccade inhibition and facilitation will be observed the hemianopic field of blindsight patients. If these patterns do present themselves in blindsight patients, then it is possible that saccades are modulated by processes that are largely unconscious for guiding and directing our covert attention to our environment. Blindsight is an unusual neurological disorder in that patients have normal to above-chance task performance in pointing, forced-choice, and

implicit processing paradigms, yet the patients themselves report being unable to consciously perceive visual stimuli (Danckert & Rossetti, 2005). The subcortical brain structures that are involved in the residual visual functions of blindsight are shared with those required to generate saccadic eye movements, which allow the eye to orient and foveate onto stimuli of interest in the external environment. In directing the eye toward environmental stimuli, these structures allow for overt shifts in visual attention. This unique feature of the oculomotor system allows researchers to gain insight into the location and timing of participant attention (Lewkowicz & Hansen-Tift, 2012).

The research we conducted used the memory-guided saccade task to investigate the neural correlates of memory-guided saccades in the presence of distractors. Additionally, since attention appears to be a prerequisite for awareness under most normal circumstances, detailing the mechanisms involved in saccadic eye movements is invaluable for understanding the mechanisms of blindsight as manifest in saccade tasks. Our findings elucidated these processes by demonstrating that changes memory-guided saccades do not appear to be associated with changes in ERP activity between distractor conditions.

Traditionally it has been argued that our visual environment is processed in two streams which operate semi-independently of one another (Goodale & Milner, 1992). These are the ventral and dorsal processing streams. The ventral stream processes objects categorically ("what" pathway), providing semantics to the object perceived; where the dorsal stream processes spatial information ("where" pathway) about objects. The primary argument for the independence of these streams derives from the apparent modularity of function between the streams, as lesion studies have implied dissociation between regions (Rossit et al., 2010; Medendorp et al., 2018). Intriguingly however, elongated objects have been identified as tool primes when compared to

the effect of continuous flash suppressed (CFS) elongated versus non-elongated objects on reaction time (RT) on tool identification; the elongated objects were found to be just as useful as a prime as a tool itself in the task (Sakuraba et al., 2012). This study suggests that general object form, which is chiefly processed in the dorsal stream, can impact the semantic processes of the ventral stream (Hebart & Hesslmann, 2012).

The interplay between spatial and semantic representation of objects can be observed in regions such as the Frontal Eye Fields (FEF), where saccades and goal relevant objects have been found to elicit increased activation in the region. As discussed earlier, transient pharmacological lesioning of FEF can significantly impact animal behavior in memory-guided saccade tasks, whereby a representation of the target stimulus must be held online until a saccade toward the target goal location is initiated. Visually-guided saccades did not appear impacted by FEF transient lesioning, possibly because the saccade was reflexive and exogenously driven. Therefore, in our future study with blindsight patients, it may be seen that patients will be drawn reflexively to or interrupted by contralateral distractors presented within their blind hemifield and the distractors will impact their saccade latency in our memory-guided saccade task, even as they exhibit increased frontal electrode activity after target offset.

The behavior and performance of patients in our memory-guided saccade study will depend on their structural and functional brain connectivity. Previous fiber tractography research has shown that residual visual functions of blindsight appears to be contingent on the integrity of tract fibers connecting the colliculus and pulvinar to V5 and between the LGN and V5, but not necessarily between the colliculus and pulvinar themselves (Ajina et al., 2015). Given these findings, it may be useful to *a priori* refine our inclusion criteria to enroll participants without colliculo-pulvinar damage for future saccade studies.

In this preliminary study, we have manipulated saccades in a memory-guided saccade task through distractor presentation and have profiled associated changes in brain dynamics and eye movement behavior. In our future directions, we aim to evaluate these parameters in hemianopic blindsight patients who lack visual awareness; in doing so, we may better profile the role of visual awareness on behavioral performance associated with healthy saccadic eye movements and blindsight.

Limitations

While this study provided some insights into the behavior and ERP components of memory-guided saccades, it is not without limitations. For instance, because of the brief time scale within which the saccadic eye movements are generated at, it was incredibly difficult to capture noiseless ERP data of the process, as eye movements tend to generate large EEG artifacts. Because of this, it is possible that the impact of distractor appearance in memory-guided saccades were distorted and masked in frontal and parietal recording sites. As we discovered, only N1 amplitude at Pz was significantly impacted under select distractor presentation conditions. Eye movements may have produced non-significant results through movement artifacts, especially in frontal electrodes where frontal eye fields are known to participate in saccade initiation. Additionally, while trials with artifacts unrelated to eye movements were visually rejected, EEG artifact rejection was performed by one experimenter and therefore may lack the internal reliability achievable through multiple reviewers. Therefore in future studies Independent Component Analysis (ICA) may be used to separate eye movement artifacts from cortical activity related to distractor processing.

In addition to movement artifacts, there also exists large saccade latency variability in the human population. In this study, our sample size was limited to just 13 participants for reasons discussed earlier, therefore it would be useful to recruit a larger number of participants for the study and refine the sample to a subset of participants who performed well on the task and retest them in a higher volume of trials. A third change could be to increase the number of trials to improve the signal-to-noise ratio. A number of participants that were involved in this study had some difficulty remembering task instructions, even after the training trial period. With a larger or more targeted population sample, the results of this study may have turned out differently.

Finally, this study lacks data from a patient population which was originally planned to be included in the study; however, because of extenuating circumstances due to COVID-19 these participants were not tested and evaluated. Future directions will include this patient population.

Future Directions

In addition to including a hemianopic blindsight patient population into the current study, there are a number of directions that can be taken with our paradigm. First off, it may be worthwhile to evaluate the impact distractors presented in the upper and lower-half of the visual field have on saccade latency, as previous research has only evaluated nasal (central visual field) and temporal (peripheral visual field) distractor influence (Rafal et al., 1990). Second, ERP analysis may investigate whether distractor and target appearances are qualitatively different from one another. Third, it would be interesting to see if there is an interaction between EEG alpha wave phase and memory-guided saccade task performance, as alpha wave phase is known to impact the perception of stimuli (Mathewson et al., 2009). Lastly of potential interest: it is

curious to see if TMS application to the parietal scalp region during distractor presentation in the memory-guided saccade task may transiently rescue saccade activity from distractor inhibition, as it has been found that TMS applied to the occipital pole can disrupt visual processing of a metacontrast mask (Ro et al., 2003). Inhibition of the parietal region may interrupt N1 activity associated with distractor presentation during the memory-guided saccade task. Together with research demonstrating that TMS application over the posterior parietal lobe may interrupt the sensory phase of stimulus processing (first 50 ms), but not memory phase (> 500ms), suggests that TMS application may be able to disrupt the effect of distractor presentation without interrupting the memory-guided saccade itself (Brandt et al., 1998).

Conclusion

The presentation of distractors during memory-guided saccades can modulate their latency, however, measures of ERP amplitude and time at Pz or Fz do not appear to differ significantly between distractors presented ipsilateral or contralateral to a target stimulus. Since we were not able to detect changes in ERP activity at these sites, it is possible that this process is mediated by subcortical structures such as the superior colliculus. Future directions of this study will include blindsight patients in order to assess whether distractor influence of memory-guided saccades is largely an unconscious process, and in doing so, we may also shed light on some of the neural mechanisms of blindsight itself.

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