

**Spatial, Selective and Sustained Attention to Motion in a Unilateral Parietal
Patient with Remediated Neglect**

A Case Study using Multiple Object Tracking with infrared Eye-tracking & Pupillometry

Anee Karin Lee



Cognitive Neuroscience Masters Program

Department of Psychology

University of Oslo

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Abstract

Patients demonstrating a syndrome called unilateral neglect will often show a striking deficit in directing attention to the visual space contralateral to the site of cortical damage, or lesion. Once unilateral neglect has remediated, some neglect patients continue to demonstrate visual extinction, in which impairments in the allocation of attention appear only in the presence of competing stimuli. In this study, a relatively novel methodology, multiple object tracking (MOT) paired with eye-tracking and pupillometry, was used to quantify attention to motion in a parietal patient with remediated unilateral neglect. Our patient LE could select and track a single target from a field of identical distractors, but this selective attention mechanism differed from that of normal age-matched controls. LE also had significantly altered cognitive load capacity as well as sustained attention in both hemifields, thereby indicating a non-lateralized impairment of attention. Previous studies show that patients with extinction have performance that is severely impaired in the contralesional field, and slightly attenuated in the ipsilesional field. Contrary to previous findings, our results suggest that sustained attention to motion can be more severely impaired in the ipsilesional than in the contralesional hemifield, and also be affected altitudinally. Most surprising was the reduced performance in the controls when attending the left hemifield in the presence of competing stimuli in the right hemifield. In conclusion, studying attention with MOT in conjunction with eye-tracking and pupillometry offers a unique possibility to further characterize specific spatial, selective, and sustained attentional functions in patients as well as in healthy aging participants.

Keywords

MOT, multiple object tracking, fMRI, unilateral, parietal, altitudinal, neglect, stroke, motion, eye-tracking, pupillometry, attention, lesion studies

Introduction

Spatial Attention

Visual attention is a cognitive process that in a dynamic environment provides a means of selecting and enhancing the perception of relevant visual stimuli, while ignoring irrelevant stimuli (Kim & Cave, 1999; Lavie et al., 2004; Posner, 1994a; Posner et al., 1994; Connor et al., 2004; Corbetta et al., 2008; Drew et al., 2009). More specifically, visuospatial or spatial attention is the selective processing of information at given locations, or regions of space (Sohlberg & Mateer, 1987; Hikosaka, et al., 1993). Spatial attention is thought to act by enhancing the processing of attended stimuli and suppressing the processing of unattended irrelevant information relative to baseline in given locations (Posner, 1994a; Posner, et al., 1994; Drew et al., 2009). For instance, spatial allocation of attention to a location improves the accuracy and the speed of detection of objects presented in that location (Bashinski & Bacharach, 1980; Downing, 1988; Hawkins et al., 1990; Sheliga et al., 1994; Hoffman & Subramaniam, 1995). Notably, because shifts of attention can occur much faster than changes in eye position (*covert attention*), spatial attention while gazing at one stimulus allows for the selection of, or *orienting* to, the next location before an actual change of eye position can occur (Posner, et al., 1984; Hoffman & Subramaniam, 1995). Furthermore, attention to motion may be described as tracking objects in given locations or regions of space over time (Alvarez & Franconeri, 2007). An important role of spatial attention is to selectively attend to objects of interest in the environment and track them as they move temporally in the visual field while ignoring irrelevant information (Verstraten et al., 2000; Battelli et al., 2001; Drew et al., 2009).

The processing of relevant stimuli by attention may be 1) selected on particular stimuli or activities either intentionally or automatically, 2) is limited in capacity, and 3) may be sustained by effort (Desimone & Duncan, 1995; Scholl, 2009). Kahneman (1973) proposed that activities which are demanding, or have high attentional load, require a large amount of mental effort. Effort is the level of demands that is required by the processing of a particular task. The mental capacity to process a particular task is limited and therefore, it is necessary to selectively allocate mental resources to various activities and to the various stages in processing. In addition, several processing of several tasks may occur simultaneously, provided that the total amount of mental effort does not exceed the inherent capacity limit of attention. However, other tasks might be relatively automatic therefore requiring less mental effort regardless of the level of attentional

load. The total available capacity for task-processing may also be influenced by factors such as arousal or the alert state. Attentional capacity will therefore reflect demands, or loads, required at the initial level of perception, the level of interpretation of perception where it is committed to memory, and at the stage where an appropriate response is selected (Kahneman, 1973; Beatty & Lucero-Wagoner, 2000; Lavie et al., 2004).

Sohlberg and Mateer developed a qualitative model of visual attention, which is useful in evaluation of pathology and development of rehabilitation programs for patients with neurological deficits (Sohlberg & Mateer, 1987, 2001). This conceptualization divides the different attentional mechanisms into hierarchical descriptive subgroups, and correlates strongly with clinical observation of patients as they recover attentional functions. At the lowest levels of their hierarchical model, sustained and focused attention recover earliest in coma patients and are involved in vigilance and working memory (Sohlberg & Mateer, 2001). *Focused attention* is involved in the discrete responses to specific visual, auditory or tactile stimuli, and *sustained attention*, or vigilance, enables the effortful maintenance of consistent behavioral responses during continuous and repetitive activity (Sarter et al., 2001; Sohlberg & Mateer, 1987, 2001). The highest levels of their hierarchical model include selective, divided, and alternating attention. *Selective attention* refers to the cognitive capacity to maintain a goal-directed behavior in the presence of distracting or competing stimuli (Sohlberg & Mateer, 1987, 2001; Connor et al., 2004). This cognitive mechanism allocates processing of attended relevant versus unattended irrelevant information. For example, selective attention acts to direct the contents of working memory to task-relevant behavior (Milham et al., 2002), and has been demonstrated to be limited in capacity both spatially and temporally (Verstraten et al., 2000; Intriligator & Cavanagh, 2001). *Divided attention* enables responses simultaneously to multiple stimuli or multiple task demands. *Alternating attention* refers to the ability of individuals to shift their focus of attention and move between two cognitively different tasks.

In Posner's model of attention, the attentional network is organized into three subsystems that perform different but interrelated functions; 1) maintaining a vigilant or *alert* state, 2) selecting, or *orienting* to, sensory input resolving, and 3) conflict among responses or *executive control* (Posner & Boies, 1971; Posner & Petersen, 1990; Corbetta et al., 2000; Fan et al., 2002; Fan et al., 2005; Posner & Rothbart, 2007; Green et al., 2008). The alerting network involves sustained attention, vigilance, alertness and arousal (Raz & Buhle, 2006) and is defined as

achieving and maintaining a state of preparedness or sensitivity to incoming stimuli. Alerting has been proposed to be the foundational attentional network on which other mechanisms of attention are based (Raz & Buhle, 2006). Arousal is the state of general non-specific excitability, whereas alertness refers to goal-directed task preparedness and may interact with the executive control network (Raz & Buhle, 2006). The orienting network consists in the directing of attention in space (Fan et al., 2002; Fan et al., 2005). The orienting of attention may occur overtly, with eye movements, or covertly without eye movements (Posner et al., 1984; Posner & Rothbart, 2007). Executive control network is implicated in tasks involving cognitive conflict and mental effort (Fan et al., 2002; Fan et al., 2005).

These theoretical models of attention are not mutually exclusive and may be complementary in characterizing attention. Indeed, these attentional theories have been quite instrumental in delineating attentional networks of the brain (Knudsen, 2007).

Attentional Networks and Control

There are multiple components of attention mediated by different cortical and subcortical networks, which interact but are largely disparate functions (Posner & Petersen, 1990; Corbetta et al., 2000; Corbetta & Shulman, 2002; Raz & Buhle, 2006; Knudsen, 2007). Posner suggested that different anatomical areas perform specific cognitive operations, and that different neural networks were involved in the three various attentional functions of alerting, orienting and executive control (Posner & Petersen, 1990; Fan et al., 2002; Fan et al., 2005; Posner & Rothbart, 2007; Green et al., 2008). Plus, there is evidence for hemispheric specialization of attention, in which the right hemisphere is biased for processing global, low-spatial frequency information, and the left hemisphere for processing local, high-spatial frequencies (Robertson & Delis, 1986; Posner & Petersen, 1990). The alerting network has been proposed to be dependent on noradrenergic innervations arising from the locus coeruleus, to the right frontal areas, dividing as they go back to the posterior parietal lobe, the pulvinar and superior colliculus, and the ventral geniculo-striate pathway (Robbins, 1997; Posner & Petersen, 1990; Aston-Jones & Cohen, 2005; Fan et al., 2005; Posner & Rothbart, 2007; Raz & Buhle, 2006). The maintenance of the alert state and sustained attention has been associated with right-hemispheric dominance (Heilman et al., 1985; Posner & Petersen, 1990; Sarter et al., 2001). Performance in tasks measuring sustained attention is also more impaired with right lesions than left hemispheric infarctions (Coslett et al., 1987). The locus coeruleus-norepinephrine (LC-NE) system has also

been implicated in outcome of task-related decision processes (Aston-Jones & Cohen, 2005). Phasic LC activation was proposed to facilitate behaviors that optimize task performance, whereas tonic LC activation led to disengagement from a current task and exploration of alternative behaviors.

In addition to having noradrenergic ascending pathways, sustained attentional mechanisms have also implicated cholinergic innervations (Sarter et al., 2001). Cholinergic innervations of the posterior superior parietal lobe (Mountcastle, 1978; Wurtz et al., 1980), the temporoparietal junction (TPJ), the lateral pulvinar nucleus of the posterolateral thalamus, superior temporal lobe, frontal eye fields (FEF) and the superior colliculus of the midbrain has been implicated in the orienting network (Posner & Petersen, 1990; Corbetta & Shulman, 2002; Posner & Rothbart, 2007; Raz & Buhle, 2006). Cholinergic stimulation has been proposed to enhance processing the impact of salient stimuli (Robbins, 1997). The parietal lobe, particularly the TPJ is thought to disengage attention (Corbetta et al., 2000; Corbetta & Shulman, 2002), while the FEF (Corbetta & Shulman, 2002) and superior colliculus shifts attention to a new target area, and the pulvinar nucleus is engaged in processing information from the indexed location and reengages attention (Posner & Petersen, 1990).

Executive control is suggested to be modulated by dopaminergic signaling targeting the anterior cingulate cortex (ACC) and the supplementary motor area of the frontal midline areas, the lateral ventral, the prefrontal regions and the basal ganglia (Posner & Petersen, 1990; Robbins, 1997; Fan et al., 2005; Raz & Buhle, 2006; Posner & Rothbart, 2007). The ACC has been suggested to resolve or monitor conflict in response level rather than in stimulus perception (Fan, et al., 2005; Raz & Buhle, 2006), and sends prominent direct inputs to the LC-NE system (Aston-Jones & Cohen, 2005). The dorsal ACC has been activated in cognitive conflict tasks, and the rostral ACC shows activation when there is an error in response (Raz & Buhle, 2006).

The control of attention has also been described as processing visual information via two distinct neural processing streams, namely, the dorsal and ventral frontoparietal networks (Corbetta & Shulman, 2002; Corbetta et al., 2008; Ting et al., 2011). Bottom-up or exogenous attentional control of the ventral frontoparietal stream is stimuli-driven, enhancing salient items in the environment and may be driven by noradrenergic ascending activation (Desimone & Duncan, 1995; Sarter et al., 2001; Raz & Buhle, 2006). Attention may increase the saliency, or intensity of an attended object by enhancing the neuronal responses of the sensory cortex

(Maunsell & Cook, 2002). This ventral system has been implicated in salience detection and is thought to be lateralized to the right hemisphere and connects the temporal parietal junction (TPJ), the inferior parietal lobe (IPL), and the ventral frontal lobe (Corbetta et al., 2000; Corbetta & Shulman, 2002).

On the other hand, top-down mechanisms of the dorsal frontoparietal stream focus or bias endogenous neural processing resources on the most relevant sensory information in order to maintain goal-directed behavior (Kim & Cave, 1999; Corbetta et al., 2000; Corbetta & Shulman, 2002; Fan et al., 2002; Connor et al., 2004; Lavie et al., 2004; Raz & Buhle, 2006; Knudsen, 2007; Corbetta et al., 2008; Ting et al., 2011). Top-down attentional control, then, is a task-dependent process that modulates low-level processes when searching the environment for specific stimuli (Connor et al., 2004; Corbetta et al., 2008; Sarter et al., 2001). This dorsal network is associated with the superior parietal lobes, the intraparietal sulci (Ips), the frontal eye fields (FEF) of the dorsal frontal lobes and is important in goal-directed top-down attentional selection (Corbetta & Shulman, 2002; Knudsen, 2007; Ting et al., 2011).

Selective attention to motion is an example of high-level motion influenced by top-down attentional control (Verstraten et al., 2000; Battelli et al., 2001). Low level motion is automatic and signals motion even in the absence of attention. In contrast, high-level motion is a top-down attention-dependent process that modulates or biases bottom-up signals of moving stimuli (Cavanagh, 1992; Connor et al., 2004; Knudsen, 2007).

Measuring Attention

Attention is a cognitive process, and thus intangible and difficult to measure, especially non-invasively in human participants. However, the processes behind visual attention may possibly be elucidated via lesion studies, using physiological responses associated with attention such as eye-movements and pupillary response, and through behavioral tasks that require selective and sustained attention over time.

Lesion Studies

As the neurobiology of attention is thought to consist of distinct and parallel functional networks distributed throughout the brain (Connor et al., 2004; Corbetta et al., 2008; Fan & Posner, 2004; Kim & Cave, 1999; Ting et al., 2011), functional dissociations in lesion studies may allow for the inference of the separation of processing pathways and organization principles.

When the attentional systems are disrupted, a person's ability to interact with and attend to the dynamic environment may be profoundly impacted. Studies in patients offer a unique possibility to improve our understanding of the causal relationship between brain activity and specific attentional functions in humans (Billino et al., 2009). Although, this approach suffers inferential limitations, such as the immense variability of cognitive impairment as well as size and location of lesion sites between patients, lesion studies have been instrumental in implicating brain regions with a particular function (Posner, et al., 1984; Posner, 1994b; Riggs et al., 2007). For instance, trauma or stroke with injury to the right parietal cortex may lead to a mainly one-sided visual perception disorder, called visual or unilateral neglect, that is characterized by a reduced awareness or inattention of stimuli on one side of space (Riggs et al., 2007). About 46%-92% of stroke patients exhibit deficits in attention as one of the most prominent neuropsychological change related to stroke (Barker-Collo et al., 2009; Feigin, Lawes, Bennett et al., 2009). Therefore, studying deficits in visual neglect patients may provide novel insights into the causal relationship between neural structures and attentional processes underlying spatial, selective and sustained attentions.

Unilateral Neglect

Unilateral neglect is described by various terms, such as visual neglect, hemispacial neglect, hemiagnosia, hemineglect, egocentric (viewer-centered) neglect, spatial neglect or neglect syndrome (Riggs et al., 2007). Patients demonstrating unilateral neglect will often show a striking deficit in directing attention to the visual space contralateral to the lesion site (Posner et al., 1984; Battelli et al., 2003). Immediately after a stroke caused by a large right middle cerebral artery infarction, patients often favor head and eye positions towards the right visual hemifield, and very rarely direct their gaze to the left, indicating a failure of attentional control (Husain, 2008). Most commonly, patients with damage to the right parietal cortex demonstrate a variety of attentional deficits contralateral to their lesion, in the left visual field (Posner et al., 1984). A patient suffering from spatial neglect may draw only the right side of an object, read only the right part of a word or the right part of sentences name items located only on the right, or eat only from the right side of a plate (see Fig. 1; image taken from Parton et al., 2004).

Damage to the posterior parietal lobe appears to affect the ability to disengage attention from a location contralateral to the lesion (Posner & Petersen, 1990). According to the biased competition model, not only will lesions to a particular cortical area result in loss of functions

mediated by the damaged region, but also result in a loss of competitive weights, or biases attributed to objects in the affected field contralateral to the lesion (Desimone & Duncan, 1995). Since the posterior parietal cortex mediates disengaging of attention, the balance of competitive weights attributed to objects in the contralesional field will be altered, so that in neglect, the midsagittal plane or egocentric frame of reference of the patient is biased towards the right (Posner, et al., 1984; Posner & Petersen, 1990; Desimone & Duncan, 1995). Thus, neglect has been implicated as a top-down process since, if specifically cued or instructed, neglect patients can attend the contralesional hemifield, which demonstrate a failure of attention rather than a loss of vision, or *hemianopia* (Duncan et al., 1999). It may also be a failure of bottom-up stimuli to disengage the top-down process (Corbetta & Shulman, 2002).

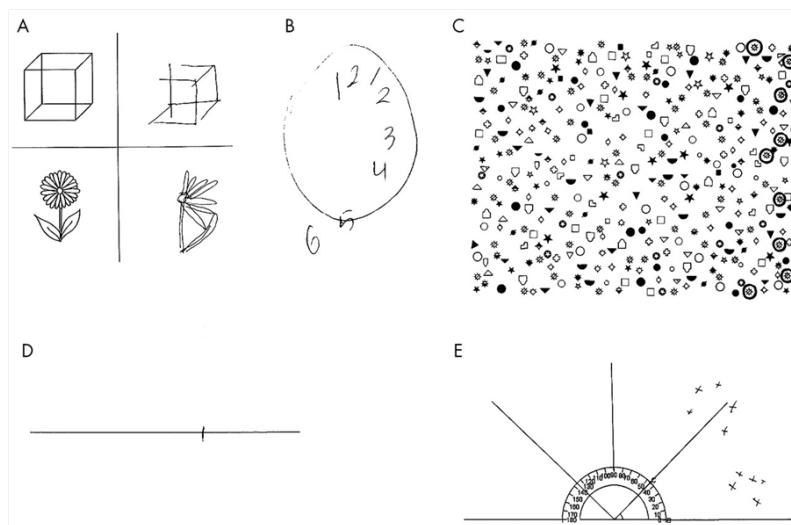


Figure 1. Attentional control of Unilateral Parietal Neglect patients. Elements in the left visual field were omitted or patients erred to the right in the following tasks: **A.** Copying simple objects **B.** Drawing a clock **C.** Weintraub & Mesulam (1987) cancelling targets among distractors task. **D.** Bisecting a horizontal line. **E.** Naming objects in their surrounding location. (image taken from Parton et al., 2004).

The balance of competitive weights may also be altered in the vertical visual space. Patients exhibiting unilateral neglect in the left versus right hemifields may exhibit *altitudinal neglect* of the upper, or *superior*, versus lower, or *inferior* hemifields (Bender & Teuber, 1948; Rapcsak et al., 1988; Butter et al., 1989; Kageyama et al., 1994; Ergun-Marterer et al., 2001). Patients with altitudinal neglect fail to attend to items located in the inferior visual field, and are most frequently found to make upward errors in bisecting vertically oriented lines (Bender & Teuber, 1948; Ergun-Marterer et al., 2001). Such altitudinal neglect has been associated with bilateral parieto-occipital infarctions (Ergun-Marterer et al., 2001; Rapcsak et al., 1988).

In addition to the lateralized deficits of neglect, there are also non-lateralized impairments in the allocation of attention of neglect patients (Robertson, 2001). Although, visual neglect is traditionally considered a unilateral disturbance, bilateral generalized impairments of attentional

capacity have also been reported (Habekost & Rostrup, 2007; Habekost & Starrfelt, 2009; Husain & Rorden, 2003). These non-lateral impairments include deficits in motion perception, spatial working memory, sustained attention, and visual extinction (see also Posner, et al., 1984; Battelli et al., 2001; Husain et al., 2001; Robertson, 2001; Parton, Malhotra, & Husain, 2004; Husain, 2005).

Visual Extinction

Visual extinction is a syndrome that is characterized by a failure to attend to stimuli on the contralesional field only when in the presence of a competing distractor in the ipsilesional visual field (Posner et al., 1984; Weintraub & Mesulam, 1987; Egly et al., 1989; Kaplan et al., 1991; Rorden et al., 1997; Robertson, 2001; Husain, 2008). This impairment has been described as both a unilateral and a non-lateralized deficit of neglect, since the impairment occurs in one hemifield and therefore seems lateralized, but the impairment appears only in the presence of competing stimuli in the opposite hemifield, thus making it also a non-lateralized deficit. Generally, the greater the number of distractors to the right, the more that visual attention is impaired on the left (Kaplan, et al., 1991). Also, while performance may be worse in the contralesional field, ipsilesional performance is also attenuated in neglect patients compared with controls (Battelli, et al., 2001).

Thus far, the effect of visual extinction or neglect on motion has not been well-defined. However, there are a few studies demonstrating extinction of motion perception in unilateral parietal patients. In instances where two or more stimuli must compete for attention, these patients with parietal lesions exhibiting extinction in the left visual hemifield were found to be impaired in top-down attention as well as high-level motion perception. This effect was found only in cases of competing stimuli, thereby indicating visual extinction of motion perception (Zihl et al., 1983; Rorden, et al., 1997).

In a unique case study, Crevits et al. (2004) reported a patient with visual extinction for motion in the left hemifield. This patient presented with a left posterior artery cerebral infarction of the occipital lobe and had had a previous incident of right parieto-occipital watershed infarction. During a monocular visual field exam, the patient was able to attend and process visual static and motion information, as he could describe locate items and movement when it was presented unilaterally in the left or right visual hemifield. However, movement was ignored or neglected on the left when motion was presented bilaterally using simultaneous finger

movements in the right and left hemifields. This extinction was repeatedly present in the left upper and in the left lower quadrants of each eye with reproducible results across multiple trials. Given that the patient could detect unilateral movement, there is no indication of a sensory dysfunction in motion perception. The authors posited that the second infarction in the left occipital region may have unmasked the visual higher-order extinction to motion that could be attributed to the earlier right occipito-temporo-parietal lesion (Crevits et al., 2004).

Cortical Damage in Neglect

No single lesion location has been sufficient to encapsulate all the symptoms of neglect following a cerebral artery infarction. Karnath et al., (2001) had previously identified the junction between the temporal, parietal and occipital lobes as the critical brain region involved in neglect, but this area has been involved in only 50% of the cases of neglect (Mort et al., 2003; Parton et al., 2004). However, the critical brain region involved in every case of neglect has been the angular (ang) gyrus of the inferior parietal lobe (IPL) (Mort et al., 2003; Parton et al., 2004). In addition, cortical damage involving the IPL or nearby TPJ has classically been implicated in neglect pathology (Husain, 2008; Parton et al., 2004; Shinoura et al., 2009; Verdon et al., 2010). The right hemisphere cortical regions associated with neglect include the angular (ang) and supramarginal (smg) gyri of the IPL (Shinoura et al., 2009), the TPJ, the superior temporal gyrus (STG) (Karnath et al., 2001; Mort et al., 2003; Parton et al., 2004), and the inferior (IFG) and middle frontal (MFG) gyri (Fig. 2; taken from Parton et al., 2004). The neural basis for the effects of increasing leftward neglect via increases in the number of items to the right in a visual presentation has been identified as being localized in the mid-intraparietal sulcus, just above the IPL (Eglin et al., 1989; Kaplan et al., 1991). Neglect patients with lesions that were located relatively inferiorly in the right parietal cortex, such as at the TPJ or in the underlying white matter were significantly associated with reductions in both visual processing speed and visual span as well as in attentional capacity (Habekost & Rostrup, 2007; Habekost & Starrfelt, 2009).

The literature suggests that contralateral hemispacial neglect was more frequent and severe following right-hemispheric lesions than following unilateral left-cerebral damage. Right-sided spatial neglect is rare since there is redundant processing of the right space by both the left and right cerebral hemispheres, whereas the left visual space is processed only by the right cerebral hemisphere (Mapstone et al., 2003; Parton et al., 2004; Ting et al., 2011). Therefore, damage to

the right cerebral hemisphere would demonstrate a deficit to the left visual field more commonly than left-sided lesions in the right visual field. Redundancy in processing of right visual space also explains why ipsilesional deficits are attenuated in comparison to contralesional impairments (Weintraub & Mesulam, 1987; Ting et al., 2011).

Notably, there is a remarkable overlap between the ventral frontoparietal network proposed by Corbetta and Schulman and neural correlates associated with visual neglect (Corbetta & Shulman, 2002). As the ventral network is thought to be involved in salience detection of exogenous stimuli, visual neglect may possibly be a bottom-up attentional deficit of salience detection which fails to disengage the top-down network. In sum, then, to the proposed ventral network correlates with the higher incidence of visual neglect following lesions to the right posterior parietal cortex.

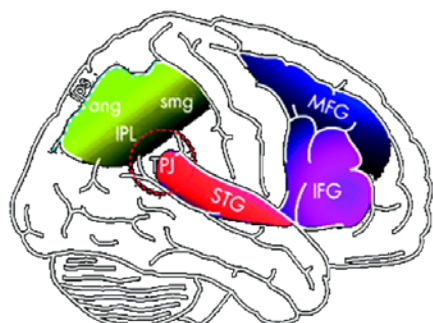


Figure 2. Right hemisphere regions implicated in neglect.

The intraparietal sulcus (Ips) separates the superior parietal lobe (SPL) from the inferior parietal lobe (IPL), which consists of the angular gyrus (ang) and supramarginal gyrus (smg). The temporoparietal junction (TPJ) is located between the IPL and the temporal lobe. The middle frontal gyrus (MFG) and inferior frontal gyrus (IFG) are anterior areas that may also be involved in neglect patients (image taken from Parton et al., 2003).

Spatial deficits associated with neglect may be due to lesions affecting the dorsal regions of the right parietal lobe, the superior parietal lobe, and/or the intraparietal sulcus (Husain, 2008; Shinoura et al., 2009). Non-spatial deficits associated with neglect, such as the previously mentioned sustained attention and salience detection, are thought to be caused by damage to the more ventral regions involving the right inferior parietal lobe and/or intraparietal sulcus. In addition, there may be similar distinctions in the functions of the dorsal and the ventral right frontal lobe (Husain, 2008; Ting et al., 2011). Also, as auditory sustained attention has been strongly correlated with and is a significant predictor of unilateral spatial neglect, this indicates that the right hemisphere-dominant sustained attention system may modulate the lateralized posterior attention system (Posner et al., 1984; Robertson et al., 1997).

Eye-tracking

Visual attention and eye movements are thought to be closely related (Sheliga et al., 1994; Hoffman & Subramaniam, 1995; Leigh & Kennard, 2004). For instance, once attention is directed to a moving object, the eyes do not stay at the initial location but follows the object as it

moves simultaneously in spatial trajectory as if attached to the object (Hikosaka et al., 1993). According to the premotor theory of attention, the mechanisms responsible for spatial attention are the same mechanisms responsible for oculomotor activation (Rizzolatti et al., 1987; Sheliga et al., 1994; Clark 1999; Corbetta, 1998; Corbetta et al., 1998; Corbetta & Shulman, 1998; Eimer et al., 2005; Van der Lubbe & Abrahamse, 2011). Sheliga et al., (1994) found that the allocation of spatial attention led to activation of oculomotor circuits. In a series of elegant neuroimaging studies, Corbetta et al. showed that visuospatial attention and eye movements shared the same cortical neuronal networks areas (Corbetta, 1998; Corbetta et al., 1998; Corbetta & Shulman, 1998).

Just and Carpenter (1976) postulated that eye fixations are intimately involved with the ability to encode visual information, and that eye fixations can also indicate how visual information is internally manipulated and attended. A fixation occurs when foveal attention lingers on a particular object or in a particular region of space; the movements of the eyes from one fixation to another are known as saccades.

There is also evidence suggesting that there is a close relationship between attention and saccades (Clark, 1999; Leigh & Kennard, 2004). Indeed, a number studies support the claim that saccades drive attention (Just & Carpenter, 1976; Hoffman & Subramaniam, 1995; Schneider & Deubel, 1995; Armstrong et al., 2006; Schafer & Moore, 2007; Gregoriou et al., 2009). Prior to a saccade, attention precedes an eye movement to the target location (Hoffman & Subramaniam, 1995). In other words, when healthy participants move their eyes to a location in space, they attend to location prior to the actual movement of the eyes. In addition, Hoffman et al, (1995) found that an inability to orient attention to one location and simultaneously execute a saccade to another location.

Thus, as eye movements and attention are so closely linked, attention may be characterized in part by measuring fixations and saccades. The brainstem reticular formation, the cerebellar dorsalvermis and caudal fastigial nucleus, the frontal eye fields, the supplementary eye field, the supplementary motor area and the parietal eye field have been identified to contribute to the programming of saccades (Leigh & Kennard, 2004).

Infrared eye-tracking is a non-invasive, video-based method of quantitative analyses of oculomotor and visual function (Laeng et al., 2007a; Laeng et al., 2007b). Eye-tracking provides a continuous record that temporally indexes the course of cognitive processing rather than

measuring only the differences in the behavioral end-products, such as in reaction times or accuracy. Current studies of eye-tracking in patients that have recovered from neglect symptoms indicate that traditional neglect assessment methods fail to register mild deficits in frequency of hemispatial neglect that remain in patients after the acute phase of stroke has remediated, (Mapstone et al., 2003). Additionally, eye-tracking, is compatible with simultaneous recording of pupillary responses, called pupillometry, which is also non-invasive and ideal to use in a patient population (Laeng et al., 2007a). Thus, the oculomotor responses as measured by eye-tracking and pupillometry may be sensitive to responses that are only partially activated and that may be below the threshold for awareness or in eliciting overt behavior (Laeng et al., 2007a).

Pupillary response

Studies have demonstrated a measureable relationship between pupillary responses to mental activity (Hess & Polt, 1964; Kahneman & Beatty, 1966; Andreassi, 1995; Piquado et al., 2010; van der Meer et al., 2010). A pupillary response is the contraction or dilation of the pupil, with constant 1 mm tonic fluctuations of the human pupil at baseline (Beatty & Lucero-Wagoner, 2000; Kim et al., 2000). Tonic changes in pupil size have been implicated to reflect arousal state, whereas phasic changes in pupil size have been implicated in cognitive and emotional processes. Thus, various perceptual and cognitive tasks have used task-evoked pupillary response (TEPR) to assess cognitive effort (Hess & Polt, 1964; Kahneman, 1973; Beatty, 1982; Winn et al., 1994; Beatty & Lucero-Wagoner, 2000; Steinhauer et al., 2000; Aston-Jones & Cohen, 2005; Porter et al., 2007).

Pupillometry is an exquisitely sensitive measure, in which differences in change of pupil diameter between conditions may be found at 0.001 mm dilations to stimuli occurring up to a rate of 3Hz (Beatty, 1988). The size and responsiveness of the human pupil is controlled by the circular sphincter and radial dilator fibers in the iris (Davson, 1984; Heller et al., 1990; Andreassi, 1995; Beatty & Lucero-Wagoner, 2000) . The radial dilator muscle, or the dilator pupillae, is innervated by the adrenergic sympathetic nervous system (Andreassi, 1995; Beatty & Lucero-Wagoner, 2000; Winn et al., 1994). This signal for dilation originates in the hypothalamus, propagates to the cervical spinal cord to a synapse with the superior cervical ganglion and is then transmitted directly via the ophthalmic nerve to the dilator pupillae (Andreassi, 1995; Beatty, 1988; Beatty & Lucero-Wagoner, 2000). The catecholamines,

norepinephrine and epinephrine, act on the adrenergic receptors of the sympathetic nervous system, affecting alertness, arousal and “flight or fight” responses (Tanaka et al., 2000).

Increases in pupil size have been most widely used as the psychophysiological measurement to characterize the processing of effort, capacity and allocation of attentional resources (Goldwater, 1972; Kahneman, 1973; Janisse, 1977; Beatty, 1982; Beatty & Lucero-Wagoner, 2000; Trillenberget al., 2004; van der Meer et al., 2010). Pupil diameter was found to increase incrementally with increasing cognitive load and effort, and to decrease with corresponding decreases in task difficulty (Kahneman & Beatty, 1966; Beatty, 1982; Beatty & Lucero-Wagoner, 2000; Porter et al., 2007).

When the cognitive process of memory or attention approaches maximum capacity, the pupil correspondingly stabilizes and reaches maximum size (Peavler, 1974; Granholm et al., 1996). For instance, in digit-span tasks, pupil size was found to increase with each successive digit, but reached maximum size after the 10th digit, which corresponds to short-term memory capacity limits of 9 digits (Granholm, Asarnow, Sarkin, & Dykes, 1996; Peavler, 1974). Thereafter, if processing capacity is exceeded, or overloaded, the pupil diameter has been shown to decrease (Poock, 1973; Granholm et al., 1996). Indeed, Poock, (1973) demonstrated that pupil size increased at 75% and 100% of maximum processing speed capacity, but decreased at 125% overload. Changes in pupil size as a function of processing capacity overload suggest that pupillometry is sensitive to the extent and limits of attentional processing capacity (Poock, 1973; Peavler, 1974; Granholm et al., 1996). Furthermore, Porter et al., (2007) found that the dilation pattern during a spatial memory task suggested little effort in the early stages of visual search and increasingly higher levels of effort towards the response. The effort associated with processing load, then, increases during trials in addition to level of difficulty.

Although dilation has been correlated with increases in mental effort, this may be caused either by dilation of the dilator pupillae or relaxation of the sphincter pupillae. Matthews et al. (1991) used an alpha-adrenergic receptor antagonist, thymoxamine, to temporarily immobilize the dilator pupillae. Despite the paralysis of the dilator pupillae, error rate and pupil dilation amplitude continued to increase with effort corresponding increases in effort required by task difficulty (Matthews, Middleton, Gilmartin, & Bullimore, 1991). These results suggest that although the sympathetically innervated dilation contributes to responses cognitive tasks

(Friedman et al., 1973; Steinhauer & Hakerem, 1992), the dilation amplitude associated with mental effort, is therefore primarily produced by the parasympathetic innervated sphincter.

Pupillary constriction is controlled by the sphincter muscle, or sphincter pupillae, and is innervated by the acetylcholinergic parasympathetic nervous system (Winn, et al., 1994; Andreassi, 1995; Beatty & Lucero-Wagoner, 2000). The parasympathetic nervous system is responsible for homeostatic activities when the body is at rest (Quigley, 2010). This acetylcholinergically innervated signal for contraction originates in the Edinger-Westphal nucleus of the midbrain, is propagated along oculomotor nerve fibers to the ciliary ganglion, which connects to the smooth circular muscles of the sphincter pupillae (Beatty, 1988; Andreassi, 1995; Beatty & Lucero-Wagoner, 2000). Increase in cortical acetylcholine levels has been associated with task performance in sustained attention during the presence of distractors (Himmelheber et al., 2000). Specifically, the nicotinic subtype of the acetylcholine receptor has been implicated in the successful processing attentional load (Espeseth et al., 2010).

Steinhauer et al., (2004) also found that sympathetic and parasympathetic pathways had differential contributions to changes in pupil diameter during sustained attentional processing. In a series of experiments, the effects of the cholinergic antagonist tropicamide, and the alpha-adrenergic antagonist dapiprazole were examined in comparison with a placebo. Tropicamide immobilized the sphincter pupillae, maintaining adrenergic innervation, while dapiprazole immobilized the dilator pupillae, maintaining parasympathetic innervations. Although all pharmacological treatments resulted in increases in pupil diameter during task performance, dapiprazole treatment had pupillary outcomes most similar to the control condition, while tropicamide differed in the pattern of pupillary response in comparison with placebo. These findings as well as those from Matthews et al., (1991) suggest that sustained attention and effort is modulated through the inhibition of the parasympathetically-innervated constriction, rather than the dilation innervated by the sympathetic nervous system. Thus, measurement of pupillary responses via pupillometry is a highly sensitive and reliable method of delineating brain networks

The relative immediacy of the pupillary response is distinctly advantageous as an objective measure of cognitive effort. Task-evoked pupillary response was originally suggested as valid and dynamic neuropsychophysiological index of attentional load by Hess and Polt (1964), and Kahneman relied heavily on pupillometry research to develop his model of the basic components

of attention and effort (Kahneman, 1973). In accordance with Kahneman's three criteria for measuring attentional load, the measurement of task-evoked pupillary responses can 1) accurately index changes in task parameters within-task variations in task demands; 2) can consistently and reliably be related to between-task differences in processing load by different mental tasks, and 3) the amplitude is responsive to individual differences in cognitive abilities. Attentional load measured by task-evoked pupillary responses has been shown to be highly sensitive, reliable and consistent. Although the pupil lacks face validity as a measure of brain function and lacks causality, correlation is high, and thus elucidating attentional functions with the use of pupillometry has yet to be fully exploited.

Modern laboratories use a low-intensity infrared video based pupillometer, which eye movements are observed through a closed-circuit monitoring system, and task-evoked pupillary responses are measured using a signal processor (Beatty & Lucero-Wagoner, 2000). The average of changes in pupil diameter is measured with respect to a task and background variations are ignored. As pupil size is affected by physiological factors such as levels of illuminance (Wyatt & Musselman, 1981; Steinhauer et al., 2000), hue (Kohn & Clynes, 1969), the ability to focus (accommodation and convergence of the eye) on an object (Marg & Morgan, 1949, 1950; Hennessy et al., 1976), age (Birren et al., 1950; Winn et al., 1994; Piquado et al., 2010), fatigue (Beatty & Lucero-Wagoner, 2000), and initial pupillary constriction in response to stimuli presentation (Kohn & Clynes, 1969; Libby et al., 1973; Steinhauer et al., 1983). Measurements of pupil size must control for such confounding factors. In addition to the physical factors, pupil size is also affected by cognitive factors such as novelty (Aboyoun & Dabbs, 1998; White & Maltzman, 1978), emotional content (Hess & Polt, 1960, 1964; Steinhauer, et al., 1983) sexual content (Aboyoun & Dabbs, 1998), and overstimulation (Poock, 1973; Peavler, 1974; Granholm, et al., 1996). Therefore, even after the confounding effect of initial physiological reactions is eliminated, and it is extremely important to have a good behavioral paradigm that will give a stable baseline, allow multiple presentations, and be able to control the number and types of stimuli presented.

Multiple Object Tracking

An appropriate paradigm should engage and measure multiple aspects of attention simultaneously. In addition, the measurements should be directly specific to processes in the

visual system, and also have high sensitivity in capturing the thresholds of attention early, as well as high reliability and validity of results across numerous trials and experiments.

Several tasks have been used in recent years for the evaluation of attentional mechanisms. For instance, the *Stroop task* has been used to study executive control (Bush, Luu, & Posner, 2000), the *Conner's Continuous Performance Test (CCPT)* has been demonstrated to assess sustained attention (Egeland & Kovalik-Gran, 2010), and the *Attention Network Test (ANT)* is useful in parsing the alerting, orienting and executive control functions of attention (Fan, et al., 2002; Fan & Posner, 2004; Green, et al., 2008) and the *Theory of Visual Attention-based assessment (TVA)* has been implemented in measuring visual threshold or span, processing speed, visual short-term memory capacity, efficiency of top-down control; and the spatial bias of attention (Habekost & Rostrup, 2007; Habekost & Starrfelt, 2009). The TVA in particular has already been used to study many different neuropsychological conditions, such as Alzheimer's disease, Huntington's disease, visual neglect and stroke in various regions of the brain (see Habekost, 2009 for a review). However, most of these aforementioned current performance measurements reveal only differences in the behavioral end-products of cognitive processing, and are not capable of measuring attention to motion as it occurs. In addition, a good behavioral paradigm should allow for the simultaneous measurement of physiological responses associated with attention, such as tracking eye movements or pupillary responses for the validation of such a paradigm and for the further delineation of attention. Thus, the multiple object tracking paradigm (MOT) may be such an ideal task for the elucidation of spatial, selective and sustained attention to motion.

The MOT paradigm allows for parsing the selectivity, capacity-limitation, and effortful components of attention (Pylyshyn & Storm, 1988; Fencsik et al., 2007; Scholl, 2009). MOT requires sustained and active attention over time, rather than brief shifts of attention and passive vigilance, and the limitation on the ability to carry out simultaneous processing may be measured by varying attentional load (Sears & Pylyshyn, 2000; Fougne & Marois, 2006; Alvarez & Franconeri, 2007; Scholl, 2009). The MOT task parameters and within-task variations in task demands can easily be varied, can consistently and reliably relate between-task differences in processing load by different mental tasks, and yet still be responsive to individual levels in cognitive abilities (Lavie et al., 2004; Alvarez & Franconeri, 2007; Scholl, 2009). In addition to this specificity, our technique provides high sensitivity and MOT is ideal for examining spatial

attention, object-based attention, as well as attention to motion (Driver & Baylis, 1989; Cavanagh, 1992; Verstraten et al., 2000). Thus, MOT may be an ideal paradigm for testing deficits in neglect as opposed to other paradigms, as MOT is easily paired with eye-tracking, pupillometry, which are non-invasive, continuous measures of attention that do not interrupt the behavioral paradigm, even in clinical patient studies (Doran et al., 2009).

In a typical MOT experiment, participants track a number of identical objects moving independently and unpredictably in a field of identical distractors. Participants are told to fixate on a point in the center of the screen. Between six to ten stationary identical items are presented, and a subset of one to five flash several times to indicate their status as targets, after which the objects are indistinguishable from those objects that did not flash, are thereafter distractors for the task. The items then move randomly and unpredictably about the screen (Fig. 1, image taken from (Scholl, 2009)). After a predetermined interval ranging from 7 to 20 seconds, the motion of all items stop, and participants must indicate, with either partial or full response, which of the items are the original targets. As the target and distractor stimuli are identical, participants are only able to only distinguish the targets from distractors by following the trajectory of each stimulus during the trial (Fencsik et al., 2007). Healthy participants have the maximum capacity to perform this task for an average of four and as many as five targets among a total of ten identical items, indicating that they can simultaneously maintain an index on each individual target (Pylyshyn & Storm, 1988; Scholl & Pylyshyn, 1999; Scholl et al., 2001; Flombaum et al., 2008; Scholl, 2009)

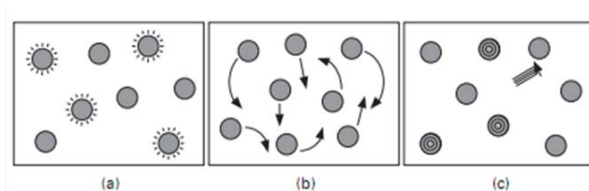


Figure 3. Multiple object tracking (MOT). **A.** Four discs flash, and return to baseline color. **B.** All discs move randomly and unpredictably. **C.** Movements stop, and participants indicate which disc was the original target (image taken from Scholl, 2009)

MOT and Neglect

To date, there has been only one published study, by Batelli et al. (2001) examining high-level attentive motion system in right parietal patients using MOT. Performance was severely impaired in the field contralateral to the lesion for patients in the tracking of more than 1 target with distractors and less severely impaired when tracking only one target with distractors. Because the participants performed normally on the low-level motion task (ability to see a motion defined rectangle in the absence of selective attention), it was postulated that these were a

direct consequence of disrupted attentional tracking rather than a loss in low-level motion processing. These results are consistent with the predicted deficit from similar objects competing for the same attentional resources, in which the contralesional side is more severely impaired. Attentional deficits were found only in the contralesional fields for selective attention and a multiple object-tracking task. This finding seems to indicate that selective attention to high level motion will be impaired in the visual field contralateral to the lesion, as opposed to being a bilateral impairment.

The Present Case Study

Multiple object tracking (MOT) used in conjunction with eye-tracking and pupillometry in a unilateral patient with neglect offers a unique combination of characterizing the role of the right parietal cortex in spatial attention, selective and sustained attention to motion, as well as the examining the capacity limits of selective and sustained attention by varying cognitive load using simultaneous measurements of physiological responses associated with attention. In this case study, we will attempt to validate this procedure as a sensitive and reliable method to measure dysfunctional selective and sustained attention.

Selective attention. The ability to select and track accurately a target in a field of identical targets in MOT during a short tracking interval of 5 seconds would demonstrate the presence or absence of preserved selective attention function. The capacity limits of selective attention may be examined by varying cognitive load of tracking between 1-4 targets. Increased effort would correspondingly increase pupil size, followed by stabilization at maximum diameter followed by decrease in pupil size once attentional capacity is overloaded. Accordingly, increasing the number of targets tracked per trial should in normal controls lead to the corresponding increase in pupil size.

Thus, accuracy and pupillary response was used as a measure ability to process selective attention in our patient to be compared with age-matched controls. Older adults have a natural decreased attentional capacity due to the effects of aging (West, 1999; Kim, et al., 2000; Kaneko et al., 2004 ; Van Gerven et al., 2004; Piquado, et al., 2010). As a result, we expected that the control group would reach maximum capacity at 3 targets rather than 4 targets.

Rorden et al. (1997) found that two unilateral parietal patients experienced extinction to motion perception when there were two separate moving objects competing for attention in the left hemifield. Therefore, we predicted that the unilateral parietal patient would be impaired in

selective attention to motion, and would reach maximum capacity, or asymptotic performance, for fewer targets than controls. No such deficit is predicted to be apparent in singly presented moving stimuli without distractors.

Sustained attention. Sustained attention may be measured by examining performance over time. In other words, preserved or impaired sustained attention may be demonstrated in the difference in ability to track a target in a field of identical targets in MOT for an early versus late tracking period. Moreover, although task-evoked pupillary response varies as a function of cognitive load, it also responds to the duration of tracking length (West, 1999; Steinhauer et al., 2004; Van Gerven, et al., 2004; Piquado et al., 2010). Therefore, we measured the change in pupil size as an index of sustained attention and effort. Thus, comparing the accuracy as well as pupil size of a particular cognitive load condition (e.g. 2 targets) over time (5 versus 10 seconds), would illustrate sustained attention. Varying cognitive load (tracking 1-4 targets) would delineate the capacity limits of sustained selective attention.

The right hemisphere-dominant sustained attention system may modulate the lateralized posterior attention system (Posner, et al., 1984; I. H. Robertson, et al., 1997). Thus, in the presence of a unilateral parietal lesion, the ability sustain attention in tracking 1 target might be affected as early as 5 seconds. Since we also expected the patient to have impaired selective attention, we believed he would show deficits in both the early (5s) and late (10s) tracking conditions for tracking more than one target.

Spatial attention. In order to examine spatial attention, MOT paradigms were created to compare the patient's ability to track in an entire field (whole field stimulation), only in left or right hemifields (unilateral stimulation), or left and right hemifields in the presence of distractors in the contralateral hemifield (bilateral stimulation). The biased competition model may be examined, as well as attentional control by testing if there is an ability to preferentially track in the left or the right visual field, compared with tracking ability in the whole screen. Preference of right or left visual fields would be indexed by comparing accuracy and eye-tracking data across the different conditions. The amount of time spent looking at different quadrants of the visual field was calculated with the percent dwell time, or percent total number of fixations and saccades in the particular area of interest (AOI) compared with other AOIs. In an eye-tracking study, patients with left neglect made fewer fixations and had shorter inspection time on the contralesional left side relative to normal subjects and to patients with hemianopia without

neglect (Behrmann et al., 1997). The neglect patients also had significantly more fixations and longer fixations on the right hemifield, ipsilateral to the lesion (Behrmann et al., 1997; Mapstone et al., 2003). Other studies demonstrated the presence of altitudinal neglect (Bender & Teuber, 1948; Ergun-Marterer et al., 2001). Therefore, we predicted that a parietal patient exhibiting unilateral neglect would likewise exhibit more fixations and longer fixations on the right side as well as the superior plane of the visual field compared to age-matched controls.

Based on the findings of Battelli et al., (2001), we predicted that the unilateral parietal patient would have more impairment than controls in the left hemifield of the visual field than the right hemifield in the whole field condition. This deficit in the left hemifield of the whole screen stimulation should be especially apparent in the unilateral left screen stimulation than unilateral right, but that unilateral right would still be attenuated (Posner et al., 1984; Eglin et al., 1989). In addition, as these previous studies have found that increases in the number of items to the right led to increased leftward neglect and visual attention is correspondingly impaired on the left (Kaplan et al., 1991), we hypothesized that impairment caused by the lesion would increase with greater processing load in the MOT task that was especially sensitive to side of allocation (left or right), and the presence of distractors on the contralateral side. Since visual extinction to motion in unilateral parietal patients is defined as the failure to attend to moving stimuli in the contralesional field only in the competing presence of moving distractors in the ipsilesional visual field, we predicted that the patient would have significantly impaired function in the bilateral stimulation condition compared with age-matched controls. Therefore, in instances where two or more moving stimuli must compete for attention, patients with parietal lesions exhibiting extinction in the left visual hemifield seem to be impaired in top-down attention to high-level motion perception.

Participants

In this case study, the recruited control group participants were age-matched to the patient (age range = 60–70, and excluded in the event of any history of brain artifacts, trauma, or stroke). All participants were informed of and instructed about the features of the task, types of stimuli, and experimental procedures, and received 100 NOK per hour as compensation for their sessions. All read and signed a consent form and were given the opportunity to withdraw at any point after participation, in compliance with the Helsinki Declaration. Each MOT session lasted

between 2-3 hours, and consisted of tracking different attentional loads on a computer in the Cognitive Laboratories at the Psychology Institute.

The Control Group

The control group consisted of 12 healthy persons (mean = 64.786, SD = 2.155), with no history of stroke. Eight of the 12 had similar education backgrounds as the patient. Two were excluded due to incidence of stroke or presence of brain artifact in the MR scanner. Therefore, ten controls were used for eye-tracking, pupillometry, and accuracy analyses.

The Patient

LE is a 64 year-old right-handed male, diagnosed with hemispatial neglect with some left hemianopia, i.e. reduced vision in the left visual field of the left eye, after a experiencing a right middle cerebral arterial infarction in June of 2007. He was admitted to Sunnaas Rehabilitation Hospital (Oslo, Norway) on October 30, 2007 to January 2, 2008, and referred to a visual specialist from KRESS/Drøbak, thereafter in January 7-29, 2008, as well as on April 8-10, 2008, to map his visual functioning. LE described his own experience of visual function to his physician as having, “difficulty with perception of things on the left side. Small details that are fixated on can disappear and then be there again....”

The visual specialist found he had good ability to fixate, track an object with his eyes as it moved in the vertical and horizontal directions, was able to inwardly rotate the eyes from a close fixation point (convergence), and had preserved ability to see contrast.

The visual field is the part of the environment that can be perceived without eye movement, and the extreme boundaries of the visual field may be systematically measured via Computerized Goldman perimetry. Visual perimetry measures the ability of a patient to detect the presence of test targets on a defined background. When presented with rapid flashes of light in the right visual field, LE’s eyes showed reduced sensitivity in the lower nasal quadrant that extends slightly into the peripheral part of the upper quadrant, which is consistent with the location of cortical damage (Fig. 4-5). In April 2008, accurate perimeter measurement showed a weak expansion of the right and left visual fields, so that the left-sided outcome now almost limited to the downward left quadrant (Fig. 4).

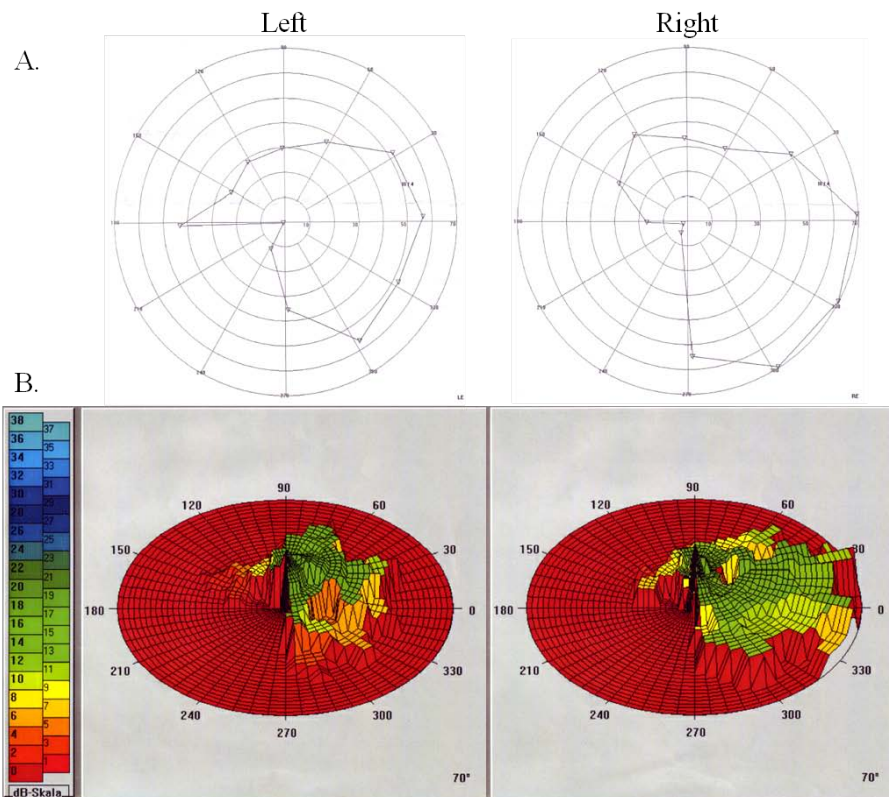
Fine eye movements of fixations, saccades and tracking were measured in January 2008 via reading short coherent texts, in which short fixations were targeted, and movements and fixations

were measured independent of text and letters. LE was found to have unstructured movements and fixations, in addition to short duration of fixations. LE required ample time to perform said tasks. After training, LE has become faster and steadier. However, during the April session, LE still displayed a tendency to start observation and remain overly focused on the right side, before he moved his attention to explore the left side.

In terms of orientation in space, LE located the center point of the room when it was straight ahead during the January 2008 testing. He did not show difficulty in crossing the center line of a 70 cm long line of letters approximately 1 meter distance away. Similarly, he did not have difficulty recognizing the letters on the line, with the exception of the first letter on the left of the starting line. However, he focused on one item at a time and had difficulty seeing wholes and similarities, and needed ample time as well as thorough verbal instructions. During the April 2008 testing session, LE did not have problems finding the indicated stimuli and was oriented, but still needed an abnormally long inspection time to complete tasks.

Figure 4.
Characterizing LE's
visual field using the
Computerized
Goldman perimetry.

A. April 10, 2008, KRESS/Drobak. LE exhibited a homonymous lower left quadrant hemianopia. The limitations in the upper quadrants may be explained by the presence of prominent brow bones. **B.** Mapping 360 deg of the left (9:12 min) and right (10:33 min) eyes on a dB scale.



By May 2011, LE performed successfully on two standard neglect tests (bisect a single line 19 cm in length, and the Weintraub & Mesulam (1987) star cancellation task), demonstrating remediation of neglect.

Magnetic resonance imaging (MRI) of the head showed extensive ischemic lesions in the right posterior parietal, occipital and temporal regions of the right cerebrum, including the intraparietal sulcus (Ips), superior and inferior parietal lobules (SPL and IPL), angular (ang) and supramarginal (smg) gyri of the IPL, the middle and superior temporal gyri, as well as a part of the middle occipital gyrus (part of V5, MT/MST) (Fig. 5; see also Fig. 3). According to the atlas of Talairach and Tournoux, the right middle cerebral arterial lesion involved parts of BA 7,19,21, 22, 37,39, 40 and 41.

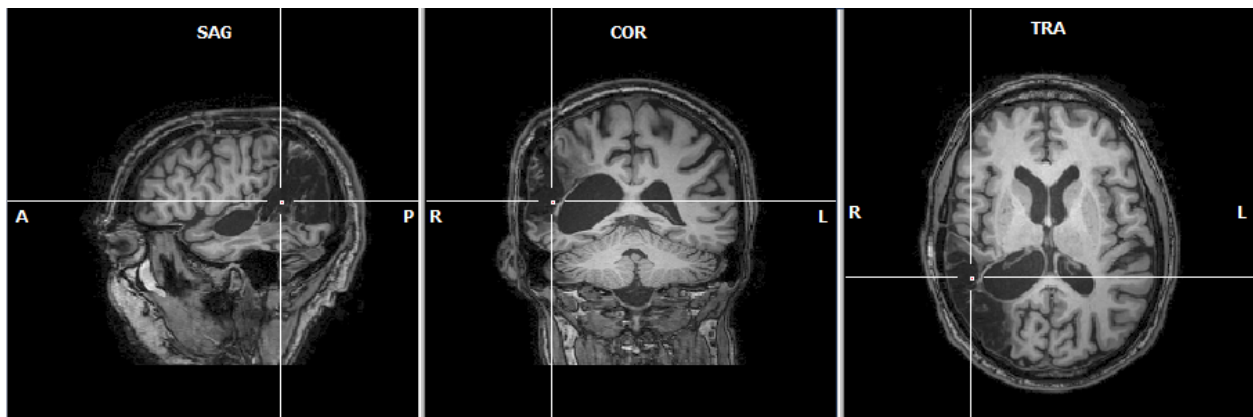


Figure 5. MRI of LE. T1-weighted 3D Turbo gradient echo sequence with SENSE, scanned on October 31, 2010. Crosshairs located on the temporoparietal junction (TPJ), Talairach coordinates (48-40, 9).

Methods

Multiple Object Tracking: Stimuli and Apparatus

Remote Eye-Tracking Device

Horizontal and vertical coordinates as well as pupillary diameter of each participant's left eye were registered using Remote Eye-Tracking Device (RED), and iView software (SensoMotoric Instruments [SMI], Teltow, Germany). The eye-tracker operated with an infrared-light-sensitive video camera, with a 2-ms sample rate and resolution less than 0.1 degree, capable of determining gaze by calculating the center between the position of the pupil and the reflection of the cornea. Eye-tracking data was recorded in .idf format, and thereafter converted to text files (txt), and accuracy data was saved in an excel spreadsheet (.xls). The illumination of the testing room was kept constant during each testing session, and the eye-tracker was calibrated between sessions. Distance from the monitor to the head was 900 mm. First fixations were excluded from analyses.

Procedure

As illustrated in Figure 6, each trial began with the appearance of a centrally presented, white 0.2° diameter fixation point (Hue 0.0, Saturation 0.0 and Lightness 1.0), on a gray whole field (Hue 0.7, Saturation 0.0 and Lightness 0.5) surrounded by a black frame (Hue 0.0, Saturation 0.0 and Lightness 0.0), or on the black background frame between two gray split screen fields, displayed on a 21" EIZO CRT monitor using the MatLab psychophysics toolbox extensions, version 3 (MathWorks, Natick, MA), with a screen resolution of 1280 x 960 pixels (Brainard, 1997). Due to hemianopia in LE, participants were not required to fixate on a point in the center of the screen. After 1 second, one or eight identical blue 0.7° diameter non-overlapping discs (Hue 0.7 Saturation 1.0 Lightness 0.5) were then presented, and a subset of one to four turned red (Hue 1.0 Saturation 1.0 Lightness 0.5) for 2.5 seconds before returning to the original blue to indicate their status as targets, after which the objects are indistinguishable from those objects that did not flash, and are thereafter distractions from the task. Duration between onset of stimuli and target assignment was also 2.5 seconds. After another 1.0 second interval, the discs started moving randomly and unpredictably about the screen with a speed of 4.0° per second, constrained only so that they could not pass nearer than 1° to each other and could not move off the display. The duration of tracking was set to either 5 or 10 seconds, after which, the motion of all items stopped, and a disc with a probe validity of 50% would turn red. If the probe was a valid in the particular trial, then one of the targets of that trial would turn red. If the probe was invalid in the particular trial, then one of the distractors would turn red.

Participants then indicated whether the highlighted disc was one of the original targets, and the correct or incorrect feedback was given after a 1 second delay. The pace of the trials was controlled by the participant indicating their readiness and each trial was initiated with a mouse click. Each session lasted approximately 2-3 hours, with sessions occurring from October 2009 to February 2011.

Behavioral Paradigms

Three conditions (whole screen, unilateral and bilateral), sides of allocation (left and right sides, except in the whole screen condition), cognitive loads (target/distractor combinations of 1/7, 2/6, 3/5 and 4/4), and tracking times (5 seconds and 10 seconds) were tested during the trials, with accuracy, change in pupil size and dwell time as the dependent variables. The order of 'whole', 'unilateral', and 'bilateral' stimulations in each session were randomized.

In regard to task difficulty for the patient, and confounding factors such as practice and fatigue, target presentation was presented starting with 1 target increasing to 4 and then decreasing to 1 in a Latin-square design (ABBA), with alternating right and left sides of allocation. Display screen size, screen resolution, distance from monitor to the head, fixation point size and gray tracking fields presented on background frames were common to all conditions.

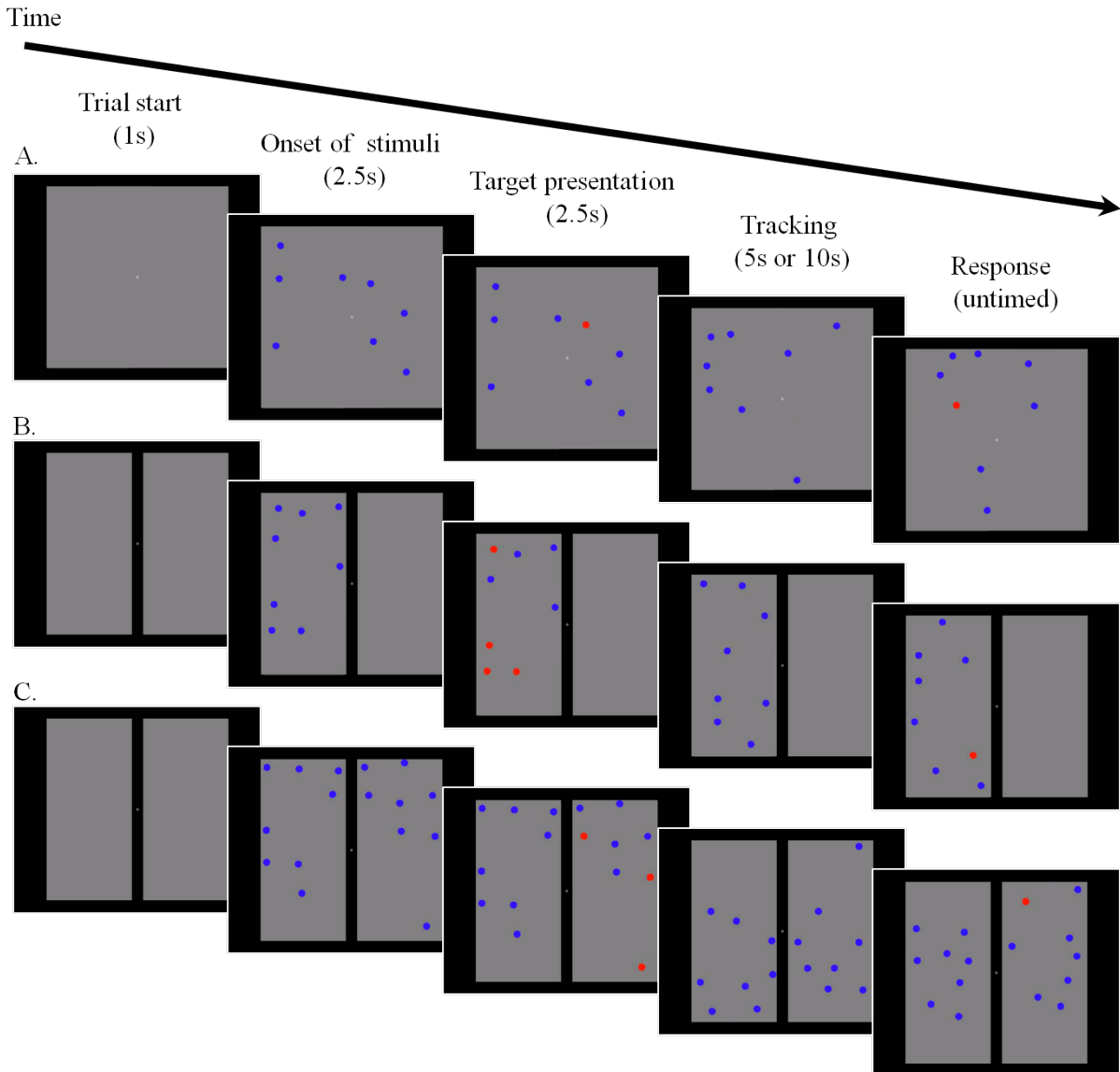


Figure 6. The multiple object tracking task procedure shown over the timeline. Trials began with an appearance of a fixation point on a gray background, followed by the onset of 8 identical discs (2.5s). The targets were assigned by flashing in red (2.5s), followed the discs started moving randomly and unpredictably for the allotted tracking time (5s or 10s). Participants then responded whether the highlighted disc was one of the original targets, and feedback was given. **A.** Whole Screen Stimulation. 1 target, 7 distractors **B.** Split-Screen Unilateral Stimulation: Left side of allocation, 4 targets and 4 distractors. **C.** Split-Screen Bilateral Stimulation: Right side of allocation, 3 targets, 5 distractors.

In the whole screen stimulation (Fig. 6A), targets and distractors were tracked on a gray field size 306.7 mm x 306.7 mm (868px x 868px) was presented centrally on the display screen, in which the fixation point was located in the center of the gray field. During the split screen paradigms (Fig. 6B-C), the fixation point was located central in the black frame equidistant between the left and right gray tracking fields. Each gray hemifield was 143.5 mm x 306.7 mm (406 px x 868 px), with 19.1 mm (54 px) distance between.

Accuracy, change in pupil diameter and dwell time (calculated by percent fixations and saccades) were measured as the dependent variables. Additionally, a training task (1 target/0 distractors) was evaluated for both tracking times.

Eye-tracking: Areas of Interest

Areas of interest were defined and dwell time (percent saccades and fixations) in each area of interest were analyzed using BeGaze software (SensoMotoric Instruments [SMI], Teltow, Germany). In order to quantify where the participants were attending, areas of interest (AOIs) were created for the whole screen and split-screen fields (Fig. 7). As we were not only interested in left versus right, or LE's ability to see superior versus inferior visual fields, but also whether he may be neglecting the upper and lower left quadrants of the respective left and right hemifields, eight areas of interest were created.



Figure 7. Attention vs. AOIs. Attention was defined as the percent dwell time (saccades and fixations) per area of interest (AOI). **A.** AOIs for the whole screen condition. Each AOI is 7.6% of the total area. **B.** AOIs for the Split-screen conditions, both unilateral and bilateral stimulation. Each AOI is 7.2% of the total area.

Therefore, left hemifield was divided into four quadrants; Bottom Left 01 (BL1), Bottom Left 02 (BL2), Top Left 01 (TL1), and Top Left 02 (TL2). The right hemifield was also divided four quadrants; Bottom Right 01 (BR1), Bottom Right 02 (BR2), Top Right 01 (TR1) and Top

Right 02 (TR2). Each AOI of the whole screen was 7.6%, and the split screen AOI was 7.2% of the total screen area.

Pupillometry: Data Pre-Processing

Pupil diameter in pixels was obtained using the eye-tracker at the same time as collecting horizontal and vertical coordinates of each participant's left eye, using RED and iView at 240Hz (see the section on Remote Eye-Tracking Device). For each sample, pupil diameter was calculated by averaging the horizontal and vertical coordinates of the left eye. The data sets were pre-processed so that, pupil diameter was translated to mm, the first and last 2s from all trials were excluded, nonstandard data as well as physiologically impossible data were removed, data was baseline corrected and converted to change in pupil diameter, data were downsampled, and trials were averaged (Fig. 8). Events were sorted according to conditions, and either patient or control population.

Raw trial data. The pupil diameter was translated from pixels (px) to millimeter (mm) data. Then, to eliminate the automatic pupillary constriction produced by the initial presentation of stimuli (Kohn & Clynes, 1969; Libby, et al., 1973; Steinhauer, et al., 1983), pupil data was analyzed for the time between 2s-5s in the 5-second tracking condition, and 2s-8s in the 10-second tracking interval. These precautions were used to control for the initial 200ms reaction time and to ensure actual tracking as well as any anticipatory response mechanisms during the late phase of tracking (Fig. 8A).

Exclude nonstandard data. Eye-blinks were filtered out on the basis of sudden drops in vertical pupil diameter. The criterion for detecting a drop was the ratio between the vertical and the horizontal pupil diameter. During a blink or semi-blink the ratio quickly drops toward 0, whereas a circular pupil has the ratio of approximately 1.0. Physiologically impossible data, such as pupil sizes outside the range of 2-7 mm, was then removed from the data set. After the removal of unacceptable pupil sizes, outlier sample points per event that were outside the range of ± 2.5 standard deviations from the mean were deleted as well as change in velocities outside the range of 0.702-3.204 mm/s. The filter size was set to 12; that is, when noise is detected, 12 points before and 12 points after the noisy value were removed together with the noisy value. Therefore, 25 points total, or approximately 100ms were removed per noisy value, and set to 'not a number' (NaN; Fig. 8B).

Baseline correction. Pupil size decreases linearly as a function of age at all luminance levels (Birren, et al., 1950; Winn, et al., 1994). Therefore, changes in pupil diameter were used to control for this variable rather than reporting absolute pupil size. A time window of 200 ms at 240hz (50 datapoints) was used to calculate changes in pupil diameter, and a baseline of 1200 periods (5s) of interest were used in calculating plots and averages. The onset position of the tracking period was first defined as the baseline period. Thereafter, the average of the baseline period was subtracted from the tracking period (Fig. 8C).

Average the horizontal and vertical pupil measurements. A single value for each timepoint was calculated by averaging the horizontal and vertical pupil values at that time point (Fig. 8D).

Trial inclusion/exclusion. Any trial that had more than 50% of the tracking period classified as artefacts was removed by setting the entire trial to NaN (Fig. 8E).

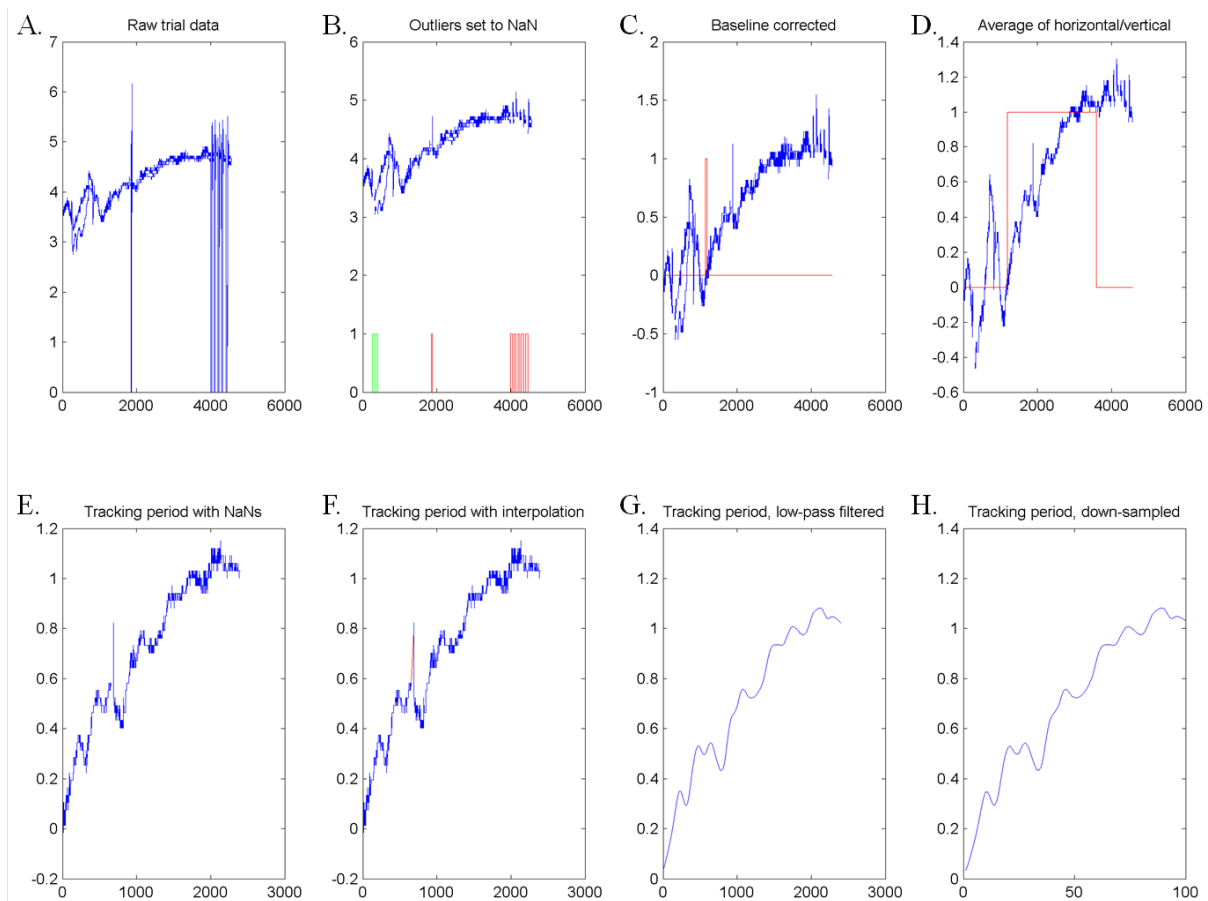


Figure 8. Pupilometry pre-processing. The pre-processing steps for the patient LE during a 10-second whole field condition, when tracking 4 targets among 4 distractors. **A.** Raw trial data. Time series between 2s-8s, after translating pupil diameter from px to mm. **B.** Exclude nonstandard data to not a number (NaN). **C.** Baseline correction. **D.** Average the horizontal and vertical pupil measurements. **E.** Remove trial from analysis if there are artefacts in more than 50% of tracking period. **F.** Interpolate between missing datapoints. (connecting line n red) **G.** Low-pass filter. **H.** Downsampling.

Interpolation. Missing datapoints were interpolated by connecting the nearest present datapoints, and marked in red (Fig. 8F).

Low-pass filter. The interpolated time series was smoothed via low-pass filter (Fig. 8G).

Downsampling. Dataset was reduced by using a downsampling factor of 24, leaving one point per 100ms (Fig. 8H).

Trial average calculation. After downsampling, a datapoint interval of 30:50 was used in the period of interest to calculate the trial average (mean time series) and standard errors across trials. Data was separated over different load levels (1-4 targets) and. Single subject and group graphs were generated.

Statistical Analysis

Comparison of an individual's test score against a small normative sample is a commonly used in the clinical neuropsychological assessments (Crawford & Howell, 1998). As this is a case study, we ran into the statistical problems commonly found in the clinical neuropsychology field of comparing a single individual to a small control group. There is no distribution for a single person, and therefore usual methods of analyses did not apply to this study. However, we compared LE to age-matched controls using the modified *t*-test designed by Crawford and Howell (1998).

$$S_2 = \sqrt{\frac{\sum_{i=1}^n (X_i - \bar{X})^2}{N - 1}}$$
$$t = \frac{X_1 - \bar{X}_2}{S_2 \sqrt{\frac{N_2 + 1}{N_2}}}$$

Figure 9. Comparing an individual's t-test to a small normative sample. The calculations involved in the modified *t*-test procedure, in which smaller normative samples required larger differences in order to reach significance. Note that this is not a *t*-test per se, but comparing a single datapoint against a single *t*-distribution. X_1 = patient value, \bar{X}_2 = control group mean, S_2 = standard deviation, N_2 = control sample size, and $df = N_2 - 1$. (Crawford & Howell, 1998)

The mean and standard deviation were used as if they were *parameters* rather than *sample statistics* so that the normative sample was treated as if it were a population. This calculation was used for comparing the patient accuracy, dwell time or pupil size against the control set accuracy, dwell time or pupil size within a particular condition. It is important to note that we are comparing a data point against a single *t*-distribution. Therefore, the issue of multiple comparisons does not apply as this formula is not a *t*-test in the strictest definition. The calculations involved in the modified *t*-test procedure, in which smaller normative samples required larger differences in order to reach significance (Fig.9). X_1 was defined as the patient

value (mean accuracy, pupil size or dwell time) for a particular condition, and is not a distribution or a mean but a single number devoid of variance or standard deviation. \bar{X}_2 was the control group mean derived from the average of the individual means in the control group, S_2 was the non-typical standard deviation, N_2 was defined as the control sample size, and df was the degrees of freedom of the control group ($N_2 - 1$).

We also used the control population confidence interval (CI) calculation in comparison with the patient to indicate the reliability of the estimate of Crawford's t-test. The CI calculated was using the typical standard deviation (σ), using a 95% confidence level ($0.95 = P(\bar{X}_2 - 1.96 \frac{\sigma}{\sqrt{N_2}} \leq \mu \leq \bar{X}_2 + 1.96 \frac{\sigma}{\sqrt{N_2}})$). Since we had several dependent variables, we used the multivariate ANOVA to answer if changes in the independent variables (5s or 10s tracking length x whole, unilateral or bilateral conditions x left or right sides of allocation x 1-4 loads) had significant effects on the dependent variables (accuracy, pupil size and dwell time). In addition, we also were interested in finding the interaction among the dependent variables, and interactions among the independent variables.

Results

The accuracy, dwell time and pupillometry results (means \pm SE) for the whole screen, split-screen unilateral and bilateral conditions will be discussed below, followed by a within-subject regression analysis of mean pupil diameter change with respect to accuracy, and attentional load. If the control group confidence intervals for the accuracy and dwell time data exceeded the range of 0%-100%, then the values were set at 0% and 100% correspondingly.

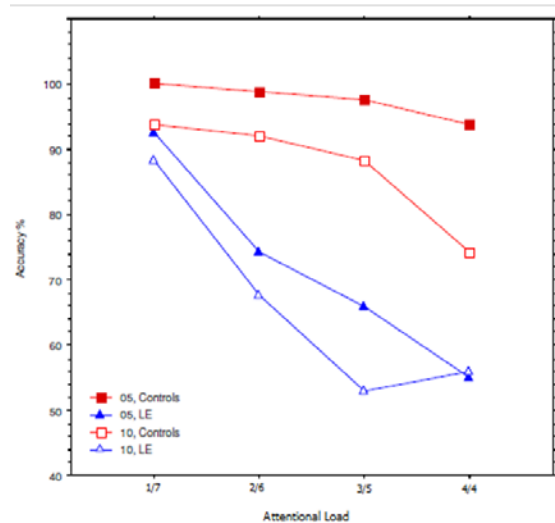


Figure 10. Whole screen: Accuracy (%) as a function of Attentional Load. Graphical representation of Table 1. Target/distractor combinations of 1/7, 2/6, 3/5, 4/4. Controls (red), LE (blue) graphed for 5 second (filled) and 10 second (unfilled) tracking periods.

Condition 1: Whole Screen Stimulation

Accuracy. In the 5-second tracking sessions for the whole screen condition, patient differed significantly from the control group mean in accuracy for all of the different cognitive

loads (Table 1, Fig. 10 filled). However, in the whole screen 10-second tracking time, LE's accuracy was significantly different from control group when tracking 3 targets.

Table 1. Accuracy (means ± SEs) for Whole Field condition

Tracking	Load	Control Group	Control 95% CI	Patient	p-value ^a
5 s	1/7	100% ± 0	0	92.5%	p<0.05
	2/6	98.75% ± 1.250	91.00% – 100%	74.17%	p<0.001
	3/5	97.50% ± 2.500	82.01% – 100%	65.83%	p<0.01
	4/4	93.75% ± 3.359	72.93% – 100%	55%	p<0.01
10 s	1/7	93.75% ± 5.017	62.65% – 100%	88.24%	p<0.05
	2/6	92.083% ± 5.063	60.70% – 100%	67.65%	
	3/5	88.33% ± 5.114	56.63% – 100%	52.941%	
	4/4	74.167% ± 7.949	24.90% – 100%	55.88%	

^a Comparing the patient to the control group (Crawford and Howell, 1998)

Pupillary changes. When measuring changes in pupil diameter for the whole screen both the 5-second and 10-second tracking period, LE showed no significant differences from the control group for any of the attentional load levels due to large variations in the control group, thus resulting in large confidence interval

Table 2. Changes Pupil diameter (means ± SEs) for Whole Field condition

Tracking	Load	Control Group	Control 95% CI	Patient	p-value ^a
5 s	1/7	-0.003 mm ± 0.028	-0.179 mm – 0.172 mm	-0.099 mm	
	2/6	0.154 mm ± 0.044	-0.119 mm – 0.427 mm	0.174 mm	
	3/5	0.286 mm ± 0.054	-0.050 mm – 0.621 mm	0.162 mm	
	4/4	0.239 mm ± 0.043	-0.025 mm – 0.503 mm	0.210 mm	
10 s	1/7	0.041 mm ± 0.044	-0.235 mm – 0.316 mm	-0.058 mm	
	2/6	0.165 mm ± 0.051	-0.149 mm – 0.478 mm	0.200 mm	
	3/5	0.243 mm ± 0.058	-0.114 mm – 0.600 mm	0.175 mm	
	4/4	0.196 mm ± 0.060	-0.175 mm – 0.566 mm	0.130 mm	

^a Comparing the patient to the control group (Crawford and Howell, 1998)

Table 3. Percent Dwell time (means ± SEs) for whole screen tracking

Tracking	Load	AOI	Control Group	Control 95% CI	Patient	p-value ^a
10s	2/6	TL1	5.32% ± 1.355	0% – 13.72%	17.47%	p<0.05
		TL2	9.65% ± 1.263	1.82% – 17.48%	19.33%	p<0.05
	4/4	TL1	4.31% ± 0.981	0% – 10.39%	10.51%	p<0.05

^a Comparing the patient to the control group (Crawford and Howell, 1998)

Dwell Time in AOI. For the whole field condition, there were no percent dwell time differences between LE and the control population in any AOI for any of the attentional loads, during the 5-second tracking periods. However, LE significantly differed from the control group dwell time for TL1 and TL2 when tracking 2 targets, and for TL1 when tracking 4 targets during the 10-second tracking (Table 3).

Condition 2: Split-Screen, Unilateral stimulation

LE differed significantly from the control group in percent mean accuracy for the condition defined by unilateral tracking within the right side (controls = 92.81% ± 3.169, 95% CI 73.17% –112.45, LE = 69.47%), but not for the left side of allocation (controls = 92.81% ± 3.187, 95% CI 73.06 –112.56, LE = 74.01%). More specifically, in the 5-sec tracking of the unilateral condition, in which the left side of the screen was stimulated, mean accuracy of LE was significantly different from the control group in percent accuracy for attentional loads of 2 and 3 targets (Table 3, Fig. 11A filled). When allocating attention to the left side of the 10-second tracking, LE was significantly different from the control group in percent accuracy for attentional loads 1-3, but not for tracking 4 targets (Table 4, Fig. 11A unfilled).

Results of the 5-second tracking of the right side of the unilateral condition revealed that LE was significantly different from the control group accuracy for 1-2 targets, but not for 3-4 targets (Table 5, Fig. 11B filled). LE was significantly different from control group in mean accuracy for the right-sided 10-second unilateral condition when tracking 1-3 targets (Table 5, Fig. 11B unfilled) however there was no difference when tracking 4 targets, especially considering the control group performance decreases dramatically with increasing load.

Table 4. Accuracy (means ± SEs) for unilateral field, left side of stimulation

Tracking	Load	Control Group	Control 95% CI	Patient	p-value ^a
5 s	1/7	100% ± 0	0	100%	
	2/6	97.5% ± 2.500	82.01% – 100%	67.24%	p<0.05
	3/5	97.5% ± 2.500	82.01% – 100%	59.32%	p<0.001
	4/4	75% ± 10.541	9.67% – 100%	66.67%	
10 s	1/7	100% ± 0	0	93.10%	p<0.05
	2/6	100% ± 0	0	89.29%	p<0.05
	3/5	97.5% ± 2.500	82.01% – 100%	46.43%	p<0.0001
	4/4	75% ± 7.454	28.80% – 100%	70%	

^a Comparing the patient to the control group (Crawford and Howell, 1998)

Table 5. Accuracy (means ± SEs) for unilateral field, right side of stimulation

Tracking	Load	Control Group	Control 95% CI	Patient	p-value ^a
5 s	1/7	100% ± 0	0	95.08%	p<0.05
	2/6	100% ± 0	0	73.77%	p<0.05
	3/5	90% ± 5.528	55.74% – 100%	58.07%	
	4/4	87.5% ± 6.719	45.86% – 100%	66.67%	
10 s	1/7	100% ± 0	0	79.31%	p<0.05
	2/6	97.5% ± 2.500	82.01% – 100%	64.29%	p<0.01
	3/5	92.5% ± 5.336	59.43% – 100%	53.57%	p<0.05
	4/4	75% ± 5.270	42.33% – 100%	65%	

^a Comparing the patient to the control group (Crawford and Howell, 1998)

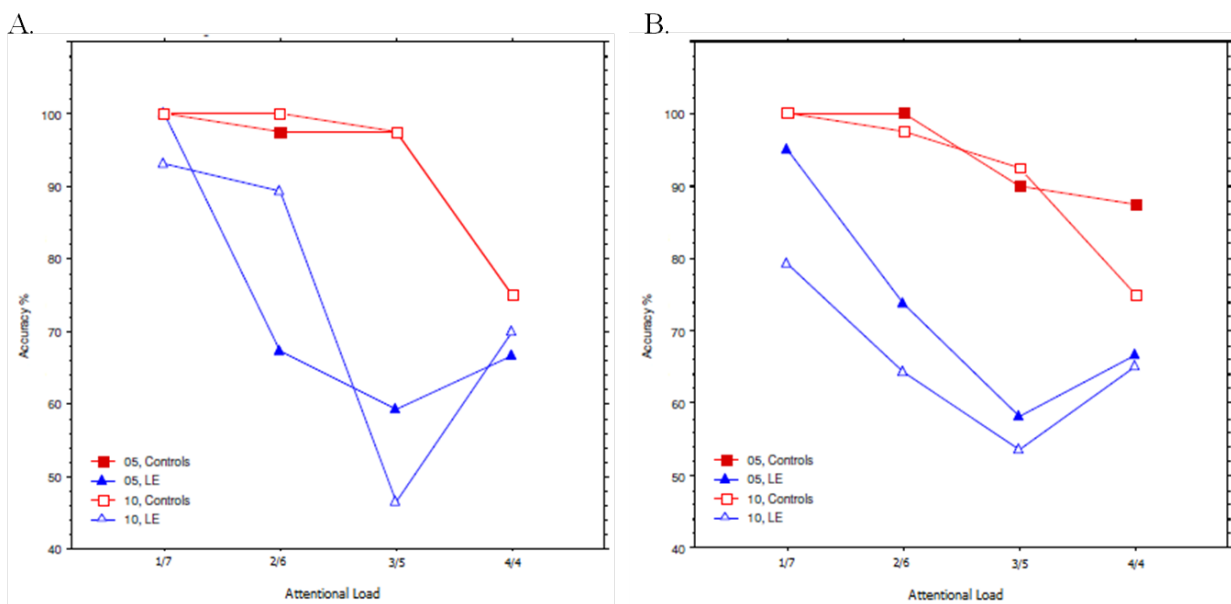


Figure 11. Split-screen: Unilateral Stimulation. Accuracy (%) as a function of Attentional Load (target/distractor combinations of 1/7, 2/6, 3/5, 4/4). Controls (red), LE (blue) graphed for 5 second (filled) and 10 second (unfilled) tracking periods. **A. Left side of stimulation** Graphical representation of Table 4. **B. Right side of stimulation.** Graphical representation of Table 5.

Table 6. Changes Pupil diameter (means ± SEs) for Unilateral condition, Left side of stimulation

Tracking	Load	Control Group	Control 95% CI	Patient	p-value ^a
5 s	1/7	0.052 mm ± 0.055	-0.290 mm – 0.395 mm	-0.079 mm	
	2/6	0.249 mm ± 0.037	0.022 mm – 0.476 mm	0.325 mm	
	3/5	0.268 mm ± 0.056	-0.082 mm – 0.618 mm	0.297 mm	
	4/4	0.295 mm ± 0.049	-0.009 mm – 0.598 mm	0.254 mm	
10 s	1/7	0.014 mm ± 0.039	-0.225 mm – 0.254 mm	-0.100 mm	
	2/6	0.103 mm ± 0.039	-0.137 mm – 0.344 mm	-0.057 mm	
	3/5	0.212 mm ± 0.045	-0.070 mm – 0.493 mm	0.072 mm	
	4/4	0.268 mm ± 0.049	-0.033 mm – 0.569 mm	0.147 mm	

^a Comparing the patient to the control group (Crawford and Howell, 1998)

Pupillary response. LE was not significantly different in mean changes of pupil diameter in any of the tracking periods, attentional loads or sides of stimulation, due to large confidence intervals in the control population (Table 6-7).

Table 7. Changes Pupil diameter (means ± SEs) for Unilateral condition, Right side of stimulation

Tracking	Load	Control Group	Control 95% CI	Patient	p-value ^a
5 s	1/7	0.001 mm ± 0.051	-0.317 mm – 0.320 mm	-0.043 mm	
	2/6	0.203 mm ± 0.040	-0.046 mm – 0.452 mm	0.207 mm	
	3/5	0.261 mm ± 0.051	-0.055 mm – 0.578 mm	0.250 mm	
	4/4	0.216 mm ± 0.048	-0.082 mm – 0.513 mm	0.140 mm	
10 s	1/7	0.019 mm ± 0.044	-0.252 mm – 0.289 mm	-0.083 mm	
	2/6	0.182 mm ± 0.036	-0.039 mm – 0.403 mm	0.206 mm	
	3/5	0.230 mm ± 0.047	-0.060 mm – 0.521 mm	0.127 mm	
	4/4	0.269 mm ± 0.046	-0.016 mm – 0.554 mm	0.194 mm	

^a Comparing the patient to the control group (Crawford and Howell, 1998)

Table 8. Percent dwell time (means ± SEs) for unilateral field, left side of stimulation

Tracking	Load	AOI	Control Group	Control 95% CI	Patient	p-value ^a
5s	2/6	TL1	4.47% ± 1.607	0% – 14.43%	14.54%	p<0.05
		TR2	0.00% ± 0	0	0.05%	p<0.05
	4/4	TL2	24.47% ± 2.874	0% – 29.53%	37.47%	p<0.001
		TR2	0.00% ± 0	0	1.81%	p<0.05
10s	1/7	TR1	0.00% ± 0	0	0.14%	p<0.05
	3/5	TL1	25.03% ± 4.611	0% – 53.61%	56.27%	p<0.05
		TR1	0.00% ± 0	0	3.42%	p<0.05

^a Comparing the patient to the control group (Crawford and Howell, 1998)

Dwell Time in AOI. There were no percent dwell time differences between LE and the control group for any of the AOIs when tracking 1 or 3 targets on the left side for 5 seconds. LE differed significantly from the control group dwell time confidence intervals in the 5- second unilateral left stimulation in TL1 and TR1 when tracking 2 targets and TL2 and TR2, when tracking 4 targets compared with the control group (Table 8). In the unilateral 10-second condition when tracking left, LE showed small but significant differences in TR1 when tracking 1 or 3 targets, and significantly different from the control group in percent dwell time for TL1 when tracking 3 targets.

In the unilateral 5-second track right condition, LE showed small but significant differences in percent dwell time for BL1 and TL1 when tracking 1 target, for TL2 when tracking 2 targets,

in BL2, TL1 and TL2 when tracking 3 targets, in BL2 and TL1, when tracking 4 targets compared with the control group. During the 10-second tracking interval, LE demonstrated small but significant differences for percent dwell time in TL2 when tracking 1 target, TL1 when tracking 2 targets, and BL1 and TL2 when tracking 3 targets when compared with controls (Table 9). None of the other attentional loads or AOIs was significant between LE and the control group.

Table 9. Percent dwell time (means \pm SEs) for unilateral field, right side of stimulation

Tracking	Load	AOI	Control Group	Control 95% CI	Patient	p-value ^a	
5s	1/7	BL1	0.00% \pm 0	0	0.09%	p<0.05	
		TL1	0.00% \pm 0	0	0.06%	p<0.05	
	2/6	TL2	0.00% \pm 0	0	0.08%	p<0.05	
		3/5	BL2	0.00% \pm 0	0	0.19%	p<0.05
			TL1	0.00% \pm 0	0	0.10%	p<0.05
	4/4	TL2	0.00% \pm 0	0	0.12%	p<0.05	
		BL2	0.12% \pm 0.115	0% – 0.83%	1.03%	p<0.05	
		TL1	0.00% \pm 0	0	0.12%	p<0.05	
	10s	1/7	TL2	0.00% \pm 0	0	0.63%	p<0.05
TL1			0.00% \pm 0	0	3.76%	p<0.05	
3/5		BL1	0.00% \pm 0	0	0.28%	p<0.05	
		TL2	0.00% \pm 0	0	0.36%	p<0.05	

^a Comparing the patient to the control group (Crawford and Howell, 1998)

Condition 3: Split-Screen, Bilateral stimulation

Accuracy. LE did not differ significantly from the control group in percent accuracy in the case of left side of allocation (controls = 88.23% \pm 4.269, 95% CI 61.77 – 114.69, LE = 77.40%), but did differ from the control group in percent accuracy for the right tracking condition (controls = 92.56% \pm 2.923, 95% CI 74.45 – 110.68, LE = 66.61%). When tracking on the left side of the bilateral condition for 5 seconds, LE was significantly different in percent accuracy from the controls for the attentional loads of 1-2, but not for 3- 4 targets (Table 10, Fig. 12 filled) . In the 10-second bilateral stimulation condition, in which participants tracked the left side, LE differed significantly from the control group accuracy confidence interval for 1 target (Table 10, Fig. 12 unfilled). None of the other attentional loads (targets 2-4) were significantly different between LE and the control group.

Table 10. Accuracy (means ± SEs) for bilateral field, left side of stimulation

Tracking	Load	Control Group	Control 95% CI	Patient	p-value ^a
5 s	1/7	100% ± 0	0	98.28%	p<0.05
	2/6	100% ± 0	0	74.58%	p<0.05
	3/5	97.5% ± 2.500	82.01% – 100%	84.75%	
	4/4	95% ± 5.000	64.01% – 100%	75.86%	
10 s	1/7	100% ± 0	0	92.86%	p<0.05
	2/6	87.5% ± 6.719	45.86% – 100%	82.76%	
	3/5	70.83% ± 7.683	23.21% – 100%	75.00%	
	4/4	55.00% ± 12.247	0% – 100%	50.00%	

^a Comparing the patient to the control group (Crawford and Howell, 1998)

Table 11. Accuracy (means ± SEs) for bilateral field, right side of stimulation

Tracking	Load	Control Group	Control 95% CI	Patient	p-value ^a
5 s	1/7	100% ± 0	0	100%	
	2/6	100% ± 0	0	77.05%	p<0.05
	3/5	95% ± 3.333	74.34% – 100%	75%	
	4/4	88% ± 5.487	53.99% – 100%	64.52%	
10 s	1/7	100% ± 0	0	82.76%	p<0.05
	2/6	100% ± 0	0	60.714%	p<0.05
	3/5	85% ± 7.638	37.66% – 100%	42.86%	
	4/4	72.5% ± 6.922	29.60% – 100%	50%	

^a Comparing the patient to the control group (Crawford and Howell, 1998)

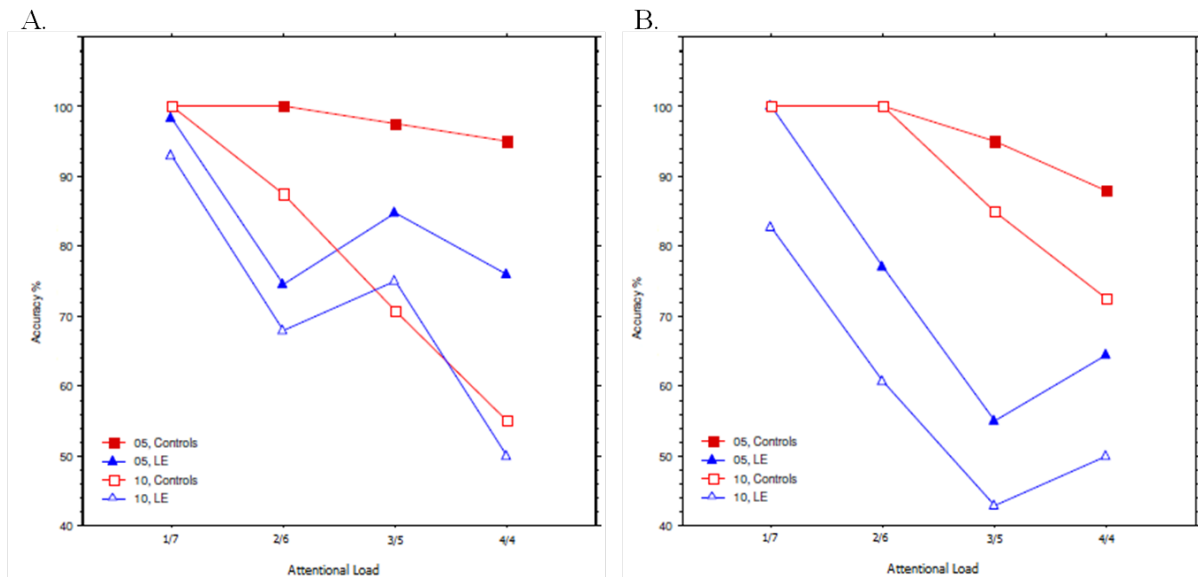


Figure 12. Split-screen: Bilateral Stimulation. Accuracy (%) as a function of Attentional Load (target/distractor combinations of 1/7, 2/6, 3/5, 4/4). Controls (red), LE (blue) graphed for 5 second (filled) and 10 second (unfilled) tracking periods. **A. Left side of stimulation.** Graphical representation of Table 8. Controls exhibit an extinction-like symptom when presented with distractors on the right hemifield for 10-second tracking. **B. Right side of stimulation.** Graphical representation of Table 9.

Right-sided tracking in the bilateral 5-second condition, showed that LE was significantly different from the control group in percent accuracy for 2 targets (Table 11, Fig. 12 filled). When tracking on the right side of the 10-second bilateral condition, LE was significantly different in percent accuracy for 1-2 targets (Table 11, Fig. 12 unfilled).

Pupillary change. There were no differences for mean change in pupil diameter across tracking times, conditions or attentional loads between LE and the control population when comparing left (controls = 0.205 mm ± 0.026, 95% CI 0.00 – 0.668, LE = 0.166) versus right (controls = 0.167 mm ± 0.023, 95% CI 0.00 – 0.547, LE = 0.164) sides of stimulation (Table 12-13).

Table 12. Changes Pupil diameter (means ± SEs) for Bilateral condition, Left side of stimulation

Tracking	Load	Control Group	Control 95% CI	Patient	p-value ^a
5 s	1/7	0.012 mm ± 0.054	-0.325 mm – 0.349 mm	-0.062 mm	
	2/6	0.197 mm ± 0.074	-0.262 mm – 0.656 mm	0.208 mm	
	3/5	0.280 mm ± 0.061	-0.100 mm – 0.659 mm	0.286 mm	
	4/4	0.319 mm ± 0.083	-0.197 mm – 0.835 mm	0.212 mm	
10 s	1/7	0.030 mm ± 0.059	-0.338 mm – 0.398 mm	-0.043 mm	
	2/6	0.294 mm ± 0.079	-0.198 mm – 0.785 mm	0.271 mm	
	3/5	0.304 mm ± 0.067	-0.109 mm – 0.717 mm	0.143 mm	
	4/4	0.207 mm ± 0.062	-0.178 mm – 0.592 mm	0.311 mm	

^a Comparing the patient to the control group (Crawford and Howell, 1998)

Table 13. Changes Pupil diameter (means ± SEs) for Bilateral condition, Right side of stimulation

Tracking	Load	Control Group	Control 95% CI	Patient	p-value ^a
5 s	1/7	0.028 mm ± 0.032	-0.169 mm – 0.224 mm	0.019 mm	
	2/6	0.194 mm ± 0.072	-0.251 mm – 0.639 mm	0.259 mm	
	3/5	0.265 mm ± 0.057	-0.087 mm – 0.617 mm	0.250 mm	
	4/4	0.235 mm ± 0.069	-0.190 mm – 0.659 mm	0.213 mm	
10 s	1/7	0.014 mm ± 0.048	-0.287 mm – 0.314 mm	-0.025 mm	
	2/6	0.203 mm ± 0.047	-0.092 mm – 0.497 mm	0.290 mm	
	3/5	0.232 mm ± 0.053	-0.095 mm – 0.560 mm	0.142 mm	
	4/4	0.231 mm ± 0.056	-0.115 mm – 0.577 mm	0.168 mm	

^a Comparing the patient to the control group (Crawford and Howell, 1998)

Dwell Time in AOI. Likewise, there were no differences in percent dwell times between LE and the control group when tracking on the left or the right side for any of the eight AOIs. However, in the 5-seconds bilateral left tracking condition, LE's % dwell time significantly differed from the control group for BL1, BR1 and BR2 when tracking 1 target, for TL1, BR1,

when tracking 2 targets, for TL1 and TR1 when tracking 3 targets, and for BR1 and TL2 when tracking 4 targets (Table 14). None of the other attentional loads or AOIs was significant when comparing LE to the control group for the 5-second bilateral left side of stimulation.

There were no differences in 5-sec bilateral right in any of the AOIs when tracking 1 target. However, there were significant differences when tracking on the right side of the bilateral stimulation condition for BL1, BL2, TL1 and TR2 for 2 targets, in TL1, TL2 and TR1 for 3 targets, and when tracking on the right for 4 targets in BL1 and TL2 (Table 15).

Table 14. Percent dwell time (means ± SEs) for bilateral field, left side of stimulation

Tracking	Load	AOI	Control Group	Control 95% CI	Patient	p-value ^a
5s	1/7	BL1	0.25% ± 0.248	0% – 1.78%	1.97%	p<0.05
		BR1	0.00% ± 0	0	0.45%	p<0.05
		BR2	0.00% ± 0	0	0.03%	p<0.05
	2/6	TL1	3.93% ± 1.629	0% – 14.02%	16.03%	p<0.001
		BR1	0.00% ± 0	0	0.47%	p<0.05
	3/5	TL1	1.61% ± 0.614	0% – 5.41%	17.88%	p<0.001
		TR1	0.00% ± 0	0	0.05%	p<0.05
	4/4	BR1	0.00% ± 0	0	0.18%	p<0.001
TL2		10.21% ± 2.573	0% – 26.15%	27.31%	p<0.05	
10s	1/7	BL2	35.94% ± 3.372	29.33% – 42.56%	28.33%	p<0.05
		BR1	0.00% ± 0	0	0.38%	p<0.05
		TR1	0.00% ± 0	0	0.76%	p<0.05
	2/6	BR1	0.00% ± 0	0	0.13%	p<0.05
	3/5	TR1	0.00% ± 0	0	0.13%	p<0.05

^a Comparing the patient to the control group (Crawford and Howell, 1998)

Table 15. Percent dwell time (means ± SEs) for bilateral field, right side of stimulation

Tracking	Load	AOI	Control Group	Control 95% CI	Patient	p-value ^a
5s	2/6	BL1	0.00% ± 0	0	0.08%	p<0.05
		BL2	0.00% ± 0	0	0.19%	p<0.05
		TL1	0.00% ± 0	0	0.19%	p<0.05
		TR2	16.85% ± 3.412	0% – 37.99%	43.95%	p<0.05
	3/5	TL1	0.00% ± 0	0	0.03%	p<0.05
		TL2	0.00% ± 0	0	0.08%	p<0.05
		TR1	19.87% ± 4.161	0 – 45.66%	50.54%	p<0.05
	4/4	BL1	0.00% ± 0	0	0.13%	p<0.05
		TL2	0.00% ± 0	0	0.09%	p<0.05
10s	1/7	BL1	0.00% ± 0	0	0.66%	p<0.05
		BL2	0.05% ± 0.158	0% – 0.26%	2.83%	p<0.05

Table 15. Percent dwell time (means \pm SEs) for bilateral field, right side of stimulation

10s	1/7	TL1	0.00% \pm 0	0	0.09%	p<0.05
		TL2	0.00% \pm 0	0	2.62%	p<0.05
	2/6	BL1	0.00% \pm 0	0	0.08%	p<0.05
		BL2	0.02% \pm 0.023	0% – 0.16%	1.11%	p<0.05
		TL1	0.00% \pm 0	0	0.42%	p<0.05
		TL2	0.00% \pm 0	0	0.51%	p<0.05
	3/5	BL1	0.00% \pm 0	0	0.16%	p<0.05
		TL1	0.00% \pm 0	0	0.33%	p<0.05
		TL2	1.43% \pm 0.809	0% – 0.76	1.43%	p<0.05
	4/4	BL2	0.00% \pm 0	0	1.51%	p<0.05
		TL2	0.00% \pm 0	0	0.67%	p<0.05

^a Comparing the patient to the control group (Crawford and Howell, 1998)

Regression Analyses

Controls

There was a significant correlation between accuracy and pupil diameter ($F(1,38) = 10.855$, $p=0.0021$). According to regression analyses, 22.2% of the variance in the change of pupil diameter change was explained by accuracy ($Y=0.586, 0.443*X, R^2 =0.222$) (Fig 15A, red). There was also significant correlation between changes in pupil diameter and attentional load (target/distractor combinations of 1/7, 2/6, 3/5, and 4/4).

The control group showed increases in pupil size as a function of time and cognitive load. Results were highly significant ($F(1,38) = 78.710$, $p<0.0001$), and 67.4% of the variance in the change of pupil diameter change is explained by increasing attentional load ($Y= -0.006, 0.074*X, R^2 =0.674$) (Fig 15B, red). When using a repeated measures ANOVA to compare all factors, there was no effect of attention to the left or right hemifields in terms of percent accuracy (Left Mean= 90.519 ± 3.473 ; Right Mean= 92.688 ± 2.272 , Fisher's PLSD $p=0.6051$), nor in pupil diameter change (Left Mean= $0.194\text{mm} \pm 0.128$; Right Mean= $0.174\text{mm} \pm 0.24$, Fisher's PLSD $p=0.5945$) between the controls.

Patient LE

There was a significant correlation between pupil diameter and accuracy ($F(1,38) = 31.069$, $p<0.0001$). According to regression analyses, 45% of the variance in the change of pupil diameter change was explained by accuracy ($Y=0.533, -0.559*X, R^2 =0.45$; Fig 15A, blue).

There was also a significant correlation between pupil diameter and attentional load. Results were highly significant ($SS=0.280$, $F(1,38) = 26.297$, $p<0.0001$), and 40.9% of the variance in the change of pupil diameter change is explained by increasing attentional load ($Y = -0.052$, $0.075 * X$, $R^2 = 0.409$) (Fig 15B, blue). When using a repeated measures ANOVA to compare all factors, LE also did not show an effect of attention to the left or right hemifields in terms of percent accuracy (Left Mean 73.475 ± 3.249 , Fisher's PLSD $p=0.2961$), nor in pupil diameter change (Left Mean $=0.128\text{mm} \pm 0.129$; Right Mean $=0.145\text{mm} \pm 0.129$, Fisher's PLSD $p=0.7075$).

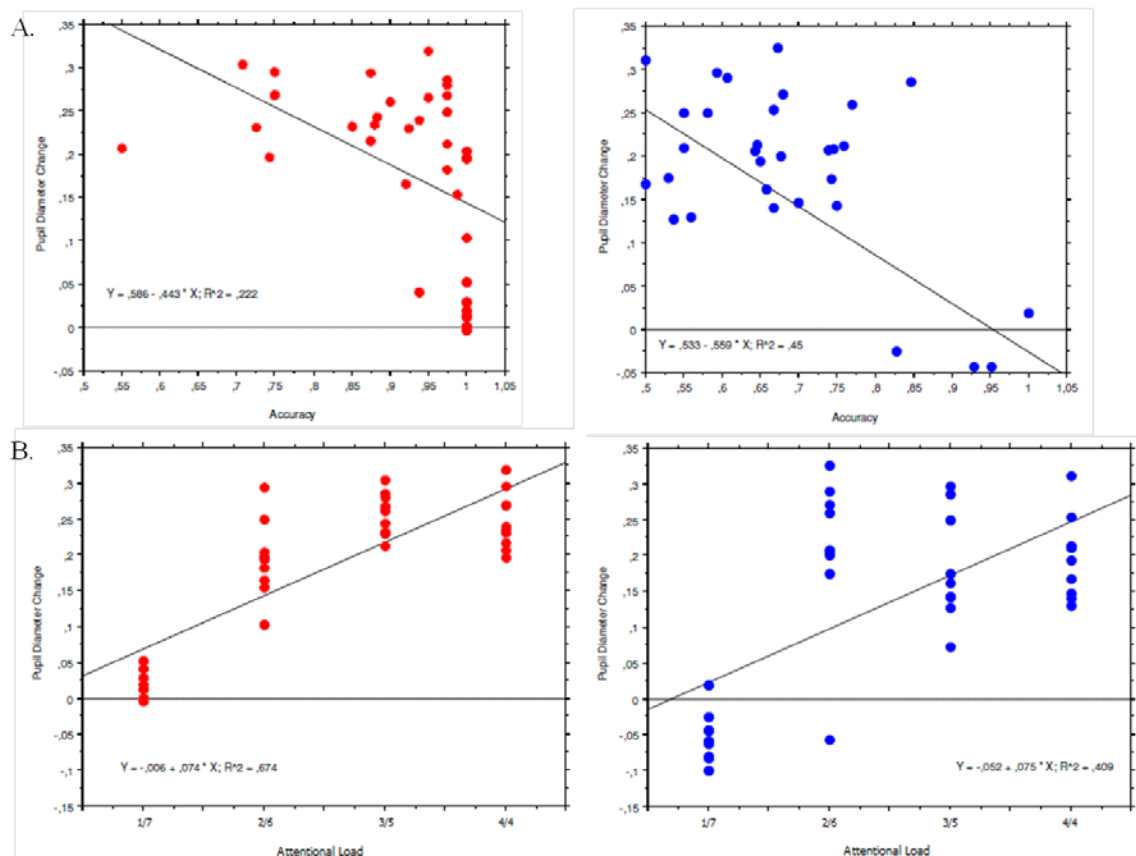


Figure 15. Regression Analyses A. Changes in pupil diameter as a function of accuracy in controls (left panels in red, $R^2 = 0.222$) and LE (right panels in blue, $R^2 = 0.45$). **B.** Changes in pupil diameter as a function of increasing attentional load, (target distractor combinations of 1/7, 2/6, 3/5 and 4/4) in controls (red, $R^2 = 0.674$) and LE (blue, $R^2 = 0.409$)

Discussion

Spatial, selective and sustained attentional mechanisms to motion were examined in a unilateral parietal patient with remediated neglect. The patient's ability to track different cognitive loads for 5 or 10 seconds in an entire field (whole field stimulation) versus left or right

hemifields only (unilateral stimulation), or left and right hemifields in the presence of contralateral distractors (bilateral stimulation) was assessed in comparison with age-matched controls using MOT in combination with infrared eye-tracking and pupillometry. Accuracy and pupillary response was used as a measure of selective and sustained attention in our patient compared with age-matched controls. The ability to select and track accurately a target in a field of identical targets in MOT during a short tracking interval of 5 seconds would demonstrate the presence or absence of a preserved selective attention function or indicate, over time, its recovery. In the present paradigm, the capacity limits of selective attention were assessed by varying cognitive load of tracking between 1-4 targets. We predicted that the present case of unilateral stroke patient would be impaired in selective attention to motion, and would reach maximum capacity, or asymptotic performance, for fewer targets than controls. Since previous studies showed that neglect patients also had significantly more fixations and longer fixations on the right hemifield (Behrmann, et al., 1997; Mapstone, et al., 2003), we predicted that our neglect patient would likewise exhibit more fixations and longer fixations on the right side of the visual field compared to age-matched controls.

Whole field stimulation. When comparing with the control group, the mean accuracy for LE in the whole field at 5 seconds significantly different across all attentional loads (Table 1). This implies that although, LE is able to select and track a target, the selective attention mechanism is altered from that of normal controls. Since the patient was significantly different from controls only for tracking 3 targets for the whole field 10 seconds, sustained attention seems to be intact, while maximum attentional load capacity is reduced compared to controls. When measuring changes in pupil diameter in either the early and late tracking periods, LE was not significantly different from the controls for mean changes in pupil diameter across any of the attentional loads (Table 2). Since pupillary responses have been implicated in the effort to sustain attention to stimuli over time, this seems to indicate that our patient and control population expended equal amount of effort in completing the MOT task in the whole field.

For the whole field condition, contrary to our predictions, there were no differences in dwell time between LE and the control population in any AOIs for any of the attentional loads during the early tracking period, except at 10-seconds. At 10 seconds, LE had more percent saccades and fixations in the upper quadrant of the left hemifield (TL1 and TL2) when tracking 2 targets as opposed to controls. The difference in the upper right of the left hemifield (TL2) disappeared

at higher attentional loads (3-4 targets); however, the difference in the upper left side of the left hemifield was significant at 4 targets (Table 3). This result may be due to altitudinal neglect rather than unilateral neglect, or possibly the effect of LE's scotoma. Targets in the lower left quadrant may be invisible to the patient, and thus his gaze may be captured by targets moving in the upper quadrant of the same field.

The control group had mean accuracy of between 93-100% across all loads at 5 seconds in the whole screen stimulation, but performance was reduced to 75% for tracking 4 targets at the 10-second interval (Table 1). The healthy age-matched controls were able to attend and track up to 4 targets for up to 5 seconds, but by 10 seconds, they exhibit an age-related reduced capacity to sustain tracking of more than 3 targets. This result is consistent with previous research, which has shown that older adults between 60-75 years have an age-related decline of selective attention so that working memory processes are disrupted by task-irrelevant information, in comparison to younger adults (May, Hasher, & Kane, 1999; Milham, et al., 2002; West, 1999). Porter et al., (2007) demonstrated that effort associated with processing load was low in early stages of a task, but increased during the trials. Therefore, it seems that there is an age-related reduced capacity limit in sustained selective attention for healthy older adults, which leads not only to decreased accuracy, but also to reaching maximum pupil size when tracking 3 targets followed by a decrease at 4 targets (Table 2).

Split-screen, Unilateral stimulation. To investigate the validity of the biased competition model, spatial attention was assessed in LE by stimulating either the left or right hemifield. Based on the findings of Battelli et al., (2001), we predicted that the unilateral parietal patient would have more impairment in the left hemifield of the visual field than the right hemifield. This deficit in the left hemifield of the whole screen stimulation should be especially apparent in the unilateral left screen stimulation than unilateral right, but that unilateral right would still be attenuated (Posner, et al., 1984; Eglin, et al., 1989).

When comparing the patient with control group performance at 5-seconds, LE was significantly impaired in tracking 2-3 targets on the left side, and was significantly different in tracking 1-2 targets on the right. For the 10-second tracking length, LE was significantly impaired in tracking 1-3 targets compared with controls. This suggests that LE has significantly altered cognitive load capacity as well as reduced sustained selective attention in both hemifields compared to age-matched controls. Since there is impairment present in both fields, these results

suggest that selective attention to motion can be a non-lateralized deficit of neglect after a right parietal lesion and that the deficit may appear as more severe in the ipsilesional hemifield. This result contradicts the expectation that any presence of ipsilesional deficits would be weaker than contralesional deficits (Weintraub & Mesulam, 1987), but our findings support the view that there is a right hemispheric dominance in attentional control. However, the patient LE is aware that his condition causes a failure to attend to the left hemifield, and an alternate explanation may be that he is overcompensating by spending more time examining the left hemifield at the expense of attending to the right hemifield during a demanding test. Again, LE demonstrated remediated unilateral neglect in the line bisection tests, and thus may only be exhibiting altitudinal neglect.

Although LE displays a different pattern of pupillary response than that of controls, LE was not significantly different from the controls for mean changes in pupil diameter across any of the attentional loads, for either the 5- or 10-second tracking intervals or in either left or right side of allocation during the unilateral stimulation condition. Consistent with findings from the whole field condition, pupillary responses between our patient and control population seem to indicate that equal amounts of effort were used in completing the MOT task.

When stimulating only the left hemifield in the absence of distractors during the unilateral screen condition, there were no differences in dwell time between the patient and the control group for any of the AOIs when tracking 1 or 3 targets for 5-seconds or when tracking 2 or 4 targets for 10-seconds. However, LE spent a significant longer period of time than controls gazing at the upper left quadrant of the left hemifield (TL1) for 2 and 4 targets in the 5-second tracking and for 3 targets when tracking for 10-seconds (Table 8), thus exhibiting altitudinal neglect.

In addition, LE had small but significant differences in dwell time than controls for gazing at the upper right quadrant of the non-stimulated hemifield (TR2) when tracking 2 or 4 targets for 5 seconds or in the upper left quadrant of the unstimulated hemifield (TR1) when tracking 1 or 3 targets for the 10-second period. This result is curious as the unstimulated hemifield was a blank screen. Thus, our patient LE seems to have a reduced oculomotor control which may cause a reduced ability to attend solely to the correct side of stimulation. During right hemifield stimulation in the absence of distractors for the split-screen unilateral condition, again, LE had small but significant differences than controls in percent fixations and saccades for various

quadrants of the unstimulated left hemifield across all attentional loads in the 5-second tracking (BL1, BL2, TL1 and TL2), and when tracking between 1-3 targets for the 10-second tracking period (BL1, TL1 and TL2). The lack of difference in dwell times when tracking 4 targets during the 10-second interval correlates to the control group's limit in accurately tracking more than 3 targets (Table 9). In addition, as in the whole screen condition, LE did not demonstrate the expected longer dwell time in the ipsilesional visual hemifield compared to age-matched controls, but did exhibit decrease in oculomotor control since there were small percentages of saccades and fixations in the unattended fields.

When comparing the split-screen unilateral left or right screen stimulation in controls only, the control population had no difference in performance for accuracy in left versus right hemifields, regardless of early versus late tracking intervals. As seen in whole field stimulation, the control group accuracy during the split-screen unilateral stimulation was between 92.5-100% in tracking 1-3 targets, but decreased to 75-87% at 4 targets irrespective of side of allocation or tracking times, which again implies an age-related reduced maximum load capacity. Unlike the whole field condition, the control group pupil size only reached maximum diameter when tracking 3 targets on the right hemifield for the 5-second condition, while the tracking left in both time intervals and tracking right during the 10-second interval showed continual increase. This also suggests that the left and right visual space is differentially processed in normal controls and not just in the patient.

Split-Screen, Bilateral stimulation. As previous studies had found that high-level motion perception was impaired in the visual field contralateral to the lesion, and that increases in the number of items to the right in a visual presentation or search array led to increased leftward neglect and visual attention or search is correspondingly impaired on the left (Eglin, et al., 1989; Kaplan, et al., 1991), we hypothesized that LE's impairment caused by the lesion would increase with greater processing load in the MOT task that was especially sensitive to side of allocation, and the presence of distractors on the ipsilesional field. Since visual extinction to motion in unilateral parietal patients is defined as the failure to attend to moving stimuli in the contralesional field only in the competing presence of moving distractors in the ipsilesional visual field, we predicted that the patient would have significantly impaired function in the bilateral stimulation condition compared with age-matched controls.

When comparing the patient to the control group, LE's performance in accuracy was significantly different for tracking lower cognitive loads (1-2 targets) than controls irrespective of tracking time or side of stimulation. Thus, although LE has the ability to attend selectively, the operation of his selective attention mechanism is significantly reduced. Also as in previous conditions, the control group was able to track up to 3 targets, and did not differ in their ability to track left versus right hemifields during the 5-second tracking interval of the split-screen bilateral stimulation condition (Tables 10-11). However, a surprising difficulty emerged at 10 seconds in the control group when tracking more than 1 target in the left hemifield than in the right hemifield (Table 10). This reduction in ability to track in the contralesional field was at the same level of performance as the patient. In the 10-second bilateral condition when attending the left hemifield, our older controls seemed to display a susceptibility to distractors in the right hemifield. Pupillary responses for the control population in both right and left bilateral stimulations mirrored the whole screen findings, where there seems to be an age-related reduced capacity limit in sustained selective attention for healthy older adults, which leads to reaching maximum pupil size when tracking 3 targets followed by a decrease at 4 targets (Table 12-13).

Similar to our findings in the unilateral condition, our patient LE seems to have a reduced ability to attend solely to the correct side of allocation, and seems to show reduced attentional control. This seeming reduction of oculomotor and/or cognitive control found in unilateral stimulation is even more visible during bilateral stimulation, in which LE had higher number of saccades and fixations in the unattended field than did controls. When stimulating only the left hemifield in the presence of distractors of the ipsilesional field for the 5-second split-screen bilateral condition (Table 14), LE had significantly more saccades and fixations for the bottom left quadrant of the attended hemifield (BL1) when tracking 1 target, or in the upper left quadrant of the attended hemifield (TL1) when tracking 2-3 targets, or in the upper right quadrant of the attended left hemifield (TL2) when tracking 4 targets. Notably, the patient had significantly less dwell time in the bottom right quadrant of the attended left hemifield (BL2) when tracking 1 target during the 10-second split-screen bilateral condition. LE also had significantly longer dwell times than controls in the upper quadrants of the left hemifield when tracking 2 targets (TR2, 43.95% vs. 16.85% respectively) and when tracking 3 targets (TR1, 50.54% vs. 19.87%) of the 5-second tracking period, once again displaying altitudinal neglect.

In addition during bilateral left side of stimulation, LE had small but significant differences in dwell times in various quadrants of the distracting unattended hemifield (BR1, BR2, TR1) for both the 5- and 10-second tracking periods across all attentional loads. These small differences were also found during right hemifield stimulation in the presence of distractors for the split-screen bilateral condition (Table 15), in which LE had small but significant differences than controls in percent dwell time for various quadrants of the unstimulated left hemifield (BL1, BL2, TL1, TL2) across all attentional loads for both early and late tracking intervals. Thus, our patient LE seems to have a reduced ability to attend solely to the correct side of allocation, seen through his decrease of oculomotor control.

These results are consistent with lesion studies in primates, which show that unilateral parietal cortex lesions cause a tendency to make voluntary eye movements into the ipsilesional field when presented with bilateral stimuli (Desimone & Duncan, 1995), but inconsistent with the finding that neglect patients have significantly more fixations and longer fixations on the right hemifield (Behrmann, et al., 1997; Mapstone, et al., 2003). The increased ability of irrelevant information to disrupt processes has been attributed to an age-related decline in the inhibitory function of selective attention (West, 1999; Kim et al., 2000; Milham et al., 2002; Kaneko et al., 2004; Van Gerven et al., 2004; Piquado et al., 2010).

Limitations and Future Directions

There were several limitations inherent in our experimental design. For instance, in this case study we looked at partial response, in which the participants respond yes or no, rather than allowing for full response, complicating the calculation of the probability of guessing correctly. Allowing for full response in a future study would control for this possibility, and also characterize accuracy more thoroughly. In addition with respect to the possible extent of impairment in LE, we did not completely randomize order of presentation. Whole, unilateral, and bilateral stimulations were randomized, but target presentation was presented starting from 1 target increasing to 4 and then decreasing to 1 in an ABBA format. Therefore, we can only describe our statistics limited to the presentation of the stimuli in an ABBA format. It should also be noted that our method of normalizing pupil size carries an implicit assumption that the change in pupil size is equivalently linear in LE versus the control group. A difference in this regard could affect the relative magnitude of the pupillary response curves on the y-axis as

measures of cognitive effort for the two groups, but it is not expected to reverse or eliminate the effects of stimulus conditions.

Functional Magnetic Resonance Imaging (fMRI)

As part of this study, a modified version of the MOT paradigm was also used in conjunction with functional magnetic resonance imaging (fMRI), in order to delineate the function after insult to the attentional networks. fMRI may be used to correlate functional neural activity of a task to a particular region of interest in the brain, and has become a popular tool of choice in the field of cognitive neuroscience due to its noninvasiveness, relative ease of implementation, high spatial and temporal resolution, and signal fidelity (Bandettini, 2009a, 2009b). However, for the purposes of this thesis in respect to time and length constraints in performing analyses, only the behavioral portion of this study was described for this thesis. Preliminary results suggest a remarkable different pattern of re-organized activity in the right MT and parietal cortex which has spread around the lesioned cortex in LE (Fig. 16, unpublished data).

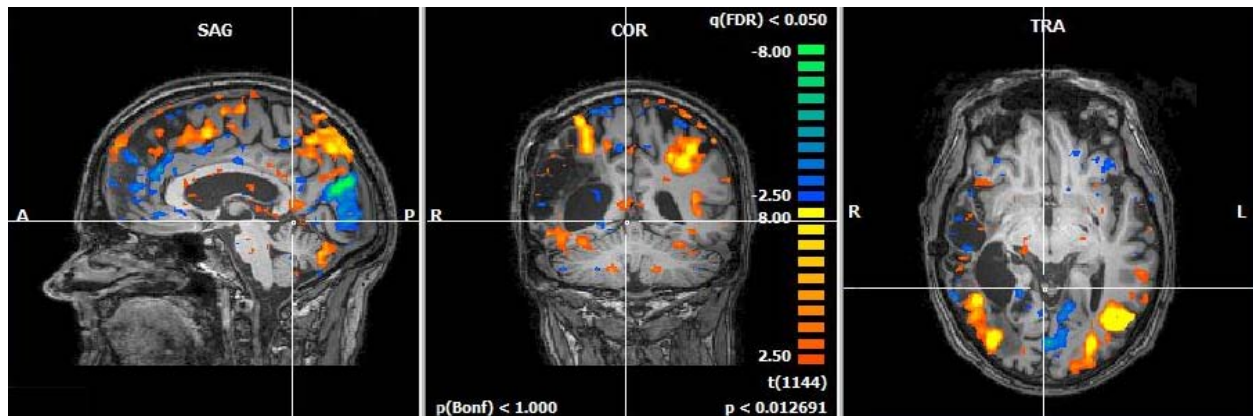


Figure 16. Neuroplasticity. fMRI of LE during whole field stimulation. Preliminary analysis using general linear model analysis of whole field tracking vs. passive viewing. Note activation near the right MT and right parietal cortex in comparison to the left.

Based on our findings, lesions in the right posterior parietal, occipital and temporal regions of the right cerebrum, including the Ips, SPL, the IPL, the middle and superior temporal gyri, as well as a part of the middle occipital gyrus (part of V5, MT/MST) are implicated in non-lateralized as well as unilateral and altitudinal neglect (Fig. 5; BA 7, 19, 21, 22, 37, 39, 40 & 41).

Finally, we would like to expand this case study to a patient population, in which case, it will be important to control for the immense variability of cognitive impairment as well as size and location of lesion sites between patients. The subsequent visual disorders may vary widely,

leading to heterogeneity and poor characterization of the neglect syndrome. MOT may itself be useful as a treatment model, since 1) the paradigm is well-grounded in attentional theory, 2) trials are easily controlled, sensitive to improved or impaired performance over time for specific components of attention, and 3) sufficient repetitions of trials are possible with high validity and reliability of results across trials. Thus, results should be reanalyzed to include LE's performance over time. Indeed, LE mentioned that over the course of the year, he noticed an increased ability to watch television. Therefore, testing MOT with eye-tracking and pupillometry may have rehabilitation significance in addition to diagnostic applications in the clinical field.

Conclusion

Overall, we have presented a new methodology to quantify spatial, selective and sustained attention to motion in a patient with remediated neglect. Standard bedside neglect tests were no longer sensitive to capture deficits, however, MOT demonstrated sensitivity for specific attentional deficits. Although the patient LE is able to select and track a target, the selective attention mechanism is altered from that of normal age-matched controls. Sustained attention seems to be intact, while maximum attentional load capacity is reduced compared to controls in the whole field condition. However, LE had significantly altered cognitive load capacity as well as sustained selective attention in both hemifields, although equivalent cognitive effort was expended in completing the MOT task by both LE and the control population. LE also seems to have a reduced oculomotor control, leading to a decreased ability to attend solely to the correct side of allocation. Since there is impairment present in both fields, these results suggest that selective attention to motion can be expressed as a non-lateralized deficit of neglect after a right-sided parietal lesion and that the deficit can be more severe in the ipsilesional hemifield. LE also displayed altitudinal neglect favoring the superior visual field. Most surprising was the occurrence of age-related reduction of attending items in the left hemifield in the presence of competing stimuli in the right hemifield in the 10-second condition for the control group.

In conclusion, studying attention with MOT in conjunction with eye-tracking and pupillometry offers a unique possibility to further characterize specific spatial, selective, and sustained attentional functions of motion perception in patients as well as in healthy aging adults.

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