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Ipsilesional Neglect: Its anatomical and behavioral correlates

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Ipsilesional Neglect: Its anatomical and behavioral correlates

Daniela L. Sacchetti

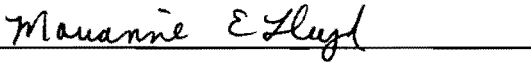
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with a concentration in Behavioral Neuroscience
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Abstract

Spatial neglect is a disorder commonly occurring after right hemisphere stroke. Typically, neglect results in an attentional impairment to contralesional space: a person with a right lesion fails to respond or orient towards stimuli on the left. In some cases however, patients display ipsilesional (right-sided) neglect. Contralesional neglect is often associated with lesions to right parietal cortex. Although it is a heterogeneous disorder, many have traditionally considered it a disorder of perceptual-attention. In contrast, the much sparser existing research on ipsilesional neglect supports an association of this disorder with damage to the right frontal lobe which may result in more motor-intentional errors. I will present the results from a case study of an 80 year old male who displayed symptoms of contralesional and ipsilesional neglect. The purpose of the case study was to determine whether a visuomotor pointing task could rehabilitate neglect symptoms. The results from this case study suggested that visuomotor pointing training alleviated functional symptoms of neglect and decreased motor-intentional bias, while having no effect on paper and pencil tasks. In a second study, I performed lesion mapping and overlap analysis of 12 participants with ipsilesional neglect. I also assessed participants' perceptual-attentional and motor-intentional biases. I hypothesized that participants would have lesions localized to the right frontal lobe and basal ganglia, because these areas are associated with the motor-intentional system. I also predict that participants would display greater motor-intentional than perceptual-attentional bias. Consistent with my hypothesis, a greater proportion of participants with ipsilesional neglect had frontal/basal ganglia damage compared to expected proportions observed in contralesional samples. However,

inconsistent with my hypothesis, participants with ipsilesional neglect had a greater magnitude of perceptual-attentional than motor-intentional bias.

Introduction

Spatial neglect is demonstrated by patients as a failure to report, respond to, or orient towards stimuli in contralesional space, which cannot be attributed to basic perceptual or motor dysfunction (Heilman, Watson & Valenstein, 2003). It is a heterogeneous disorder of spatial cognition in which patients may manifest symptoms in one or more of the cognitive processing stages of stimulus encoding, imagery and memory (e.g., Coslett, 1997), and movement planning (Heilman, 2004). Neglect usually results from and is most severe following right hemisphere brain damage, with a reported incidence rate of 13-81% of right hemisphere stroke patients displaying with this disorder (reviewed in Barrett et al., 2006).

Individuals suffering from spatial neglect may act as if half of their world does not exist but many of the behavioral characteristics of this disorder differ between individuals. Some individuals with neglect are unable to 'see' or 'hear' people who approach them on the left side or may even collide with objects on their left. Other times, an individual with neglect may not eat the food on the left side of their plate or reach for a drink in the left side of space. Some individuals only shave or apply make-up to the right side of their face, while others will forget to dress their left half leaving their left arm outside of a shirt. In severe cases of neglect, it is even possible for individuals to claim that their left extremities do not belong to them. These behaviors all vary depending on the individual, no two cases of neglect are exactly the same.

Patients with neglect are usually also unaware of their deficits and because of this are unable to compensate for their deficits by voluntarily changing the orientation of their attention (Rodes, Klos, Courtois-Jacquín, Rossetti & Pisella, 2006). Individuals who

suffer from spatial neglect are also more likely to have longer rehabilitation hospitalizations and are more impaired than those individuals without neglect on measures of disability (Kalra, Perez, Gupta & Wittink, 1997). Although spontaneous recovery from the obvious symptoms of neglect have been demonstrated in most patients both acutely (less than 6 weeks after stroke) and post-acutely (less than 3 months), in more than 25% of cases neglect can persist for several years (Farne et al., 2004). Due to these extra hurdles faced by the stroke survivor with spatial neglect, it is increasingly important that researchers try to understand the behavioral and anatomical components of this disorder.

Characteristics of Contralesional Neglect

Common ways of testing for neglect include drawing and copying tasks, line bisection tasks, and cancellation tasks (e.g., Rossetti et al, 1998; Serino, Bonifazi, Pierfederici, & Làdavvas, 2007; Pisella, Rode, Farnè, Boisson, & Rossetti, 2002). In drawing and copying tasks, patients with contralesional neglect may omit certain features from the left side of objects or fail to draw the entire left side of an image. In line bisection tasks, patients are asked to mark (with a pen) the center of a horizontal line. Patients tend to indicate that the center of the line is right of the true center; this may be because they underestimate the length of the left side of the line. In a cancellation task patients are presented with a paper that is full of either different letters of the alphabet, lines, different objects, or different shapes and are asked to locate and mark with a highlighter or pen one specific symbol. For example, a patient completing a letter cancellation task would be presented with a paper containing many letters of the alphabet but are only asked to identify the E's and R's. When completing a cancellation

task, patients will typically not mark objects on the left. Clinical testing for the presence of neglect has focused on these types of paper-and-pencil tests, with research suggesting that multiple tests are more sensitive than just one because of the variability in performance from person to person (Azouvi et al, 2002).

Types of Neglect

Research has also shown that the tasks used for testing neglect are not necessarily correlated, suggesting that these tasks may place qualitatively different demands on the patient and may assess different neural or cognitive systems that contribute to the disorder (Na, Adair, Williamson, Schwartz, Haws & Heilman, 1998). Although symptoms of neglect have classically been considered deficits of visual attention, spatial biases may be observed in all sensory systems including audition (Pavani, Làdavas & Driver, 2003), touch (Faglioni, Scotti & Spinnler, 1971), proprioception and olfaction (reviewed in Vallar, 1998), as well as motor (Coslett, Bowers, Fitzpatrick, Haws & Heilman, 1990) and oculomotor functions (Walker & Findlay, 1996). In addition to lateralized biases in these attentional and exploratory functions, neglect patients often experience non-lateralized biases, including deficits in sustained temporal attention (Husain, Shapiro, Martin & Kennard, 1997), spatial working memory (Husain, Mannan, Hodgson, Wojciulik, Driver & Kennard, 2001) , and temporal perception (Danckert et al., 2007).

Among the commonly recognized subtypes of neglect are intentional (motor), and sensory (perceptual) neglect (Heilman, Watson & Valenstein, 2003). Perceptual-attentional deficits are demonstrated by a lack of awareness or attention to stimuli in space opposite the brain damage, while motor-intentional deficits are a failure to

respond to or initiate an action towards the space opposite the brain damage (Heilman, 2004).

Neglect patients may demonstrate either perceptual-attentional, motor-intentional spatial biases or both (Adair, Na, Schwartz & Heilman, 1998; Buxbaum et al., 2004) but it has also been found that symptoms of neglect in all subtypes are highly inconsistent and change over time (Hamilton, Coslett, Buxbaum, Whyte, & Ferraro, 2008); one individual with neglect can present with any combination of these symptom subtypes during various stages of the disorder (Hamilton et al, 2008; Barrett & Burkholder, 2006).

Assessing Neglect Subtypes

Researchers have developed a number of mechanisms for teasing apart these subtypes of neglect (e.g., Bisiach, Geminiani, Berti & Rusconi, 1990; Hamilton, Coslett, Buxbaum, Whyte & Ferraro, 2008; Na, Adair, Williamson, Schwartz, Haws & Heilman, 1998). A video apparatus created by Na and colleagues (1998) manipulates visual feedback during a line bisection task to differentiate motor-intentional from perceptual-attentional neglect. Using this apparatus, patients perform line bisections while direct view of their hand is blocked, but they watch a video-screen onto which their hand movements are projected. The video image is manipulated so that there are two conditions: In the Natural condition the right side of the paper (and the participant's hand) appears on the right side of the screen and vice versa – the left side appears on the left. However, in the Reversed condition the right side of the paper (and the participant's hand) appears on the left side of the screen: Rightward movements of the hand appear leftward and vice versa – leftward movements of the hand appear rightward. In the Natural condition patients show the typical line bisection errors

associated with contralesional neglect, erring to the right. In the Reversed condition those individuals who have motor-intentional deficits will have rightward deviations on the line bisection because of a failure to move leftward. Those individuals with perceptual-attentional deficits, however, will have leftward deviations in the Reversed condition because their error is dependent upon the reversed visual feedback (Na, Adair, Williamson, Schwartz, Haws & Heilman, 1998).

Although Na and colleagues (1998) used this apparatus to categorically label patients as having primarily motor-intentional errors or primarily perceptual-attentional errors, others have pointed to the fact that a single patient may have both perceptual-attentional and motor-intentional biases (Barrett & Burkholder, 2006). These researchers developed a method for simultaneously quantifying both biases of patients. Algebraically solving the following equations allows for the simultaneous and independent calculation of “aiming” (i.e., motor-intentional) bias and “where” (perceptual-attentional) bias:

$$\text{Natural Error} = \text{Motor-intentional} + \text{Perceptual-attentional} \quad \text{Eq. 1}$$

$$\text{Reversed Error} = \text{Motor-intentional} - \text{Perceptual-attentional} \quad \text{Eq. 2}$$

Garza, Eslinger, and Barrett (2008) demonstrated the validity of these algebraically fractionated terms in a study with healthy young and aged participants. They showed that motor cueing (i.e., starting a line bisection at either the left or right upper- corner of a screen) had an effect on motor-intentional but not perceptual-attentional bias. When participants started their movement from the upper left corner of the screen they displayed motor-intentional bias that was further to the left than when they started from the upper right corner of the screen. Perceptual cueing (i.e., having a

visual distracter present at either the left or right side of the screen) had an effect on perceptual-attentional but not motor-intentional bias. Participants who were exposed to a left distractor had increased leftward error, while those who were exposed to a right distractor had decreased leftward error (Garza, et al., 2008).

This apparatus, because of its ability to separate motor-intentional and perceptual-attentional bias, may help to determine which deficits in neglect are more sensitive to certain types of rehabilitation techniques. Specifically, researchers may be able to tell which types of rehabilitation techniques are more useful for individuals who display primarily more motor-intentional bias or more perceptual-attentional bias. Furthermore, there is potential for a neglect treatment to improve one type of bias while worsening the other (e.g., Barrett & Burkholder, 2006).

Theories on the Neurological basis of Contralesional Neglect

Neglect is a complex and heterogeneous disorder not only in its behavioral characteristics but also in its neurological basis. One of the main discrepancies seen in neglect is that it occurs far more frequently and severely following right hemisphere stroke than left hemisphere stroke (reviewed in Barrett et al, 2006). This phenomena gave rise to the use of the hemispheric dominance hypothesis of attention when trying to explain neglect symptoms (Weintraub & Mesulam, 1987); this theory suggests that the left hemisphere contains the neural machinery to direct attention only to contralateral right hemispace, but the right hemisphere has the ability to direct attention not only to the contralateral left hemispace but also (to a lesser extent) the ipsilateral right hemispace. In a normal functioning brain, the hemispheres work together to spread attention over an entire work space. When left-hemisphere injury occurs the right

hemisphere can direct attention to contralateral as well as some ipsilateral space but when the right hemisphere is damaged we would expect severe contralateral neglect to occur because the left hemisphere cannot compensate. One theory surrounding the hemispheric dominance hypothesis attributes the increased incidence of neglect after right hemisphere damage to the left-sided language dominance in humans which then allows for the right-hemisphere to become dominant in spatial attention (reviewed in Hillis, 2006).

A similar hypothesis suggests that within each hemisphere there is a bias for attention to the contralateral side so that there is a gradient for spatial neglect, but that gradient is steeper in the left hemisphere (Barton, Behrmann & Black, 1998). Under this hypothesis more neurons in the left hemisphere have contralateral receptive fields, while more neurons in the right hemisphere have bilateral receptive fields. When damage occurs to right hemisphere neurons are more likely to lose the ability for bilateral attention (right and left space), while the left hemisphere is still able to attend to contralateral -right space. A third hypothesis suggests that there is similar contralateral bias of spatial attention in both hemispheres but that the right superior temporal gyrus and right tempoparietal junction are specialized for nonspatial attention, specifically vigilance and reorienting (Corbetta, Kincade, Ollinger, McAvoy & Shulman, 2000). Under this theory, neglect is most severe when a lesion causes damage to these right hemisphere functions resulting in an inability to reorient attention to unattended locations.

Anatomical Correlates of Contralesional Neglect

Studies looking at the anatomical correlates of contralesional neglect have resulted in a wide range, and often contradicting, set of information. It is important to note here that neglect usually results from a larger set of tissue damage which may also play a role in why it is so difficult to pinpoint specific anatomical locations of this disorder (reviewed in Hillis, 2006). Specifically, it seems that this disorder is mainly associated with lesions located in the parietal lobe (Vallar & Perani, 1986) the temporal-parietal-occipital (TPO) junction (Leibovitch et al, 1998) and the superior temporal gyrus (STG) (Karnath, Himmelbach & Rorden, 2002; Karnath, Berger, Kuker & Rorden, 2004; Karnath, Rennig, Johannsen & Rorden, 2011).

In the early 1970s and 1980s most of the research conducted on contralesional neglect resulted in the belief that this disorder manifested most often from damage to the frontal lobe (Heilman & Valenstein, 1972) and subcortical grey matter structures like the thalamus (Watson & Heilman, 1979) and basal ganglia (Healton, Navarro, Bressman & Brust, 1982) but that view was soon abandoned after a study by Vallar and Perani (1986). Their study investigated the anatomical correlates of contralesional neglect in 110 right-brain-damaged stroke patients and sought to provide evidence that neglect was much more likely to occur when posterior regions of the right hemisphere are damaged. Their study found that contralesional neglect as defined by a cancellation task was much more likely to occur after parietal lobe damage. The authors suggest that the involvement of the parietal lobe in neglect may be due to a deficit in orienting attention which is not associated with the frontal region. Further support of the parietal lobe's involvement in contralesional neglect came from a study of 120 stroke patients

(82 with neglect) which found that 38% of participants with neglect had suffered damage to their parietal lobe (Leibovitch et al, 1998). These results were particularly interesting because the participants in this study underwent structural (CT) and functional (SPECT) imaging. The results from the SPECT scan supported the role of the parietal lobe in contralesional neglect and suggested that the only significant functional predictor of neglect was decreased perfusion in the right parietal lobe. This study also implicated the temporal-parietal-occipital (TPO) junction, an area which may connect with visual, tactile and auditory association areas. Of the individuals suffering from neglect, extensive damage was seen in white matter fiber bundles including the posterior-superior longitudinal and inferior-frontal fasciculi which pass through the temporal-parietal-occipital (TPO) junction.

Focus has also been placed on a number of subcortical structures and their involvement in contralesional neglect. It appears that neglect most frequently occurs from damage to grey matter subcortical structures, specifically the thalamus and basal ganglia which are believed to be involved by disrupting ipsilateral cortical activation and motor activation (Vallar & Perani, 1986). A study which focused solely on the implications of subcortical regions in contralesional neglect looked at 16 participants who had damage to the thalamus and basal ganglia. These results suggest that the putamen, pulvinar and caudate nucleus are the subcortical regions most associated with contralesional neglect (Karnath, Himmelbach & Rorden, 2002). The authors suggest that the involvement of these subcortical regions in contralesional neglect occur because of their connection with the superior temporal gyrus (STG). A large 140 participant study (78 with neglect) also supported the involvement and connection of the

STG with the basal ganglia (Karnath, Berger, Kuker & Rorden, 2004). These results suggest that damage to the STG is the most frequent cortical correlate of contralesional neglect followed by subcortical damage to the caudate and putamen. A voxel-wise longitudinal study of 54 neglect participants found that the right superior and middle temporal gyri predict both acute and chronic symptoms of contralesional neglect (Karnath, Rennig, Johannsen & Rorden, 2011). The authors point to the close anatomical connection between caudate and putamen with the STG; the caudal portion of the STG projects dorsally to the caudate and putamen while the middle portions of the STG is connected with the ventral portions of the putamen. The authors suggest that the right putamen, caudate and STG may form a network representing spatial perception and awareness (Karnath, Berger, Kuker & Rorden, 2004).

It has also been suggested that the behaviors associated with motor-intentional neglect or “aiming” bias and perceptual-attentional neglect or “where” bias may result from damage to specific brain locations. A study which sought to better understand the behavioral and anatomical relationships of perceptual-attentional and motor-intentional neglect in 10 participants found that there were primary brain regions associated with each bias (Na et al, 1998). Participants who displayed with a perceptual-attentional bias suffered from more parietal lobe injuries, while participants who displayed with a motor-intentional bias had more damage to frontal and subcortical structures. The frontal lobe may be more associated with motor-intentional neglect because of its association with exploration, scanning, reaching and fixating (Mesulam, 1981), as well as motor behaviors regarding goal oriented actions (Schwartz, Barrett, Kim & Heilman, 1999). The parietal lobe may be more associated with perceptual-attentional neglect because

of its association with providing an internal sensory map (Mesulam, 1981) and spatially directed attention (Schwartz, Barrett, Kim & Heilman, 1999). Recently it has also been suggested that individuals with the perceptual-attentional subtype of neglect are two times more likely to have damage to the temporal lobe than those with the motor-intentional subtype (Buxbaum et al, 2004). This result is consistent with emerging research that implicated the superior temporal gyrus (STG) in contralesional neglect (Karnath, Rennig, Johannsen & Rorden, 2011). It is important to recognize that perceptual-attentional and motor-intentional systems are not anatomically or functionally separate: the frontal, parietal and temporal lobes are interconnected and interact with each other.

Characteristics of Ipsilesional Neglect

Although contralesional neglect occurs more frequently, cases of ipsilesional or right-sided neglect have been described (e.g., Kwon & Heilman, 1991; Robertson et al, 1994; Beschin, Basso & Della Sala, 2000). Ipsilesional neglect is a phenomenon where an individual shows a tendency to make omissions or errors on the ipsilesional side of one or more tests while showing clear contralesional neglect on other tests (Robertson et al, 1994). Ipsilesional neglect usually occurs in a task dependent manner; which means that some individuals display with this disorder on cancellation tasks, while others show the deficit only on line bisection tasks, and other individuals may display with the disorder only on drawing tests (Na, Adair, Choi, Seo, Kang & Heilman, 2000).

The literature on ipsilesional neglect has highlighted the variable properties of the disorder and has provided researchers with various ways to define the syndrome.

Robertson and colleagues (1994) describe a neglect patient who missed 40% of the

targets on the left side of a cancellation task but none on the right, a clear case of contralesional neglect. That same individual, when asked to draw a clock face from memory neglected to draw the right side of the image- a clear case of ipsilesional neglect. A study which used two forms of the line bisection task, one where the line was solid and two where the line was either made of letters or shapes, showed that 5 participants presenting with neglect bisected solid lines towards the left (ipsilesional) while 4 out of 5 participants bisected non-solid lines towards the right (contralesional; Na, Adair, Choi, Seo, Kang & Heilman, 2000). A case study of a 67 year old man with a right hemisphere stroke found that he presented with ipsilesional neglect on all tasks including cancellation, reading, and copying tests but showed clear contralesional neglect when he was drawing something from memory (Beschlin, Basso & Della Sala, 2000). Sometimes ipsilesional neglect may not present on any of these tests; the case study of a 62 year old male who suffered from a right-sided stroke and presented with contralesional neglect on line bisection, cancellation, and drawing tests also showed he was unable to inhibit contralesional ocular saccades when he was cued to look rightward (i.e., ipsilesionally; Kwon & Heilman, 1991).

Theories on the Neurological basis of Ipsilesional Neglect

Five hypotheses that may account for why ipsilesional neglect occurs were described and tested in 1994 by Robertson and colleagues. First mentioned was the poor reliability of neglect testing, suggesting that the rightward errors seen on some tests appeared by chance and were due to random fluctuations in attention. This hypothesis claims that if one person is given a battery of tests there always is the possibility that the individual will make right-sided errors. In order to accept this

explanation for ipsilesional neglect we would have to assume that there would be random rightward errors on all tests, but ipsilesional neglect is often seen on one test and not others. Similarly the second hypothesis is based on the neglect tests being too task specific. In other words, ipsilesional neglect is a feature of one test instead of being a more general phenomenon. The third hypothesis focuses on neglect severity, claiming that individuals with ipsilesional neglect have less severe general inattention which makes their rightward errors seem magnified compared to their total errors. This hypothesis has also been disproven because there is no evidence suggesting that individuals with ipsilesional neglect are less attentionally impaired than those participants with contralesional neglect. The fourth hypothesis suggests that participants with ipsilesional neglect may actually have some undetected left brain pathology causing them to ignore rightward space. Although this hypothesis is definitely plausible in some instances, it cannot be the cause for the cases for which we have brain scans that disprove this idea. The final hypothesis is that participants with contralesional neglect are learning to compensate for their neglect by scanning over the left resulting in omissions made on the right. This compensatory scanning technique makes the most sense when trying to understand how ipsilesional neglect may occur, especially because this disorder exists in combination with contralesional neglect. Unfortunately there is still one main problem with this hypothesis, why does compensatory scanning occur on some tests and not others?

The five hypotheses listed above attempt to provide an explanation for the basis of ipsilesional neglect but fall short, so what are some theories on this disorder that have stood strong? Just like with contralesional neglect, the hemispheric dominance

hypothesis plays a large role in understanding why ipsilesional neglect may occur. When thinking about the right hemisphere's involvement in modulating attention to both contralateral and ipsilateral space we can understand how damage to the right hemisphere may result in not only contralesional neglect but also some neglect for ipsilateral right space (Weintraub & Mesulam, 1987). Another main theory that has merit is that this disorder may be due to a widespread attentional deficit rather than a hemisphere specific disorder of attention (Gainotti et al, 1990). The belief surrounding this theory is not that the right hemisphere has bilateral receptive fields, but instead that ipsilesional neglect is due to a lowering of general attention. This lowering of general attention may be due to non-specific factors like old age or severity of the cerebral lesion (Weintraub & Mesulam, 1987).

It has also been suggested that different types of attentional tasks would result in the display of two different types of neglect: contralesional and ipsilesional (Na, Adair, Choi, Seo, Kang & Heilman, 2000). Evidence for this theory comes from a study that tested the difference between performance on a solid line bisection task versus a non-solid line bisection task with stars and letters (Na et al, 2000). Participants in this study did in fact display with different types of neglect depending on the task and the authors attribute these differences to the suggestion that the right hemisphere modulated global attention, while the left hemisphere modulated focused or local attention. The authors believed that some tests like cancellation and drawing tasks, place greater demand on focused attention and after the right hemisphere is damaged the left hemisphere dominates processing local features towards the right hemispace resulting in left-sided neglect (contralesional). In contrast, when a solid line bisection task is performed it puts

little demand on focused attention so that line bisection performance can be normal or even to the left of true midpoint resulting in ipsilesional neglect. This theory could explain how the same subject could present with both ipsilesional and contralesional neglect at the same time.

Anatomical Correlates of Ipsilesional Neglect

There have been very few case studies and far fewer large-scale studies looking into the anatomical correlates of ipsilesional neglect, and because of this there is a great deal of discrepancy and uncertainty within the literature. Case studies of patients with ipsilesional neglect have produced a wide variety of lesion locations including the right dorsolateral frontal lobe (Kwon & Heilman, 1991), the right temporal-occipital lobe, the right MCA territory including the frontal lobe and temporal lobe (Schwartz, Barrett, Kim & Heilman, 1999) and the right thalamus and caudate (Barrett, Peterlin & Heilman, 2003). Larger scale studies have implicated the frontal lobe (Na et al 2000; Kim, Na, Kim, Adair, Lee & Heilman, 1999; Robertson et al, 1994), temporal lobe (Na et al, 2000; Robertson et al, 1994), parietal and occipital lobe (Robertson et al, 1994), insula (Na et al, 2000), basal ganglia (Na et al, 2000; Kim et al, 1999) and thalamus (Kim et al, 1999).

An important study on this topic aimed to not only identify the anatomical correlates of ipsilesional neglect but also attempted to learn whether this disorder was caused by perceptual-attentional (“where”) bias, motor-intentional (“aiming”) bias or both (Kim et al, 1999). The researchers identified 5 participants with ipsilesional neglect based on leftward deviation scores from center on a line bisection task which exceeded the 95% confidence intervals of control subjects. All five participants underwent testing on a video apparatus that separated motor-intentional and perceptual-attentional bias.

From this assessment the participants were classified as having either bias or both. Brain scans were also looked at to classify their lesion location. The results from this study found that all five participants had lesions involving the frontal and subcortical circuits, four restricted to the basal ganglia and one to the thalamus. There were however, no significant findings associated with neglect bias: three participants displayed with a primarily attentional bias while the other two presented with a primarily intentional bias. The results from this study suggest that the frontal-subcortical circuits play an important role in ipsilesional neglect, which may be because the frontal lobe mediates both attention and intention. This result does not follow the theory that perceptual-attentional bias is controlled by the parietal lobes and motor-intentional bias is controlled by the frontal lobes. Because the five participants did not share a particular bias, it is possible that these systems are functionally independent and may be why we see different performance on different tests. The performance of the same individual may reflect ipsilesional neglect on an intentional bias and contralesional neglect on an attentional bias. The demand of the task may determine the bias and the type of neglect. The inconsistency of the results may also be due to the small sample size and the method at which they were classified as having ipsilesional neglect.

Overview of Current Studies

The results of two studies will be reported in this paper: the first is the case study of an 80 year old male undergoing a visuomotor pointing rehabilitation for his spatial neglect. Behavioral testing of this individual suggested he may have ipsilesional neglect and sparked the second study. The second study is an attempted replication and extension of the study conducted by Kim and colleagues in 1999, to confirm whether the

frontal-subcortical circuits are indeed an integral part of ipsilesional neglect, and to determine the relative presence of motor-intentional versus perceptual-attentional biases in these patients. This was an archival study of ipsilesional neglect in 12 right-brain stroke patients screened by the Stroke Laboratory of the Kessler Foundation Research Center. After each participant was identified, their CT/MRI scans were used to classify the participants' lesion locations. I predicted that participants displaying symptoms of ipsilesional neglect would have lesions sites localized to the frontal lobe and basal ganglia. These areas are believed to be associated with the motor-intentional system (Heilman, Valenstein & Watson, 1994) and therefore, I also predicted that participants with ipsilesional neglect would display more motor-intentional than perceptual-attentional bias.

Study 1

Methods

Participant. The participant, S1, was an 80-year old male who suffered from a right hemisphere stroke and left spatial neglect. He was enrolled from an inpatient rehabilitation hospital where right-hemisphere stroke patients, admitted on average five to ten days post-stroke, were continuously screened (2008-2011) for eligibility in research studies on left neglect conducted by the Stroke Laboratory at the Kessler Foundation Research Center. Participants were not able to enroll in studies if they were more than 60 days post-stroke, had bi-lateral or left hemisphere damage, were pregnant, had dementia, past strokes, or past head trauma with loss of consciousness. Participants were asked to participate in a study if they 1) were right handed as assessed by the Handedness Questionnaire (Raczkowski, Kalat, & Nebes, 1974), 2) had unilateral right-hemisphere brain damage with no detectable left-hemisphere damage, 3) this was their first stroke event, and 4) if they scored less than 129 (the cutoff for categorization of “neglect”) on the Behavioural Inattention Test (BIT); Wilson, Cockburn & Halligan, 1987). Meeting these inclusion criteria, S1 was identified as a possible candidate for inclusion by a member of the Stroke lab and then was referred by his doctor as a potential candidate for the study. The patient was then approached by a lab member, who discussed possible enrollment into the experiment. Once the patient agreed to participate, he was then consented into the study.

General Procedure. For all practice, testing, and treatment sessions, two experimenters were present to work with the participant and to record performance. In an effort to ease the demands of the research participation, the majority of testing took

place in the participant's hospital room when possible. However, all testing on the desktop apparatus (described below) was done in the Stroke laboratory.

Assessment of Neglect Pre and Post Visuomotor Therapy. Pre-training assessment of the participant's neglect symptoms occurred prior to visuomotor pointing training on day one and post-training assessment occurred after visuomotor pointing training on day four. Pre-training assessment included the Behavioural Inattention Test (BIT; Wilson, Cockburn & Halligan, 1987), which consists of a line bisection test, three cancellation test (lines, stars, and letters), and three drawing tests (figures, shapes, and representational drawing). This test was presented to the participant aligned with his body's midline and without a time limit. Assessment included the participant's performance on the Geriatric Depression Scale (GDS; Yesavage et al., 1983), one functional test of neglect, the Catherine Bergego Scale (CBS) (Azouvi, Marchal & Samuel, 2003), and two paper and pencil tests: bell cancellation (Gauthier, Dehaut & Joannette, 1989) and copying of a complex drawing (Gainotti, Messerli, & Tissot, 1972). See the Appendix for examples of these tests. In the bell cancellation test the participant was presented with a sheet of paper filled with 315 figural items of which 35 were bells. The paper was placed on an empty table and aligned with the midsagittal plane of the participant. The participant was then asked to cross out all the bells. The participant's score reflects how many bells were canceled (range 0-35). The figure copying task included a complex drawing of two trees (left), a house (center), and two pine trees (right). Each item was scored as 2 points for a flawless copy, 1.5 points for partial omission of the left hand side, 1 for complete omission of the left hand side, 0.5

for complete omission of the left hand side and part of the right side, and a 0 for a drawing that was deemed unrecognizable (total score could range from 0 to 10).

The Catherine Bergego Scale (Azouvi, Marchal & Samuel, 2003; see Appendix for a full copy of the scale) was administered to assess the participant's function specific to left neglect, and was performed by an occupational therapist blind to the purpose of this study. This scale assesses how well a participant performs actions and orients to stimuli on the left side of space. For example, this scale assesses participants' ability to groom or dress themselves, as well as how well the individual maneuvers in space while walking or driving their wheelchair. Scores on this scale can range from 0-30, with 0 indicating no deficits and 30 indicating maximum impairment.

“Where” and “Aiming” Bias. Both Pre and Post assessments also included testing for “where” and “aiming” spatial bias (as described in the Introduction and in Na et al., 1998). The participant performed line bisections, marking the center of twenty horizontal lines (240mm X 2mm). Each line was printed alone on a standard sheet of 8.5 in. x 11 in. paper and was placed on a table in front of the participant. The participant's direct view of the line was blocked by a black curtain placed between the participant and the table. A camera (Sanyo, VCC-5884) was located above the table, at a distance of 37cm. This camera transferred the image of the line and the participant's hand onto a video screen centered in front of the participant at a distance of 80 cm. In order to avoid interference or cues, the borders of the paper containing the line were not visible on the screen.

A black cloth was draped around the participant to block the view of his arm. Therefore, in order to carry out the bisection the participant had to watch his hand

motions on the video screen. The line bisections were performed under two different conditions; each condition was preceded by two practice trials. In the Natural condition, eight lines were bisected with rightward and leftward movement on the screen unaltered. In the Reversed condition, the participant bisected eight more lines in which rightward movements appeared leftward on the screen and vice versa. Because individuals with neglect are often easily distracted by stimuli and sometimes have difficulty with attention it was important to avoid one-sided directional cuing from the experimenter. Thus, two experimenters were present during this task, one standing to the right of the participant and one standing to the left of the participant. Each experimenter took turns giving instructions and collecting completed line bisections from the participant, so as to not continuously pull the participant's attention to only one side.

In order to familiarize the participant with the apparatus and avoid fatigue, confusion, and agitation, the participant practiced the line bisection task in the week prior to starting the visuomotor pointing training. This practice took place for 30 minutes in one session. During the practice session the participant was asked to move his hand across the line in both the Natural and Reversed conditions in order to get familiar with the visual feedback. Several trials of the line bisection were performed in each condition until the participant showed an ability to reach each side of the line and perform the bisection task. When the experimenter noticed that the participant was having a difficult time moving his hand across the line she would physically move the participants hand for him until he could perform the task on his own. The experimenter also asked the participant to trace the line and write his name along the length of the line to help his progression.

Using Equations 1 and 2, it was possible to separate “where” and “aiming” spatial bias contributions to participants’ line bisection performance. Scoring was completed by computing the deviation (in mm) of the marked center from the actual center of the line; with positive values denoting errors to the right of center and negative values denoting leftward errors. Only the 16 experimental line bisections were scored.

Visuomotor Pointing Therapy. The participant received four consecutive days of visuomotor pointing training. During these training sessions he wore plain goggles that prevented vision of the peripheral visual field. While wearing the goggles, the participant performed a series of 60 pointing trials within a timed 15 minute period. He used his right index finger to point to a visual target (tip of a red pen) appearing at the distal side of a board. The board was marked with a ruler visible only from the experimenter’s side so that the pointing error could be recorded. The visual targets were presented one at a time in the right (+21cm), center (0cm), or left (-21cm) position relative to the participant’s midsagittal plane. The visual targets were presented 20 times in each position in a pseudorandom order, such that each group of 6 trials included two instances of right, center, and left positions. Deviation of the finger position from the target was recorded in degrees, with negative values indicating deviations to the left of center and positive values indicating rightward deviations.

Results

S1 was an extremely pleasant and friendly man who was very compliant towards the study. He was alert during all testing and training procedures, although he had a very difficult time paying attention and understanding some of the directions. Often times I would have to repeat the directions multiple times or actually show him what I

wanted him to do. Once he understood the purpose of the task, he always excelled in his attempt to complete it. Although memory performance was never tested in this study it was obvious that S1 did have some memory issues related to the stroke which could have affected his performance.

Prescreening. Prescreening results supported that participant S1 did in fact meet all of the criteria for this study. He had a perfect score on the Handedness Questionnaire, answering right-handed to all ten questions. CT scan as well as his radiology report both confirmed that this was S1's first stroke, which was confined to the right frontal lobe and insula. Lastly, S1 received a score of 25 out of 146 possible points on the BIT; this was far below the 129 cutoff score for neglect. It was during this prescreening phase, specifically on the BIT, that I began to notice some abnormal properties of the participant's test. S1 displayed with classic contralesional neglect on the cancellation portion of the BIT, but when he was asked to complete the drawing portion S1 seemed to neglect the right-side of the image which is consistent with ipsilesional neglect.

Neglect Assessment. Pre-training neglect assessments took place on Day 1 before the visuomotor pointing training. Similarly to S1's poor performance on the BIT, he also had great difficulty with the Bells Cancellation Task and the drawing task. On Day 1, S1 was only able to select 11 out of 35 bells and received only a 4 out of the 10 on the drawing task. He scored 25 out of 30 on the CBS, which suggests severe leftward neglect. At post-training on Day 4, S1 continued to display with strong neglect symptoms on the paper and pencil tests. His performance on the Bells Cancellation Task actually worsened, he was only able to select 7 out of 35 bells and received the

exact same score on the drawing task, a 4 out of 10. Interestingly S1's performance on the CBS increased to 13 out of 30 which suggest that his functional skills and neglect in daily activities were actually improving. In order to set up an emotional control to support that tests results were a function of the participant's neglect and not his mood, S1 was also given the Geriatric Depression Scale on pre and post training days, both times he scored a 1 which suggests that his mood was stable over the course of the 4 days of testing and he was not depressed as far as this scale could measure. It is important to note in this section that S1's abnormal testing sessions continued into pre and post-training. During both Bell Cancellation Tests, the participant selected bells that were in the center or right side of the page and ignored those on the left side which clearly fits the behaviors of contralesional neglect (see Figure 1). On the drawing test, both times he drew the two trees on the left side ignoring the objects on the right side of the page which suggests an ipsilesional neglect.

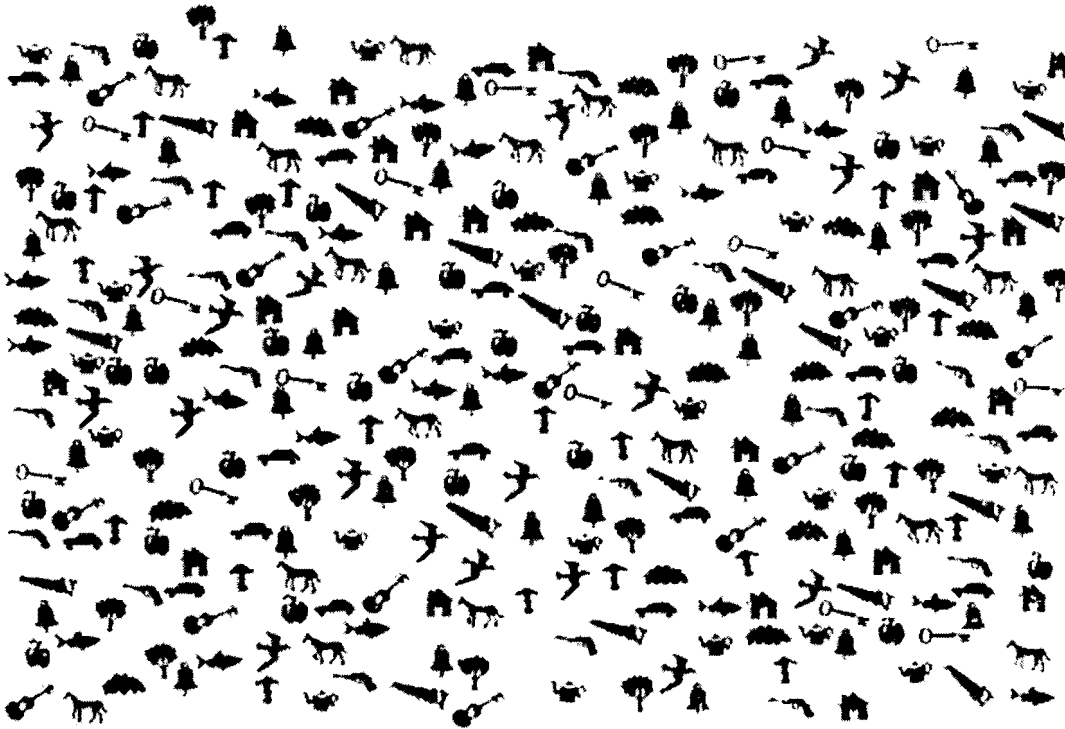


Figure 1. The Bell Cancellation test performed by participant S1 during the pre-training phase.

“Where” and “Aiming” Bias. On Day 1, pre-training, S1 displayed with an average Natural error (which deviated from the true center of the line) of -1.63 and a Reverse error of -35.88. These results suggest that S1 was bisecting lines towards the left of true center which is consistent with ipsilesional neglect. From these scores, it was mathematically determined that S1 had a rightward “where” error of 17.13 and a leftward “aiming” error of -18.75. On Day 4, post-training, S1 displayed with an average Natural error of 3.88 and a Reverse error of -22.5. These results suggest that after visuomotor pointing training, S1 was beginning to bisect lines right of true center in the Natural condition but continued to bisect lines left of true center in the Reverse condition to a lesser degree. From these scores, it was mathematically determined that S1 still had a rightward “where” error which decreased to 13.19 and a leftward “aiming” error

that also decreased to -9.31. It appears that the visuomotor pointing training may have actually helped to decrease the participant's errors in both the perceptual-attention and motor-intentional domain, but had a much greater impact on motor-intentional neglect symptoms.

Visuomotor Pointing Training. Improvement in visuomotor pointing was assessed by averaging the first six points on Day 1 and comparing that to the average of the last 6 points on Day 4. On average, S1 was relatively accurate at pointing to the target and only deviated from center an average of 1.5 cm to the left on Day 1. On Day 4, S1 improved to a rightward deviation of only .5 cm.

Overall, the results from this study suggest that four consecutive days of visuomotor pointing training may help to better rehabilitate motor-intentional neglect symptoms over perceptual-attentional neglect symptoms. It also seems that visuomotor pointing training may help to alleviate the symptoms of neglect which are affecting activities of daily living (the CBS) but have no effect on alleviating neglect symptoms as seen on paper and pencil tests (the bell cancellation task).

Study 2

Methods

Participants. Participants were selected from an existing dataset, the Neglect Screening Database, of the Stroke Laboratory of the Kessler Research Foundation. This dataset (N = 132) reflected a consecutive sample (December 2, 2008 to June 15, 2011) of right-hemisphere stroke patients with suspected left neglect. Like in Study 1, all participants who were selected from this database were enrolled from an inpatient rehabilitation hospital where most patients are admitted five to ten days post-stroke. Based on the previous inclusion and exclusion criteria of the original study they were enrolled in, all participants were between the ages of 18-100, were able to give informed consent, and were willing to comply with the study protocol. As in Study 1, participants were not able to enroll in the study if they had bi-lateral or left hemisphere damage, were pregnant at the time, had dementia or Alzheimer's disease, were blind in one or both eyes, had uncontrolled glaucoma, or experienced past head trauma with loss of consciousness.

All 132 participants underwent prescreening to test for eligibility which included the Mini-Mental Status Examination (MMSE; Folstein, Folstein, & McHugh, 1975), Behavioural Inattention Test (BIT; Wilson et al., 1987), Catherine Bergego Scale (CBS; Azouvi et al., 2003), Geriatric Depression Scale (GDS; Yesavage et al., 1983), Barthel Index (Mahoney & Barthel, 1965), Handedness questionnaire (Raczkowski et al., 1974). As in Study 1, once the patient was deemed eligible, the study continued with a neglect assessment that included the BIT and CBS, in addition to other assessments that will not be reported here. The BIT consists of a line bisection test, three cancellation test

(lines, stars, and letters), and three drawing tests (figures, shapes, and representational drawing). This test was presented to the participant aligned with his body's midline and without a time limit by a research assistant. The CBS was used to evaluate the participant's abilities in functional activities, specific for the left side of space, and was performed by an occupational therapist blind to the purpose of the study.

The 132 participants in this study also underwent testing for where and aiming bias, but none of them used the video-apparatus as was described for participant S1. These participants were assessed for where and aiming bias using a computerized line bisection task. The participant was positioned centrally in front a computer screen (40cmX30cm) that was 60 cm away. The participant's right hand was placed on a computer mouse under a wooden board covered with a black cloth so that the participant could not see his/her hand. On this screen appeared a black horizontal line (240mmX2mm) and the participants were told to move their cursor to either the top left or top right of the computer screen, the order of which was predetermined by a randomized testing sheet. Once participants moved the cursor to the given location they were asked to bring the cursor to the middle of the line. The location of the cursor was recorded by the computer. Like with the desktop apparatus for Study 1, there were two conditions to the computerized line bisection task: the natural and reversed condition. In the natural condition the cursor moved in the same direction as the mouse, so that rightward movement on the mouse produced rightward movement of the cursor and visa-versa. In the indirect condition, the cursor moved in the opposite direction of the mouse, so that rightward movement of the mouse produced leftward movement of the cursor. The participants completed 16 line bisections for each condition.

Using the existing data from these 132 participants I identified patients with ipsilesional neglect. Participants were categorized as presenting with ipsilesional neglect on the basis of their computerized line bisection task performance under the natural viewing conditions. Cut off values for defining abnormal leftward error were created from a study conducted by Chen and colleagues (Chen, Goedert, Murray, Kelly, Ahmeti, & Barrett, 2011), which assessed age-related and sex-specific differences in the spatial bias of normal participants completing a line bisection task. Patients were categorized as having ipsilesional neglect if their line bisection error was more than two standard deviations to the left of the mean of age- and gender-based healthy groups (see Table 1). Each gender and age group was given its own cutoff score because there is a difference in normal line bisection performance with age and gender: older men made greater rightward line bisections than young men and women made greater leftward errors than men regardless of their age (Chen et al., 2011). The cutoff for what determined pathological line bisection performance depended upon the participants age and sex, with young participants ranging from 22 to 56 years old and old participants ranging from 57 to 93 years old.

Table 1

Cutoff Line Bisection Scores (mm) for Ipsilesional Neglect

Sex	<u>Young</u>		<u>Old</u>	
	Healthy M (SD)	Cutoff	Healthy M (SD)	Cutoff
Males	-.91 (3.03)	-6.97	2.53 (2.88)	-3.18
Females	-3.06 (2.71)	-8.48	-4.15 (6.09)	-16.37

Note. M = mean, SD = standard deviation

Procedure

Lesion Mapping. In order to identify the anatomical correlates of ipsilesional neglect, lesion mapping of each participant's brain was created. To map out the participant's individual lesions MRIcro, a publically available image processing software (<http://www.sph.sc.edu/comd/rorden/micro.html>) (Rorden and Brett, 2000), was used. MRIcro provides an extensive toolbox to identify lesions, compute lesion volume, and categorize regions of mutual involvement (Rorden and Brett, 2000). To overcome the individual difference with the brain images, we mapped lesions onto a manually rotated template which was manipulated to closely match the participants' clinical scans. MRIcro-based free rotation toolbox allowed rotation in 3D space (i.e., with respect to pitch, yaw and roll axes) using cerebellum, eyes and head orientation as landmarks. The lesions drawn on rotated templates were then realigned with stereotaxic Montreal Neurological Institute (MNI) space to overlay them on the standard brain template available in MRIcro. This allowed for all the participants lesions to be mapped onto the 'same' brain and therefore, they could be compared to each other.

For this study, clinical radiology scans, which included computed tomography (CT or CAT) and/or magnetic resonance imaging (MRI) scans, were obtained from the participants' acute care hospitals. Ten clinical scans were on compact discs (CD) and two were film x-ray copies. Authorization for medical records and HIPAA regulations set forth by the Kessler Foundation Research Center and the participants' respective hospitals were thoroughly followed. Clinically available scans closest to pre-screening dates from the original neglect experiment were used for identifying the lesions. Each brain lesion was manually mapped out on a transverse plane.

Results

I identified 14 participants (10 male, 4 female) with ipsilesional neglect. It was later determined that one participant had bi-lateral stroke damage and one participant did not meet the BIT criteria for neglect. These two participants were removed from the data set, leaving 12 participants. Seven participants were in the 'old men' category, one participant in the 'young men' category, two participants in the 'old women' category and two participants in the 'young women' category. Table 2 shows the demographic and clinical data of all twelve right-brain damaged participants with ipsilesional neglect.

Table 2

Demographic and clinical data of twelve right-brain damaged participants with ipsilesional neglect

	Sex	Age	Edu.	MMSE	BIT	Barthel	CBS	Where	Aiming	FLBG
P2	M	74	11	22	114	65	17	-1.76	-1.60	Yes
P3	M	66	12	25	26	5	23	-1.42	-6.75	Yes
P4	M	53	16	29	67	10	5	-4.00	-1.65	Yes
P5	F	59	12	21	65	35	23	-1.68	-1.05	Yes
P6	F	41	18+	26	67	30	-	-15.40	-3.24	Yes
P7	M	67	9	21	58	15	20	-6.90	2.26	Yes
P8	M	68	8	13	104	10	21	-5.40	4.27	Yes
P9	M	76	12	23	59	0	27	-11.49	-9.38	Yes
P10	M	76	18	29	129	60	-	-1.01	-7.33	Yes
P11	F	76	8	17	101	20	-	-1.17	-3.16	Yes
Mean	-	65.60	11.78	22.60	79	25	19.43	-5.02	-2.76	-
SD	-	11.60	3.42	5.04	31.57	22.48	7.07	4.94	4.23	-
P1	F	30	14	30	128	90	2	-12.36	-0.85	No
P12	M	78	12	16	93	30	5	-5.59	-3.44	No
Mean	-	54	13	23	111	60	3.5	-8.98	-2.15	-
SD	-	33.94	1.41	9.90	24.7	42.43	2.12	4.79	1.83	-

Note. F= female, M=male; Edu.=Education in years; Where and Aiming error in mm, Z-score reported; FLBG= whether the participant had a frontal lobe or basal ganglia lesion.

Lesion Analysis. To identify the brain areas which are associated with ipsilesional neglect I analyzed the entire sample of twelve participants with right hemisphere brain damage. Each participant's brain scan was carefully mapped onto a

standardized template using MRICro which allowed for the comparison and overlapping of all twelve scans. I then created a lesion checklist (see Table 3) indicating which areas of the brain were damaged in each patient. A neurologist looked over each mapped lesion in comparison with the original brain scan in order to ensure that the lesion was drawn in the proper location. The neurologist confirmed the accuracy of the lesion checklist. The results from the lesion analysis indicated that ten out of the twelve participants (83%) suffered damage to the right frontal lobe and/or basal ganglia.

Table 3

Lesion locations of the 12 participants identified with Ipsilesional Neglect

Subject	Image	Frontal	Parietal	Temporal	Occipital	Insula	Basal Ganglia
S1	MRI	0	0	1	1	0	0
S2	MRI	1	1	1	0	0	1
S3	CT	1	1	1	1	1	1
S4	CT	1	0	0	0	0	1
S5	MRI on film	1	1	1	0	0	1
S6	MRI	1	1	0	0	1	1
S7	MRI	1	1	0	0	0	0
S8	MRI	1	1	1	0	1	1
S9	CT on film	1	1	0	0	1	0
S10	MRI	0	1	1	0	0	1
S11	CT	1	1	1	1	0	1
S12	MRI	0	1	0	1	0	0
Total		9	10	7	4	4	8
%		75%	83%	58%	33%	33%	67%

Note. Values of 1 indicate that the lesion was present; values of 0 indicate that the lesion was not present.

A χ^2 goodness of fit analysis was conducted in order to determine whether participants with ipsilesional neglect had a greater incidence of right frontal lobe or basal ganglia damage relative to the incidence that is typically observed for contralesional

neglect. In order to run this analysis I needed to derive expected values for how often right frontal or basal ganglia lesions occur in contralesional neglect. To come up with this value I gathered evidence from anatomical studies on contralesional neglect that indicated either the number or percentage of patients exhibiting lesions in these sites (Leibovitch et al, 1998; Karnath, Himmelbach & Rorden, 2002; Mort et al, 2003; Karnath, Renning, Johannsen & Rorden, 2011; Chen et al, under review). All five studies used in this analysis included patients who were in the acute stage of stroke recovery. The weighted average proportion of contralesional patients exhibiting frontal or basal ganglia lesions across all five studies was .273. This proportion was used to derive the expected values for the Chi-square that appear in Table 4. The results of the Chi-square analysis indicate that a greater proportion of participants with ipsilesional neglect had frontal or basal ganglia damage compared to expected proportions observed in contralesional samples ($\chi^2(1, N=12) = 18.95, p < .001$).

Table 4

Observed and Expected Values Derived from the Overall Weighted Average

	<u>Observed</u>	<u>Expected</u>
Frontal Lobe or Basal Ganglia Damage	10	3.28
Other Damage	2	8.72

Using the weighted average of all five studies may not be the best comparison because of differences in the exclusion criteria; the decision was made to run a second Chi-square goodness of fit analysis excluding the two studies conducted by Karnath and colleagues (Karnath, Himmelbach & Rorden, 2002; Karnath, Renning, Johannsen &

Rorden, 2011) because unlike our participant sample and those of the Leibovitch et al. (1988), Mort et al. (2003), and Chen et al. (under review) studies, the Karnath studies excluded individuals with visual field deficits. The weighted average proportion of contralesional patients with frontal or basal ganglia damage from these three studies was .347. The expected values derived from the weighted average of the three select studies are shown in Table 5. The results of the second Chi-square analysis supports the results of the first analysis; a greater proportion of participants with ipsilesional neglect had frontal or basal ganglia damage compared to expected proportions observed in contralesional samples ($\chi^2 (1, N=12) = 12.55, p < .001$).

Table 5

Observed and Expected Values Derived from the Select Weighted Average

	<u>Observed</u>	<u>Expected</u>
Frontal Lobe or Basal Ganglia Damage	10	4.16
Other Damage	2	7.84

Lesion overlapping was also done in order to visually display the brain regions that are most commonly affected in ipsilesional neglect. Figure 2 illustrates the overlapping of all twelve participants' lesions with colors denoting increasing numbers of participants having a lesion overlap in that region, from "purple" (n=1) to "bright green" (n=9).

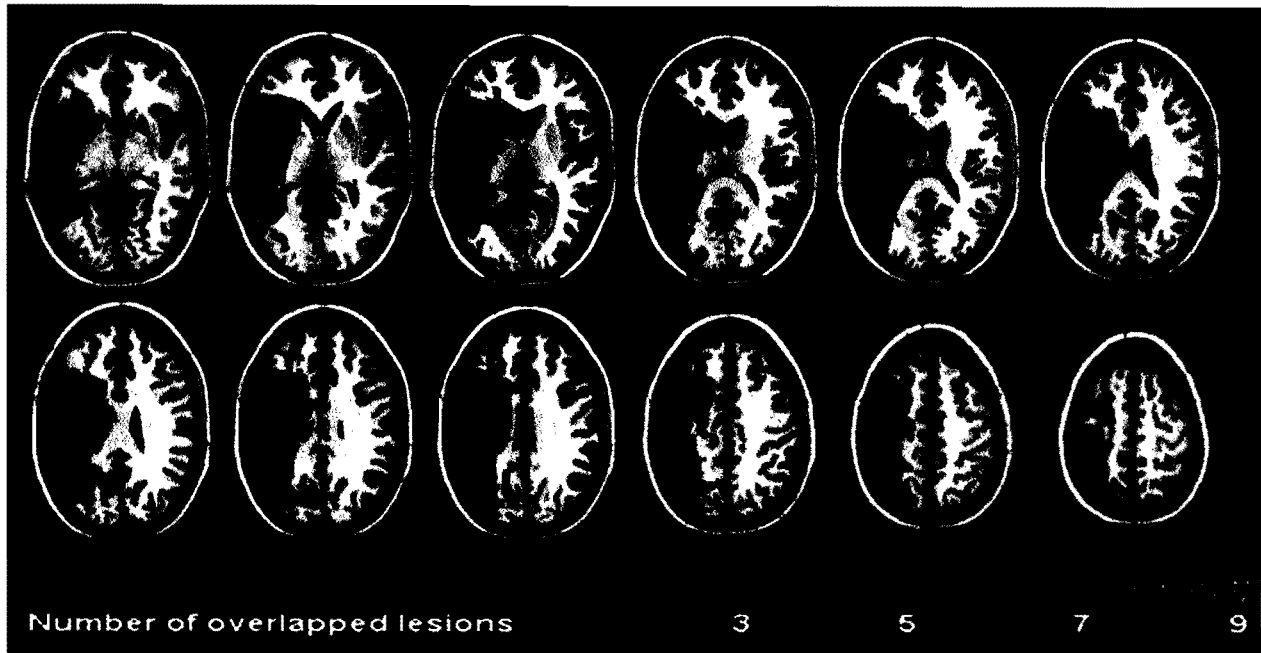


Figure 2. Lesion overlap of the 12 participants identified with ipsilesional neglect plotted onto a normal template brain using MRIcro software (Rorden & Brett, 2000). Lesions were drawn onto axial slices, and because this is a radiological image the left side of space represents the right hemisphere.

The lesion overlap shows the greatest areas of overlap in the right basal ganglia (specifically the caudate) and frontal lobe white matter. The caudate had an overlap for 6 out of the 12 participants, while the frontal lobe region had a maximum overlap for 9 out of the 12 participants. The results from the lesion overlap are also in support of my original hypothesis, implicating damage to the frontal lobe or basal ganglia as an important anatomical correlate of ipsilesional neglect.

“Where” and “Aiming” Bias. In order address if participants with ipsilesional neglect also had greater “aiming” errors than “where” errors, a Wilcoxon signed-rank test was used. I used this nonparametric statistical analysis because of the small sample and non-normal distribution of the “where” and “aiming” measures. Due to the general phenomenon of “where” errors usually being greater than “airning” bias, I transformed all the raw scores into Z-scores using the means and standard deviations

from the healthy participants' "Where" and "Aiming" bias from the Chen et al. 2011 paper (see Table 6).

Table 6

"Where" and "Aiming" Bias Means and Standard Deviations of Healthy Participants

	"Where" Bias		"Aiming" Bias	
	<u>Mean</u>	<u>SD</u>	<u>Mean</u>	<u>SD</u>
Old Males	2.71	2.49	-.19	1.45
Young Males	.40	2.85	-.51	1.77
Old Females	-4.07	5.90	.08	2.16
Young Females	-2.48	2.66	-.58	1.23

This allowed me to compare the scores relative to each other without being confounded by the general tendency of "where" bias to be greater. The results from the analysis show that there was a statistically significant difference between "where" (Mean= - 5.83, SD= 5.05) and "aiming" (Mean= - 2.04, SD= 3.75) errors ($Z = -1.96, p = .050$), such that individuals with ipsilesional neglect had greater magnitude of perceptual-attentional than motor-intentional bias. This result goes directly against my hypothesis that individuals with ipsilesional neglect would have greater motor-intentional bias because of the frontal lesions and frontal involvement in motor-intentional neglect.

Discussion

The major finding from the case study, Study 1, was that visuomotor pointing training may help to alleviate motor-intentional neglect to a greater extent than perceptual-attentional neglect, and that this benefit may only be observed on functional measures of neglect, as suggested by CBS scores, as opposed to paper and pencil tests of neglect. The idea that it may be possible to improve functional recovery of neglect patients using spatial cueing during a motor activation task has been previously reported (Kalra, Perez, Gupta & Wittink, 1997). It may be that because visuomotor tasks incorporate a motor component that this type of therapy may be more effective at improving “aiming” bias. The findings from Study 1 are also in accordance with other studies that have looked to answer whether other visuomotor tasks (prism adaptation) are better suited to rehabilitate motor-intentional or perceptual-attention neglect. It appears that performing a visuomotor task while wearing rightward shifting prism goggles can help to ameliorate motor-intentional “aiming” bias in both healthy (Fortis, Goedert & Barrett, 2011) and neglect participants (Striemer and Danckert, 2010; Fortis, Chen, Goedert, & Barrett, 2011). Thus, our findings support the claim that performing a visuomotor task improves neglect in patients and that this improvement may be related to changes in the aiming spatial systems.

It is important to note that this was a case study and that S1 was an abnormal case of spatial neglect who also presented with some ipsilesional neglect. If we take this variable into consideration, it is also possible that the improvement seen in the motor-intentional deficit was in part because of the ipsilesional neglect. It is also important to note that this participant did have some very obvious issues with following directions and memory, because of this it is possible that we would not be able to replicate these

results in a larger sample. Lastly, it is also possible that the restriction of the peripheral visual field caused by the goggles being blacked out on the sides could also be what is causing improvement in this participant. Taking into consideration the results from Study 1 and those of the previous studies mentioned using prism adaptation techniques, visuomotor pointing training may serve as a wonderful rehabilitative technique but a large scale study, with a normal neglect population would have to be conducted in order to determine if there is any usefulness in this technique.

The major finding of Study 2 is that individuals with ipsilesional neglect have more right frontal lobe or basal ganglia lesions than expected from studies of contralesional neglect participants. This result is in direct support of the original hypothesis that damage to the frontal lobe or basal ganglia is an important anatomical correlate of ipsilesional neglect and gives some strong insight into the anatomical basis of this disorder. The frontal lobes are part of a system that are thought to mediate attention in respect to exploration, scanning (Mesulam, 1981) and goal oriented action (Schwartz, Barrett, Kim & Heilman, 1999). It is then plausible that if ipsilesional neglect is caused by compensatory scanning as suggested by Robertson et al. in 1994, then the damage to the frontal lobe that is special in ipsilesional neglect may be the reason why the individual cannot pull their attention back towards the right. It may be that all individuals with contralesional neglect adopt this compensatory strategy but only those individuals with frontal lobe damage develop ipsilesional neglect because they are vulnerable to getting attentionally 'stuck'.

Another theory that may explain why the frontal lobe is so important in ipsilesional neglect is because the frontal lobes are thought to mediate avoidance

behavior in the attentional domain (Kwon & Heilman, 1991). Without the frontal lobe to inhibit attention from wandering because of stimulus overload, a lesion to the frontal lobe may lead to an increase in approach or stimulus-dependent behaviors. This idea suggests that an individual suffering from contralesional neglect may habituate to rightward stimuli, and once this occurs the inability of the frontal lobe to keep the attentional window directed to rightward space causes the individual to explore the left side: ipsilesional neglect. If this is true, an individual may actually be approaching the contralateral portion of a stimulus, rather than neglect the ipsilateral side. This is an interesting explanation of ipsilesional neglect, especially if one considers the fact that ipsilesional and contralesional neglect occur together, which may be a great way to explain why ipsilesional neglect is task dependent. It is possible that some tests require a greater attentional demand and have more stimuli that can act as attentional distractors which pull the individual's attention leftward. If ipsilesional neglect is not neglect at all, but instead the approach of contralesional space then researchers should definitely look into this idea more because it may be possible to exploit it for rehabilitative purposes.

As for the involvement of the right basal ganglia in ipsilesional neglect, research is still needed to postulate why this area is implicated. The basal ganglia is an important subcortical area that makes connections with cortical areas all over the brain including the frontal (Heilman, Valenstein & Watson, 1994) and temporal lobes (Karnath, Berger, Kuker & Rorden, 2004). Perhaps, the right basal ganglia is working with right frontal lobe to mediate attention. Another interesting aspect of the function of the basal ganglia, specifically the caudate, is that it is an important correlate of preservative behaviors in

patients with spatial neglect (Nys, van Zandvoort, van der Worp, Kappelle & de Hann, 2006). More specifically, it appears that perseveration in neglect is lateralized more towards the ipsilesional side of paper-and-pencil tests in patients. This may suggest that the link between the basal ganglia and ipsilesional neglect is stronger than previously thought. It is also important to note that the basal ganglia, like other brain regions, are made up of grey and white matter; it would be interesting to look into the importance of the white matter fibers in the basal ganglia in order to determine what kind of connections are being made. Just in the current sample of twelve participants, four had lesions that were localized to only the white matter. This result may suggest that ipsilesional neglect is a disorder of the white matter and not grey matter. If this is true, we might then be able to explain ipsilesional neglect by describing the specific white matter tracts that give rise to this disorder.

The second major finding of Study 2 goes directly against my hypothesis; individuals with ipsilesional neglect had greater perceptual-attentional bias than motor-intentional bias. It is difficult to explain these results if we use evidence from Na et al. (1999), which suggests that motor-intentional neglect results from damage to the frontal lobe. But if we look at the frontal lobe as a region that mediates both attentional and intentional systems, it is possible that an individual's performance may be reflecting ipsilesional neglect on an intentional bias and contralesional neglect in a perceptual bias (Kim et al, 1999). Under this view it is possible that the participants in the study reflected contralesional neglect on a greater level than ipsilesional neglect which resulted in the higher perceptual bias. It is also extremely important to point out that even though there was a greater incidence of frontal lobe damage in our ipsilesional population in

comparison to what we would expect from contralesional samples, 83% of our participants also had damage to the parietal lobe. It may be because of this large amount of parietal lobe damage that we are seeing a greater perceptual-attentional bias in this sample.

One limitation of this study is that historically, researchers have not been consistent in the way they have identified ipsilesional neglect, which means different studies of ipsilesional neglect may have samples of participants with very different characteristics. I chose to use leftward deviations on a line bisection test that was two standard deviations from the normal populations mean, but this method has not been used before. Many other studies on ipsilesional neglect used 95% confidence intervals for line bisection errors of control subjects¹ (Kim et al, 1999) or displaying with ipsilesional (right sided) neglect on one out of three different types of neglect assessments (Robertson et al, 1994). Since no one has yet implemented a standardized way of selecting for ipsilesional neglect it is possible that if I altered my inclusion criteria I would have gotten a very different participant sample with very different results.

Another limitation is with the lesion technique that was used; the MRIcro program relies greatly on the interpretation of the individual who is rotating the brain image to match the standard template and who is drawing the lesions by hand. Because of the direct influence of human perception it is expected that not all images will be created perfectly. Unfortunately when you are interpreting brain images, exact accuracy does

¹ A confidence interval is based on a distribution of means and because of that it would be statistically inappropriate to use a 95% confidence interval to identify whether a single score is outside the range of normal.

matter. In these regards, it is then possible that some lesion locations were not identified properly. However, the confirmation of lesion mapping accuracy by the neurologist lessens the potential impact of this limitation.

Conclusion

The results from this two part study suggest that individuals with ipsilesional neglect may have a greater proportion of damage to the frontal lobe or basal ganglia and may also have greater perceptual-attentional bias. Additionally, it appears that four consecutive days of visuomotor pointing training may help to alleviate the symptoms of neglect which affect the individual's activities of daily living. It also appears that visuomotor pointing training may better rehabilitate motor-intentional neglect symptoms over perceptual-attentional neglect symptoms. The implications of these results for therapists and doctors suggest that each individual with spatial neglect may require a specific type of rehabilitative treatment which is tailored to the individual's specific deficits. It is also important to note that testing for rehabilitative success using paper and pencil tests may not expose the true benefits of certain rehabilitations. Although it is important to have standardized tests to measure neglect, the real life implications of visuomotor pointing training may be more useful for an individual suffering from neglect.

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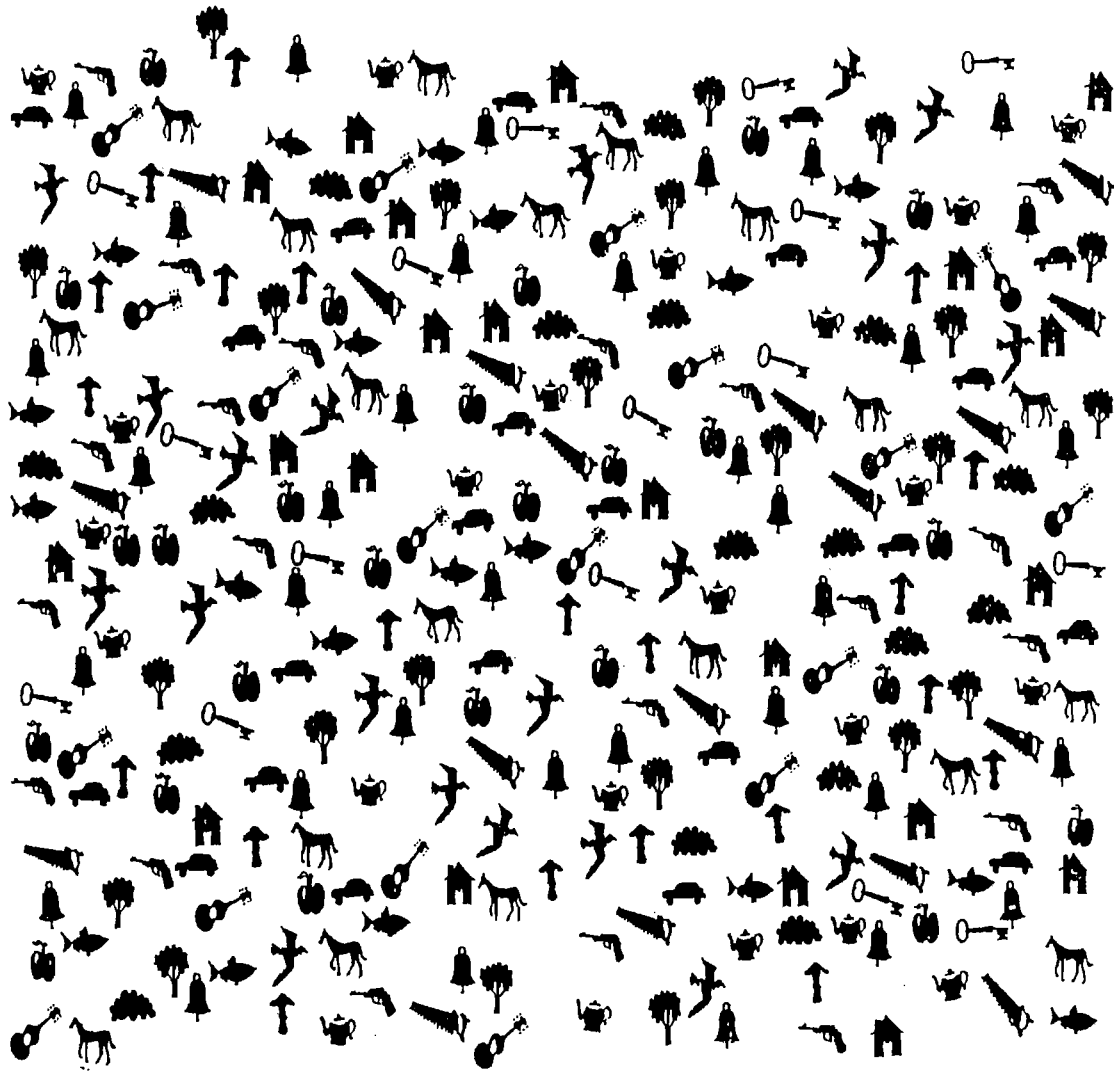
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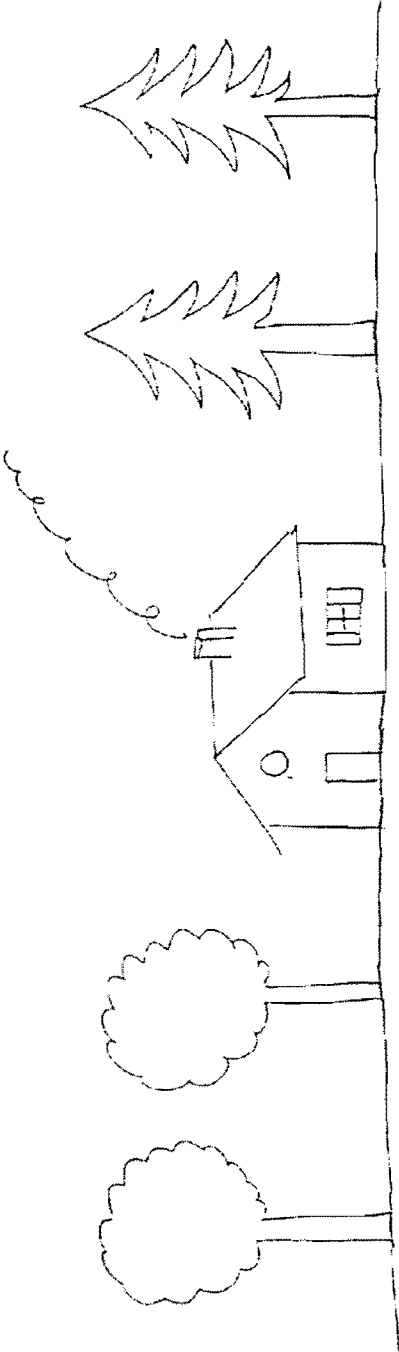
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Appendix

Bell Cancellation Task



Drawing Task



Catherine Bergego Scale (CBS)

Score

- 1. Experiences difficulty in adjusting his/her left sleeve/slipper/pant leg _____
- 2. Forgets to groom or shave the left part of his face _____
- 3. Experiences difficulty in spontaneously looking towards the left _____
- 4. Forgets about left part of his/her body (eg: forgets to put his/her left upper limb on the armrest, on his/her left foot on the wheelchair rest, or forgets to use his/her left arm when he/she needs to) _____
- 5. Has difficulty in paying attention to noise or people addressing him/her from the left _____
- 6. Collides with people or objects on the left side, such as doors or furniture (either while walking or driving a wheelchair) _____
- 7. Experiences difficulty in finding his/her way towards the left when traveling in familiar places or in the rehabilitation unit _____
- 8. Experiences difficulty finding his/her personal belongings in the room or bathroom when they are on the left side _____
- 9. Forgets to eat food on the left side of his plate _____
- 10. Forgets to clean the left side of his/her mouth after eating _____

Total Score _____ / 30