Statistical learning in brain damaged patients: A multimodal impairment

by

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AUTHOR'S DECLARATION

I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

I understand that my thesis may be made electronically available to the public.

Abstract

Spatial neglect has mainly been described through its spatial deficits (such as attentional bias, disengagement deficit or exploratory motor behavior), but numerous other studies have reported non-spatial impairments in patients suffering from this disorder. In the present thesis, non-spatial deficits in neglect are hypothesized to form a core impairment, which can be summarized as a difficulty to learn and benefit from regularities in the environment.

The different studies conducted and reported in the present thesis have converged to support this hypothesis that neglect patients have difficulty to interact with environmental statistics. The two first studies, which tested the visual modality (Chapters 2 and 3), have demonstrated that neglect patients have difficulties to become faster to respond to targets that appear successively at the same location (position priming). This difficulty is also more generic, as neglect patients do not learn that some things occur more often than others, such as for example that a target has a high probability to be repeated at a specific region. Those two studies have shown that neglect patients are impaired in position priming and statistical learning, which corresponds to difficulties benefiting from regularities presented in the visual domain.

This difficulty may be explained by patients' impairment in working memory or temporal processing. Several studies have reported the implication of those two mechanism in statistical learning: if patients tend to underestimate the time that a target is presented on the screen and have difficulties keeping in memory its precedent location, this translates into a difficulty to benefit from the repeats of the target position as well as a difficulty to benefit from transition probability.

In order to verify if priming and statistical learning impairments were specific to the visual modality or if neglect patients present a multimodal difficulty to learn the transition probability in general, brain damaged patients were tested in the auditory domain (Chapter 5), with a paradigm that has shown statistical learning in infants. This study confirmed that for the auditory modality too, brain damaged patients are impaired in statistical learning. The different results of the studies reported in Chapters 2, 3, 4 and 5 converge to support the hypothesis that spatial neglect patients have difficulties benefiting from regularities of their environment.

Nevertheless, this impairment is not irreversible, as it was demonstrated by a chronic neglect patient who was trained with three sessions distributed over three days (Chapter 2). Although having similar results to the other patients for the first session, this patients' performance improved over the sessions to show a faster reaction time for the targets presented on the high probability region (his

contralesional side). Therefore, priming and statistical learning investigated in this thesis are worth exploring further for their potential outcome in the rehabilitation domain.

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As I am about to complete the final lines of this thesis, I finally have the opportunity to stop and think about what an incredible journey it has been.

It has all started with a Neuroanatomy class, where I was too intimidated to be in a class that was above my poor English level at that time. I was only supposed to be there for an exchange term of 4 months, while I was finishing my Masters at the University of Lausanne. Finally, it became an achievement that I am proud of and that I was able to share with incredible people.

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Dedication

Mesiguri se nuk do të ishte e mundur të mbaroja këtë punim pa mbështetjën e familjen sime. Dashurija e tyre, durimi dhe inkurajimet ishin arsyja që unë arrita këtu ku jam sot.

Ndjehem jashtzakonisht me fat që kam shembullin e përsosur të dashurisë, kurajos, njerzimit dhe sidomos punës, prej prindërve. Ata kan një aftësi të përparojnë në jetë me një butësi por po ashtu me një qëndrueshmëri që është dhurata më e qëmueshme që na dhanë motrave të mia dhe mua.

This thesis would have not been possible without the support of my family. Their love, patience and encouragement are the reasons that I am here today.

I feel immensely lucky to have the perfect example of love, courage, humanity and hard work from my parents. They have this incredible ability to go through life with a balance between gentleness and strength, which is the most beautiful gift they gave to my sisters and me.

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Chapter 1: General Introduction[1]

The spatial impairments of neglect are striking and have dominated most research until the past few years (Corbetta et al., 2005; Danckert and Ferber, 2006; Karnath and Rorden, 2012; Pisella and Mattingley, 2004). As a result, a large number of rehabilitation programs, such as prism adaptation and vestibular stimulation, have focused on correcting those deficits (Luauté et al., 2006; Kerkhoff and Schenk, 2012; Redding and Wallace, 2006; Bowen et al., 2007). Unfortunately, success has been limited. This suggests that non-spatial impairments in neglect may contribute to its rehabilitory recalcitrance and should be investigated more. Based on the results of recent studies, we have hypothesized that numerous non-spatial deficits in neglect make it difficult for those patients to use regularities from the environment to guide their behaviour (Shaqiri et al., 2013; Danckert et al., 2012b).

The ability to successfully interact with the environment depends on a number of interdependent sub-processes, where one of the most important is statistical learning: the ability to learn that some elements occur more often than others. Statistical learning in turn requires other, more elemental processes, such as priming. In addition, priming and statistical learning rely on intact temporal processing and working memory; to detect regularities in our environment, as for example whether something is frequently repeating its position, we must remember what has happened and be accurate in judging if it has occurred recently.

Working memory or temporal processing deficits, as well as difficulties in position priming and statistical learning, can all lead to an impairment in noticing and using regularities from the environment. Those processes have also been demonstrated to be impaired in spatial neglect, which points the way to new tactics and targets that can be the focus of rehabilitation for this disorder.

In the present thesis, neglect is accepted as a phenomenally heterogeneous disorder, and spatial impairments are assumed to form its definitional core. Spatial components of neglect will be described briefly in this introduction (e.g., Danckert and Ferber, 2006; Karnath and Rorden, 2012), but this thesis will principally focus on non-spatial deficits in neglect. More specifically, Chapters 2 and 3 will examine the effects of right hemisphere lesions on priming. Then, in Chapter 3 and in

[1] A version of this chapter was originally published in *Frontiers of Human Neuroscience* (Shaqiri, Anderson and Danckert, 2013)

subsequent sections of this introduction, it will be described how an impairment in temporal processing affects the ability to accumulate information from priming and statistical learning. Then, statistical learning will be described in detail in Chapters 2 and 3, as it has been investigated in parallel with priming. Also, spatial working memory is impaired in neglect patients and can explain their difficulty in learning statistical regularities. A few studies that support this hypothesis will be described in subsequent sections of this introduction. Finally, Chapters 4 and 5 will examine auditory statistical learning: Chapter 4 will investigate its robustness in healthy participants. Once auditory statistical learning is explored in control participants, Chapter 5 will then report a similar paradigm used to test brain damaged patients. This paradigm was chosen to investigate if statistical learning is preserved in brain damaged patients when aspects such as spatial working memory or timing are not involved. Other non-spatial impairments in neglect, such as a prolonged attentional blink and decreased sustained attention, will also be described in this introduction. Lastly, evidence that those different impairments of priming, temporal processing, statistical learning and spatial working memory should be taken into consideration to create new approaches for rehabilitation, will be reviewed.

1.1 Spatial aspects of neglect

During the acute stage, spatial neglect is easily observable and diagnosable, as patients tend to shift their gaze and direct their actions toward ipsilesional space (Karnath and Roden, 2012). This observable behavior defines the core and most studied aspect of neglect: the shift of attention and exploratory behaviors towards ipsilesional space, which in turn leads to a loss of awareness for contralesional events (Husain and Rorden, 2003; Fellrath et al., 2012). A dramatic demonstration of this bias comes from paper-and-pencil tests of line bisection and cancellation. Neglect patients systematically cancel targets on their ipsilesional side, failing to cancel contralesional targets, and judge the middle of a line to be shifted ipsilesionally (Ferber and Karnath, 2001; Halligan et al., 1989; Vallar, 2001; Anderson, 1996). This impairment is also demonstrable in visual search paradigms, where patients' exploratory eye and hand movements are deviated towards ipsilesional space, leading to a failure to fully search contralesional space (Behrmann et al., 1997).

A study with chimeric faces (face shown with one half smiling and the other half showing a neutral emotion) has also demonstrated this deviation towards ipsilesional side. In that study, healthy controls reported the left-smiling face as being happier (Heller and Levy, 1981), contrary to neglect subjects, who systematically reported the face with the smile on the right side as being happier, presumably due to the patients' preferential exploration of the right side of the stimulus (Mattingley et al., 1993). This bias has also been confirmed when patients do not have any point of spatial reference. Hornak (1992) recorded neglect patients' eye movements and asked them to find a non-existent light while they were seated in a dark room. The author found that patients' fixations were directed mostly towards the right, in contrast to the control group, which showed balanced search behavior throughout left and right space. Even in the absence of any task, when at rest and asked to remain still, neglect patients demonstrate gaze deviations (Fruhmann-Berger et al., 2008).

As Parton and colleagues (2004) report in their review, this ipsilesional bias can be explained by several aspects: it could be due to difficulty disengaging attention from the ipsilesional side (Posner et al., 1984; Losier and Klein, 2001), or due to a greater salience of right sided stimuli compared to left sided items (Duncan et al., 1997) or simply to a graded attentional bias from left to right (Kinsbourne, 1993). The notion of a greater attentional weight for right-sided objects or of an attentional gradient from right to left is captured by the concept of a priority map (Fecteau and Munoz, 2006; Ptak and Fellrath, 2013). The priority map theory explains attentional biases as the combination of top-down evaluations of relevance and the bottom-up salience of object features. For neglect patients, elements presented on their contralesional side are underweighted, as the salience and relevance of items does not influence the allocation of attention to the same extent as it does in controls. For example, Bays and colleagues (2010) asked neglect subjects to look at task relevant or task-irrelevant, but salient, items while they monitored patients' eye movements. The authors found a gradient of patients' gaze shift with a preference toward the ipsilesional side for both task relevant items as well as salient but irrelevant items, demonstrating that salience and relevance were both affected by the bias inherent in spatial neglect (Bays et al., 2010).

Most rehabilitation approaches for neglect have targeted these lateralized spatial symptoms. This approach made sense, as the spatial aspects of neglect have been the focus of most research, are easily observed, and afford direct measures of success. Unfortunately, rehabilitation strategies developed from this perspective have had only limited success.

1.2 Spatially directed rehabilitation strategies for neglect

Rehabilitation strategies for neglect have a long history. Luauté and colleagues (2006) listed more than 18 different approaches that have been tried in order to facilitate patients' cognitive rehabilitation and improve their quality of life. These rehabilitation strategies can be divided into two different approaches (Bowen and Lincoln, 2006): those that have a bottom-up emphasis and do not require patients to be aware of their deficits, and those that focus on top-down aspects with the intent to train patients to consciously and voluntarily overcome their spatial impairment. The bottom-up approach will be described in the next section, because it is the one that is the most explored by rehabilitation techniques.

One of the first methods tried for the rehabilitation of neglect, published in 1941 by Silberfenning, was caloric vestibular stimulation. This technique consists of infusing warm or cold water into the external ear canal to stimulate the vestibular system via convection (Rubens, 1985; Luauté et al., 2006; Karnath, 1994; Vallar et al., 2003). It has been reported to improve neglect by enhancing visual exploration, improving straight-ahead bias and reducing somatosensory impairments (Rode et al., 1998). Other methods that implicitly target spatial biases include optokinetic stimulation (Thimm et al., 2009; Schroder et al., 2008), neck-muscle vibration (Schindler et al., 2002), and limb activation (Robertson and North, 1992).

Another method used in rehabilitation of spatial neglect and that has been extensively investigated is prism adaptation (Rossetti et al., 1998; Saevarsson et al., 2009; Luauté et al., 2012; for a review see Redding and Wallace, 2006; Danckert and Ferber, 2006). Helmholtz (1867) first investigated this method, which consists of wearing left or right-shifting wedge prisms. Prisms shift visual perception in one direction or another (for neglect patients, right-shifting prisms are used to shift visual perception further towards ipsilesional space; Rossetti et al., 1998). Patients then point to targets to the left and right of their body midline. Initial pointing movements demonstrate errors in the same direction as the prismatic shift. Patients then adjust their pointing movements leftward to account for those errors. When the prisms are removed patients now demonstrate an after-effect such that pointing movements are shifted leftward into previously neglected space (Rossetti et al., 1998). Prism adaptation has several advantages over other techniques as it is easy to apply, non-invasive, and influences a broad range of symptoms sometimes for hours or days post adaptation (depending on the method used; Farné et al., 2002).

Various studies have demonstrated a range of benefits arising from prism adaptation, such as a reduction of the bias patients display when they attempt to point straight-ahead (Pisella et al., 2002) and an improvement in visual exploration of contralesional space (Saevarsson et al., 2009; Ferber et al., 2003). But it has also been reported (Danckert and Ferber, 2006; Luauté et al., 2012) that although prisms improve observable exploratory biases toward ipsilesional space, they do not necessarily improve patients' perceptual biases (Ferber et al., 2003; Dijkerman et al., 2003; Striemer and Danckert, 2010; Sarri et al., 2008).

Unfortunately, all the methods tried – those reported above and others, such as transcranial magnetic stimulation (TMS), transcranial direct-current stimulation (tDCS) or virtual reality – produce benefits that are short lived and use techniques that are difficult to implement in everyday life (Katz et al,. 2005; Oliveri et al., 2000; Song et al., 2009; for a review, see Utz et al., 2010). Further, their benefits appear to be limited to the spatial impairments of neglect (Luauté et al., 2006; Rossetti and Rode, 2002; Kerkhoff and Schenk, 2012). Results of the past few years have demonstrated that neglect is more than a spatial disorder, therefore therapeutic success has been limited. Further, the non-spatial impairments contribute significantly to performance deficits. Rehabilitation approaches (some of which were first tried a half century ago) predicated on neglect as a disorder of predominantly *spatial* attention, could potentially be improved by incorporating new ideas from recent research that more comprehensively demonstrate the full extent of the psychological impairments associated with neglect.

1.3 Non-lateralized deficits in spatial neglect

Numerous recent studies have demonstrated deficits in neglect that are not lateralized spatially, but that contribute to the complexity of this disorder (Becchio and Bertone, 2006; Malhotra et al., 2006; Husain et al., 1997; Ptak et al., 2007). Husain and Rorden (2003) suggest that a combination of non-lateralized and lateralized deficits might explain the difficulty in finding effective rehabilitation strategies.

The interest in non-lateralized deficits in neglect has grown in recent years with studies demonstrating a number of fundamental non-spatial impairments, such as decreased arousal, problems with sustained attention, spatial working memory impairments and non-spatial attentional bias (for a review, see Corbetta and Shulman, 2011; Danckert et al., 2012b; Husain and Rorden, 2003).

Many neglect patients show decreased arousal and vigilance; this translates into a lower level of sustained attention (Farné et al., 2004; Corbetta and Shulman, 2011; Robertson et al., 1997). Several studies have implicated the right hemisphere in deficits of arousal or alertness (Fimm et al., 2006; Corbetta et al., 2005; Robertson et al., 1995; 1997, Grahn and Manly, 2012; Sturm and Willmes, 2001; Rueckert and Grafman, 1996). A correlation between neglect and a decreased level of sustained attention was first shown by Heilman and colleagues (1979) and has been confirmed by multiple studies (Barrett et al., 2007; Hjaltason et al., 1996; Samuelsson et al., 1998, Robertson et al., 1997). In a study in which right brain damaged patients were asked to count a series of tones, Robertson and colleagues (1997) found a correlation between sustained attention and a bias in spatial attention, confirming a connection between spatial and non-spatial aspects of neglect.

Another non-lateralized deficit that could contribute to spatial biases in neglect is a deficit of spatial working memory. Husain and colleagues (2001) recorded a neglect patient's eye movements while the patient judged whether a stimulus had been seen before. The authors found that a patient suffering from left neglect revisited old targets and identified them as new, even when they were presented on the right, ipsilesional side. Neglect patients were also impaired when tested in vertical spatial working memory tasks, even though there was no left-right spatial component (Malhotra et al., 2006; Ferber and Danckert, 2006). The working memory deficit predicted the general degree of impairment in patients with neglect: the less patients can retain of their previous actions, the less liable they are to undertake new actions (Husain et al., 2001).

An additional non-spatial impairment in neglect is a prolonged attentional blink (Johnston et al., 2012). The attentional blink refers to the observation that when a person must detect multiple targets, the correct detection of one target impairs the ability to detect a subsequent target that follows it shortly thereafter in time. A recovery interval of between 200 to 500 ms is necessary for the detection of a second target to return to baseline (Dux and Marois, 2009). For many neglect patients, this interval is two to three times longer: after they have detected the first target, neglect patients are not aware of the second target unless there is an interval of about 1200 ms (Johnston et al., 2012; Raymond et al., 1992; Husain et al., 1997; Shapiro et al., 1997; 2002).

The non-lateralized deficits just highlighted demonstrate that neglect is more than a spatial disorder. We suggest that many of these different symptoms are related and reflect a mutual dependence. Data demonstrating that neglect patients also have impairments in priming, temporal processing, statistical learning and working memory are reviewed in the next sections and suggest that those different deficits sum to prevent patients from interacting adequately with their environment.

1.4 Neglect as a disorder of noticing and using regularities from the environment

1.4.1 Position priming

Studies in visual search are greatly influenced by the research in priming and how the effect of the repetition of the target position or features influence participants' reaction time (for a review, see Kristjansson and Campana, 2010; Kristjansson, 2008). Maljkovic and Nakayama (1994; 1996) were the first to report that when the features or the position of a target are repeated, participants are faster to detect it. Other studies have since confirmed those results for the priming of context, object features, movement, and presentation interval (Chun and Jiang, 1998; Los and Van Den Heuvel, 2001; Goolsby and Suzuki, 2001). The priming effect has also been tested in neglect patients (Saevarsson et al., 2008; Kristjansson et al., 2005; Shaqiri and Anderson, 2012). Saevarsson and colleagues (2008) repeated or switched the overall context in which a target was presented. They found a preserved priming effect in neglect. In their second experiment, they tested the priming effect in contralesional and ipsilesional space by repeating the context in both visual fields. Patients were faster to detect targets when the context was repeated, even when the presentation was in contralesional space.

In the present thesis, Chapter 2 will examine the effects of color and position priming in neglect, with patients discriminating the color of a dot that could be either black or white (Shaqiri and Anderson, 2012). In the study reported in this chapter, neglect patients demonstrated preserved color priming, but their results for location priming were less consistent, which is in accordance with Kristjansson and colleagues (2005), who found preserved color and position priming when participants had an unlimited time to respond to the target, although one of the two patients needed at least three repeats of the same position to show a priming effect. Moreover, when the duration of the display was limited to 200 ms, patients did not show a position priming effect, unless they indicated that they had consciously detected the target, whereas color priming remained intact regardless of stimulus duration. Kristjansson and colleagues (2005) concluded that awareness was necessary for patients to show position priming on their left side.

These studies included a spatial aspect in their design, as they presented stimuli on the contralesional and ipsilesional side. This complicates the interpretation of the impairment. Chapter 3 will describe how, in order to avoid a spatial bias, Maljkovic and Nakayama's study (1996) was adapted by presenting the target and distractors vertically aligned in central space. We assessed whether patients had preserved position priming, that is, if they were faster when the target repeated the same position successively (Shaqiri and Anderson, 2013b). In that study, a deficit in position priming was revealed in a task that eliminated lateral spatial biases. A generic priming deficit was not present though, as most studies, including our own, have demonstrated preserved color priming.

The brain regions associated with neglect may explain the differential results for color and position priming. In an fMRI study investigating the neural correlates of priming, Kristjansson and colleagues (2007) found different brain regions activated by color and position priming conditions. Whereas both of these priming effects were associated with regions traditionally linked with the control of attention, the so called "attention network" that includes the intraparietal sulci (Corbetta and Shulman, 2002; 2011), the color repetition condition also showed suppression of activity in the inferior temporal region. Position priming was more related with regions such as the right inferior parietal cortex and frontal areas. Kristjansson and colleagues (2007) also found a greater involvement of the right hemisphere for position priming than for color priming. Although there is no single brain region where damage is both necessary and sufficient for causing spatial neglect, the right inferior parietal and the frontal lobes are frequently involved in the strokes that produce neglect (Corbetta and Shulman, 2002; Ricci et al., 2012). The correspondence between the regions involved in position priming and those involved with spatial neglect may explain why patients do not show as robust position priming effects as do controls and why different studies might find varying results.

1.4.2 Temporal deficits in neglect

The results discussed above reveal that neglect patients have difficulties benefiting from successive repeats of the same position by the target, and therefore demonstrate attenuated position priming. This difficulty might be explained by the temporal processing impairments demonstrated by neglect patients, who underestimate all durations, showing an impairment for estimating the passage of time (Merrifield et al., 2010; Danckert et al., 2007; Berberovic et al., 2004). For example, in a study in which they had to estimate the duration of the trials, Danckert and colleagues (2007) found that neglect patients estimated all trials to be under 10 seconds and this was even true for trials that could last 60 seconds.

The temporal processing impairment is intrinsically linked with priming, as the importance of timing in priming has been demonstrated by Maljkovic and Nakayama (2000), who tested the ability of participants to benefit from position priming with different inter-trial intervals. Whereas a break of

30 seconds between two trials did not affect priming magnitude, a break of 90 seconds did, as it reset any possible benefit from target position repetition to its initial pace and demonstrated that priming was cumulative. The difficulty neglect patients have in benefiting from more than one repeat of position in a priming task might be accounted for by temporal and memory impairments. To restate, because neglect patients have slower response times for any task in general (Kaizer, 1988; Shaqiri and Anderson, 2012), it means that they have to keep in mind the association between the trials for a longer period of time and therefore, they experience fewer trials from which they can accumulate information, compared to healthy controls. A problem in keeping the relation between the trials in their implicit memory might prevent patients from extrapolating to a more general regularity about their environment.

The importance of timing in the priming effect and the demonstration of an impairment in temporal processing in neglect affects other processes as well, such as statistical learning. Indeed, as will be demonstrated in the subsequent sections, priming and statistical learning are closely related, to the point that some authors (Walthew and Gilchrist, 2006) have questioned whether statistical learning is not simply a form of priming, or if the latter is a necessary step for statistical learning to occur (Jones and Kaschak, 2012). In the subsequent sections and chapters, different studies that have investigated the relation between priming and statistical learning and how they are involved in the interaction with the environment, are reported.

1.4.3 Statistical learning

Statistical learning is a form of implicit learning that occurs through mere exposure and observation and does not involve explicit feedback (Turk-Browne et al., 2008; Aslin and Newport, 2012). It has been demonstrated for both auditory and visual modalities. Bulf and colleagues (2011) found that newborn infants were able to extract the transitional probabilities of simple visual structures, as they demonstrated preferential looking towards novel sequences, compared to sequences with high transition probabilities that they had seen before. The authors concluded that newborns have the ability to detect regularities from the environment and learn which elements are being repeated more often. A similar result was found by Fiser and Aslin (2002), who tested 9-month-old babies in a more complicated paradigm of visual statistical learning. They presented four base pairs of shapes combined with four noise elements, so that each baby was presented with consecutive base pairs and a noise element during the task. The data revealed that babies showed a greater preference for base pairs over non-base pairs, and the authors suggested that the infants learned the co-occurrence of the shapes.

Although the phenomenon of statistical learning is well established, its relation to priming is complex. When a statistical distribution leads to frequent repeats there are also more primed trials. Walthew and Gilchrist (2006) suggested that claims of statistical learning of spatial probability distributions in neglect might be explained on this basis; rather than learning underlying distributions, faster responses in areas of high probability could merely reflect the influence of a greater number of primed trials in those regions. In order to address this issue, a study was conducted in our lab (Druker and Anderson, 2010). In this paradigm, the target was biased to appear 80% of the time in a high probability region. The results showed that participants were faster to respond to targets presented in the high probability region than the other regions of the screen. Given that exact locations were rarely if ever repeated, it is difficult to explain this result as simply a consequence of position priming. Furthermore, participants were not aware of the biased location for the target, demonstrating that the statistical learning of the high probability target zone was achieved implicitly.

Statistical learning has also been assessed in neglect patients. Geng and Behrmann (2002, 2006), found that neglect patients were faster at detecting targets that appeared in the high probability region compared to the other regions of the screen, even if this was in contralesional space. Those results give promise for the use of statistical learning as a rehabilitation strategy for neglect patients. This technique does not need supervision or feedback. Patients' observations lead to an implicit learning of the distribution of elements in their environment. This could facilitate the direction of attention and help to overcome the ipsilesional attentional bias.

The two studies reported in Chapters 2 and 3 were conducted from this perspective, in which we tested statistical learning in neglect patients (Shaqiri and Anderson, 2012, 2013a, b). In the first study reported in Chapter 2, the paradigm of Druker and Anderson (2010) was adapted in order to test whether neglect patients could learn a spatial statistical distribution and use it as an attentional cue (Shaqiri and Anderson, 2012). We biased the target to appear 75% of the time in a high probability region on the left side of space. Overall, we found that neglect patients were slower to respond to targets in the high probability region in left space, when compared with a low probability region in the mirror symmetric location in right space. But neglect patients demonstrated a certain sensitivity to statistical distribution, as they were faster to respond to targets on the high probability region, compared to the other targets on the left (although their RTs were slower compared to the RTs for the right sided targets).

Chapter 3 reports a second study, conducted in order to investigate whether the spatial elements of the task were central to the results. In that paradigm, the targets were presented vertically in the middle of the screen (Shaqiri and Anderson, 2013). To examine statistical learning, the transitional probability of stimulus positions was biased to include a high repeat condition (an 80% probability of repeating target location), or a low repeat condition in which targets changed location on 80% of trials. As with our previous task, results for this study showed that neglect patients did not learn the statistical distribution of the targets independently from the spatial position of stimuli. This occurred despite the fact that *primed* trials were faster. In other words, the magnitude of the position priming effect was the same whether repeated trials were very likely or very unlikely and this was not simply a consequence of left-right biases of attention.

All these different paradigms tested the visual modality, but if such an impairment is generic, it ought to be present for other sensory modalities, given that numerous studies have reported multimodal impairments in neglect, including auditory and tactile deficits (for a review, see Jacobs et al., 2012; Pavani et al., 2003). For example, Cusack and colleagues (2000) found that neglect patients show auditory impairments for temporal aspects of stimuli, mapping a visual bias to the auditory modality (Bisiach et al., 1984; Tanaka et al., 1999), and they demonstrate a greater uncertainty for the location of sounds compared to healthy controls (Pavani et al., 2002).

Those studies, which demonstrated multimodal impairments in neglect, motivated our assessment of neglect patients' ability to learn the transition probability of nonsense words in an auditory statistical learning paradigm that is reported in Chapter 5 (Shaqiri et al., 2013). This procedure relied on decades of results on auditory statistical learning exemplified by Aslin and colleagues (1998). They exposed 8-month-old infants to tri-syllabic nonsense words (for example bidaku, padoti, golabu) where the transitional probability of syllables within words was 100%, (e.g., "go" was always followed by "la", "la" by ""bu" to create "golabu" etc.). In contrast, the transitional probability for syllables between words was 33% (e.g., "bu" of "golabu" was followed by "pa", "bi" or "go" equally often). The words had no breaks between them and were presented by computer to avoid clues to the word borders other than the statistics of syllable transitions. The continuous stream of speech presented to the children lasted 2 minutes. Aslin and colleagues (1998) found that 8-month-old infants were able to identify the words, extracting information about the word boundaries solely on the basis of the transitional probability of those words. This effect has been confirmed for adults. Gebhart and colleagues (2009) used a similar paradigm for university undergraduates and found that they were able to correctly identify the words with 80% accuracy in a forced choice test. When presented with two languages, they learned both as long as they had a break between the exposures to each. We too, found similar results when we replicated the study of Gebhart and colleagues (2009) with undergraduate students, and this will be presented on Chapter 4. This study demonstrates the robustness of auditory statistical learning in healthy participants.

Chapter 5 will describe how the paradigm of Gebhart and colleagues (2009) was adapted in order to test neglect patients for their ability to learn the transitional probability of the tri-syllabic nonsense words (Shaqiri et al., 2013). After listening to the language streams, participants were tested in a forced-choice format in which the words they heard were paired with part words made-up of syllables that spanned word borders. Neglect patients did not show any learning effect. Indeed, patients did not perform the task above chance, contrary to our healthy controls who learned the transition probability between syllables and identified the correct words about 80% of the time (Chapter 4). These results demonstrate that the difficulty neglect patients have in learning statistical distributions is multimodal and is neither limited to visual nor spatially presented material. Our study did not involve spatial aspects, but tested the general ability of those patients to be sensitive to the transitional probability between the syllables within the word, an ability shown to be present in 8-month-old infants (Aslin et al., 1998).

1.4.4 Working memory and statistical learning

The different studies we conducted on statistical learning (Shaqiri and Anderson, 2012; 2013; Shaqiri et al., 2013) confirmed that neglect patients have difficulties benefiting from statistical regularities. We hypothesized that this might be, in part, because of the temporal processing impairment demonstrated by those patients (see above), and in part from working memory impairments. Spatial working memory has been shown to be deficient in neglect patients (Johnston et al., 2012; Husain et al., 1997; Ferber and Danckert, 2006) and this deficit might be related to patients' impairement on statistical learning.

A study conducted by Valadao and colleagues (2013) tested working memory in statistical learning, in order to investigate whether these processes were interdependent and to what extent working memory plays a role in statistical learning. This study (Valadao et al., 2013) required participants to complete an n-back working memory task and a prediction task simultaneously. Participants had to predict the location of a target that was biased to appear in a specific quadrant of the display. They also had to do a 0-back or 2-back task based on the shape, location or color of the target, which tested feature and spatial working memory. The authors report that when participants did the 2-back task, they were not as accurate in learning the biased probability distribution of the target location, particularly if spatial working memory was involved. Another study that tested working memory while manipulating the statistical distribution of the target also found a close relation between these two aspects: participants were better at storing in working memory targets that were presented within a high probability area, without necessarily being aware of this facilitation (Umemoto et al., 2010). These studies demonstrate that for statistical learning to occur, participants need free working memory resources. The impairment that neglect patients demonstrate in spatial working memory (Johnston et al., 2012; Husain et al., 1997) might extend and affect working memory more generally, which could contribute to the difficulty patients have in learning and benefiting from statistical regularities in their environment. If neglect patients cannot keep in memory the recent information about target locations and features, then they will not have access to the information necessary for statistical learning. This difficulty in holding information in mind could also affect their ability to notice changes in the environment and to adapt to those changes.

1.5 Thesis purposes

The different elements reviewed above demonstrate that neglect is a heterogeneous disorder. Until the last few decades, most of the studies conducted on this disorder have focused on its spatial aspects, and have highlighted a large scope of impairments that are easily observable: a shift of attention and exploratory behavior towards the ipsilesional side, as well as a difficulty in disengaging attention from the latter in order to orient to the contralesional side (Corbetta and Shulman, 2011; Danckert and Ferber, 2006). This focalisation on the spatial aspects of neglect also explains why most of the rehabilitation strategies tested until now have been principally oriented towards rehabilitating the spatial impairments of the disorder (Luauté et al., 2006; Bowen et al., 2007). Indeed, approaches such as vestibular stimulation or prism adaptation have tried to train participants to overcome their spatial bias and orient towards their neglected side, but their efficiency is temporally limited and difficult to implement in everyday life (Luauté et al., 2006). Recent studies have started investigating other aspects of spatial neglect, revealing that the disorder is also characterized by non-spatial impairments, that can explain why those rehabilitation strategies have not fully succeeded (Husain and Rorden, 2003; Shaqiri et al., 2013). Impairments such as decreased arousal, prolonged attentional blink or mechanisms such as working memory and temporal processing, have been demonstrated to be present in those patients, without necessarily reflecting any spatial aspect (Danckert and Ferber, 2006; Husain and Rorden, 2003). Non-spatial impairments are therefore an important aspect of the disorder. In order to investigate further those impaired aspects, we have conducted different studies that are the basis of this thesis. Chapter 2 and 3 will report two paradigms that have tested visual priming and statistical learning in neglect patients. Finding that priming and statistical learning were impaired in those patients, we have decided to conduct an additional study to investigate if those impairments were limited to the visual domain or if they were multimodal. To that end, the paradigm of Gebhart and colleagues (2009) was adapted and replicated with university students first (Chapter 4) and then tested with brain damaged patients (Chapter 5). This last study also revealed an impairment in the auditory domain for neglect patients. Taken together, these studies reveal the difficulty of neglect patients to accurately notice and use regularities from the environment. It is a difficulty that most rehabilitation techniques available have not addressed yet. We have demonstrated that with enough time and information, some neglect patients can be trained to become more sensitive to the statistical distribution and regularities from their environment and use that information to their benefit. As such, this may be a fruitful avenue for developing novel rehabilitative techniques for what has proven to be an extremely difficult disorder to treat.

Chapter 2: The influence of statistical learning for the direction of attention in right brain damaged patients.[2]

2.1 Introduction

The visual world is formed by a complex combination of features and contains more information than the visual system can process. Therefore, we need mechanisms that help us select what is behaviorally relevant. This selection of incoming stimuli, more specifically called visual attention, is guided by mechanisms such as the salience map - where the most salient object attracts attention thanks to its physical distinctiveness (Itti et al., 1998, 2001; Fecteau and Munoz, 2006) - or by the use of spatial, temporal and statistical information in order to facilitate the direction of attention (Maljkovic and Nakayama, 1994, 1996; Perruchet and Pacton, 2006; Roser et al., 2011). The combination of those two elements forms what Fecteau and Munoz (2006) called the priority map, which unites the salience and relevance of the target. In the present paper, we explore how diverse forms of statistical regularities, such as priming and distributional learning, can be used as cues to direct attention and whether lesions in the right hemisphere (RH) impair this ability.

2.1.1 Statistical learning and priming in visual search

Our sensitivity to the statistical structure of our environment has long been recognized (Estes, 1950), and has recently been extended to attentional phenomena. For example, Chun and Jiang (1998; Chun, 2000) found that learning contextual information drives spatial attention and speeds the identification of the objects that occur in repeated, common contexts. Other researchers (Geng and Behrmann, 2002, 2006; Walthew and Gilchrist, 2006; Jiang et al., 2012) have found that detecting or identifying items is quicker when they are biased to repeat the same position. In those studies, the authors have concluded that our classification of items in visual search tasks is sensitive to the statistical structure of targets but also to the structure of distractors (Al-Aidroos et al., 2012; Vincent et al., 2009; Vincent, 2011). Even a classical attentional phenomenon like inhibition of return is modulated by the probability that target locations will be repeated (Farell et al., 2010).

[2] A version of this chapter was originally published in *Brain and Cognition* (Shaqiri and Anderson, 2012)

Typically, spatial probability learning is inferred when there is quicker identification of targets in high probability regions. However, if the number of high probability regions of a display is limited then those locations will have many sequential repeats and therefore faster identification might be more related to location priming (Maljkovic and Nakayama, 1994, 1996), unless specific efforts are made to avoid this (Walthew and Gilchrist, 2006; Jones and Kaschak, 2012).

Being the first to report position priming, Maljkovic and Nakayama (1996) had a target repeat or switch its location on subsequent trials. The authors found that when the stimulus repeated the same position, participants were faster to detect it than when the position was switched, and this facilitation lasted for five to eight successive trials. The finding that positional repetition speeds detection has been replicated in different conditions and studies (Kristjansson, 2010; Hillstrom, 2000), and has led some researchers (Walthew and Gilchrist, 2006) to suggest that improved target detection in regions of high probability might be explained by positional priming.

However, positional priming does not appear to be a sufficient explanation, because reducing the frequency of sequential repeats (by either increasing the number or possible positions where targets can appear or by not repeating the same position for successive trials) still results in faster reaction times (RT) in high probability regions (Druker and Anderson, 2010; Jiang et al., 2012; Jones and Kaschak, 2012). The extent of position priming's contribution to spatial statistical learning remains unclear.

We hypothesize that statistical learning relies on detecting sequential regularities, though it is not simply an expression of priming effects. This hypothesis predicts that an impairment of priming will lead to impaired statistical learning. The evidence for this interpretation follows from the demonstration that the learning of spatial statistical distributions (Geng and Behrmann, 2002) is lessened when spatial repeats are limited (Walthew and Gilchrist, 2006), and that the demonstration of statistical learning depends principally on adjacent elements. For example, the robust learning of word borders depends on the relation of adjacent syllables and does not occur for non-adjacent syllables (Newport and Aslin, 2004). In addition, this relationship is bound up with attentional systems, since the ability to learn adjacency relations, especially if irrelevant distractors appear, is absent for unattended sequences (Turk-Browne et al., 2005).

2.1.2 Neural network for priming and statistical learning

A possible confirmation of the correlation between priming and statistical learning can be provided by functional Magnetic Resonance Imaging (fMRI) studies focusing on the neural correlates of those two phenomena, as well as by studies of patients suffering a lesion in those particular regions. In a study in which they reproduced the paradigm of Maljkovic and Nakayama (1994; 1996), Kristjansson and colleagues (2007) found repetition-suppression of blood oxygenation level dependent (BOLD) activity in regions responsible for attentional control, including the intraparietal sulci. The authors also discovered a difference in the activation of the brain regions associated with color and location priming: Location priming was associated with a reduction in the contralateral inferior parietal and frontal areas, whereas color priming was associated with an inferior temporal region. The authors also revealed that the right inferior parietal cortex was activated for both the left visual field and right visual field, which was not the case for the left hemisphere, highlighting a greater implication of the RH in spatial attention. The role of the RH in statistical learning was also confirmed in a study conducted by Roser and colleagues (2011) on a split-brain patient during a visual task. The authors presented random and fixed pairs of shapes either on the left or right visual field, and they found that the patient was able to report the statistical link between the shapes only when they were presented in the left visual field.

In order to investigate whether a lesion in the RH affects position priming and statistical learning to the same extent, and to probe the relation between spatial priming, priming in general, spatial probability learning and brain attentional systems, we undertook a study of target classification contrasting two different forms of priming (spatial and color) with overall spatial probability learning in participants who suffered RH damage with and without attentional impairment.

2.1.3 Spatial neglect

Spatial neglect is a multifaceted deficit characterized by a variety of symptoms (Danckert and Ferber, 2006) making a global understanding of the disorder difficult. However, certain trends can be discerned. Neglect patients with a lesion in their RH generally have some attentional impairment, e.g., they often fail to explore or direct their attention to contralesional visual space (Halligan et al., 2003).

In addition, people with neglect have difficulty in detecting environmental regularities underlying spatial probability learning. They show spatial working memory impairments, prolonged attentional blinks, and impaired *covert* spatial priming (Danckert et al., 2007; Ferber and Danckert, 2006; Husain and Rorden, 2003; Samuelsson et al., 1998; Husain et al., 2001).

2.1.4 Our study

The present study aims to compare priming and statistical learning in a set of RBD patients with and without neglect, as well as a comparison group of older controls. Our procedure used a simple visual discrimination task with no distractors to prevent neglect participants from becoming fixated on distractors on the right side of the screen. To improve our confidence that participants had actually detected the target, we had them report the color of the stimuli. We adapted the method of Druker and Anderson (2010) to include a large number of target locations, allowing us to assess both positional priming and statistical learning. Furthermore, the location of the lesion of our participants in the RH allowed us to investigate the implication of this region in priming and statistical learning, for directing spatial attention, and to determine if a distinction exists between neglect and non-neglect patients. As a difference exists between color and location priming (Kristjansson et al., 2005; 2007), our hypothesis was that patients with and without neglect will show color priming but will be impaired for location priming, an impairment that should extend to statistical learning. Lastly, as we found impairment in our mild neglect participants, we extended our study and undertook a single case study to see if this deficit in statistical learning was absolute or remediable. We tested a single participant with chronic, stable, severe neglect on three separate days with the same paradigm.

2.2 Methods

The study received approval from the University of Waterloo Office of Research Ethics and all participants gave written informed consent to participate in the experiment.

2.2.1 Participants

Sixteen subjects participated in the main study. All participants had normal or corrected-to-normal vision. There were five healthy control participants (four females and one male, average age of 67.6 years, standard deviation (sd) of 2.2), recruited through the Waterloo Research in Aging Participant Pool (WRAP). The control group was chosen to generally match the age range of our two brain damaged groups. We did not control for gender. There were 11 (Table 1) brain-damaged participants (five females and six males of average age of 60.8 years and sd of 13.9 years): Five without neglect (RBD), and six with signs of mild clinical neglect (RBD+N). The presence of neglect was established by falling outside the normal range for any two of three neglect tasks from the Behavioural Inattention Test (BIT) (Table 1; further details below). Additionally, one chronic neglect participant (RR, 69 years old male) was recruited from the Neurological Patient Database (NPD) and was studied as a single case. All our patients had their stroke within the last five years, but we qualified RR as a chronic neglect patient because, contrary to the other patients who had shown fluctuations or improvement in their neglect, RR had been regularly tested since his stroke in 2008 and has shown consistent impairment on diverse tests of neglect.

2.2.2 Spatial neglect

The majority of participants from the two brain damaged groups had lesions of the right cerebral hemisphere. The lesions of each patient are presented in Table 1.

Table 1. Twelve brain damaged participants*: 5 without signs of spatial neglect, 6 with signs of mild clinical neglect and 1 participant with chronic neglect.*

Patient	*Sex*	*Group*	*Age*	*Handed ness*	*Lesion*	*Line bisection (–mm for L and mm for R)*	*Mean deviation in % for line bisection*	*Letter cancellation (L, R)*	*Shape copying*
1. DM	M	RBD	64	R	L thalamus	-17, -5, 1	7.6%	20/20, 20/20	OK
2. DO	F	RBD	67	R	R parietal	8, 3, -2	4.2%	20/20, 20/20	OK
3. RS	F	RBD	69	R	R basal ganglia	9, 7, 0	5.17%	20/20, 19/20	OK
4. JH	M	RBD	30	L	R parietal	4, 4, -5	4.2%	20/20, 19/20	Cube different shape on the left

									side
5. GP	M	RBD	54	R	R basal ganglia	-7, 0, -11	5.83	20/20, 18/20	OK
6. RB	M	RBD+N	82	R	R parietal occipital	1, 12, 9	7.12%	20/20, 19/20	Cube shorter on the left
7. CP	M	RBD+N	49	R	R basal ganglia	-14, -20, 9	13.9%	18/20, 17/20	Cube bottom part missing
8. BR	F	RBD+N	65	R	R temporal	28, -10, -18	18.19%	9/20, 9/20	Cube left part missing
9. CB	F	RBD+N	70	L	R parietal	5, -3, -10	5.85%	17/20, 18/20	Cube left side missing
10. DB	F	RBD+N	68	L	R fronto parietal	45, 14, -19	25.36%	12/20, 14/20	Cube and flower left side missing
11. TC	M	RBD+N	51	R	R basal ganglia	4, 44, 55	33.3%	14/20, 17/20	OK
12. RR	M	RBD+N Chronic	68	R	R fronto parietal	1st Session: 27, -4, -30	19.80%	0/20, 17/20	Cube and flower missing the left part
						2nd Session: 32, 5, -22	19.18%	7/20, 20/20	Star, cube and flower missing the left part

2.2.3 Neglect Assessment

To determine if participants manifested signs of clinical neglect or a possible neurological deficit, they all performed three subtests of the BIT (Wilson et al., 1987): line bisection, figure copying and letter cancellation. Based on the convention for the BIT test, performance was classified as abnormal when participants had a mean deviation of more than 5% from the center of the lines for the lines bisection test, omitted more than 10% of the “E” and “R” letters on the left side or failed to copy the left side of the star, cube and flower for the figure copying test. Following Halligan and colleagues (1989), spatial neglect was determined to be present when participants fulfilled at least two of these diagnostic criteria.

2.2.4 Experimental Task

The experiment was created with the Python programming language, using PsychoPy, a psychophysics module for Python (Peirce, 2007). We used a 17 inch screen with a resolution of 1366x768. The computer background was grey (Fig. 1). Each trial began with a white fixation cross at the center of the screen for 800 ms followed by a 300 ms blank (grey) screen before the stimulus was presented. The stimulus was a circle of 0.24 degrees of visual angle that was white on 50% of trials and black on 50% of trials. The choice of the black or white color for the target was distributed randomly. Dots were presented on the screen for 3 sec (or 7 sec for the chronic neglect participant). Participants were asked to report the color of the target and they used a key press to indicate if the circle was white or black. They did so by pressing the left or right arrow on the computer keyboard, and because the color of the target was chosen randomly, the left or right key presses were equally likely for left and right-sided targets.

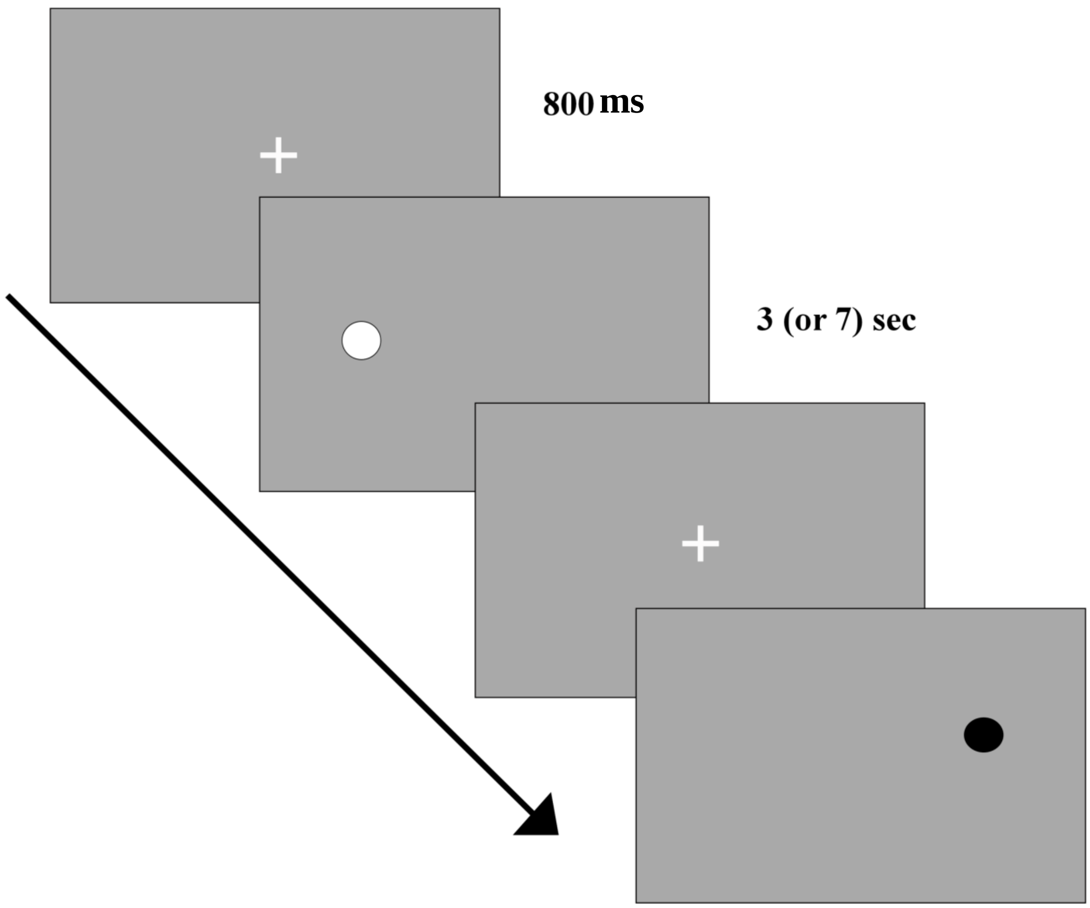

Figure 1: Experimental design. *Participants saw a white fixation cross for 800 ms, then the fixation cross disappeared and a black or white dot appeared for 3 or 7 sec. Participants had to push the right arrow on a computer keyboard if the dot on the screen was black, and the left arrow if the dot was white. Dots in the experiment were smaller than depicted here.*

The primary manipulation was a non-uniform, cone shaped distribution (as previously described by Druker and Anderson, 2010) of target locations. Seventy-five percent of the time targets came from a distribution centered 6.9° of visual angle to the left, which we called the "hot spot" (Fig. 2). 12.5% of the time the target location was selected from the same distribution but mirrored, so that it was located on the participant's right side, centered 6.9° visual angle to the right, which we called the “warm spot”. Finally, 12.5% of the time, the target location was selected from the uniform distribution, called “background”.

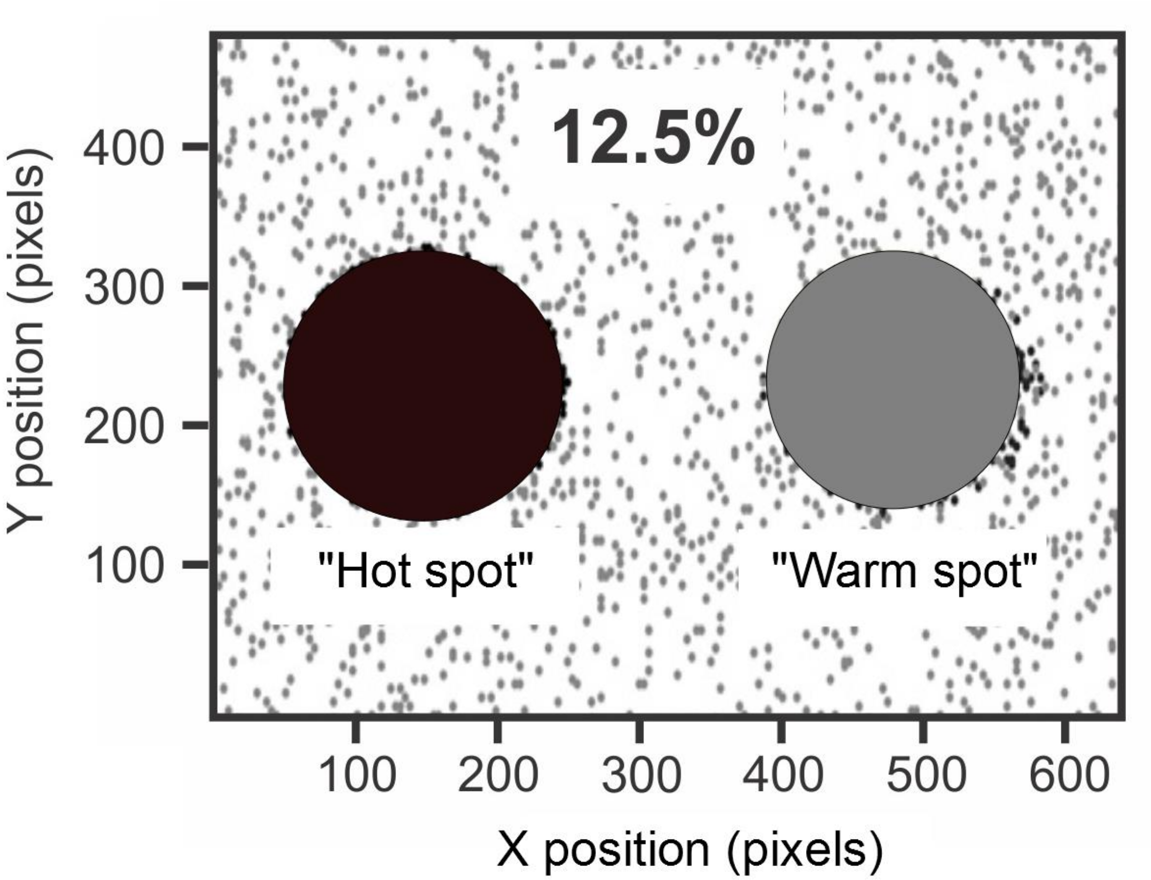

Figure 2: The distribution of the stimuli. *The dots were biased to appear 75% in the hot spot (black), 12.5% of the time in the warm spot (grey) and 12.5% for the background, all over the screen.*

Participants sat approximately 70 cm away from the computer screen. All trials were completed in a single session with the exception of those of the chronic neglect participant. There were four blocks of 200 trials. Participants were instructed to complete trials as fast and as accurately as possible.

The chronic neglect participant, RR, participated in three sessions on three different days. For the first session, RR failed to complete most trials because the three-second response window was too brief, and trials frequently timed out. Although he was presented with the complete number of trials, response data were generally lacking and could not be evaluated. For the second testing session, RR completed three blocks of 200 trials with 7 sec to respond to each and for the third session, he completed two blocks of 200 trials and one block of 81 trials, as he was too tired to complete the 200 trials forming the full block.

2.2.5 Statistics

The primary analytic method was linear mixed effect modeling (Baayen, 2008). In spirit, the method is similar to conventional analysis of variance (ANOVA); one examines for linear relations between independent variables and a dependent variable. However, for the linear mixed model there are both fixed effects, similar to the factors of a conventional ANOVA, and random effects, which in our case includes the participants, as they represent a random sample from the pool of all potential participants. With the mixed effect models, the standard deviation and coefficients are estimated for the random and the fixed effects, respectively (Baayen, 2008). The use of mixed models increases the power of the analysis and reduces the inter-subject variability unrelated to group assignments. This method is increasingly being used in psychological studies. For example, Marangolo and colleagues (2010) used this analysis approach in their study of brain damaged participants to overcome small sample size limitations. Baayen (2008) provides an excellent tutorial review, and software packages are available. We used R, a statistical program (version 2.13.2, R Development Core Team, 2011) with the lme4 and the languageR packages (version 0.999375-42 and version 1.2). The last package contains the Markov Chain Monte Carlo (MCMC) analysis, which reports the p-values and confidence intervals of the t-statistic (Baayen, 2008).

2.3 Results

Healthy controls performed the computer-based task with a small number of errors; 1.4% of responses were incorrect and 0.2% were no-answers (NAs). The group of brain damaged participants without neglect had 2.7 % errors and 0.52 % of NAs. The group of neglect participants had 2.5 % errors and 4.6 % of NAs. Finally, RR, the chronic neglect participant, made 8.1% errors and missed 67% of the targets when the display timed out after 3 s. For the second session, RR made 3.1% errors and 4.7% NAs, and 0.83% errors and 5.4% NAs for the third session. For RT analyses, we used only correct trials. We eliminated NAs and anticipations (trial responses faster than 0.1 sec). Given the high number of NAs for the first session for the chronic neglect participant, only the data from the second and the third session were analyzed.

2.3.1 How different are the RTs of the three groups on the left and right sides?

We analyzed the RTs of the three groups by isolating stimuli that were presented on the left side of the screen or on the right side. For each group, participants were considered as a random effect and the side of the screen was analyzed as a fixed effect. Controls and RBD participants were faster for left-sided stimuli, contrary to RBD+N participants that showed the opposite effect, consistent with their clinical condition.

Demonstrating a sensitivity for the main manipulation of the experiment, the group of healthy controls was 60.3 ms faster for targets presented on the high probability left side of the screen compared to the targets on the right side ($p=0.0001$, 95% confidence intervals (CI) 44-76 ms). The RBD participants were also 35 ms faster for stimuli on the left ($p=0.0006$, 95% CI 14-54). RBD+N participants demonstrated a different effect, as they were 66.3 ms slower for stimuli on the left side (Fig. 3), which represents their contralesional side, compared to the trials on the right side ($p=0.0001$, 95% CI 42-90).

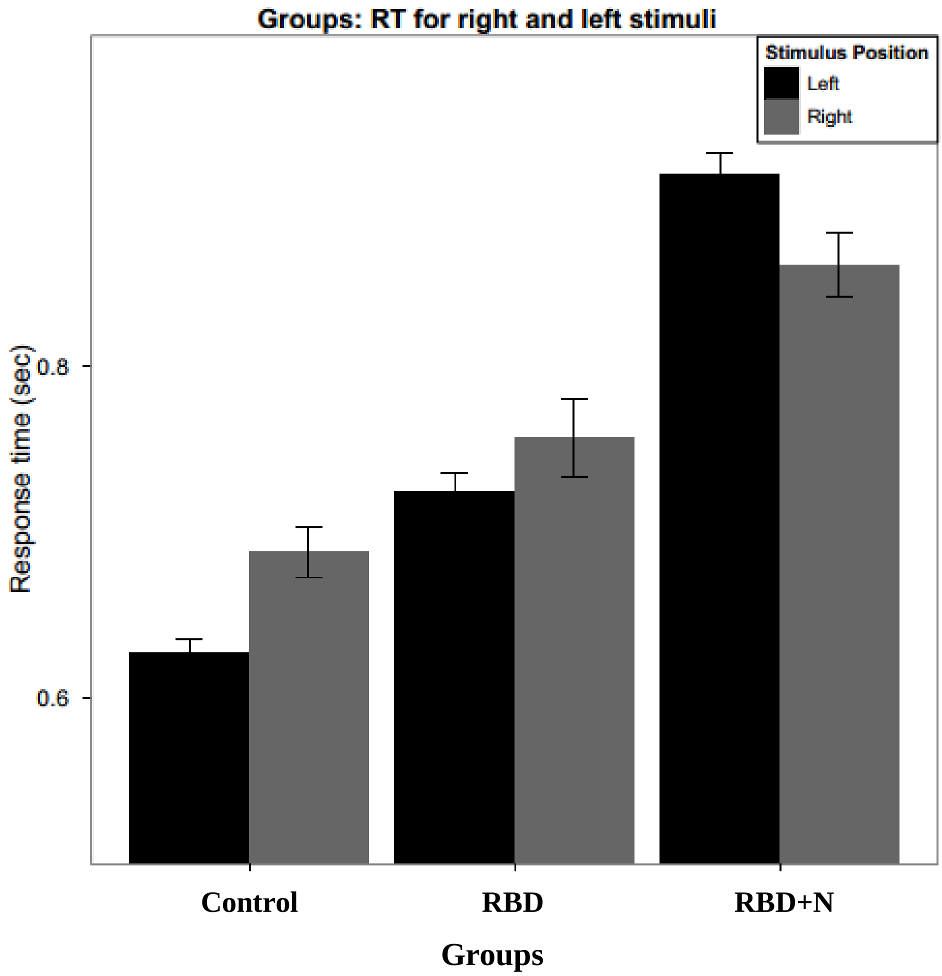

Figure 3: RT based on the position of the stimuli for each group. *Healthy control participants and brain damaged without neglect (RBD) are faster for targets presented on the left side of the screen, where stimuli were biased to appear, contrary to neglect participants (RBD+N), who are faster for targets presented on their ipsilesional side. Error bars represent 95% confidence intervals.*

2.3.2 Priming effects

We isolated consecutive trials that were either of the same color or that had been located near each other (defined as within 5 degrees of visual angle). All three groups showed significant priming effects for color repeats. The results reveal (Fig. 4a) that the healthy control group was 28.8 ms faster to detect consecutive targets of the same color (p=0.0001, 95% CI 16-41 ms). The two groups of brain damaged participants also demonstrated preserved color priming. The group RBD was 47 ms faster (p=0.0001, 95% CI 31-63 ms) and RBD+N participants were 29 ms quicker (p=0.002, 95% CI 10 – 49 ms) when the color of the stimulus was repeated.

Controls and RBD showed significant decreases in RT when trials were repeated in the same location. The control group was 36.5 ms faster (p=0.0001, 95% CI 24-49 ms) and RBD was 26.8 ms quicker (p=0.0006, 95% CI 10-42 ms) for targets repeated at the same region. However, this was not true for RBD+N, who failed to show positional priming (they were 5 ms faster when the target repeated location p=0.56).

To assess if this depended on the side of the screen, we repeated the analysis separately for hot-spot trials (left side of the screen) and warm-spot trials (right side of the screen). Within neither area was there a significant positional priming effect for the RBD+N, but on the left, there was a trend towards significance (24 ms faster, p=0.075). These negative results are in contrast to those for color priming, which was present in regions of the display that did not show position priming. For example, when restricted to targets in the high probability region on the their left side, RBD+N were 36 ms faster when a hot spot trial was preceded by a similarly colored trial than when it was not (p=0.001, 95% CI 13-58 ms).

As can be seen in Figures 4a, 4b and 4c, the effect of increasing the number of times a stimulus is repeated strengthens the priming effect, but there are differences between the groups. Here “repeat number” refers to the number of consecutive repetitions. For example, if the target color sequence were White-Black-Black-Black this trial would have a repeat count of 3 for color.

All three groups showed an increased priming effect as the number of consecutive color repeats increased, at least out to five trials. For positional priming, the effect for RBD subjects was attenuated and the effect was carried by trials with multiple repeats and not just a single, isolated repetition, as appeared the case for controls. This was more pronounced for RBD+N subjects who did not show any statistically significant position priming with an increased number of consecutive positional repeats (for one repeat compared to no repeats (p=0.35); for two repeats compared to one repeat (p=0.8)).

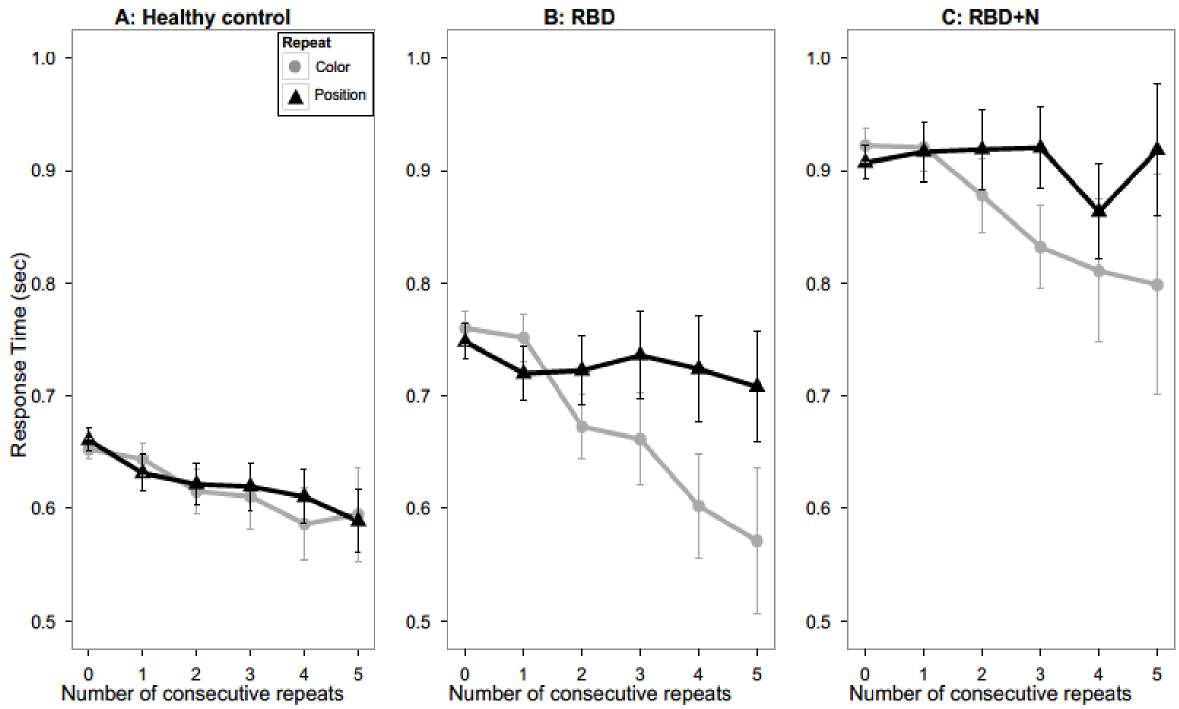

Figure 4 (A-C): Priming effect for the position and the color. *(A). Healthy control participants improved their RT for more than 50 ms when the same color or the same position was repeated 1 to 5 times. (B). Brain damaged participants without neglect demonstrated a higher improvement of their RT when the color of the target was repeated 1 to 5 times compared to when the position was repeated. (C). Neglect participants, who are slower overall compared to the two other groups, also demonstrate a better improvement of their RT when the color of the target is repeated 1 to 5 times, but they do not have a significant improvement for the repetition of the same location. Error bars represent 95% confidence intervals.*

2.3.3 Distribution learning

To investigate if participants learned the probability distribution of the targets separately from the effect of positional priming, we evaluated how the RT for particular screen locations evolved across blocks. We also repeated analyses for the subset of trials that were not repeats (i.e., did not match the prior trial for color or location).

The linear mixed model analysis for the healthy control group showed a significant effect on RT for stimuli presented on the hot spot area; participants were 42.3 ms faster overall to detect targets located in the high probability region (p=0.002, 95% CI 14-72 ms) compared to targets falling in the mirrored image warm spot, but the warm spot was not faster than the background (p=0.16).

To further evaluate if participants were learning the probability distribution, we examined if RT decreased across blocks for trials falling in the high probability hot spot as compared to other screen regions. The following analysis reports the comparison of the RT in the first block compared to the second and third block, in order to investigate if participants were getting faster for the hot spot during the blocks.

The results showed that healthy control participants very rapidly learned to favor the high probability region within the first block. By the second block, trials located in the hot spot were detected 70 ms faster during the second block than trials in the hot spot in the first block (p=0.005, 95% CI 23-120 ms) while improvement for the less probable warm spot had not significantly changed (18 ms faster than for the first block, but p=0.5). Control participants were 91 ms faster during the third block (p=0.0001, 95% CI 43-142 ms) and 93 ms in the fourth block (p=0.0001, 95% CI 46-140 ms) when comparing trials falling in the high probability region to similar trials in the first block.

Contrary to the results from the hot spot area, control participants did not show a significant improvement of their RT for the warm spot during the third block (73 ms slower than trials located on the warm spot during the first block, but p=0.8) or the fourth block (57 ms faster but p=0.07) compared to trials presented on the warm spot during the first block.

We conducted the same analysis for RBD. This group revealed faster RTs for trials presented at the high probability region (51.4 ms faster for the hot spot area compared to the warm spot; p=0.02, 95% CI 6-90 ms). We also compared their RT across the blocks and found that RBD participants were 136 ms faster (p=0.01, 95% CI 38-243 ms) to detect targets during the fourth block compared to the first block for the warm spot region. The trend was similar, but not statistically significant for the hot spot area (53 ms faster; p=0.12, 95% CI 13-122 ms). In sum, for RBD participants the improvement in response times across blocks was greater for the high probability region, of the screen than the lower probability background region. But those results were driven by the benefit on the RT across blocks for the warm spot, which highlights a spatial attention deficit on this group.

RBD+N participants demonstrated a different pattern. There was a suggestion that some degree of statistical learning may be intact, as the RBD+N group was 93 ms faster for non-repeated trials presented on the warm spot (which is their ipsilesional side; p=0.0001, 95% CI 50-136 ms).

There was no change for trials in the hot spot region. Although their neglect makes RBD+N participants slower to report left sided targets, it might still be the case that they are sensitive to the non-uniform spatial distribution of targets within their impaired hemi-space. To assess for local effects, we analyzed trials falling within the hot spot (or warm spot) and compared them with trials from background region on the same side only. We did this for all three groups.

The controls were 51.7 ms faster for left sided hot spot trials compared to left-sided background trials (p=0.0002, 95% CI 26-77 ms). And although only 12.5% of the targets were presented on the warm spot, the group of older healthy controls was also 31.5 ms faster for those targets compared to right-sided background trials (p=0.02, 95% 5-65 ms).

As we reported earlier, the group of RBD participants was also sensitive to the probability distribution, but not to the same extent as healthy participants. When we compared the RT of RBD participants for trials falling in the hot spot to the other trials presented on the background, we did not find a statistically significant difference on their RT (p=0.69). As RBD participants were substantially faster for left sided targets in general compared to the right sided targets (Figure 3), the present result and the one showing a faster RT for the hot spot than the warm spot interpreted together suggest a possible decrease in spatial precision.

Interestingly, RBD+N participants did show that hot spot trials were faster than other left sided trials (65.5 ms; p=0.0008; 95% CI 25-106 ms), even though these participants were slower on the left side overall (which is after all their contralesional side). This leaves open the possibility that neglect subjects may still be partially sensitive to probability structure, as they were not faster than the warm spot. This result motivated us to examine these effects in a patient with more severe neglect where we could acquire a larger number of trials.

2.3.4 Chronic Neglect

As this was a single participant, analyses used conventional ANOVAs. Similar to our group of RBD+N participants, the chronic neglect participant did not show any detectable location priming. During the second session (first session trials were not evaluable due to the high number of NAs), RR was 313 ms *slower* when the position of the target was repeated within 5 degrees visual angle of the prior trial; this was significantly different from trials that were not repeated at the same location (F(1, 534)=11.41, p=0.0007). But again, like the RBD+N group, RR did benefit from color priming. He was 297 ms faster when the color of the stimulus was repeated (F(1, 534)=10.29, p=0.001).

For the third session, RR again failed to demonstrate any benefit from spatial repetitions: he was 436 ms slower for targets that were repeated at the same position ($F(1, 441)=24.52$, $p<0.0001$), but showed a trend to be faster when color primed, (150 ms, $F(1, 441) = 2.8$, $p=0.09$).

To assess for RR's ability to learn the spatial probability distribution, we conducted a conventional ANOVA with location and block factors. For the second session, RR had a significant RT effect for the target distribution factor ($F(2, 527) =39.90$, $p<0.001$) and for the blocks ($F(2, 527)=20.8$, $p<0.001$). RR also showed a target distribution by block interaction ($F(4, 527)=4.34$, $p=0.001$).

For the third session, although he did only 81 trials during the second block because of fatigue effects, RR again demonstrated an effect for target distribution factor ($F(2, 434)=95.95$, $p<0.001$), and for block ($F(2, 434)=23.87$, $p<0.001$), as well as a significant interaction between the two ($F(4, 434)=2.42$, $p=0.04$). This result is not affected by the fewer trials of the second block, as the final results of this session are not affected, even if we disregard this block (indeed, without the second block, RR would still show an effect of block $F(1, 360)=33.83$, $p<0.0001$, an effect of target distribution $F(2, 360)=80.14$, $p<0.0001$ and an interaction between the two $F(2, 360)=4.7$, $p=0.009$). Since there was a consistent pattern of results across the two sessions, we collapsed across sessions and assessed how RR was learning the spatial distribution of targets for left and right sides by conducting an ANCOVA with hemispace as a factor and trial number as the covariate. If RR is learning something about the probability of targets per se, as opposed to just learning the task in general, we would predict a greater effect of experience on his RT for targets falling on the left side, despite left sided trials being slower overall (consistent with his neglect; $F(1, 977)=246.56$, $p<0.0001$).

To illustrate this relationship in more detail, we performed a general linear hypotheses test for the RT based on the trial number and the side (Figure 5). We found a significant effect of the side ($t= -3.28$, $p=0.001$), demonstrating a difference in the improvement in RT for the left side compared to the right side over trials. In summary, the greatest gain from experience for RR was in his neglected hemispace: the hemispace toward which we had systematically biased the target location probability.

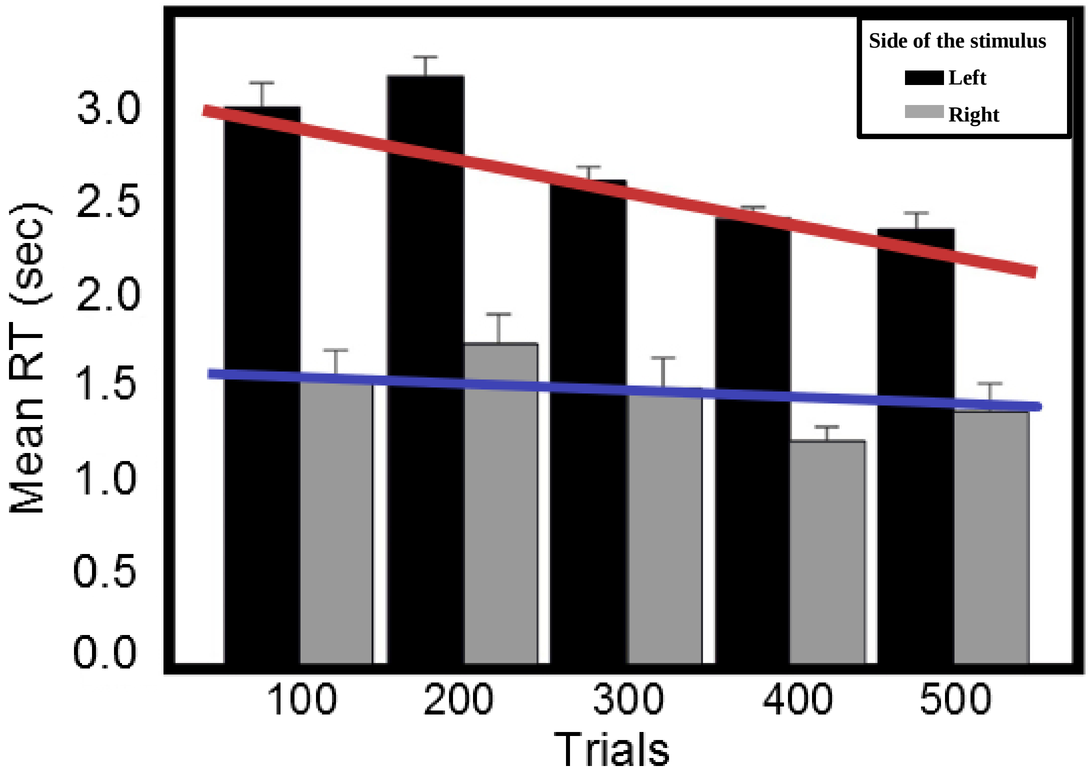

Figure 5: *Neglect patient's RT for the hot spot (black) and the warm spot (grey). There is a difference on the RT for the left and right-sided targets over the sessions. The patient improved his RT over the sessions for the targets presented on the hotspot (red line), which was not the case for the targets presented on the warm spot (blue line).*

2.4 Discussion

In this experiment we studied color priming, spatial priming, and the learning of a spatial probability distribution in Controls, RBD, and RBD+N. Our goal was to investigate how priming and statistical distributions can be used as cues to direct attention. The design of our paradigm allowed us to consider these two functions separately. Sequential trials that were of the same color or in the same position allowed us to assess priming effects, and by eliminating such trials and comparing regions where the target was biased to appear, we could assess the ability to learn the probability distribution of target locations. Finally, because two of our groups suffered damage in the RH, an impairment in attentional functions would highlight the involvement of the RH in priming and statistical learning.

A simple scenario for the development of spatial top-down attentional effects is that statistical inhomogeneity leads to spatial repeats. This short time repetition leads to priming, and from an accumulation of priming effects a higher order map of target probabilities is constructed and biases spatial expectancy. To explore the implications of our data for this simple model, we consider in turn our priming and statistical results from the different participant groups.

2.4.1 Priming effects

Our definition of priming is based on that of Maljkovic and Nakayama (1994, 1996). We tested if our participants were faster when the target color or position repeated. All our participant groups; the healthy controls and the RBD participants with and without neglect, showed a sensitivity to repeating target characteristics on a short time scale. All groups showed a robust color priming effect, demonstrating that priming per se is not affected by either brain injury or neglect.

Only a few researchers have investigated priming in brain damaged participants before (for example Kristjansson et al., 2004; 2005), and those studies have also shown a preserved color priming effect. Furthermore, Saevarsson and colleagues (2007) found that priming was preserved in the contralesional side in neglect patients when distractor sets were repeated; the authors highlight that repetition improved search ability on the neglected side.

Whereas we did not find an impairment for priming per se, we did find impairments for spatial priming. This was partial in our RBD group, who seemed to require more than one repeat to benefit from spatial repetition, and was complete in our RBD+N participants, who showed no spatial priming. These data are at some variance with the results of Kristjansson and colleagues (2005), who did find intact spatial priming. The differences in experimental procedures may well account for the different findings. In their study, there were only three relevant locations and each location was always occupied by a relevant token. In our task, the location of targets was unpredictable and varied widely from trial to trial. Of note, Kristjansson and colleagues (2005) failed to find position priming when shortening the display time and preventing overt recognition of the target. Thus, of the two forms of priming, color and position, Kristjansson and colleagues (2005) also found position priming to be the weaker. Although a larger group of patients with lesion analyses would have addressed the question of the possible implication of specific brain regions in priming and statistical learning, a basic inspection of the lesions from the patients' files did not show obvious differences in the brain regions injured. Thus, the absence of a position priming effect correlates better with the presence of persistent attentional impairment in the form of spatial neglect than it does with any one brain region.

2.4.2 Statistical learning

Our paradigm was also designed to test for probability learning separate from position priming effects. We did this by having a large number of potential target positions and a large number of trials. This meant that even after we excluded trials that were spatial repeats, we still had sufficient numbers of trials for statistical analysis. Because all screen locations were not equally probable, these remaining trials differed in their spatial probability. We chose five degrees of visual angle as the cut off for spatial repetition because of evidence that position priming effects are gradual (Maljkovic and Nakayama, 1996).

Considering first the older controls, they replicate our earlier work in young healthy controls (Druker and Anderson, 2010). Our older healthy participants prime for color and position, and when eliminating such trials, show performance benefits across blocks that are greater in the high probability regions of the screen. In addition, these participants are faster for screen regions of high probability than are their responses to ipsilateral, lower probability, locations.

Is this benefit secondary to shifts in gaze? Although we instructed participants to maintain central fixation, we did not train them nor measure their eye position. So, we cannot exclude this as a *mechanism* whereby learning statistical information contributes to improved attentional processing, since attention and gaze generally correlate (Corbetta, 1998). However, we emphasize that while such a shift, if present, would be a mechanism for improved response speed, it would not explain away the fact that statistical learning does take place, spontaneously, without specific instruction, and when participants are generally not overtly aware of the target distribution (Druker and Anderson, 2010). Lastly, eye position biases cannot be a complete mechanism, since our older healthy participants were simultaneously faster for both the right and left sided high probability locations than for ipsilateral lower probability screen locations.

We began our discussion by suggesting a simple sequence for the development of spatial attentional expectancies: spatial repeats are associated with positional priming and this leads to the development of an attentional bias. Our data however, are more ambiguous. For example, although our RBD participants were faster for trials presented on the left higher probability side of the screen, they were not faster in the left-side hotspot compared to other left sided locations, and they showed an impoverished position priming effect that appeared to require multiple sequential repeats. Our RBD+N participants showed no position priming, but still demonstrated some retained ability to learn to a partial degree how likely targets were to appear in different regions of the computer screen.

The RBD+N patients were faster for targets presented in the hot spot compared to other left sided target locations. And our single patient showed a retained ability to improve his response more in the high probability, left side of the screen, despite being slower overall on this side, and also having no position priming effect.

Our finding of a retained ability for probability learning in people with spatial neglect is in accordance with earlier work by Geng and Behrmann (2002, 2006). These authors found that neglect patients were able to learn the statistical distribution of the position of the target on their contralesional side and use it as a cue to direct their attention and improve their performances. Because there were relatively few target locations in those studies, the risk that the effect was being mediated by position priming was suggested (Walthew and Gilchrist, 2006). But in light of our retained evidence for probability learning and the absence of evidence for position priming, the most parsimonious explanation for all the data is that patients with spatial neglect retain an ability to learn target probabilities and that this retained ability is not simply a consequence of position priming, contrary to our initial hypothesis. Further, although our data demonstrate a relation among RBD, attention, and statistical learning, the nature of that relation requires further investigation. A central question is whether RH systems for spatial attention and statistical learning overlap or are distinct.

Given our demonstration of some preserved statistical learning in the contralesionsal hemispace for RBD+N participants, it is possible that their attentional impairments simply act as a mask on their retained statistical learning abilities. Determining whether the statistical learning impairments are primary or secondary could have practical implications for rehabilitation.

One-way forward on this question will be to look at performance with non-lateralized stimuli, to see how priming and statistical learning are affected for items near fixation. A second approach would be to combine the present methods with eye tracking. Although Karnath and Perenin (1998) have shown that neglect patients are equally likely to make leftward and rightward saccades, they tend to not explore the left visual space (Girotti et al., 1983). If the way control participants benefit from knowing the statistics of spatial distributions is through facilitating exploratory eye movements, then this could explain the impairment of RBD+N subjects without requiring a primary impairment in statistical learning. Answers to these questions will require further experiments.

In summary, the analyses we conducted for statistical learning show varying results for the ability of RBD patients, with or without neglect, to learn spatial statistical distribution and to use that as a cue to direct their attention. While the RBD participants were faster on the high probability side, they did not show an improvement confined to the highest probability area on that side. The RBD+N patients despite being slower on the left, did show an advantage for the hotspot region. These results are ambivalent and there is a risk they reflect chance variation or are a consequence of the size of our brain damaged subject pools.

Despite our small group size, our results contribute to the literature on priming effects after brain injury. We find a category specific impairment for spatial but not color priming. More importantly, we do find evidence of a retained ability to learn statistical features of the environment after RH injury. This is interesting in light of recent results of the RH's importance for statistical learning. This has been demonstrated in previous studies by Danckert et al., (2011); Roser et al., (2011) and Turk-Browne et al., (2009). If, as our data and these other studies suggest, similar RH systems contribute to the learning of spatial probability and positional salience, then efforts to rehabilitate neglect could make spatial statistical learning a therapeutic target.

Chapter 3: A limited priming and impaired statistical learning in right brain damaged patients[3]

3.1 Introduction

Spatial neglect is frequently associated with attentional impairments, and the failure of patients to orient or respond to contralesional stimuli (Heilman, 1979; Halligan et al., 2003) is often characterized as a spatial attentional failure. However, neglect is also associated with deficits that are not obviously spatial, for example working memory impairments (Ferber and Danckert, 2006), increased attentional blink duration (Husain et al., 1997) and impaired temporal estimation (Danckert et al., 2007; Merrifield et al., 2010). We have suggested (Danckert et al., 2012a; Shaqiri et al., 2013) that performance on such tasks is an indirect reflection of impaired systems for learning environmental probabilities (Shaqiri and Anderson, 2012) and failing to update them when they change (Danckert et al., 2012a). In this report, we investigate how these functions relate to right lateralized attentional systems by assessing spatial priming for midline targets in patients with right brain damage without (RBD) or right brain damage with neglect (RBD+N) and evaluating how the magnitude of spatial priming is modulated as positional repeats become more likely and then less likely.

Studies have shown that we are faster to respond to targets in search tasks when features, locations or contexts are repeated (Maljkovic and Nakayama, 1994, 1996, 2000; Kristjansson et al., 2005). Maljkovic and Nakayama (1994) first studied this priming effect by having participants detect an odd-colored diamond from two distractor stimuli. The authors biased the trials to successively repeat their color or location and found that participants demonstrated a faster reaction time (RT) when the target color or position was repeated.

This priming effect has also been found when targets have the same movement profile before a trial as within a trial (Goolsby and Suzuki, 2001) or when targets are presented within a predictable interval (Los et al., 2001). Contextual cuing can also be conceived, broadly, as another example of how repetition - in this case the context or distractor sets - may improve detection performance (Chun and Jiang, 1998; Saevarsson et al., 2008).

Studies in clinical populations have found some of the priming effects to be preserved. In Kristjansson and colleagues (2005), for example, the same paradigm as used by Maljkovic and

[3] A version of this chapter was originally published in *Neuropsychologia* (Shaqiri and Anderson, 2013).

Nakayama (1994) was employed to demonstrate preserved color priming in two patients with spatial neglect. For spatial priming, their neglect patients had to have been given sufficient time to consciously detect the target in order to benefit from spatial repetitions, suggesting that priming effects can fractionate because of RBD and that spatial priming is particularly vulnerable, possibly as a result of spatial neglect. We, too, found preserved color priming in RBD+N patients and a more fragile spatial priming effect in a task where participants discriminated colored circles (black or white) presented one at a time at a biased location (Ch 2; Shaqiri and Anderson, 2012).

Whereas both these studies found an impairment of spatial priming in participants with neglect, the interpretation of a priming deficit per se is complicated by the utilization of tasks in which the targets can appear from left to right of the participants with a spatial attentional deficit worse on the left. The results of Saevarsson and colleagues (2008) suggest that spatial attentional deficits are not a sufficient account for priming deficits, but the mixture of horizontally extended priming tasks in people with spatial attentional deficits makes it difficult to reach an unambiguous conclusion.

Although priming is a relatively short time scale effect that emphasizes repetition, statistical learning deals with similar notions and emphasizes transition. Turk-Browne and colleagues (1996) for example, tested the learning of transition probabilities and its relation to attention. The authors constructed visual triplets with two separate sequence sets coloured distinctly. Participants viewed a single sequence of pictures with items from each coloured sequence randomly interleaved and intermingled. The task was to monitor for repeated shapes of a particular colour. As in the language task, participants were tested for their ability to recognize the "triplets" statistically encoded in each colour family. Even though uninformed of the statistical nature of the stimuli, participants learned implicitly to recognize the triplets, but only for the colour that they had been instructed to monitor. The authors concluded that attention was necessary for selecting content, but that after this selection, statistical learning mechanisms could operate autonomously. Although attention is a prerequisite for statistical learning, it appears that statistical regularity may also be a cue for attentional allocation (Zhao et al., 2013).

Studies in clinical populations have found many statistical learning effects to be right hemisphere dependent. In a study that was conducted on a split-brain patient, Roser and colleagues (2011) presented fixed pairs of shapes to the left or right visual field where the shapes had defined statistical relationships. When stimuli were presented to the left visual field (right hemisphere), the patient had no trouble learning the visual features or statistical properties of the stimulus, which was not the case when the target was presented to the right visual field (left hemisphere). In Danckert and colleagues (2012b), control and brain damaged participants played the children's game Rock, Paper, Scissors against a computerized opponent that was biased to gradually increase the proportion of plays it chose one choice over the others, such that at the end, one option (for example, rock), was played 80% of the time. Control participants and left-brain damaged (LBD) learned to exploit this bias, but RBD participants did not.

In contrast to an assertion of right hemisphere dominance for statistical learning, Geng and Behrmann (2002; 2006) showed intact probability cuing in people with spatial neglect. The authors tested healthy controls and spatial neglect patients on a simple search task: participants had to look for the letters L and F (with T and E as distractors). The targets appeared on the left half of the screen 80% of the time. Both controls and neglect patients used probability as a cue to direct their attention, even though the stimuli were on the patients' contralesional side.

Walthew and Gilchrist (2006) challenged those conclusions by questioning if instead of distributional learning, the results of Geng and Behrmann (2002; 2006) might not simply be the expression of spatial priming. Walthew and Gilchrist (2006) highlighted that biasing the target position to be repeated mostly on one side of the computer screen would favor spatial priming on that side as well. While attempting to reproduce the results of Geng and Behrmann (2006) with control participants, Walthew and Gilchrist (2006) failed to find evidence for probability cueing when they guarded against unequal distributions of spatial repeats. But when successive repeats were unlikely, the authors found uneven transition probabilities of exactly the type purported to be the object of statistical learning (Druker and Anderson, 2010; see Discussion at Section 3.4). Also, Jones and Kaschak (2012) have since reported that statistical distributions can be used to improve performance, even without inter-trial repetitions.

Our investigation of the relation between statistical learning, priming, and attentional systems was motivated by their important role as aids to prioritization. The world around us contains more information than we are able to process, therefore we depend on mechanisms that help us to select the items or locations where important items are most likely to occur. Such considerations are the motivation behind salience maps (Itti and Koch, 2001; Wolfe, 1994) that emphasize particular stimuli or spatial locations for perceptual processing.

Supporting the idea that prioritization takes place, Bichot and Schall (1999) had monkeys perform a simple visual search task using eye movement responses. The monkeys' errors were more likely to be to distractors that shared target features (which maps onto the concept of priming effect) and to distractors that resembled targets from earlier sessions (mapping on to the concept of statistical learning). These patterns of errors matched firing rate profiles from neurons recorded in frontal eye fields. Fecteau and Munoz (2006) combined these estimates of salience, driven by bottom-up stimulus features, with top-down estimates of relevance in order to generate the concept of *priority* maps. Studies in clinical populations have also demonstrated that priority map can be present in neglect patients (Ptak and Schnider, 2010; Danckert et al., 1999; Snow and Mattingley, 2006). But priority maps must integrate prior experience and stored memories (Hutchinson and Turk-Browne, 2012), therefore two contributors to the notion of priority are persistence and statistical expectancy.

In summary, although we certainly can learn transitional statistics (Saffran et al., 1996), it is not clear how integral priming effects are for apparent demonstrations of statistical learning and probability cuing, or whether the impairment of those functions is explained by RBD.

The objective of the present study was to test controls and RBD participants for repetition priming in the short term, as well as to assess their ability to learn longer time scale distributions. To do this, we had our participants perform a simple visual discrimination task of vertically aligned stimuli presented centered on the computer screen. We could determine the magnitude of repetition priming by comparing RTs for repeated (which we call repeats for short) and non-repeated trials. In addition, we assessed these priming effects under three different probability distributions. First, to develop familiarity with the task, was the uniform condition, in which the location of the target was chosen uniformly from all three positions and independent of prior trials. Second was a *high repeat* condition in which target position was picked dependent on the prior trial, in order to increase repeats of target position. Third was a *low repeat* condition, in which spatial repeats were improbable. Based on prior results (Ch 2; Shaqiri and Anderson, 2012), we expected RBD and RBD+N participants to show impaired spatial priming, even for mid-line stimuli. We expected that control participants, contrary to RBD groups, would show modifications of RTs that demonstrated knowledge of repeat probability.

3.2 Methods

3.2.1 Participants

The experiment was performed on four groups of participants: 20 healthy undergraduate university students (14 males, mean age = 21 years and standard deviation (sd), 3 years), 20 healthy older participants (11 males, mean age = 73, sd = 8), 4 right brain-damaged (RBD) without neglect (2 males, mean age = 64 years, sd= 17, Table 2) and 5 right brain damaged patients (RBD+N) with signs of clinical neglect (3 males, mean age=67 years, sd=5, Table 2).

The university students were obviously younger than our stroke participants. We tested if the stroke groups were similar in age to each other and with our normal older controls by pairwise comparisons. There were no significant differences in age ($t(7)=0.38$, $p>0.05$; $t(23)=1.7$, $p>0.05$ and $t(24)=1.6$, $p>0.05$), between RBD and RBD+N and then between those two brain damaged groups and older controls, respectively. The ethics committee of the University of Waterloo approved the protocol and all the participants gave a written informed consent.

Participant	*Sex*	*Group*	*Age*	*Handedness*	*Lesion*	*Line bisection (–mm for L and mm for R)*	*Mean deviation in % for line bisection*	*Letter cancellation(missed for the 4 parts from L to R)*	*Shape copying*
1. CB	F	RBD	71	L	R parietal	5, 2, -5	0.28%	0/10, 0/10, 0/10, 0/10	Cube, bottom left missing
2. GP	M	RBD	58	R	R basal ganglia	6, -3, 0	0.42%	0/10, 0/10, 0/10, 0/10	Cube shorter on the right
3. MS	F	RBD	83	R	R fronto parietal	-10, -7, 0	2.4%	2/10, 1/10, 2/10, 1/10	OK
4. LG	M	RBD	44	R	R fronto parietal	2, -1, 3	0.56%	0/10, 0/10, 0/10, 0/10	Start tilted to the right, cube longer on the left.
1. RR	M	RBD+N	69	R	R fronto parietal	59, 35, 0	13.27%	9/10, 3/10, 1/10, 1/10	Cube left side missing
2. JI	M	RBD+N	70	R	R fronto-parietal, temporal and basal ganglia	-31, 3, 30	0.28%	3/10, 2/10, 2/10, 3/10	Cube left side missing
3. GH	F	RBD+N	63	R	R temporo parietal	59, 61, 82	28.53%	10/10, 10/10 10/10, 0/10	Cube and flower left side missing
4. EG	F	RBD+N	74	R	R parietal	-25, -7, 16.5	2.2%	3/10, 0/10, 6/10, 1/10	Cube left side missing
5. BM	M	RBD+N	60	R	R parietal	3, -12, -17	3.7%	10/10, 9/10, 9/10, 2/10	Star, cube left side missing

***Table 2. Two groups of brain damaged patients**. We tested four right brain damaged patients without neglect (RBD) and five right brain damaged with neglect (RBD+N).*

3.2.2 Tests to assess spatial neglect

Selection criteria for patients with spatial neglect were identical to those described in section 2.2.3.

3.2.3 Apparatus and stimuli

For this experiment, we adapted the protocol originally created by Maljkovic and Nakayama (1994, 1996) and also used by Kristjansson and colleagues (2005) in order to test priming in healthy subjects and patients with brain damage. We adapted and extended this protocol in order to be able to test statistical learning in addition to the priming effect. The protocol was designed using PsychoPy, a psychophysics software library written in Python (Peirce, 2007). Stimulus presentation and response recording were carried out by a Gateway NV53 computer laptop with a 17-inch monitor and 1366x768 resolution. The experiment was divided into 3 blocks (conditions) of 150 trials each. Each trial began with a white fixation cross presented on a grey background. After 1 sec, two white and one black diamond (or vice versa) appeared vertically in the middle of the screen. One of the diamonds, the target, was odd-colored and had a notch cut off at its top or bottom (Figure 6). The colour of the target was determined randomly. The diamonds were squares of 2° visual angle rotated 45°, and they were located at 5° down from the center of the screen (position 1), at the center of the screen (0° visual angle, position 2) and the last one at 5° visual angle up from the center of the screen (position 3). The size of the cutoff on the targeted diamond was a triangle of 0.4° base and 0.2° height of visual angle. The task required searching for the odd-colored diamond and responding as quickly and as accurately as possible as to whether the top or the bottom part was missing. Participants had 3 seconds to respond and made their report by using a Logitech Dual Action gamepad. If the top or the bottom part of the diamond was missing, participants pushed “up” or “down” on the right analog joystick of the gamepad, respectively.

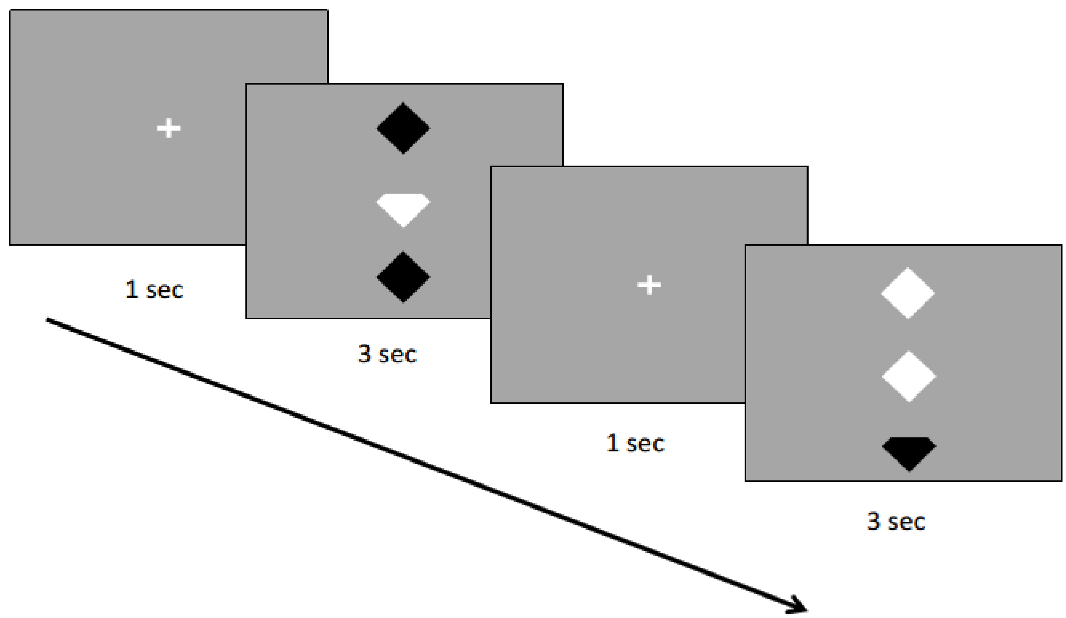

***Figure 6. Presentation of the 3 diamonds on the screen**. Participants first saw a white fixation cross on a grey background. After 1 sec, the fixation cross disappeared and 3 diamonds were presented vertically on the center of the screen. The targeted diamond was odd-colored and had a notch cutoff at the top or the bottom (the schematic here exaggerates the actual physical distinction). Participants had to detect the diamond that was from a different color than the two others and decide if it had its top or bottom missing. They had 3 sec to make their decision.*

The location of the targeted diamond was the main manipulation of the experiment. Participants did 3 blocks of 150 trials each, and each block consisted of a different probability of the target repeating its position. The first block served as a baseline and familiarized the participants with the task procedures. The position of the target for this block was distributed randomly: regardless of where the target was located on the current trial, every potential target position had an equal likelihood of 33% to be the location of the target on the next trial.

For the second block, called the "high repeat condition", the distribution was biased so the repeat probability of the same position was high (0.8). Therefore, whichever of the three positions the target was located at for the current trial, 8 out of 10 times it would be located in the same location on the next trial.

The last session was the "low repeat condition". Repeat probability was 0.2. This means that whichever of the three positions the target was located at for the current trial, 2 out of 10 times it would be located in the same location on the next trial. Whenever a target did not repeat its location, it switched to one of the other two locations with an equal likelihood.

The order of the different conditions was fixed for all participants and all groups. The heterogeneity of patient groups, the challenges of recruiting brain damaged participants, and the large number of potential orders for the tasks (6), made counterbalancing impractical. As task order was the same for all groups, it cannot, as a single factor, explain group differences, but it is possible that different results might be observed with different orderings of block probabilities.

3.2.4 Data analysis

Our RT analyses were restricted to correct responses. The data were analyzed using conventional ANOVAs to evaluate and visualize significant differences within groups and individuals. All analyses were conducted with R (version 2.15.2; R Development Core Team, 2011).

3.3 Results

3.3.1 Priming effects

Do participants have a faster RT when the target location is repeated? For all groups, we compared the RT for trials that were in a repeated position to the trials that switched their position. The RT distributions were skewed, so we first log-transformed them and used the median as a report of the average performance. In addition to the difference for RT across groups (Figure 7), there was also a significant effect of spatial priming. The detailed results for each group are reported in the subsequent sections.

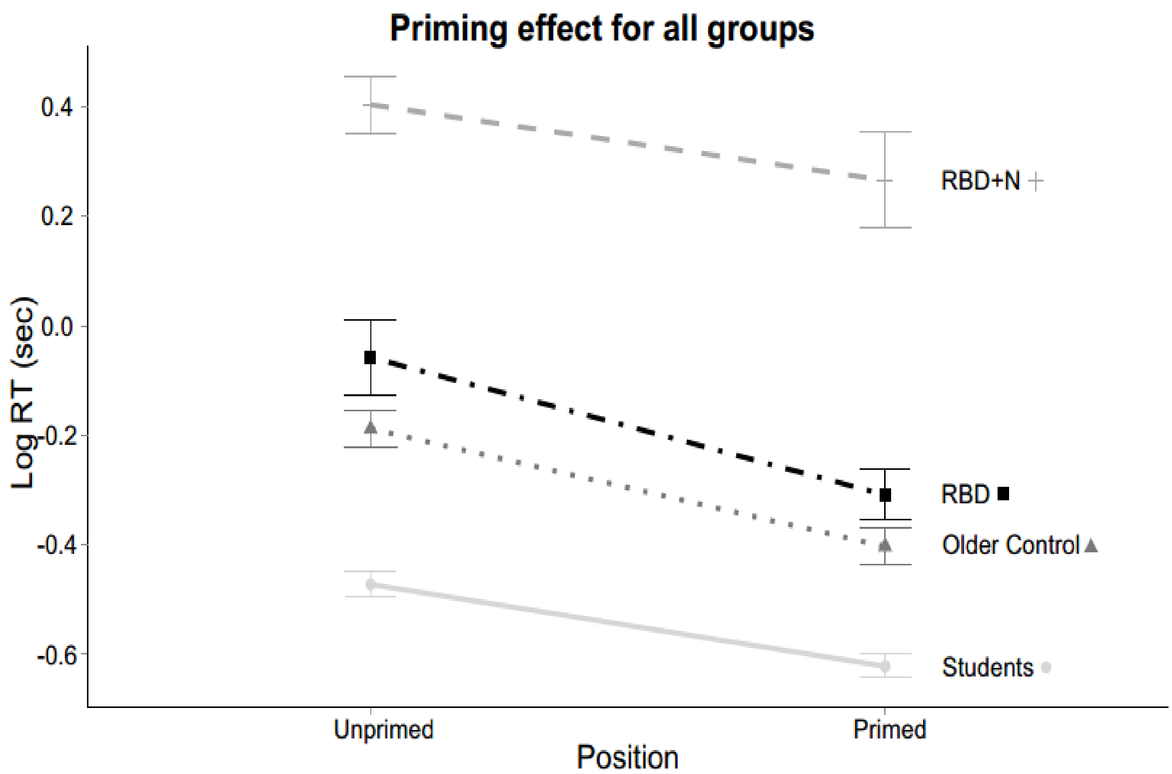

Figure 7. Priming effect for the four groups of participants. *The figure reports the log-transformed RT, as the RT distributions were skewed. All participants had a faster RT when the target was repeated at the same location compared to when it was not-primed and the target was presented in another location. Error bars correspond to standard errors. While there is a large overall effect of participant group on RT, the relative benefit of a spatial repeat seems consistent across groups.*

University students were faster for all trials that successively repeated their position (Figure 7; $F(1, 19) = 116.51$, $p<0.0001$). Increasing numbers of repeats led to significant decreases in RT; trials with exactly one repeat were faster than trials with no repeats ($F(1, 19) = 102.63$, $p<0.0001$), and two consecutive repeats were faster than trials with a single repeat ($F(1, 19) = 14.63$, $p = 0.001$). Finally, when the target was presented three times at the same location, students were faster to respond compared to two repeats (Figure 8; $F(1, 19) = 4.86$, $p = 0.03$).

Healthy older controls showed a similar pattern (Figure 7; $F(1, 20) = 258.27$, $p<0.0001$). Controls responded faster to exactly one repeat compared to no repeats ($F(1,20) = 116.61$, $p <0.0001$), and also to two repeats compared to one repeat (F(1,19) = 33.57, p < 0.001; Figure 8). Although there was a trend towards a faster RT when the number of repeats increased, the results were not statistically significant.

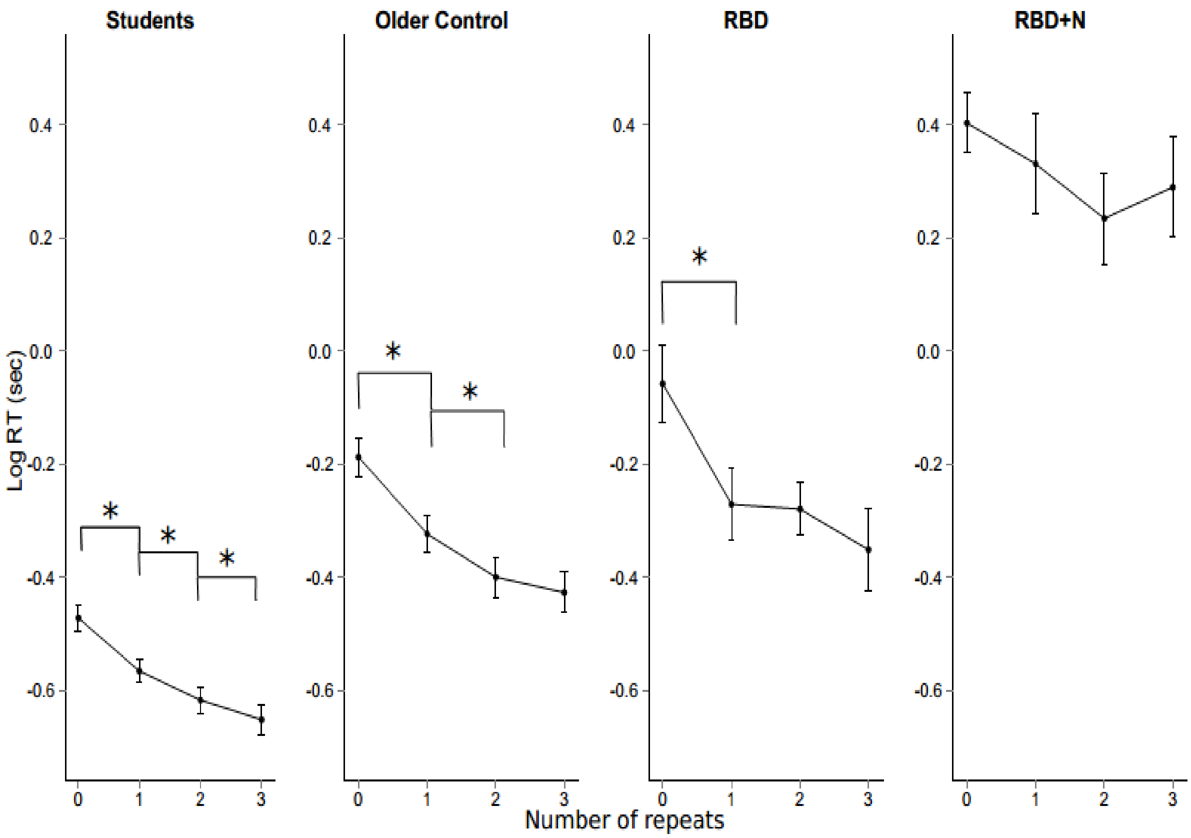

Figure 8. Log-transformed RT of the four groups when the target repeated spatial locations on subsequent trials (up to 3 repeats)*. RBD patients show reduced priming relative to the two control groups, who show increased priming over successive repeats, as the asterisks (indicating statistically significant results; p values in text) highlight. In contrast, RBD+N patients show no incremental priming benefit, and this group has the slowest average RT. Error bars correspond to standard errors.*

RBD participants who had no clinical signs of spatial neglect had a priming effect when aggregating across all trials with a repeat of position ($F(1, 3) = 103.51$, $p = 0.002$). Comparing trials with increasing numbers of repeats (Figure 8) showed the same trend. Trials with exactly one repeat were faster than trials with no repeats ($F(1,3) = 96.71$, $p = 0.002$). RBD patients also showed a trend towards a faster RT when the number of repeats increased, but without reaching statistical significance.

RBD+N patients demonstrated an aggregate spatial priming effect: comparing all trials of the task in which target position switched to all trials with one or greater repeats of target position showed a priming effect ($F(1, 4) = 9.65$, $p = 0.003$). Comparisons between individual trials with no repeats and 1, 1 and 2 repeats, or more repeats, failed to show significant stepwise declines, and the qualitative pattern is also of a less consistent decline (Figure 8).

For comparing the magnitude of the priming effect between groups, we performed an interaction analysis with a two-way ANOVA with group as a factor and with the number of sequential repeats as a covariate. There was a main effect of group ($F(3, 45) = 65.41$, $p<0.0001$), and a significant effect for the number of sequential repeats ($F(1, 45) = 382.32$, $p<0.0001$). The interaction was also significant ($F(3, 45) = 5.61$, $p = 0.002$), and as can be seen in Figure 8, this interaction can be accounted for by the failure of the RBD+N group to have progressively faster RTs with increasing numbers of spatial repeats.

In summary, all participant groups were faster to respond when trials were spatial repeats, that is, when there was spatial priming. However, the RBD+N was the slowest of all the groups; patients' decreases in RT with increasing number of repeats was the least consistent and robust, and the magnitude of the priming effect was less than the healthy older control group.

3.3.2 Statistical Learning Effects

The second goal of the present experiment was to investigate statistical learning and its relation to spatial priming. Although all groups had a faster average RT in the high repeat condition, concluding that this is due to statistical learning is challenging, as the high repeat condition also has the greatest number of primed trials. A more informative comparison is to look at the magnitude of the priming effect and its variation as a function of repeat probability (Figure 9).

For simplicity, we report the statistical analysis of each group individually first and then as a second step, we will report an overall comparison between groups. We started by comparing response speed as a function of whether the trial repeated its position (spatial priming), and whether the trial was in the random block, the block with a high repeat probability or in the block with a low repeat probability. As for the priming effect analysis above, we log-transformed the RT distributions and used the median as a report of the average performance.

Undergraduate students showed a main effect of spatial priming ($F(1,19) = 221.8$, $p < 0.0001$), probability condition ($F(2,38) = 4.6$, $p = 0.02$), and a significant interaction ($F(2,38) = 30.8$, $p < 0.0001$). The interaction can be visualized in Figure 9 (panel A), which shows a crossover. Repeated trials in the high repeat condition are faster than repeat trials in the low repeat condition. And switch trials are faster in the low repeat condition than switch trials in the high repeat condition. In both probability conditions, repeated trials were still faster than non-repeated trials. This resilience of the priming effect is a consistent observation since the study of Nakayama and Maljkovic (1994), who demonstrated that even when participants were informed that switches of the target location or color were highly probable, they were still slower to respond to those trials compared to the primed ones.

Older healthy controls demonstrated a similar pattern of performance for spatial priming ($F(1,19) = 272.7$, $p < 0.0001$). They also showed an interaction between trials that repeated their position with the probability condition ($F(2,38) = 30.2$, $p < 0.0001$).We did not find a main effect of probability condition ($F(2,38) = 0.86$, $p = 0.4$). The interaction is shown in Figure 9 panel B and is qualitatively similar to that of student participants. It also shows that trials with a switch of target position were faster during the low repeat condition, and that trials with a repeat of target position were faster during the high repeat condition.

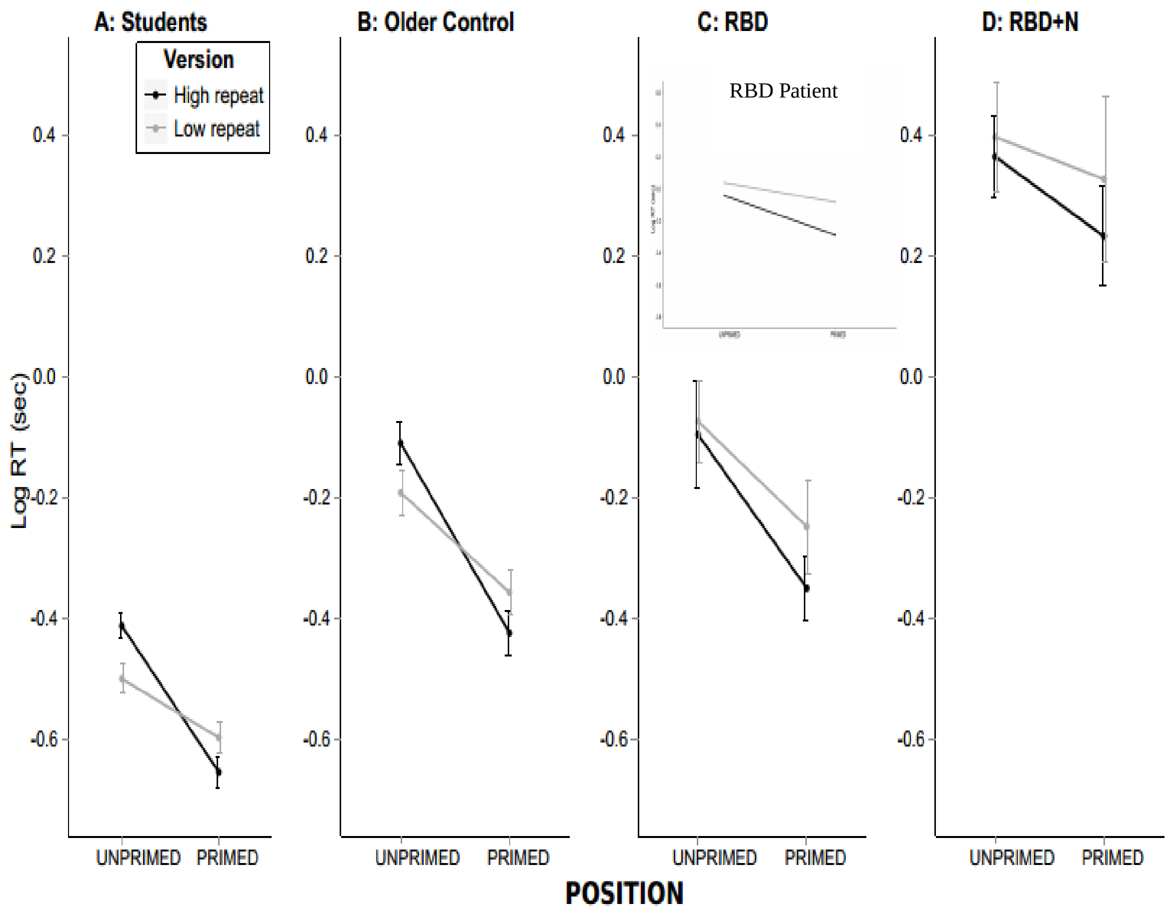

Figure 9: The magnitude of the priming effect as a function of high repeat or low repeats conditions based on the log-transformed RT*. Students (panel A) and older healthy controls (panel B) show an interaction of repeats and condition, as they are faster for repeats of position during the high repeat condition and faster for switches of position during the low repeat condition. RBD patients (panel C) do not show an interaction effect between priming and condition. This group only enhances the magnitude of the priming effect when repeats are frequent. We also plot the results of the one RBD patient whose individual ANOVA yielded a statistically significant interaction (inset panel C); this patient's pattern of performance was qualitatively similar to the RBD group as a whole. There is an improvement for primed trials when repeats are frequent but no increase for unprimed trials when repeats are rare. RBD+N patients (panel D) have a pattern similar to the RBD group, except that no*

individual neglect patient shows any statistically significant effect for priming, condition or an interaction.

RBD participants showed a different pattern: those patients demonstrated an effect of repeated position ($F(1,3) = 70.16$, $p = 0.004$), and a trend for an interaction ($F(2,6) = 4.11$, $p = 0.07$), but RBD patients did not have a main effect of probability condition ($p > 0.16$). However, as can be seen in Figure 9 panel C, there is no crossover for this group, but only the tendency to enhance the magnitude of the priming effect when repeats are frequent.

Because the RBD group has only four participants, and patients' brain injury might make this group heterogeneous, we tested for the consistency of this result by performing ANOVAs on the data of each participant. All four patients showed a main effect when the target position was repeated (all patients have a significant p value < 0.0001), and two patients showed a main effect of probability condition (both patients have a significant p value that was < 0.0003), but only one patient showed an interaction effect ($F(2,424) = 4.28$, $p = 0.01$). This participant is shown as the inset in Figure 9 panel C and demonstrated the same pattern as the group. The group shows that a preserved repetition priming effect is not a sufficient condition for demonstrating statistical learning effects on the RT independent of spatial priming, because there is no apparent effect on non-primed, switch trials, when these trials become frequent.

For RBD+N, the results were different. Whether analyzed at the group level or for each individual participant, neglect patients did *not* show a main effect of repeated position ($F(1,4) = 3.84$, $p = 0.12$; all p values for individual patients were higher than 0.17). This confirms the results we observed for the spatial priming. In addition, neither at the group level nor at the individual level was there a main effect of probability condition (all $ps > 0.07$) or an interaction (all $ps > 0.49$). Figure 9 panel D shows the interaction plot for this group, and is visibly similar to the pattern of the RBD participants.

Individual analyses of the groups revealed that both control groups showed an interaction between the priming effect and condition, but this was not the case for the RBD and RBD+N patients, who only had a main effect for the spatial priming. In order to demonstrate that the two latter groups are impaired in statistical learning and have different results compared to the control groups, we investigated the magnitude of statistical learning across all groups by conducting a three-way ANOVA with group as a factor, whether the trials were primed as a factor, and whether the trial was in the high repeat or low repeat block was a factor. As expected, we found a main effects for group ($F(3, 45)=65.01$, $p<0.0001$), priming ($F(1, 45)=402.38$, $p<0.0001$) and probability condition ($F(2, 90)=5.07$, $p=0.008$). Importantly, the three-way interaction ($F(6, 90)=2.17$, $p=0.05$) demonstrates that the magnitude of the change in priming effect as a function of probability condition is different across the participant groups. As can be seen in Figure 9, this was due to the fact that both control groups showed a cross-over pattern in which unprimed trials were faster during the low repeat condition and primed trials were faster during the high repeat condition, but neither the RBD nor RBD+N groups showed this effect.

3.3.3 Accuracy

In order to determine if accuracy can explain the group differences that we found for priming and statistical learning, we conducted an analysis to test the overall accuracy for priming and statistical learning. There was a significant effect of group on the proportion of correct answers ($F(3,45) = 20.64$, $p < 0.0001$). This was principally due to the performance of the RBD+N group that averaged 85% correct answers, whereas the three other groups were always more than 95% accurate in their responses. In the RBD+N group, two participants had accuracy measures greater than 94%. These two participants showed no appreciable difference from the other three neglect patients on their RT measures for spatial priming, probability condition or their interaction. A three-way ANOVA with group, priming and condition as factors confirmed this group effect ($F(3, 45) = 19.39$ $p<0.0001$), and a very small (~ ½ %), but statistically significant benefit for primed trials ($F(1, 45) = 8.58$, $p = 0.005$), but no higher order interactions (p values > 0.15), and so accuracy effects were not further pursued. As a summary, these results reveal that the fact that repeats were more or less probable did not change participants' accuracy. Thus, although the RBD+N group made more mistakes on the task overall, accuracy cannot provide a simple account of the priming and statistical learning effects observed here.

3.3.4 Timing differences

Our four groups each showed an overall priming effect and each participant improved their RT when the target location was repeated, at least numerically, if not always to a statistically significant degree. This priming effect was robust in the RBD group and less in the RBD+N, and neither group showed the crossover interaction seen in young and older controls (Figure 9). The difference in priming effects coupled with similar statistical learning deficits suggests that a deficit in spatial priming is not sufficient to explain the poor results of the RBD+N group.

It has been observed since the original work of Maljkovic and Nakayama (1994) that priming effects are short lived (lasting for about thirty seconds or 5 to 8 repeats of the same location in a task like ours). Could it be that because our brain damaged participants were slower to respond, the longer interval between two trials made it harder for them to benefit from what they observed in the trial before?

In order to evaluate this hypothesis, we plotted the participants' RTs for trials as a function of the RT on the preceding trial (Figure 10). Except for the general speed advantage of university students, who typically responded in less than 1 sec (see grey areas in the Figure 10 that show the density of the trials based on participant’s log-transformed RT), all participant groups, except for the RBD+N group, showed a similar relation for primed and unprimed targets: fast trials were followed by fast trials and slow trials by slow trials. Confirming that this relation differed across groups, the three-way interaction ANOVA with previous RT as a covariate and group and priming as factors was significant ($F(3, 21821) = 3.226$, $p = 0.02$, all lower order interactions were also significant with all ps < 0.0001). The RBD+N patients showed a different pattern from the other three groups, as can be seen in Figure 10, RBD+N were most different when stimuli switched their position from one trial to the next, as fast trials were followed by slow trials. In addition, the relation between RT and prior RT was flatter for primed trials.

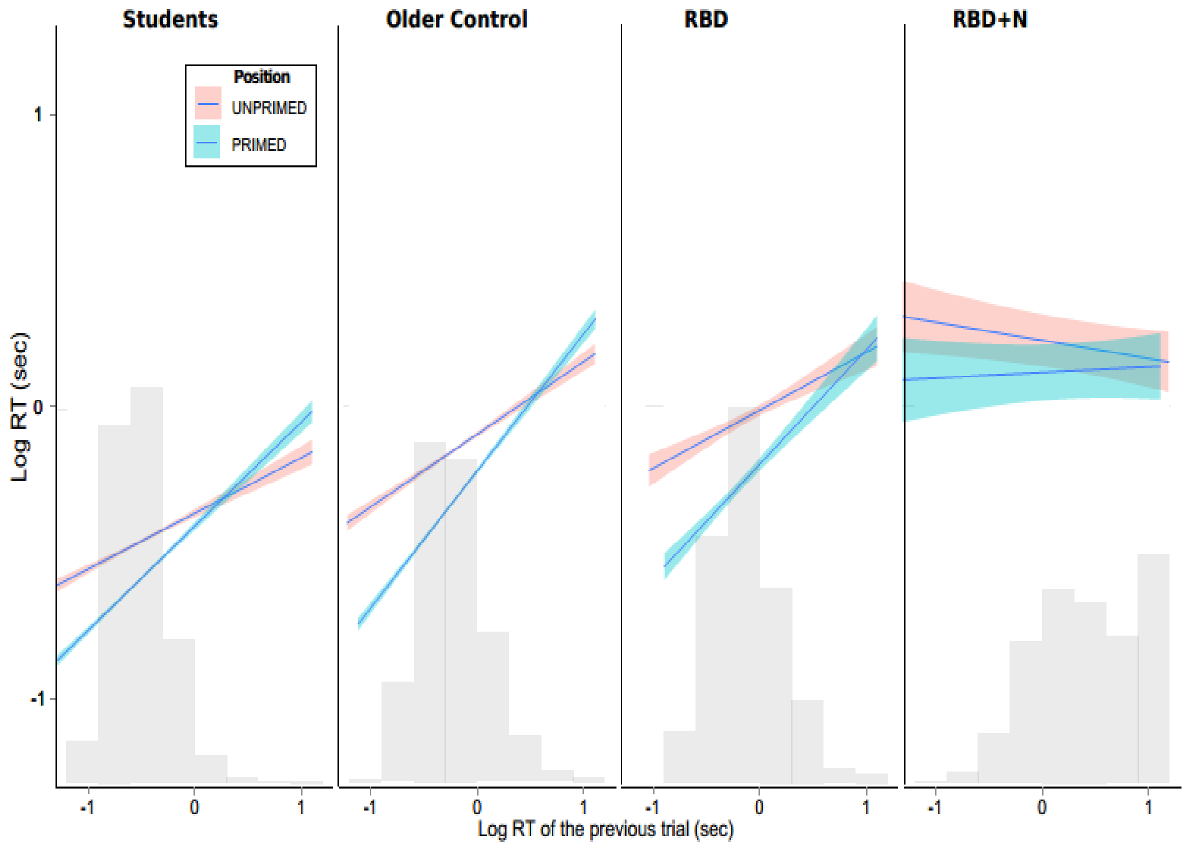

Figure 10. Log-transformed RT compared to the log-transformed RT on the previous trial*. The grey bars are the histograms for the proportion of trials at each time interval, and are included to give a general overview of RT distributions. University students responded to most of the trials in under 1 sec and therefore had a shorter interval between trials. Healthy older participants had almost an identical pattern where the regression line of repeated targets is almost parallel to the non-primed trials for most of their trials. But the RBD and RBD+N showed the largest difference between the primed and non-primed trials. When they responded fast to a prior trial, those two groups benefited more from the priming effect than when they were slow to respond. Finally, the RBD+N group shows a different pattern from the other groups, participants are greatly affected by the switch of the position, as well as by their RT on the previous trial. When the prior trial was fast, and the location switches, there is a large cost for RT. As RBD+N patients had the slowest RT of all the groups, we hypothesize that their poor statistical learning may be in part an artifact of their overall slower response time profile.*

3.4 Discussion

We tested location priming and statistical learning in four groups: university students, older healthy controls, RBD and RBD+N participants. The four groups performed three conditions; random, high repeat and low repeat, that allowed us to investigate if each group showed a priming effect, and whether this effect was modulated by repeat probability. The design of our experiment, in which we presented all the stimuli in the middle of the screen, made it possible to examine for these effects without having to consider lateralization effects due to the side of the patients' lesions. This experiment was motivated by our prior work that showed an anomaly of statistical learning (Shaqiri and Anderson, 2012), and by other studies that demonstrated a variety of non-spatial impairments in patients with neglect (Husain et al., 2001; 2003; Danckert and Ferber, 2006; Samuelsson et al., 1998).

We started by testing students and healthy older participants in order to replicate, with our modified version of the task, the main findings of prior studies on the spatial priming effect. In accordance with previous research (Maljkovic and Nakayama, 1994; 1996; Kristjansson et al., 2005; 2007; Hillstrom, 2000), both our control groups demonstrated a priming effect for up to two repetitions of the same location, which is less than the 5 to 8 trials reported by Maljkovic and Nakayama (1994). This difference could have several causes, such as the total number of trials that were presented or the interval between them. We also varied the sequences of trials, which could have affected the overall benefit from spatial priming.

The RBD group also demonstrated an overall priming effect, and each individual patient in this group had a significant statistical benefit for spatial priming as well, showing a sensitivity for the repeat of the position, despite their lesion. This was not the case for the neglect patients. Although the RBD+N group demonstrated an overall priming effect, an individual analysis of each patient revealed that none of the neglect patients achieved a statistically significant spatial priming effect. This highlights an important difference between the two groups: although RBD and RBD+N both have lesions of the right hemisphere, clinical neglect is an important predictor of a greater impairment in benefitting from short term environmental regularities.

One possible explanation for the difficulty that RBD+N patients have in benefiting from spatial priming may be timing. Maljkovic and Nakayama (2000) tested the importance of timing in the priming effect and found that short-term implicit memory is involved in this process. The authors discovered that priming is cumulative, but can decay if the interval between the trials is too long (between 30 and 90 sec). Although the authors did not find a difference in priming if the interval between the trials was from 1 to 3 sec, they reported that if participants directed their attention somewhere else or made eye movements during that interval, or if they performed a distracting task, the priming effect was affected and decayed faster.

Although our participants were not subjected to any distractors between trials, the fact that they benefited less from the priming effect during slow trials might reveal that they had more time to make eye fixations somewhere else on the screen, and this could have contributed to a decreased priming effect. Even though the spatial dimensions of our displays are small, a slight adjustment of eye position, as a consequence of learning when targets were likely to repeat or switch, could translate into faster responses. Measuring eye movements in brain damaged participants is challenging though, and the apparatus for eye position recording can influence gaze patterns as well. Therefore, we did not measure eye position for these studies. Now that we have confirmed an effect, additional experiments incorporating eye movement recording would provide useful information for understanding the absence of statistical learning observed in our brain damaged participants.

Another possible explanation for our group effects are “resetting” differences - as theorized by Serences and Yantis (2006) - who suggested that the attentional network is recruited every time there is a new state, as for example a switch of the position after a few repeats. This reset might explain the additional time needed by some participants when responding to trials that changed position. These effects are most visible for RBD+N patients, who exaggerate this pattern until it is observed after a single switch of position. RBD+N patients showed some benefit when a relatively fast trial was followed by a spatial repeat, but not when the stimuli changed location - the RBD+N group became very slow when the position was switched, even though the previous trial was fast. This was not the case of any of the three other groups. The underlying deficit of the attentional network for these patients might explain why the resetting action (Serences and Yantis, 2006) is more prominent for the patients suffering from spatial neglect.

Task demand could also contribute to the results of RBD+N patients. Dukewich and colleagues (2012) tested visuospatial neglect patients on a RT cued task and on a temporal order judgment (TOJ) task, by asking them to respond to a red or blue pinwheel. After finding a disengagement deficit for the RT task but not for the TOJ task, the authors hypothesized that because the action system needed to be recruited for the RT task, but not for the TOJ, there were different task demands. Our paradigm required our participants to disengage from the previous position (if the target location switched) and they also needed to recruit the action system in order to respond to the trial as quickly as possible. A disengagement deficit, a major symptom of neglect (Posner et al., 1982; Dukewich et al., 2012), might be most apparent on trials where target positions switch.

In addition, neglect patients have difficulty selectively attending to task relevant information, even in their "good" visual field. This has been shown previously for flanker type tasks (Ptak and Schnider, 2010; Snow and Mattingley, 2005; Danckert et al., 1999). In our task, the relevant target is defined by its color relative to the other two distractors. A failure to selectively attend to the target position could obscure the pertinent statistical relation. The difficulty of keeping in mind sequential relation between trials could have consequences for the capacity to learn longer time frame statistical distributions.

In summary, the present study showed that RBD+N in particular have a deficient spatial priming effect, even when targets are presented at the mid-line in a small number of predictable positions. Further, both RBD+N and RBD have an impairment in statistical learning of spatial information. Patients with an impairment in these functions will be less sensitive to environmental regularities and as a result, could be reasonably expected to have increased difficulties in functional activities and rehabilitation. Thus, impaired implicit learning of environmental regularities and sequential effects is a potential target for rehabilitation

Chapter 4: Primacy of auditory statistical learning[4]

4.1 Introduction

Our environment contains a multitude of stimuli and events that occur simultaneously and that challenge our perceptual and sensory systems. Because we are faced with more information than we can process, we have developed strategies to access relevant or targeted objects faster. One of those strategies consists of using prior experience or regularities from the environment to guide behavior, a phenomenon known as statistical learning (Saffran et al., 1996; for review see Turk-Browne, 2012; Aslin and Newport, 2012). Statistical learning implicitly directs attention towards regularities in the environment – without any information or feedback – as the learning occurs only through exposure (Aslin and Newport, 2012). Although statistical learning is robust and domain general, its saturation point or limits are not well known. Are we able to learn numerous structures if they have a regular distribution? Does learning a first structure interfere with learning a second one? Moreover, does explicit information influence the learning process? In order to investigate the latter aspect, as well as the limits of statistical learning, we tested participants' ability to learn two structurally different languages. The results will inform us about the possible limits of statistical learning and if explicit information influences this robust process and its use as an attentional cue (Shaqiri and Anderson, 2012; Druker and Anderson, 2010).

The benefit of statistical learning for directing attention has been extensively investigated in multiple domains and within different populations. Saffran and colleagues (1996) studied the ability of 8-month-old infants to extract the underlying structure of a language from a continuous stream of speech made up of nonsense words, composed of three syllables each. The only information about the "words" in this language was the transitional probability between syllables and between words. After only 2 minutes of exposure, infants were able to correctly identify the words, demonstrating an early ability to use statistical information for speech segmentation. Those results have been confirmed in neonates in event related potential (ERP) studies that used a similar stream of words. Teinonen and colleagues (2009), found that babies' ERP negativities were different based on the position of the syllables in the words and concluded that neonates were able to notice the transitional probability that marked the word boundaries. Other studies using tones with non-linguistic structures (Saffran et al., 1999), visual stimuli (Fiser and Aslin, 2002; Bulf et al., 2011, Turk-Browne et al., 2005), tactile

[4] A version of this chapter has been submitted at the Quarterly Journal of Experimental Psychology (Shaqiri, Danckert and Anderson, under review).

stimuli (Conway and Christiansen, 2006), or using backward transition probability (given AB, the probability that B has been proceeded by A; Perruchet and Desaulty, 2008; Pelucchi et al., 2009; Jones and Pashler, 2007) have shown similar results.

We recently extended this research to a visual discrimination task in which we examined young adults' abilities to learn the spatial distribution of targets that we manipulated to appear 80% of the time within a high probability region (Druker and Anderson, 2010). We found that although participants were not explicitly aware of the biased distribution of target locations, they were faster and more accurate to detect targets presented within the high probability region, demonstrating a learning of the underlying spatial distribution. This was not the case in patients with right hemisphere lesions, who were impaired in this task (Shaqiri and Anderson, 2012; 2013).

The aforementioned studies (Bulf et al., 2011; Fiser and Aslin, 2002; Druker and Anderson, 2010) and others have demonstrated that statistical learning is a robust phenomenon found in different modalities (Mitchel and Weiss, 2011; Conway and Christiansen, 2006) and present in different subject populations, from newborn infants to older participants (Bulf et al., 2011; Shaqiri and Anderson, 2012; Conway et al., 2010; Karuza et al., 2013). Most of those studies have nevertheless presented continuous and unique stimuli to participants, and have demonstrated the robustness of statistical learning when participants had to learn a single structure. As we will show in subsequent sections, statistical learning can be subject to interference when more complex paradigms are used.

4.1.1 Influence of initial context

The majority of studies investigating statistical learning have used stimuli with a unique distribution (for a review, see Turk-Browne, 2012; Newport and Aslin, 2012), but in everyday life, we are faced with multiple structures, and it is often necessary to switch from one set of regularities to another, in order to successfully interact with the environment (Danckert et al., 2012a, b). Because statistical learning has been shown to be a robust and long-lasting phenomenon (Jiang et al., 2012), recent studies have explored its malleability by investigating the influence of initial context and the interference from prior and subsequent statistical structures (Gebhart et al., 2009; Conway and Christiansen, 2006; Franco et al., 2011).

In a very elegant study, Jiang and colleagues (2012) demonstrated that statistical learning occurs really fast but it has a slow extinction once the learning has occurred. In their study, participants responded to a target among distractors, with targets appearing 50% more often in one quadrant of the computer screen than the rest of the screen. Results showed that participants only needed about 100 trials to become significantly faster to respond to targets presented in the high probability quadrant compared to the rest of the screen. But when, during the second part of the experiment, the location of the target became uniform, participants persisted in showing shorter reaction times for the previously biased quadrant. This bias in responding took more than 500 trials to extinguish, and persisted for at least one week. This study shows the persistence of statistical learning, and raises the question of whether it is possible to learn a distinct second statistical structure after a first structure has already been acquired (i.e., a primacy effect; Staudingel and Bücher, 2013; Werker and Curtin, 2005).

To test this question, Conway and Christiansen (2006) presented participants with two sets of stimuli in both the visual and auditory modality. In a first set of experiments, the authors tested multimodal statistical learning by presenting participants with pure tones generated from one grammar and colored shapes generated from a second grammar. The authors found that participants learned the two different statistical distributions presented in different modalities with the same efficiency. They also found that participants learned the statistical distribution of two stimuli that were presented in the same sense modality but that were perceptually different (such as shapes and colors for the visual stimuli). Interestingly, this was not the case when the stimuli were presented within the same perceptual dimension (for example two set of shapes). In this condition, participants learned only one structure and failed to learn the second one. The authors suggested that this could have occurred because the shapes were too similar and participants perceptually confused them (Conway and Christiansen, 2006). Other studies have also demonstrated that when two structures are presented within the same perceptual dimension, participants learn the first structure better than the second one (Weiss et al., 2009; Gebhart et al., 2009; Franco et al., 2011). Those results correspond to what Perruchet and Pacton (2006) call interference, or the difficulty to learn the underlying distribution of the target due to prior or subsequent information.

Although most of those studies report a primacy effect, this condition does not seem to be immutable. In a specific condition in which the two structures were separated by a 30 second pause and participants were informed of the significance of the pause, Gebhart and colleagues (2009) found that the primacy effect could be overcome and participants were able to learn two language structures to the same extent. Does explicit information given to participants help their learning ability? As we reported earlier, the study of Druker and Anderson (2010) and numerous other studies have reported the implicit nature of statistical learning (Fiser and Aslin, 2002; 2005). Indeed, Conway and

Christiansen (2006) have even merged those two expressions to "*implicit statistical learning*", showing, as Perruchet and Pacton (2006) reported, that those two phenomena are often considered as similar, as they both occur automatically and without awareness (Turk-Browne et al., 2005). Nevertheless, Franco and colleagues (2011) have questioned if we can consciously control the information acquired via statistical learning. Testing participants with two different artificial languages, the authors found that subjects were able to correctly identify the words of each language and then exclude the words from a language when instructed to do so. The authors concluded that participants have conscious knowledge and control over the learned information. As it will be reported below, the implicit or explicit aspects of this phenomenon are important and will be explored in the present study.

4.1.2 Our study

The different studies discussed above reveal that statistical learning is a fast and robust phenomenon when subjects are first confronted with structured stimuli, but also that there are limitations in adapting to new information. In order to investigate this aspect further and motivated by the condition mentioned above, in which participants were able to overcome the primacy effect, we replicated and extended the paradigm of Gebhart and colleagues (2009). We presented participants with two structurally different but perceptually similar languages, with or without a break, and also manipulated whether they were informed about the significance of the break in the auditory stream (i.e., it signaled the transition from language one to language two). We chose this paradigm because previous studies have demonstrated that participants have difficulties learning two perceptually similar structures (Conway and Christiansen, 2006) and our goal was to investigate if this difficulty can be overcome with a break between the two languages, explicit information about the presence of two languages, or both. The most important aspect of this study is the information given to participants: would this explicit information about the second structure influence their learning ability? Moreover, we manipulated the break between the two languages in order to investigate if having an extremely short (2 seconds) or longer break (30 seconds) will also have an influence on this phenomenon. Given the results of Gebhart and colleagues (2009), we made the hypothesis that in the conditions when participants are given information about the two languages, they would be able to learn both languages to the same extent. We did not believe that this would hold true for the conditions in which participants had only a break between languages, without being informed about its significance. As has been demonstrated in different studies (Conway and Christiansen, 2006; Jiang et al., 2012), statistical learning is a robust phenomenon that lasts for days, therefore we conjectured that a 2 or 30 seconds break would be too short to interfere with the learning and retention of the first structure and should allow participants to also learn the second language.

4.2 Methods

We report six different experiments that investigated auditory statistical learning in university students. The experiments and their methods are described briefly, as they replicate methods from published studies (Gebhart et al., 2009) and used identical stimuli (kindly provided by Dr. Richard Aslin, University of Rochester). Experiments 1, 2 and 6 replicate the experiments reported in Gebhart and colleagues (2009), whereas Experiments 3, 4 and 5 extend the paradigm and will be described in more detail. Experiments 2 and 6 were done in order to lay the groundwork for using the same materials and methods in a subsequent study of older healthy controls and brain damaged patients, tested for the presence of statistical learning (Shaqiri et al., 2013).

Ninety-two (60 female; mean age=20 years, SD=2.25) undergraduate students from the University of Waterloo participated in the experiments for course credit. All participants reported English as their principal language. The Office of Research Ethics of the University of Waterloo approved the research and all participants gave written informed consent to participate in the study.

4.2.1 Apparatus and stimuli

The different experiments used two languages, A and B, composed of 16 tri-syllabic nonsense words that were made using the same combination of six vowels (a, ae, e, i, o, u) and six consonants (b, d, k, p, s, t). The vowel frame was kept constant and the consonants could vary between the words, with two possible consonants for each vowel frame (See Table 3: for example, some of the words from language A were "*dakube*", "*pagute*", "*dokibae*" or "*pogitae*", where the vowels a, u, e and o, i, ae formed a constant frame, and the consonants changed). The syllables of Language A and B overlapped by 50%. Each language was formed by six blocks, with a constrained order for each of the 16 words of the language (the same word was never repeated twice).

The main manipulation of the experiment was the transitional probability of the constant vowel[5] frames within and between words. First of all, the vowels within words had a transitional probability of 100%, such that the first vowel was always followed by the same second vowel, and the second vowel by the same third vowel. In contrast, the transitional probability between words was 50%, such that the last vowel of a word could be followed by 2 different vowels.

Table 3*: Language A and D both have 16 words each. Words were made using a vowels frame that is constant and consonants varied. For language A The first 8 words are made using the vowels A, U, E and the consonants d, k, b, p, k, t and the next 8 words use the same consonants with the vowels frame O, I, AE. For language B, the same consonants and vowels were used in a different order: 8 of the words were made using the vowels frame U, AE, I and 8 other words used the vowel frame E, O, A and the consonants fillers were b, p, g, t, d, k.*

LANGUAGE A		***LANGUAGE B***	
16 words		***16 words***	
Consonants: D, K, B, P, G, T		**Consonants: B, P, G, T, D, K**	
Vowels frame:	Vowels frame:	Vowels frame:	Vowels frame:
A, U, E	O, I, AE	U, AE, I	E, O, A
Da Ku Be	Do Ki Bae	Bu Pae Gi	Be Po Ga
Da Gu Be	Do Gi Bae	Bu Dae Gi	Be Do Ga
Da Ku Te	Do Ki Tae	Bu Pae Ki	Be Po Ka
Da Gu Te	Do Gi Tae	Bu Dae Ki	Be Do Ka
Pa Ku Be	Po Ki Bae	Tu Pae Gi	Te Po Ga
Pa Ku Te	Po Ki Tae	Tu Pae Ki	Te Po Ka
Pa Gu Be	Po Gi Bae	Tu Dae Gi	Te Do Ga
Pa Gu Te	Po Gi Tae	Tu Dae Ki	Te Do Ka

[5] Although some studies have demonstrated that probability based on consonants are more easily learned than probability based on vowels (Bonatti et al., 2005; Hochmann et al., 2011), Gebhart and colleagues (2009) did not find any difference between consonant or vowel frames in their study, therefore we decided to use vowel frames here.

The goal of the study was to test participant's abilities to learn to recognize the words using only the information contained in the transition probabilities. Therefore, there were no cues to word boundaries other than the statistical distribution of the constant vowel frame. Breaks between the words were removed and the words were produced by a speech synthesizer, avoiding any clue given by the tone of the reader (see Gebhart et al., 2009, for more details). The condition for the composition of each language was that the same word would not be successively repeated and the last syllable of each word would be followed by the initial syllable of the two other possible words.

We used an mp3 player and two pairs of headsets (that were linked to the mp3 player with a headphone splitter) to present the stimuli. This was done so the experimenter could listen to the stimuli along with the participants, and make sure they were hearing the sounds correctly and without interference. Participants were seated in a quiet testing room and were instructed to listen attentively to the continuous speech sound that sounded like a foreign language. After participants listened to one or two languages (based on the experiment), they did a two alternative forced choice test. The forced choice test was made by pairing words with part-words. The latter were made by changing the word borders. Part-words had a pattern of 3-1-2 or 2-3-1: meaning that a part-word was made with the last syllable of a word (3) and the two initial syllables of another word (1-2), or made with the last two syllables of a word (2-3) and the initial syllable of another word (1), respectively. Pairing 4 nonsense words with 4 part-words resulted in a test of 16 pairs, when participants listened to only one language, or 32 pairs when they were presented with two languages. For the forced-choice test, participants heard a series of "questions" structured as two speech streams separated by a short break. After hearing each pair of words, the participant was asked which sounded more familiar.

4.2.2 Experiments

Our undergraduate students were tested in six different experiments (see Table 4). Each participant was tested only in one experiment. Three of the experiments (1, 2 and 6, indicated with asterisks in Table 4) replicated the methods of Gebhart and colleagues (2009), and three other experiments (3, 4 and 5) represented modifications, including adjustment of the duration of the break between the two languages.

4.2.3 List of the 6 experiments

Table 4: *List of the six experiments conducted for this study. Experiments 1, 2 and 6 (indicated with asterisk) are direct replications of the study of Gebhart and colleagues (2009). Whereas experiments 3, 4 and 5 are modifications of the duration of the break (experiment 3 and 4) or the information given to participants about the presence of a break separating two different languages (experiment 5). The number in parenthesis next to each experiment indicates the number of participants. We tested more participants for experiment 2 and 6, as those are replications of Gebhart and colleagues (2009), and also, in order to compare those results with brain damaged patients to be tested in a subsequent study.*

	One Language	**No Break**	**2 Sec Break**	**30 Sec Break**	**Information**
Experiment 1* (N=12)	X				
Experiment 2* (N=25)		X			
Experiment 3 (N=10)			X		
Experiment 4 (N=10)			X		X
Experiment 5 (N=10)				X	
Experiment 6* (N=25)				X	X

The number of participants differed for some of the experiments for two main reasons; First of all, we found that there were no statistical differences when participants heard language A first or when they heard language B first (see below), thus we fixed the order of the languages to be played and this allowed us to reduce the recruitment for some of the experiments. The second reason why we had a larger number of participants for experiments 2 and 6 is that these two experiments were key replications of Gebhart and colleagues (2009).

In experiment 1, we tested 12 participants for five minutes with one language (7 participants with language A and 5 participants with language B for five minutes). The second experiment consisted of 25 participants listening to a language A and B presented without a break, for 10 minutes. The third experiment involved 10 participants listening to a first language, and after a 2 second break, the second language. Participants were not informed about the break. The fourth experiment was similar to Experiment 3, except that the 10 participants were informed that a break of 2 seconds would divide the two languages. Finally, the two last experiments were similar to Experiments 3 and 4, except that we prolonged the duration of the break to 30 seconds, in order to replicate the study of Gebhart and colleagues (2009) exactly. For the fifth experiment, we had 10 participants listen to the first language for 5 minutes, followed by a 30 sec break before they listened to the second language. For the sixth experiment, participants were informed of the break, as was the case in the study of Gebhart and colleagues (2009). Twenty-five participants listened to the first language, they were told they would have a break of 30 seconds, followed by presentation of the second language.

4.3 Results

The goal of the present study was to investigate whether young adults learn implicitly the word borders of a synthetic language after only a few minutes of passive listening. If they do, is this capacity limited to one language or can it be done for more, and is this learning of two languages also implicit or does it require explicit information about the presence of more than one language? Largely, these experiments are an effort to replicate the study of Gebhart and colleagues (2009) but we also extended the protocol further, and this was motivated by our interest in using this same protocol to test the statistical learning of older individuals with and without focal brain damage (Shaqiri and Anderson, 2012; 2013).

4.3.1 Experiment 1: One language presented

When participants listened to only one language, they recognized as familiar the words from the synthetic language. Participants were not different in their performance for language A and language B ($F(1, 10) = 0.01$, $MSE = 448.44$, $p = 0.9$). When we investigated their performance for each language, we found that participants learned both language A (81.25% correct) and language B (82.5%) at above chance levels (for language A $t(6) = 3.17$, $p = 0.01$, $d = 1.2$; for language B $t(4) = 7.07$, $p = 0.002$, $d=3.16$). Our results are similar to those reported by Gebhart and colleagues (2009), as the authors found an average of 79.30% of correct answers when they had participants listen to only one language (blue line represented in Figure 11).

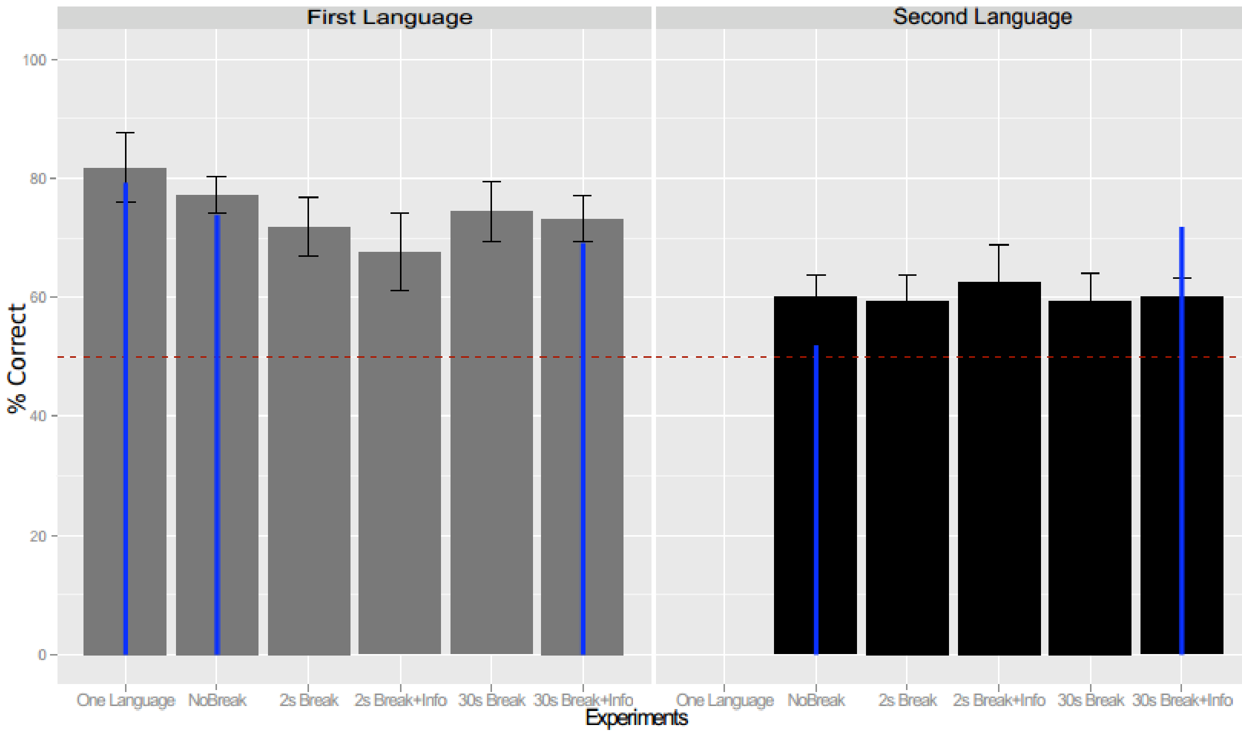

Figure 11. Participants' performance for the six experiments. *The left panel represents the percent of correct identifications of words for the language presented first and the right panel for the second language. For the first experiment, participants identified more than 80% of the words of the language. This performance dropped when they were presented with two successive languages, although the first language still remained above chance (50% is represented by the red dotted line). But as can be seen on the right panel, the performance for the second language was highly impaired, once a first language had been learned. The breaks or information between languages did not make any difference in participants' performance and their difficulty learning the second language. The blue lines represent the results of Gebhart and colleagues (2009): only the second language for the 6th experiment (30 second break and information) was different from our studies.*

4.3.2 Overall performance in all Experiments (2, 3, 4, 5 and 6) with two languages

In order to explore the impact of the break or explicit information for the different experiments, we started by investigating whether participants performed differently in all five experiments, in which we presented both languages A and B (Figure 11). Participants did not show a statistically significant difference on the forced choice test based on the experiment ($F(4, 155) = 0.19$, $MSE = 338.75$, $p = 0.94$). They also did not show a difference based on the break between the two languages ($F(2, 157) = 0.37$, $MSE = 334.48$, $p = 0.7$) or whether they were informed that the break separated two distinct languages ($F(1, 158) = 0.23$, $MSE = 334.46$, $p = 0.62$). Finally, participants' overall performance revealed that they were better at recognizing the words from the first language presented compared to the second language presented ($F(1, 158) = 25.74$, $MSE = 338.76$, $p<0.0001$). This is also highly visible in Figure 11, where it can be seen that the first language is always learned better than the second, and this holds true for all the conditions where two languages were presented. Although participants were better at recognizing words from the first language and learned them above chance (with 73.75% of correct answers, $t(79) = 12.24$, $p<0.0001$), they also learned the second language above chance (with 60.15% of correct answers, $t(79) = 5.49$, $p<0.0001$).

As a second step, we performed an interaction analysis on the different factors mentioned: condition, order, break and information given to the participants. None of the 2x2 first order interactions based on those factors were significant (all p values > 0.37).

Finally, because all of our experiments indicated that participants learned the first language better than the second language, we conducted an analysis to investigate whether having a break or having information about the break would influence participants' ability to learn the first language or the second language differently based on the condition. Participants did not learn either the first or second languages differently across the different experiments (language 1 – $F(4, 75) = 0.64$, $MSE = 307.19$, $p = 0.6$; language 2 – $F(4, 75) = 0.05$, $MSE = 286.98$, $p = 0.9$; Figure 11).

4.4 Discussion

In the present study, each of the healthy young participants participated in one of the six experiments: participants were tested for their abilities to learn the underlying statistical structure of two languages, in conditions in which the transitional probability was the only information available or when participants were explicitly informed about the presence of a second structurally different language. The goal of our research was to investigate to what extent participants were able to learn the statistical distribution of each language and whether explicitly informing them about a second language would influence their learning abilities. This research was motivated by the study of Gebhart and colleagues (2009) in which the authors demonstrated that, when faced with two different languages, participants were not able to learn the second language as well as the first one (demonstrating therefore a primacy effect; Dennis and Ahn, 2001; Werker and Curtin, 2005), unless they had a break between the two languages and were informed of that. When the experimenter made explicit the presence of the second language, participants learned both structures to the same extent. The authors concluded that we tend to learn the underlying statistical structure of the first stimuli that we are faced with, and that the second structure is only learned if we explicitly know that the two structures are different and separated by a noticeable cue.

In the present study, we manipulated the presence of the break, its duration and the information given to participants in order to test for the possible limits of statistical learning (in the second experiment, when the two languages were presented without a break) and also, the influence of explicit information (in experiment 4 and 6, when we informed participants about the break and the two languages). The results of the experiments demonstrated that based on the condition, both the first and the second language can be learned at a level that exceeds chance, despite the first language being learned to a higher level than the second. Moreover, the experiments have shown that the difficulty in learning the second language to the same extent as the first cannot be overcome by breaks of varying lengths or by giving participants explicit information regarding the breaks and the presentation of two distinct languages. Therefore, neither a break, nor information status, fundamentally alters the primacy effect and demonstrates the robustness of the first structure learned.

Our study replicated the results of Gebhart and colleagues (2009) for the experiments where the two languages were presented without a break, as we also found that participants learned the first language better than the second one. Those results correspond to a primacy effect (Dennis and Ahn, 2011; Collins and Shanks, 2002), where learning a first structure influences the learning of the structure presented later on. Numerous other studies have also found similar results. For example, Franco and colleagues (2011) also presented participants with two artificial languages; they presented a first language that was immediately followed by a second one. The authors found that subjects learned the first language significantly better, although both languages were learned above chance. Comparable results were also found by Conway and Christiansen (2006) who found that when participants were asked to learn two perceptually different structures between or within modalities, they performed the task perfectly and learned both structures above chance. But this was not the case when perceptually similar structures were presented within modalities. In that case, only one structure was learned. Finally, Jungé and colleagues (2007) also demonstrated the importance of the structure to which we are exposed first. In their study, participants were exposed to a predictable environment first then a noisy or unpredictable environment (and vice versa). The authors found that when participants were exposed to the predicable environment first, they learned the underlying statistical distribution of the target, but not when they were exposed to the noisy environment first, although participants had the same overall exposure.

Those different studies highlight the limits of our ability to learn statistical distributions. We are only able to learn a single structure within the same perceptual dimension, but in return, this ability is extremely robust and long lasting, as has been demonstrated by Jiang and colleagues (2012). The authors found that it takes only a few hundred trials to learn the statistical distribution of a target, but this learning can last for weeks and influence subsequent behaviors. This robustness of the first structure learned can also explain why our participants did not perform differently for the second language when they were exposed to a 2 or 30 seconds break: this interval was too short to affect the first structure learned and allow for a second structure to be acquired with the same efficiency as the first one. This is also in accordance with a study of Maljkovic and Nakayama (2000), who found that participants could accumulate information about the spatial position of a target if the break between the trials was less than 90 seconds. When the interval between two trials exceeded that time, participants did not benefit from the previous target location anymore and did not demonstrate a benefit in their reaction time when the same location was repeated. Maybe in future studies, longer breaks should be considered in order to test the robustness of the statistical structure that was learned first.

Finally, those different studies are also in line with our second set of results, in which we found that explicitly informing participants about a second structure did not improve learning of the second language, which is different from the finding of Gebhart and colleagues (2009). When we informed participants about a break separating two structurally different languages, they did not learn the two languages with the same efficiency. Statistical learning is considered an implicit phenomenon and numerous authors report it as being a synonym of implicit learning (for a review, see Perruchet and Pacton, 2006), which implies that it occurs without awareness. This phenomenon is also sometimes referred to as incidental learning (Saffran et al., 1997), as the learning occurs without real intention to learn the structure of a language, while participants perform a primary or main task (such as creating computer illustrations while listening to the stimuli in the study of Saffran and colleagues, 1997). Because of its implicit nature, this phenomenon might be difficult to influence explicitly and that could explain why we did not find that participants performed better on the second language when they were made aware of it. Similar results have also been found by Maljkovic and Nakayama (1994) who tried to explicitly inform participants about the recurrence of a target position, without successfully influencing their performances. Indeed, in their paradigms, the authors biased the probability that the target would repeat position or switch position. The authors revealed that when the target was set to switch its position every other trial and they informed participants about it, subjects were not able to benefit from this information and adapt their behavior to this bias. Franco and colleagues (2011) results also confirm this aspect: although the authors found that participants had a conscious control over the learned statistical structure, they still learned the first structure better than the second one. This demonstrated that conscious information and awareness have little influence over the implicit phenomenon that is statistical learning.

In conclusion, we demonstrated that statistical learning is a phenomenon that has limitations and that can be saturated after one underlying structure has been learned. In our study, participants learned the first and the second language above chance, but the acquisition of the second language was worse than the first language. We believe that statistical learning is robust when the information to learn is simple, predictable and presented alone, but when other perceptually similar structures have to be learned, the first structure is favored in this phenomenon. Moreover, our study confirms the robustness of this implicit phenomenon, as we did not find that explicit information or a break influenced participants' performances compared to when they were not given any information.

Chapter 5: Auditory statistical learning and brain damage

5.1 Introduction

Brain damaged patients fail to detect and use regularities from the environment to guide their behaviour. For example, patients with right hemisphere lesions tend to forget which locations they have searched and may treat old, revisited items as new (Husain et al., 2001). They may also be unaware of their deficits, although they are confronted daily with the effects of their brain lesion (McGlynn and Schachter, 1989). These difficulties may explain why rehabilitative prospects are worse for right brain damaged patients (RBD) than for patients with left brain damage (LBD), as most rehabilitation techniques rely on repetition (Shimodozono et al., 2013; Bowen et al., 2007; Appelros et al., 2002; Cassidy et al., 1998). These examples emphasize why deficits in statistical learning may be a critical component of brain injury and why statistical learning may need to be considered when designing and planning rehabilitation programs.

As discussed in the previous chapters (2, 3 and 4), statistical learning is the ability to learn, through exposure and without any feedback, contingent relations. Only a limited number of studies have investigated statistical learning in brain damaged patients. Those studies, reported in Chapters 2 and 3 (such as for example the studies of Geng and Behrmann (2002, 2006)), have found that neglect patients can use spatial probability as an aid to direct their attention. But some authors (Walthew and Gilchrist, 2006) questioned if the benefit on the RT was due to the position priming effect or due to statistical learning.

As reported in Chapter 2, we tested patients for their ability to use probability as a cue to direct their attention (Shaqiri and Anderson, 2012). Patients with a right hemisphere lesion failed to show a RT benefit for the targets that appeared in the high probability region, contrary to healthy controls, who were faster to respond to those targets. Although this experiment demonstrated an impairment for RBD in learning an underlying statistical structure of target location, it did not determine if the deficit was general or concerned only the patients' contralesional sides.

Then in Chapter 3, we reported a study in which we tested whether RBD patients were generally impaired for priming and visual statistical learning when tested in a baseline, high repeat and low repeat condition. Control participants were faster to respond to targets for the high repeat condition compared to the two other conditions. Controls were also faster to respond to targets that repeated the same location successively during the high repeat condition than they were for repeated trials in the low repeat condition. This was not the case for the RBD group. RBD patients benefited from only one repeat of the target location and did not show a difference in their RT for repeated trials compared across the high and low repeat conditions. This study demonstrated that RBD patients were impaired in statistical learning for visual material, and this was true for material presented vertically aligned to body midline.

The studies cited above have only tested spatial aspects and in only the visual domain. In order to investigate if the impairment demonstrated by RBD patients extends beyond the visual and spatial scope, we tested statistical learning in its auditory form, because this has been the most widely studied domain, as we reported in Chapter 4 (Saffran et al., 1996; Aslin and Newport, 2012). The ability to learn the underlying statistical structure of auditory stimuli has been shown across species (monkeys; Meyer and Olson, 2011), across age groups (in infants and adults; Saffran et al., 1996; Gebhart et al., 2009) and also modalities (non-linguistic sounds; Fiser and Aslin, 2002). As reported in Chapter 4, Gebhart and colleagues (2009) also tested university students with an auditory statistical learning paradigm. Participants listen to two different languages (of 5 minutes duration) in four conditions. The authors found that participants learned the first language, as they correctly identified the words 80% of the time. In most of the conditions, Gebhart and colleagues (2009) found that participants learned the first language better than the second. We replicated this basic result and also found that first language superiority was not modified by information or break duration (Ch 4; Shaqiri et al., under review).

This paradigm has been used to demonstrate that auditory statistical learning is a domain-general phenomenon present from infants to adults (Saffran et al., 1996, Gebhart et al., 2009). In general, participants need only a few minutes of exposure to learn the transition probability of words. Importantly, for its use with brain damaged participants, the task is passive and all participants groups receive the stimuli at the same pace. Numerous studies have demonstrated the importance of timing and temporal processing in paradigms in which participants need to accumulate information over time to learn and use statistical information, and this is particularly important for studies with brain damaged patients (Maljkovic and Nakayama, 2000; Shaqiri et al., 2013). Because they tend to be slower overall compared to healthy controls (Shaqiri and Anderson, 2012; Kaizer et al., 1988), brain damaged patients need to retain information longer between trials, which also makes it difficult to accumulate a large amount of information about the target location and learn spatial distributions (Shaqiri et al., 2013). Maljkovic and Nakayama (2000) have shown that beyond an interval of 90 seconds, the benefits from repeated target position fade away and healthy participants cannot accumulate information to improve their reaction time. The paradigms of auditory statistical learning eliminate this potential confound as stimuli are presented to all participants at the same rate.

These elements (no spatial involvement, short and accessible stimuli, no involvement of timing) have motivated the present study in auditory statistical learning. We adapted the paradigm of Gebhart and colleagues (2009) in order to test brain damaged patients and investigate if their lesions affect auditory statistical learning. In addition to a healthy control group, we tested three brain damaged patient populations: LBD, and RBD without and with signs of spatial neglect (RBD+N). The present study provides valuable information about the phenomenon of statistical learning in brain damaged patients. Our first goal was to determine if the statistical learning impairment we demonstrated was restricted to visual material or whether it was general (Shaqiri and Anderson, 2012; 2013). Second, we wanted to determine if brain damage in general affects the ability to benefit from regularities, or if this is limited to RBD patients and whether it is limited to those RBDs who also have spatial neglect (Shaqiri and Anderson, 2012; Shaqiri et al., 2013; Danckert et al., 2012).

5.2 Methods

We report three experiments that tested auditory statistical learning in four groups of participants: older healthy control, LBD, RBD and RBD+N patients. The two first experiments replicated methods that have been previously tested and published (Gebhart et al., 2009, Shaqiri et al., under review), whereas Experiment 3 tested if it was possible to improve statistical learning with prolonged exposure. The testing materials were kindly provided by Dr. Richard Aslin from the University of Rochester.

5.2.1 Participants

Four groups of participants were tested for this study. Thirty older healthy controls were recruited from the Waterloo Research in Aging Participant Pool (13 males, mean age = 75, SD = 7.95). Fifteen left brain damaged patients (9 males, mean age = 67, SD = 10.42), 17 right brain damaged (8 males, mean age = 66, sd = 11.09), and 9 neglect patients (4 males, mean age = 69, SD = 11.67) were recruited from the Neurological Patients Database in Waterloo, Ontario (see Table 5). The ethics committee of the University of Waterloo approved the protocol and all participants gave a written informed consent.

Some of the patients who participated in this study were also tested with the paradigms reported in Chapters 2 and 3. For example, patients RBD5 and RBD6 and RBD+N9 were part of the study reported in Chapter 2, whereas RBD12, RBD+N1, RBD+N3, RBD+N6 and RBD+N7 were previously tested with the paradigm reported in Chapter 3.

Different control participants and RBD patients were used for each experiment. Some LBD (n = 2) and RBD+N (n = 3) participants participated in more than one experiment (see Table 5; patients are marked with asterisks). Testing sessions for repeat participants were conducted at least one year apart and these participants did not demonstrate better results than other participants in their groups.

Table 5: List of patients. *We tested 15 left brain damaged (LBD), 17 right brain damaged patients (RBD) and 9 right brain damaged with neglect (RBD+N). Two patients from the LBD and three patients from the RBD+N groups were tested twice, but with at least a year interval and are marked with asterisks. The table reports the patient code (Patient), their age (Age), their gender (sex), the experiment they performed (Exp), the location of their lesion, (when scans were available, otherwise we indicated with the number "[1]" when we only had the reports from radiologists), Lesion: Fr=Frontal, T= Temporal, BG=Basal Ganglia, P=Parietal, RO= Rolandic Operculum, Th= Thalamus, Cereb= Cerebellum, Ins=Insula. MoCA reports the results of the Montreal Cognitive Assessment. RTT reports the results from the Revised Token Test. Line reports the results from the Line Bisection test from the Behavioral Inattention Test (BIT). Star is the results from the Star Cancellation test from the BIT. Letter reports the results from the Letter cancellation test of the BIT and finally, Copy reports the results from the Copy of shapes test from the BIT.*

Patient	Age	Sex	Exp	Lesion	MoCA	RTT	Line	Star	Letter	Copy
LBD1*	69	M	1, 3	T, P[1]	16	11.71/	3.95%	3/28, 1/28	1/10 6/10 5/10 2/10	OK
					18	-	0.7%	0/28, 4/28	0/10 0/10 0/10 1/10	Cube left bottom missing
LBD2	71	F	2	T, O	20	13.01	1.69%	0/28, 0/28	4/10 1/10 3/10 2/10	Ok

LBD3*	65	M	2,3	Fr, RO, T, O, Ins	16 (Aphasia) -	12.86 13.09	1.97% 1.27%	Ok Ok	Ok Ok	Ok Ok
LBD4	60	F	2	Fr, Pra	21	13.94	0.7%	Ok	Ok	Ok
LBD5	73	M	2	Fr, RO, Ins	16 (Aphasia)	12.16	1.27%	1/28, 0/28	1/10 3/10 2/10 2/10	Cube misses top part
LBD6	60	M	1	P	3 (Severe aphasia)	11.93	3.53%	4/28, 1/28	1/10 3/10 1/10 0/10	Cube is a square
LBD7	72	F	1	Fr, RO, T, Ins	26	13.95	1.69%	Ok	2/10 1/10 3/10 1/10	Ok
LBD8	65	M	1	P, O, T, RO	21	13.23	0.56%	Ok	Ok	Ok
LBD9	66	F	2	Fr, T, RO, Ins	28	14.40	2.96%	Ok	Ok	Ok
LBD10	77	F	1	Ins	27	13.7	1.97%	0/28 1/28	Ok	Ok
LBD11	68	M	2	Fr, RO, Ins	29	14.5	2.68%	Ok	Ok	Ok
LBD12	88	M	2	Fr, RO, Ins	8 (Aphasia)	13.31	6.77%	0/28 11/28	-	Cube and flower bottom part missing
LBD13	79	M	3	Fr, P[1]	30	-	0.84%	Ok	0/10 0/10 1/10 0/10	Ok
LBD14	48	M	3	P, T, O, Ro	26	-	0.56%	0/28 1/28	1/10 1/10 1/10 0/10	Cube right side missing
LBD15	50	F	3	Fr	29	14.65	1.55%	1/28 0/28	0/10 0/10 0/10 1/10	Cube and flower left side missing
RBD1	66	F	2	Fr, BG, O, P, T, RO, Th, Ins	29	14.56	2.4%	1/28 3/28	Ok	Ok
RBD2	67	F	1	P	27	14.8	1.97%	Ok	Ok	Ok
RBD3	57	F	2	Fr, P, T, O, RO, Ins	27	14.06	1.69%	2/28 2/28	0/10 0/10 1/10 2/10	Cube left side is distorted
RBD4	83	F	1	Fr, BG, T, RO, Th, Ins	29	14.21	0.56%	1/28 0/28	0/10 0/10 0/10 1/10	Star left side distorted
RBD5	70	F	2	Fr, T, RO, P,	28	14.66	0.56%	9/28 5/28	0/10 1/10	Ok

				Ins					2/10 2/10	
RBD6	72	F	1	Fr, T, RO, Ins	28	14.66	1.12%	0/28 1/28	1/10 0/10 1/10 1/10	Ok
RBD7	67	M	1	Fr, BG, T, Th, Ins	30	14.44	4.5%	1/28 3/28	Ok	Ok
RBD8	67	M	2	Fr, BG, O, P, T, RO, Ins	28	14.8	1.27%	Ok	1/10 0/10 2/10 3/10	Ok
RBD9	90	M	1	O, P	26	14.06	0.7%	4/28 2/28	2/10 0/10 2/10 2/10	Ok
RBD10	59	M	2	Fr, BG, O, P, T, RO, Th, Ins	29	14.79	0.98%	1/28 0/28	1/10 0/10 2/10 0/10	Ok
RBD11	75	F	3	P, BG[1]	29	14.505	2.54%	Ok	0/10 0/10 1/10 0/10	Ok
RBD12	45	M	3	P, T, O, RO, Ins	28	14.42	0.98%	Ok	1/10 0/10 1/10 0/10	Ok
RBD13	80	F	3	P, O[1]	29	14.53	5.08%	Ok	Ok	Ok
RBD14	58	M	3	T, BG, RO, Ins	24	14.05	1.12%	Ok	0/10 0/10 1/10 0/10	Ok
RBD15	57	M	3	T, RO, Ins	30	14.815	1.97%	Ok	Ok	Ok
RBD16	59	M	3	P	23	14.53	3.81%	0/28 1/28	0/10 0/10 2/10 0/10	Ok
RBD17	62	F	3	T, RO, Th, Ins	27	-	2.4%	4/28 2/28	Ok	Ok
RBD+N1	59	M	1	P, O[1]	18	12.68	6.49%	6/28 4/28	7/10 9/10 5/10 5/10	Star left side distorted. Cube and flower left side missing
RBD+N2	84	F	2	Fr, T, RO, Ins	21	14.4	5.22%	18/28 0/28	9/10 1/10 6/10 2/10	Cube and flower left side missing
RBD+N3 *	64	F	1	P, Fr, T, RO, O, Ins	22	14.07	28.53%	28/28 13/28	10/10 10/10 10/10 0/10	Cube and flower left side missing
					-	-	15.81%	28/28	10/10	Cube

								2/28	10/10 1/10 0/10	bottom part missing
RBD+N4	66	F	2,3	Th	22	13.94	9.88%	28/28 13/28	10/10 10/10 10/10 2/10	Star, cube and flower left side missing
					-	-	10.02%	28/28 15/28	10/10 10/10 4/10 0/10	Star, cube and flower left side missing
RBD+N5	86	M	2	P, T, O, RO, Ins	26	14.11	6.07%	12/28 8/28	1/10 1/10 0/10 2/10	Star and cube left side missing
RBD+N6	71	M	1	Fr, T, BG, O, P, RO, Th, Ins	25	-	9.03%	17/28 0/28	3/10 2/10 2/10 3/10	Cube left side missing
RBD+N7 *	75	F	1,3	Fr, T, BG, P, RO, Ins	11	14.24	7.76%	3/28 1/28	4/10 0/10 3/10 1/10	Cube left side missing
					-	-	15.96%	27/28 5/28	10/10 10/10 10/10 1/10	Cube left side missing
RBD+N8	71	F	2	Fr, T[1]	27	14.9	4.37%	8/28 1/28	2/10 0/10 0/10 0/10	Cube left side missing
RBD+N9	49	M	3	Fr, T, BG, P, RO, Th, Cereb	28	-	4.23%	1/28 0/28	2/10 2/10 0/10 0/10	Ok

5.3 Clinical Tests

5.3.1 Behavioral Inattention Test

As reported in section 2.2.3, we used the Behavioral Inattention Test (BIT, Wilson et al., 1987) to test for the presence of spatial neglect.

5.3.2 Five-item Revised Token Test

In order to confirm that our patients were able to understand and follow task instructions, we used the five-items Revised Token Test (RTT, McNeil and Prescott, 1978; Arvedson et al., 1985) to test for auditory processing and comprehension impairment, especially as some of our LBD patients were diagnosed with aphasia. This test has been designed to investigate auditory processing disorders due to brain damage, aphasia or other language disabilities. The five-item version is a shortened version of the RTT and has been shown to be highly reliable and correlated with the original RTT (Arvedson et al., 1985; Park et al., 2010). For the interpretation of the RTT results, we compared the overall results of our participants with the normative data of 90 normal participants reported by McNeil and Prescott (1978). The authors report the percentile scores for the overall results on the RTT: an overall score of 14.14 corresponds to 1 percentile for normal subjects, whereas a score of 15 spans from the 84th to 100th percentile.

5.3.3 Montreal Cognitive Assessment

All our participants also performed the Montreal Cognitive Assessment (MoCA), which tests for mild cognitive impairments (Table 1; Nasreddine, 2012). Based on the normative data of 90 subjects reported by the authors, a score of 27.2 (SD=2.2) corresponds to normal healthy participants, a score of 22.1 (SD=3.1) corresponds to a mild cognitive impairment, and finally, a score of 16.2 (SD=4.8) corresponds to dementia.

5.3.4 Apparatus and stimuli

The two first experiments of this study used two languages, A and B, and for the third experiment, we only used language A. Each language was formed by 16 tri-syllabic nonsense words, formed by a combination of six possible vowels (a, ae, e, i, o, u) and six consonants (b, d, k, p, s, t). The latter was variant between the words, but the vowels remained constant (for example, language B was formed with the words "*bupaegi*", "*tupaeki*", "*tedoka*" or "*bedoga*", where the vowels u, ae, i and e, o, a, were constant but the consonants changed, Table 3). Language A and B were made by syllables that overlapped by 50%.

We tested participants on their ability to learn the transitional probability of the vowels frame within the words, which was high (100%), and the low (50%) transition probability of the vowels between the words. In order to investigate if participants were able to perform a speech segmentation task and identify the words by just using the high transition probability - all other cues - such as tone, pauses or breaks between the words were removed and a speech synthesizer produced the words. Therefore, when listening to the two languages, one heard a monotone "song." The only rule for forming a language was that a word would not be successively repeated (for details, see Gebhart et al., 2009; Shaqiri et al., under review).

The same procedure as described in section 4.2.1 was used to present the stimuli and test the learning of the underlying statistical structure by the participants.

5.4 Experiments

Our four groups were tested with three experiments. In the present study, Experiments 1 and 2 replicated Experiments 2 and 3 from the study of Gebhart and colleagues (2009), whereas Experiment 3 was conducted in order to investigate if it is possible to improve statistical learning with prolonged exposure. The first experiment presented both languages A and B without a break, for a duration of about 10 minutes, whereas Experiment 2 consisted of a presentation of language A, a 30 second break and then a presentation of language B. Participants were informed about the break and that they would hear a second language after the 30 second break. Finally, for the third experiment, participants listened to language A three times: They started by listening to the language A for 5 minutes and then they were tested with the forced-choice test, before listening to language A for a second and then a third time, with a forced-choice test presented after each listening.

Table 6: *List of experiments and number of participants per group and per experiment. Two participants of the LBD group and three of the RBD+N group were tested for two different experiments (see Table 5, indicated with asterisks). Experiments 1 and 2 (indicated with asterisk) were replications of the Experiments 2 and 3 from the study of Gebhart and colleagues (2009).*

	Older Control	LBD	RBD	RBD+N
Experiment 1* Language A and language B without break	N=10	N=5	N=5	N=4

Experiment 2* **Language A + 30 sec break+ language B**	N=12	N=7	N=5	N=4
Experiment 3 **3 times language A with a test after each listening**	N=8	N=5	N=7	N=4

5.5 Results

We started by analyzing the results of each group per experiment. Then, as a second step, we report the statistical analysis of between group comparisons.

5.5.1 Experiment 1: Language A and language B without a break

Healthy controls recognized the words from the first language with 69.37% accuracy and had 66.25% correct answers for the second language. Moreover, both languages were learned above chance (Figure 12: first language $t(9) = 3.08$, $p = 0.01$ and second language $t(9) = 4.99$, $p = 0.0007$). An ANOVA revealed that the two languages were not learned at statistically different levels ($F(1, 18) = 0.19$, $MSE = 250.21$, $p = 0.66$). These results demonstrate that when faced with two languages, controls have the capacity to learn both structures to the same degree.

LBD patients showed different results from healthy controls, as they did not learn any of the languages above chance (Figure 12: first language was reported with 47.50% accuracy, $t(4) = -0.27$, $p = 0.79$ and second language with 52.5%, $t(4) = 0.33$, $p = 0.75$). LBD patients also did not demonstrate any difference on their performance between the first and the second language ($F(1, 8) = 0.18$, $MSE = 343.75$, $p = 0.68$). Because some of the patients in this group suffer from aphasia (Table 5), it can be hypothesized that their performance might be due to language impairments, but as we will report below, this seems an incomplete account for the impairment in statistical learning.

RBD patients did not learn either the first or second language above chance (Figure 12: first language was learned at 55%, $t(4) = 0.66$, $p = 0.54$ and second language was learned at 52.5%, $t(4) =$

0.78, p = 0.47). This group's performance was not different for the language heard first or second (F(1, 8) = 0.09, MSE = 166.01, p = 0.76).

Finally, RBD+N patients were not different from the two other brain damaged groups, as they did not perform above chance for either the first (48.43%) or second (54.68%) language (Figure 12: with t(3) = -0.29, p = 0.78 and t(3) = 1, p = 0.39, respectively). An ANOVA did not show any differences on their performances for the two languages (F(1, 6) = 0.77, MSE = 100.91, p = 0.41) .

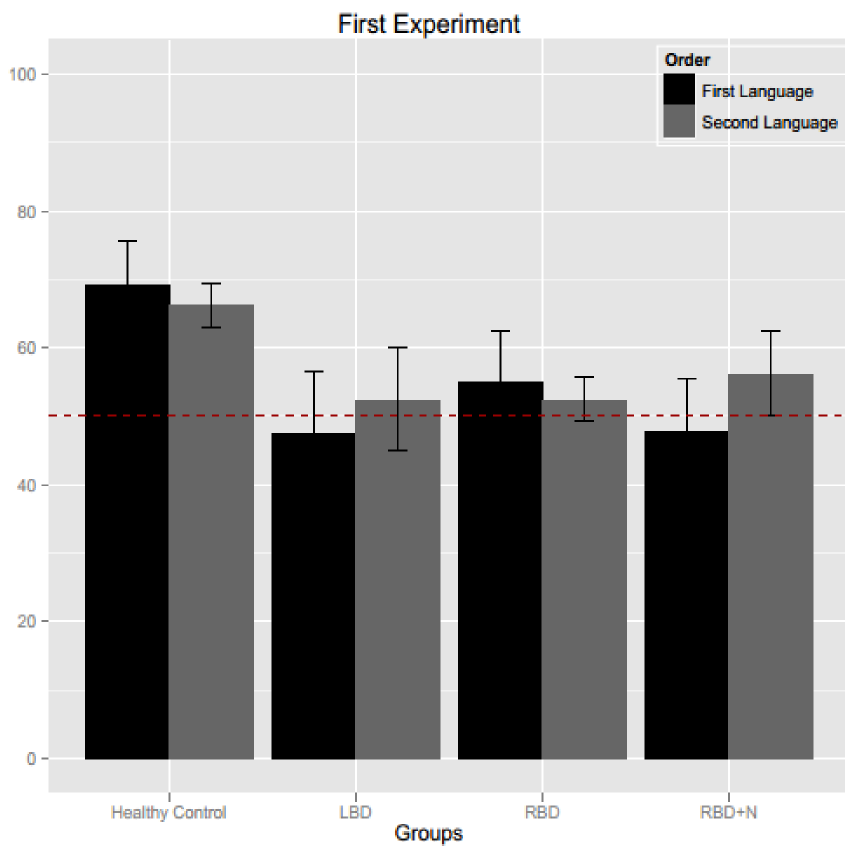

Figure 12*: Performances of the four groups in the first experiment (language A and B without a break). The group of healthy control was the only group to learn any of the languages above chance (red dotted line represents performance at chance). Error bars represent standard errors.*

As a second step, we conducted a between group comparison for this first experiment and found that the four groups performed differently (F(3, 44) = 4.79, MSE = 213.47, p = 0.005). Pairwise comparisons found that the healthy control group performed differently from RBD, RBD+N and LBD groups: ($F(1, 28) = 6.26$, MSE = 210.59, $p = 0.01$ and $F(1, 26) = 7.49$, MSE = 201.4, $p = 0.01$ for the healthy controls compared to RBD and RBD+N respectively, and $F(1, 28) = 8.04$, MSE = 263.04, $p = 0.008$ for pairwise comparison between healthy controls and LBD group). The three brain damaged groups were not different in their performance for this first experiment (all p.values >0.4).

5.5.2 Experiment 2: Language A, 30 second break and Language B.

To investigate if the length of the listening sequence and the lack of break between languages affected participants' performance, we introduced a break of 30 seconds between the first and second language.

Healthy control participants did not perform differently between the first and the second experiment ($F(1, 42) = 0.049$, MSE = 288.21, $p = 0.81$). This was also demonstrated by their overall results on the first and second language. Both languages were learned above chance (Figure 13: 69.79%, $t(11) = 3.61$, $p = 0.004$ for the first language and 63.54%, $t(11) = 2.68$, $p = 0.02$, for the second). As for the first experiment, controls did not show a difference between their performance on the first and second language ($F(1, 22) = 0.70$, MSE = 332.62, $p = 0.41$).

LBD also did not perform differently from the first experiment ($F(1, 22) = 0.17$, MSE = 432.22, $p = 0.68$), therefore having a break in the middle of the 10 minutes of listening did not help to improve their performance. LBDs did not learn any of the languages above chance (Figure 13: 55.35%, $t(6) = 0.61$, $p = 0.56$ for the first and 51.78%, $t(6) = 0.19$, $p = 0.85$, for the second language, respectively).

The RBD group was the only group to perform differently from the first experiment ($F(1, 18) = 6.67$, MSE = 154.73, $p = 0.02$). This was due to the fact that for the second experiment, RBD patients learned the second language above chance with 72.50% correct answers ($t(4) = 7.06$, $p = 0.002$), but this was not the case for the first language, with 63.75% correct answers, $t(4) = 1.9$, $p = 0.13$). The difference on their performance on the first and second language was not significant (Figure 13: $F(1, 8) = 1.25$, MSE = 156.25, $p = 0.30$). This group demonstrated that having a break after 5 minutes of listening helped them improve their performance and learn the second language above chance. Although we did not do lesion overlay analysis, we had radiologists' reports for the patients' lesions. Therefore, to see if this heterogeneity of RBD reflected different lesions for the two groups of RBD participants tested in Experiments 1 and 2, we compared brain lesion maps. The two groups were not different for the brain regions affected (Table 5). RBD patients for both Experiments 1 and 2 had lesions predominantly of the frontal lobe, rolandic operculum and insula.

RBD+N patients did not show any difference on their performance between the first and second experiment ($F(1, 14) = 1.08$, $MSE = 182.41$, $p = 0.31$). They did not learn the first or the second language above chance (Figure 13: they had 60.93% of correct answers for the first language, but this did not correspond to a performance above chance: $t(3) = 1.06$, $p = 0.36$ and 56.25% correct answers for the second language, $t(3) = 0.93$, $p = 0.42$).

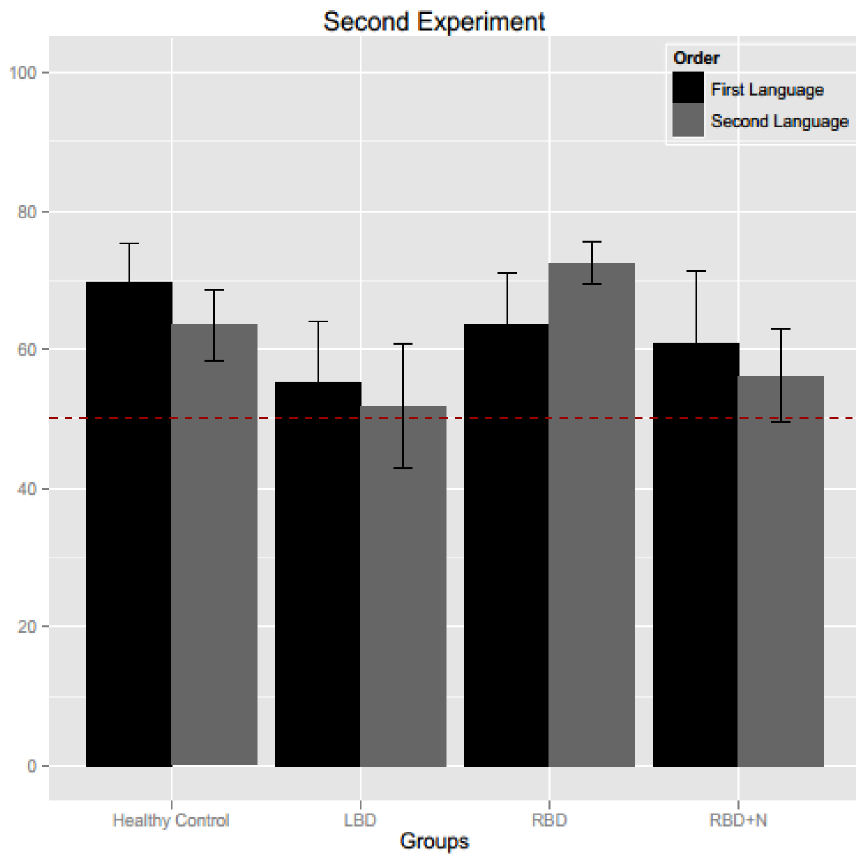

Figure 13*: Performances of the four groups in the second experiment (language A and B with a 30 seconds break). The group of healthy control performed above chance for both languages (red dotted line represents a performance at chance). Surprisingly, the group of RBD patients also performed above chance for the second language. This was not the case for the LBD and RBD+N groups, who did not learn any of the languages. Error bars represent standard errors.*

When we compared the performances between groups, we found that the results for four groups did not statistically differ in the second experiment, though there was a trend, ($F(3, 52) = 1.95$, $MSE = 337.69$, $p = 0.13$). Participants' performance on the first or second language did not influence those results, as adding the order of the language as a covariate was not significant ($F(3, 48) = 0.38$, $MSE = 355.12$, $p = 0.76$). Pairwise comparisons did not show any statistically significant difference on this task between groups (all p values > 0.06). The healthy control group was not different from LBD ($F(1, 36) = 3.83$, $MSE = 395.79$, $p = 0.06$) and with $F(1, 32) = 0.05$, $MSE = 281.04$, $p = 0.78$ and $F(1, 30) = 1.24$, $MSE = 314.07$, $p = 0.27$ for healthy control compared to RBD and RBD+N, respectively. Then the LBD and RBD groups were also not different ($F(1,22) = 3.34$, $MSE = 369.9$ $p = 0.08$). Finally, $F(1,16) = 1.95$, $MSE = 206.97$, $p = 0.18$ for comparison between RBD and RBD+N and $F(1,20) = 0.3$, $MSE = 428.33$, $p = 0.6$ for a comparison between RBD+N and LBD.

In summary, the RBD group had a performance close to the healthy control group. This demonstrates that brain damage per se is not uniformly associated with a statistical learning deficit, but the failure of the other brain damaged groups to improve shows that it is pervasive, and not easily improved with a small rest and additional information.

5.5.3 Experiment 3: Language A listened three times, with forced-choice test after each listening

In the last experiment, we investigated if we could improve statistical learning with prolonged exposure. Each participant heard language A for 5 minutes followed by a forced-choice test for three cycles.

We performed a repeated measures ANOVA and found that healthy controls did not show a difference on their performances for the three listening sessions ($F(2, 21) = 0.09$, $MSE = 211.81$, $p = 0.90$). Their scores for the three sessions were very similar: they had 62.5% correct answers for the first session, 60.15% for the second and 59.37% for the third (Figure 14). We then evaluated if any of the three sessions showed learning above chance by performing a t test on each session, which revealed a trend for above chance performance for the three sessions (p values ranging from 0.05 to 0.09).

LBD patients failed to show above chance performance for any listening session and no trend to improve across sessions ($F(2, 12) = 0.02$, $MSE = 332.03$, $p = 0.97$). They had 58.75% of correct answers for the first session, 57.50% for the second and 56.25% for the third.

The group of RBD patients did not perform differently on the three listening sessions as well ($F(2, 18) = 0.1$, $MSE = 295.76$, $p = 0.90$). Their performances did not exceed chance, as they had 58.03% of correct answers for the first session ($t(6) = 1.21$, $p = 0.27$), 54.46% for the second session ($t(6) = 0.63$, $p = 0.55$) and 58.03% for the last session (Figure 14: $t(6) = 1.4$, $p = 0.21$).

Finally, the RBD+N patients were not different from the three other groups, as they did not show a difference between the sessions ($F(2, 9) = 0.5$, $MSE = 133.46$, $p = 0.6$), and their performances did not exceed chance for any of the three listening sessions (Figure 14: first session 53.64% correct, $t(3) = 0.39$, $p = 0.71$; second session, 54.68% correct, $t(3) = 0.42$, $p = 0.78$ and finally, third session, RBD+N patients had 59.37% correct answers, with $t(3) = 1.73$, $p = 0.18$).

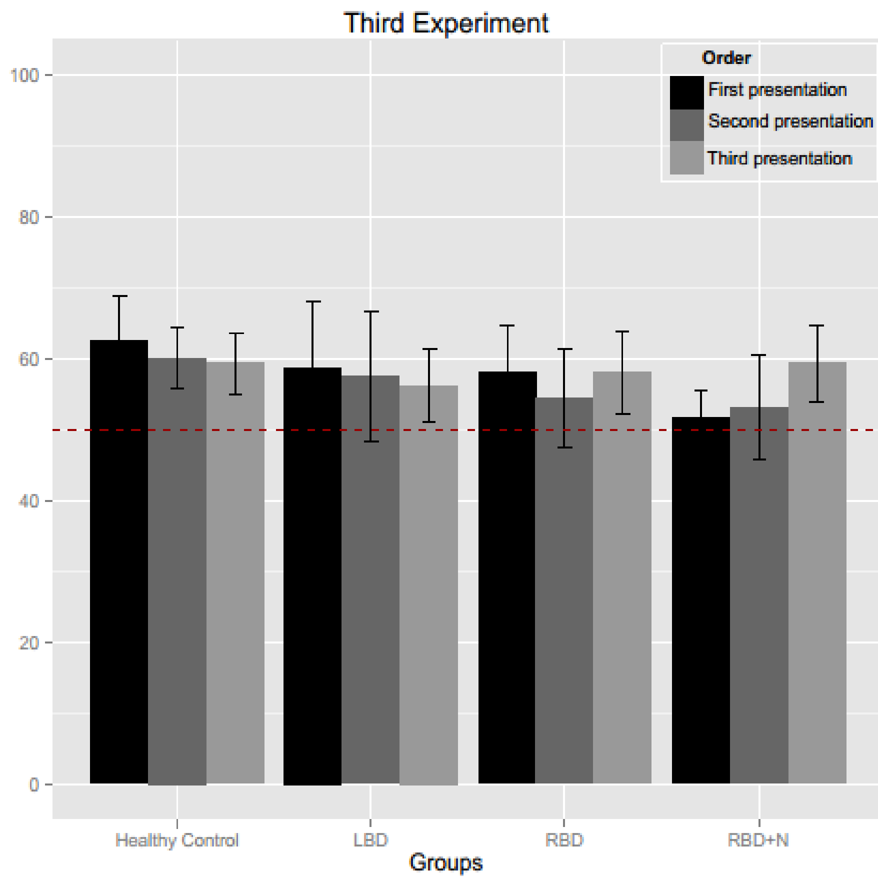

Figure 14*: Performances of the four groups in the third experiment (language A listened three times). None of the four groups learned the language A above chance, even when they were exposed to it three consecutive times. This demonstrates that statistical learning cannot be trained. Error bars represent standard errors.*

Finally, for this third experiment in which patients listened to language A three times, a between group comparison demonstrated that the groups showed no difference for their overall score ($F(3, 68) = 0.49$, MSE = 223.7, $p = 0.68$), or for the first, second or third listening, as adding the order of the language as a covariate did not show significant interaction ($F(3, 64) = 0.24$, MSE = 234.92, $p = 0.86$). Pairwise comparisons between groups confirmed those results, as none of them was statistically different (all $p>0.2$).

This third experiment demonstrated that prolonging exposure beyond the five minute training did not improve performance, and in some cases the prolongation seemed to worsen it.

5.5.4 RTT and MoCA with the results on each experiment correlations

In order to determine if cognitive or language impairments could affect participants' results in the auditory statistical learning task, we investigated the average results for the RTT and MoCA tests. For the five-item RTT, the healthy control group had an average score of 14.63 (SD = 0.33), which corresponds to 34% of the normalized data (McNeil and Prescott, 1978). The group of LBD had an average score of 13.21 (SD = 1.01), which is lower than 1%. RBD patients had an average score of 14.49 (SD = 0.26), which corresponds to 13 percentile and finally, RBD+N patients had an average score of 13.89 (SD = 0.69), which is lower than one percentile, compared to the normalized data of healthy controls. Overall, the four groups were different on their RTT results ($F(3, 158) = 48.66$, MSE = 0.33, $p<0.0001$), and pairwise comparisons also showed that every group was different from each other (with all $p<0.04$, Table 7).

***Table** 7: Details of the ANOVA analysis for pairwise comparisons of the RTT results.*

	Older control	**LBD**	**RBD**
LBD	F(1,99)=108.12, MSE=0.4, p<0.001	-	-
RBD	F(1,104)=4.18, MSE=0.09, p=0.04	F(1,69)=56.47, MSE=0.5, p<0.001	-
RBD+N	F(1,89)=43.43, MSE=0.2, p<0.001	F(1,54)=7.95, MSE=0.8, p=0.006	F(1,59)=22.31, MSE= 0.22, p<0.001

The RTT results demonstrated that LBD and RBD+N patients were below the 1% level of the normal control group. To test if comprehension deficits explained our results we correlated patients' RTT values and their statistical learning performance. The LBD patients showed no statistically significant relation between their RTT results and their performances on the statistical learning task for the three experiments ($r = -0.41$, $r = 0.11$ and $r = -0.10$ for the first, second and third experiment, respectively, and all p.values were >0.1). For example, the LBD patients with the lowest (11.61) and highest (14.65) RTT scores had virtually identical statistical learning scores (66.67 and 65.58% respectively). Similar results were found for the RBD group ($r = 0.46$, -0.31 and 0.21 for the first, second and third experiment, and all p.values were >0.23). For the RBD+N, RTT scores were not correlated with patients' performances in our task (for the first experiment, $r = 0.23$, $p = 0.54$ and for the second experiment, $r = 0.27$, $p = 0.36$), and for the third experiment, patients' results were *negatively* correlated with their RTT results ($r = -0.65$, $p = 0.03$). This was driven by the patients who were tested twice (Table 5), and EG's low score on the statistical learning task and high score on the RTT. Thus, the overall results demonstrated by the LBD, RBD and RBD+N patients on statistical learning task cannot be easily explained by RTT scores or language comprehension difficulties.

The same procedure was also followed for the results on the MoCA test. Healthy controls and RBD patients had a mean score of 27.57 (SD = 2.89) and 27.60 (SD = 2.02), respectively, which corresponds to healthy participants (Nassreddine, 2013). This was not the case for LBD and RBD+N patients, who scored 20.84 (SD = 7.5) and 20.75 (SD = 5.68), respectively. Those scores correspond to mild cognitive impairment. For the LBD patients, those results can be explained by the fact that some patients suffered from expressive aphasia, and could not complete the speech part of the test. For RBD+N patients, a difficulty completing the visuospatial section of the test can explain some of their overall lower scores. Based on those results, the four groups were different on their overall MoCA score ($F(3, 172) = 29.40$, $MSE = 21.63$, $p<0.0001$), but those results are driven by the differences between the healthy controls group and RBD, which are very different from the LBD and RBD+N groups. There was no statistical difference in the MoCA results between healthy controls and RBD ($F(1, 107) = 0.005$, $MSE = 6.77$, $p = 0.94$), or between LBD and RBD+N patients ($F(1, 65) = 0.003$, $MSE = 46.09$, $p = 0.95$), but the other pairwise comparisons showed significant differences between the groups (with all $p<0.0001$). None of the performances on the statistical learning task were correlated with participants' performance on the MoCA test, as for all groups and all experiments, p values were greater than 0.08.

5.6 Discussion

In the present study, we tested healthy and brain damaged participants in an auditory statistical learning paradigm. Our goal was to investigate if the four groups tested were able to learn the underlying statistical distribution composing the auditory stimuli, and also, if the groups were different in their performances, based on their condition (healthy versus brain damaged), or based on their lesion location.

This paradigm was chosen because it tested statistical learning with a non-spatial stimulus. Previous studies have mostly used visual stimuli. Because many patients, especially those with RBD will have co-existent spatial processing deficits (Danckert and Ferber, 2006), it has not been possible to determine the generality of the statistical learning impairment based only on experiments testing visual aspects (Shaqiri and Anderson, 2012; 2013).

Our groups performed three different experiments that tested different aspects of auditory statistical learning. The first experiment presented two structurally different languages successively for ten minutes. The goal of this experiment was to investigate if participants can learn the language, and whether there is a capacity limit that might favor either the first (primacy) or second (recency) language. Our results demonstrated that healthy controls learned both languages above chance and to the same extent. This was different from what we found in a previous study, in which we tested undergraduate students with a similar paradigm (Shaqiri et al., under review). In our work with younger participants, we found that the first language was learned significantly better than the second one. The comparison across groups revealed that the main difference resided within the first language performance. The younger group averaged close to 80% correct on the assessment, while our older participants were below 70%. When second languages alone are compared, the results are more comparable. Thus, the difference between the two experiments seems to be due to the greater ability of younger participants to learn a first language than our older controls. These results are in accordance with previous studies that have shown that younger participants are more efficient in implicit learning than older adults and also, they learned long and higher order sequences better compared to older adults (Howard and Howard, 2001; Howard et al., 2004).

In contrast, our three brain damaged groups did not demonstrate any learning of the underlying structure of the two languages. The three groups performed at chance for both languages and were not statistically different in their performance. This demonstrated that independent of which hemisphere was damaged, or whether they did or did not have neglect, our patient participants were not able to learn the underlying structure of the languages. A few studies have tried to identify the brain regions involved in statistical learning. For example, Roser and colleagues (2011) tested a brain-split patient in visual statistical learning and highlighted that the right hemisphere is involved in this phenomenon. Turk-Browne and colleagues (2009) identified the striatum, the medial temporal and ventral occipito-temporal cortex. In an fMRI study using a paradigm similar to the one we used, Karuza and colleagues (2013) found activation mainly in the left inferior frontal gyrus. Our three groups of brain-damaged patients have lesions at different brain regions, some patients have lesions at the frontal lobe, others at the temporal or parietal lobe, or the insula, or some patients have lesions at several of those regions (Table 5). Nevertheless, patients do not succeed in learning the two languages, which demonstrates that lesions at different brain regions affect this domain-general phenomenon.

Gebhart and colleagues (2009) performed another condition during their experiment, in which they provided information to participants and introduced a 30 second break between the two languages. The authors found that young participants improved their performances on the second language, as they learned both the first and the second language to the same extent. Therefore, the break and information helped them with their performance in the second language. We too, tested our four groups with a similar experiment. With the break and information, we observed an improvement in the RBD patients. This was the only group to perform differently and this might simply be due to patient heterogeneity. It is also interesting to note that in Howard and Howard (2001), intentional instructions disturbed the performances of older normal participants for implicit pattern learning, which was not the case with young participants (Howard et al., 2004).

Combining the current results with our prior research, we have demonstrated a multi-modal statistical learning impairment with brain damage (Shaqiri and Anderson, 2012; 2013). Because many of our patients also had neglect, we specifically examined if this deficit predicted worse statistical learning. This was not the case, and our LBD group had equal difficulties, or worse than our RBD without neglect.

The ability of some brain damaged participants to learn one or the other language might give us some information about the processes that take place during this task. Participants who can learn the words for the last language they heard, but not the first one, might implicate memory systems (Kasselimis, 2013; Geldorp, 2013). Many brain damaged patients, both right and left sided, have important working memory impairments (Streimer et al., 2013; Ferber and Danckert, 2006; Husain et al., 1997), and working memory is a process that is highly involved in statistical learning. Umemoto and colleagues (2010) found that participants were better at keeping in their working memory targets that were presented in a high probability region, compared to targets presented randomly in all the possible regions of the screen.

With our last experiment, we aimed to test if this impairment is definitive or if it can be overcome with training. This could have important implications for rehabilitation. None of our groups improved their performances on this task between the first and the third listening session. A difficulty with the ability to learn environmental regularities, as we demonstrate here, might underlie some of the failure to benefit from standard rehabilitation techniques, as most of those techniques rely on repetition (Shimodozono et al., 2013; Bowen and Lincoln, 2007; Appelros et al., 2002; Cassidy et al., 1998). And as we showed with our third experiment, training and repetition was not effective in our three brain damaged groups, which might explain the difficulty of those patients to be trained in some of the rehabilitation techniques.

In conclusion, in the present study, we demonstrated that brain damage impairs the ability to learn and use statistical regularities in the auditory modality. This study completes previous research that has shown that right brain damaged patients are impaired in visual statistical learning and confirms that this impairment is multimodal. Moreover, we have shown that lesions at different brain regions and in the left or right hemisphere affect this phenomenon and can prevent patients from benefiting from environmental statistics. Nevertheless, all the results were not discouraging, as some of our participants were able to learn the language that they heard last when they had a break. Therefore, we believe that statistical learning can be a useful tool to measure patients' ability to benefit from regularities of the environment and maybe the outcome of rehabilitation strategies.

Chapter 6: General Discussion[6]

Strokes are one of the main causes of disability in adults in North America (Kim et al., 2013), and the outcomes for rehabilitation of patients who suffered a stroke are often worse for right brain damaged compared to left brain damaged patients (Bowen and Lincoln, 2007; Cassidy et al., 1998). One suggestion for why right hemisphere strokes result in greater disability is that right hemisphere strokes are associated with spatial neglect (estimates of the frequency vary between 35-85%; Stone et al., 1991), a deficit in which patients fail to orient or attend to their contralesional side (Heilman and Valenstein, 1979; Danckert and Ferber, 2006). Numerous rehabilitation strategies have focused on the spatial aspects of neglect, but with only limited success (Bowen and Lincoln, 2007; Luauté et al., 2006). In addition, a large number of studies have demonstrated that neglect patients also have a large palette of non-spatial deficits (such as impairments in spatial working memory, temporal estimation or decreased arousal; for a review, see Corbetta and Shulman, 2011; Danckert et al., 2012b; Husain and Rorden, 2003; Shaqiri et al., 2013). Therefore, there is a need for rehabilitation techniques that focus on the entire spectrum (spatial and non-spatial) of deficits that follow right hemisphere damage.

This was the motivation for this thesis: explore the preserved abilities in brain damaged patients by testing them with different paradigms using priming and statistical learning. This goal was motivated by the studies of Geng and Behrmann (2002, 2006), in which the authors demonstrated that neglect patients were able to benefit from a biased distribution of target locations and that patients could use this statistical information as a cue to direct their attention. Those results seemed promising in the domain of rehabilitation and raised the question of a possible training of neglect patients, in order to help them direct their attention to the contralesional side. Although Walthew and Gilchrist (2006) questioned if patients were really learning the probability of the target distribution or if they were only demonstrating a priming effect, we believe that both priming and statistical learning will be important for patients' rehabilitation.

To investigate probability effects in patients with brain lesions, the study reported in Chapter 2 was conducted. In that study, the target location was biased so 75% of the targets would appear on left side of the computer screen (which was the patients' contralesional side). Because of the high probability of the target to appear in a biased region, we were able to investigate if patients' benefit from the biased target location and the contribution of position priming. The results showed that

[6] Parts of this chapter were originally published in *Frontiers of Human Neuroscience* (Shaqiri, Anderson and Danckert, 2013).

position priming in patients is precarious. Right hemisphere patients did not learn the underlying statistical distribution of the target location. As a second step, we investigated in a single case if this impairment could be overcome with training. We found that a chronic neglect patient, who was tested over three days, was able to benefit from the biased statistical distribution, as he demonstrated faster RT for targets presented in the high probability region. Therefore, the difficulty to learn the transition probability demonstrated by the patients could have been a confirmation of their spatial impairment, but not necessary a general deficit of the ability to learn and benefit from statistical regularities.

To try and separate effects on priming from statistical learning, the second study, presented in the third chapter of the thesis, tested right hemisphere patients with and without neglect on a paradigm of priming and statistical learning. This time, all the targets were presented at the centre of the screen, which avoided any spatial bias related to the target location. Priming was quantified by comparing trials repeated successively at the same location to those presented in different locations. Statistical learning was investigated comparing three conditions varying in their repeat probability. As in our previous study, we found that neglect patients did not have settled results for position priming. Contrary to healthy subjects, the brain damaged patients with neglect did not learn the statistical distribution of targets across repeat conditions. This was also the case for the right brain damaged without neglect, although this group demonstrated a short priming effect of one repeat of the target position. This study confirmed that position priming and statistical learning were both impaired in right brain damaged patients, even when no spatial aspects were involved.

Those two studies both assessed visual statistical learning. But statistical learning also exists for other sensory modalities. For the study reported in the fifth chapter, our goal was to investigate if a deficit of statistical learning extended to the auditory modality as well. As a first step toward the novel application of this methodology in brain damaged participants, we first wished to verify basic, well-established statistical learning effects. We conducted a replication of the study of Gebhart and colleagues (2009) in university students. Participants learned nonsense words that formed two artificial vocabularies. In this study (reported in the fourth chapter), we found that our participants were able to learn two artificial vocabularies above chance. This basically replicated the study of Gebhart and colleagues (2009). Nevertheless, our results did differ in some particulars: we found that providing information or breaks of different lengths to participants did not change their performance on auditory statistical learning, as students were always learning the first language better than the second. This study did confirm that the paradigm worked in our hands and justified our expansion to brain damaged participants.

In Chapter five is reported a study that tested if left and right brain damaged patients, with or without neglect, have preserved auditory statistical learning abilities. The results demonstrated that none of the brain damaged groups learned the two languages. We also tested if it was possible to train patients in this task by prolonging the language exposure. We found that patients' results did not change with repeated training. With this study, we demonstrated that brain damaged patients are impaired in auditory statistical learning and that this impairment is multimodal. Moreover, we also found that this impairment cannot be overcome with a simple short-time increase in exposure.

In the next section, will be outlined the precise contributions of the results presented throughout this thesis (and summarized above) for contributing to an understanding of statistical learning in brain damaged patients and the importance of statistical learning deficit as an overall impairment that covers the majority of non-spatial disorders of spatial neglect and that can be summarized as a difficulty in learning and benefiting from environmental regularities.

6.1 Contributions of the present work

As described above, the four conducted studies thoroughly investigated the phenomenon of statistical learning in brain damaged patients. Statistical learning is of great interest, because of its possible relevance for rehabilitation. This thesis demonstrates data valuable for addressing questions about clinical populations, and also about the general processes of statistical learning. These contributions are reviewed separately below.

6.1.1 Distinction between priming and statistical learning

As reported in the second and third chapters of the thesis, numerous studies have made a parallel between priming and statistical learning (Walthew and Gilchrist, 2006; Druker and Anderson, 2010) and have questioned if the results of neglect patients reported by Geng and Behrmann (2002; 2006) were due to priming effects or because patients had learned and benefited from probability cueing. Although priming effects have been extensively investigated in brain damaged patients (Kristjansson et al., 2005; Saevarsson et al., 2008), only a limited number of studies have studied statistical learning and its relation to priming in clinical populations (Geng and Behrmann, 2002; 2006). The design of the studies conducted and reported in the present thesis allowed to untangle this question and investigate the two phenomena separately. In the first study, primed trials as successive repeats of color or position were identified. For the statistical learning analysis, only trials that were not primed were analyzed. This was made possible by the high number of possible target positions in the paradigm, and the low chance for the target to repeat its exact same location.

With this paradigm, it was shown that neglect patients were not impaired in color priming, which was in accordance with the study of Kristjansson and colleagues (2005), in which the authors found that it was not necessary for neglect patients to be aware of the presence of a target on their contralesional side in order to benefit from color priming. We too, found that right brain damaged patients with or without neglect benefited from repeats of the same color and responded faster to those targets. This was not the case when the position of the target was repeated. In this case, patients did not benefit from the position priming. Kristjansson and colleagues (2005) also found a more precarious position priming effect in neglect patients. Those patients were able to benefit from position priming only when they consciously reported seeing the target, but not when the time was limited.

In the study of Geng and Behrmann (2006), patients had an unlimited time to report the target, which might explain why these authors found a benefit from the repeat of the target location. We did not find such results: for both studies that investigated position priming, the results showed that patients experienced little benefit from spatial repetitions. With this paradigm, we were able to respond to the issue raised by Walthew and Gilchrist (2006) about whether the benefits seen by Geng and Behrmann (2006) could be priming alone. This brings us to the second contribution of the thesis, the joint investigation of the relation between priming and statistical learning.

6.1.2 The relationship between position priming and statistical learning

The second contribution of the present thesis is the clarification of the relation between priming effect and statistical learning and the implication of those phenomena for brain damage. As the studies described in Chapters 2 and 3 have reported, our brain damaged groups were impaired in position priming. This might explain why it is difficult for patients to learn the statistical distribution of target locations. If a basic route for statistical learning is via position priming, than an impairment of position priming will necessarily impair statistical learning. Statistical learning requires information accumulation and storage, in order for participants to be able to learn stimulus regularities. In the present thesis, the hypothesis that priming is a necessary step for statistical learning to occur was advanced. This hypothesis is supported by the data, as well as by other studies that have investigated temporal processing and working memory in neglect patients (for a review, see Shaqiri et al., 2013; Danckert, 2013).

For example, neglect patients underestimate time intervals (Merrifield et al., 2010; Danckert et al., 2007; Berberovic et al., 2004). Impaired temporal processing could contribute to a difficulty adequately accumulating information over time about stimulus location. Information accumulation is further exacerbated by working memory deficits. In a review, Kristjansson and Campana (2010) showed that priming is a basic phenomenon that helps the direction of visual attention. Priming, report the authors, depends on implicit memory and guides attention to recently visited items. This review highlights the relation between priming and memory: working memory impairments in neglect patients are related to the difficulty neglect patients have in benefiting from position priming (Husain et al., 2001; Malhotra et al., 2006; Danckert and Ferber, 2006). To learn environmental statistics, it is necessary to keep information in working memory. A working memory deficit could explain the connection between priming and statistical learning, as those two aspects are closely related to working memory. Indeed, Umemoto and colleagues (2010) have shown that free working memory resources are necessary for statistical learning to occur.

The generality of the issue is demonstrated by showing that the impairment extends to other modalities. We found that brain damaged patients were also impaired for auditory statistical learning. Although Christiansen and Conway (2006) suggested that statistical learning was closely related to the perceptual characteristics of the stimuli, our studies show that statistical learning impairments following brain damage are multimodal.

This aspect brings us to the third and most important contribution of this thesis: the hypothesis that there exists an extremely close relation between all of the non-spatial deficits in neglect patients: working memory, temporal estimation, position priming and statistical learning can all be grouped as impairments in learning environmental regularities.

6.1.3 Statistical learning as an impairment of learning from regularities in the environment

Numerous deficits present in neglect patients can be regrouped to form a single deficit: learning environmental statistics (Shaqiri et al., 2013). The studies conducted for the present thesis all demonstrate the same results: neglect patients (as well as brain damage more generally) are impaired in statistical learning. This impairment is not limited to the visual or spatial aspects. It is multimodal.

The importance our studies have for rehabilitation is that they show that neglect patients do not benefit from basic repetitive information present on a trial to trial basis (priming) and that they cannot extrapolate to use probability cueing. Neglect patients' performances appear similar to a reset of the perceived information at every trial. This resetting theory was originally suggested by Serences and Yantis (2006) for describing normal attention. For these authors, the attentional network is recruited every time there is a new state. An extension of their idea to neglect patients would be to assert that because of working memory and temporal estimation impairments, neglect patients effectively reset their attentional system at every trial, from moment to moment, and fail to accumulate information about stimuli over time, as well as learn the regularities that are presented in their environment.

Combining the results of our studies with the others reviewed, neglect can be described as a disorder of learning and updating information from the environment (Shaqiri et al., 2013; Danckert et al., 2012, 2012b). Consequently, rehabilitation strategies need to address this deficit. Patients need to be trained to improve their ability to detect and exploit regularities within their environment. To interact efficiently with the environment, a representation of recent perceptual information is required (Tenenbaum et al., 2011). As Valadao and colleagues demonstrate (2013), keeping in mind information that may be relevant for detecting changes in environmental statistics can affect the ability to learn the statistical distribution that gave rise to that data. An impairment in patients' abilities to integrate information, or to keep it in mind, will impair their abilities to learn statistical regularities of the environment. This will impact everything from adapting to new surroundings to benefiting from rehabilitation programs.

These ideas can be extended. A neglect patient's inability to learn regularities from the environment will also impair the ability to form a mental model and to appropriately update mental models when necessary.

One of the first studies demonstrating that neglect patients have a representational impairment is the very elegant and famous study of Bisiach and Luzatti (1978). Patients were asked to imagine how they would see a famous square in Milan. The authors found is that patients could represent all the buildings present on their imagined right, but failed to report those on their left. When the experimenters asked patients to imagine themselves standing on the opposite side of the square, so that the buildings they had previously neglected were now on their right, the patients reported those building but missed (i.e., neglected) those they had previously reported. Bisiach and Luzatti (1978) concluded that patients demonstrate neglect even for their mental representations and are not aware of the fact they neglect part of those representations. They have difficulties adapting to their surroundings or imaging them. For example, another demonstration of a representational impairment in neglect comes from motor imagery. Danckert and colleagues (2002) have shown in one neglect patient that imagining and creating mental representations of motor movements is impaired, while the patient did not show any impairment while actually *performing* those movements. In their study, the researchers asked one neglect patient to imagine a motor action, such as pointing towards targets of different sizes. The patient demonstrated normal movements that conformed to expected speed-accuracy trade-offs (i.e., movement duration decreased with increasing target size; Danckert et al., 2002), whereas imagined movements did not show such a pattern. That is, contrary to the actual movement, for which the patient was faster to point to larger targets – which corresponds to the performance of healthy participants – when asked to imagine a movement for a given target, the patient did not show a relation between the time to imagine the movement and the size of the presented target, further demonstrating the challenge neglect patients have in creating accurate representations – in this instance a model of an intended action (Danckert et al., 2002).

Another study demonstrating an impairment of using incoming information to adapt behavior is the double step saccade task (Duhamel et al, 1992). In this task, participants saccade to two successive targets that are extinguished in under 200 msec (i.e., prior to initiation of the first saccade). In order to accurately acquire the second target, an individual must anticipate the sensory consequences of the first saccade to update a mental representation of space. Results with neglect patients demonstrate inaccurate saccades to the second target when the first target was presented in contralesional space and the second target is in ipsilesional space. This demonstrates an impairment in using environmental information for adapting eye movements (Duhamel et al., 1992; see also Heide et al., 1995; 2001).

6.1.4 Brain regions involved in priming and statistical learning

Many studies investigating which brain regions are involved in updating, decision-making, statistical learning and novelty detection have found sets of structures that overlap those injured in neglect. For example, the right hemisphere generally appears critical for priming and statistical learning (Kristjansson et al., 2007; Turk-Browne et al., 2009). Roser and colleagues (2011) presented sequences of shapes with varying transitional probabilities in the left or right visual field of a split-brain patient. The patient could learn the statistical relation of the shapes when they were presented to his left visual field (right hemisphere), but not when they were presented on his right visual field (left hemisphere). The authors concluded that the right hemisphere plays an important role in statistical learning (Roser et al., 2011).

The temporo-parietal junction (TPJ), a region commonly involved in neglect, has been identified in several studies as being important for representational updating (Mort et al., 2003; Downar et al., 2002; Clark et al., 2000; for a review, see Corbetta and Shulman, 2002; Husain and Rorden, 2003). In a study in which changes in event related potentials (ERP) were studied based on novel or unusual events, it was shown that the P300 component, localised to the TPJ, increased in amplitude for novel events (Dien et al., 2003). The authors found that when information coming from the environment required an update of existing mental models, the electroencephalographic activity at the TPJ increased. The TPJ is also believed to be activated when attention needs to be directed towards behaviourally relevant events (Corbetta and Shulman, 2002). In their review, Corbetta and Shulman (2002) suggest that the TPJ acts as a "circuit breaker", important for redirecting attention toward salient information in the environment. Therefore, a possible hypothesis is that the TPJ might be a critical region for orienting attention towards information that is useful to adapt to new information. Additional studies in clinical populations have identified the parietal cortex as being an important region involved in representational updating (Danckert et al., 2012; 2012b; Vuilleumier et al., 2007), as most of the patients who had lesions at this region failed to show adaptation to environmental regularities. But TPJ has not been the only region of interest for spatial neglect, the superior temporal gyrus (STG, Karnath et al., 2001, Karnath et al., 2004) has been identified as being involved in this disorder as well.

Other studies conducted in our lab have supported the hypothesis that neglect patients have difficulties learning and benefiting from regularities in the environment. For example, Stoettinger used ambiguous figures (Stoettinger et al., 2013; Christman and colleagues, 2009) to test a population of right brain damaged patients. A sequence of pictures began with one unambiguous representation of a common object (e.g., swan) and then gradually progressed through successive altered images that eventually showed a completely different, unambiguous item (e.g., cat). The number of pictures for which patients retained their initial report of the original unambiguous figure was used as a measure of updating. Results showed that right brain damaged patients persisted in their original report for more pictures than did controls. Importantly, all subjects correctly identified the beginning and ending pictures, as well as catch trials in which simple geometric figures were inserted into the sequence. These data are in good agreement with those of Vocat and colleagues (2012), who tested right brain damaged patients with anosognosia on a riddle test. Participants listened to five increasingly specific clues (for example, for the targeted word "*airplane*", they were given the clues: "*I have wings*", "*I can fly*" and then the last clue was "*I have wheels*"). The authors found that anosognosic patients with right hemisphere strokes reported higher levels of certainty regarding their initial guesses associated with the first clue (even those that were not particularly informative) and preserved their response through the subsequent clues even when this disconfirmed their guess. For example, with the clue "*my weight is approximately 300 grams*" and the target word "*heart*", a patient guessed the word "*bread*" and then with the next clue, "*I produce a regular sound*", he persisted with the answer "*bread*" but justified it by saying it's the noise that the knife makes when we cut bread (Vocat et al., 2012). The authors concluded that patients were impaired in creating and adapting beliefs to new information: they were overconfident about their initial guesses and failed to revise those guesses when successive clues were incongruent with that guess. Data from a rock, paper, scissors task (Danckert et al., 2012), the ambiguous figures task (Stoettinger et al., 2013) and Vocat's riddle task (2012) are all consistent with the hypothesis that right brain damaged patients have difficulties in creating and updating models of the regularities present in the environment (Danckert et al., 2012; 2012b). So whereas previous rehabilitation attempts may succeed to some degree in improving deficits of spatial attention (Striemer and Danckert, 2007; 2010), they are unlikely to improve the more generic deficit in building accurate mental models and updating those models as environmental changes dictate.

6.2 Limitations of our work

Although we have tried to control most of the aspects in the studies conducted in the present thesis, a few elements were difficult to implement, for example eye-tracking in the studies that tested priming and visual statistical learning (Chapters 2 and 3). Our main reason for not controlling for eye movements was the difficulty to implement such apparatus to test brain damaged patients (especially as some of the testing was done at the patient's bedside at the hospital). But eye movements are a potentially important contributor to our results. For example, in the study reported in Chapter 2, detailed information about patients' eye movements could have informed us if after a few trials, neglect patients were making more saccades to the high probability region, even though the behavioral data did not show any benefit for the biased target location. Patients could have learned the biased probability for target location, but not succeeded in responding to the targets, notably because of motor impairments or a slow capacity to initiate a movement (Robsertson and North, 1992).

Moreover, the use of an eye-tracking device would have helped us to confirm that the difficulty of neglect patients to benefit from position priming is not due to a remapping impairment, as it has been suggested by Pisella and Mattingley (2004). In their review paper, the authors suggest that patients' gaze-shifts towards their contralesional side degrade all previously visited and remembered locations, creating a remapping problem. Whereas contradictory data were reported by Vuilleumier and colleagues (2007), who tested how gaze-shifts affect the memory of location in neglect patients, this could have been because of procedural details. Vuilleumier and colleagues (2007) found that only gaze-shifts to the far right affect location information in neglect patients, but when patients had to make a left gaze-shift, they showed a preserved ability to maintain and update the location information (see also Vasquez & Danckert, 2008, for similar results in healthy individuals). The results of Vuilleumier and colleagues (2007) are consistent with our results on position priming. We presented 75% of the targets on the patients' contralesional side (Shaqiri and Anderson, 2012), therefore, we believe that patients' difficulty to benefit from position priming is not just a remapping impairment, but is a more generic impairment of benefiting from regularities of the environment. This conclusion would have benefited from a confirmation by eye-tracking data, however.

Our studies in the visual domain could have shown different results if the timing of the targets was different (for example, if patients had unlimited time to respond to the stimulus). In this condition, patients might have shown some degree of position priming, as this was the case in the study of Kristjansson and colleagues (2005). In order to test for statistical learning, we needed to accumulate a large number of trials within a short period of time for the patients to remain alert and focused. Patients with brain injury are often older and are known to be prone to fatigue. Moreover, Majlkovic and Nakayama (2000) have shown that if the inter-trial timing is greater than 30 seconds, it becomes difficult for participants to benefit from position priming, as they cannot accumulate information from successive trials in such a long interval. Therefore, the timing of our targets was a trade-off. Further work with longer exposure times would be valuable.

Another limitation in this thesis is that we only tested a few participants with prolonged exposure. In Chapter 2 were reported the results of a chronic neglect patient who was tested over successive days and found promising results. He demonstrated a benefit in his RT over days for the high probability target region (Shaqiri and Anderson, 2012). In the study reported in Chapter 5, an attempt to improve statistical learning performance with an exposure three times as long as usual was made, but we found no benefit. However, this was a single exposure of about half an hour. Maybe a longer exposure, distributed over days, would have been better? Moreover for all these tests, we never evaluated functional tasks or tasks other than the one trained on. This seemed reasonable in these early exploratory studies. Now that we have better evidence that the deficits are pervasive and persistent, studies investigating prolonged training and transfer effects are justified.

6.3 Implications for rehabilitation strategies

Whereas neglect patients have trouble creating and updating mental models (Danckert et al., 2012; 2012b), this difficulty is not absolute. As the aforementioned studies of ambiguous figures (Stoettinger et al., 2013) and riddle tasks (Vocat et al., 2012) have shown, patients eventually get the correct answers; it just takes them longer to get there. The patients' need more information and longer periods of time compared to healthy controls and this is where the rehabilitation strategies should focus.

If statistical learning is inefficient in neglect, then massing trials would be one approach for training a corrective bias in patients' attention. As a preliminary test of this idea, we trained a chronic neglect patient by testing him over three days on the statistical learning paradigm adapted from Druker and Anderson (2010; Chapter 2). We analyzed whether the patient showed greater improvement in RT over trials for targets presented on the left compared to those on the right and found that after training, the patient was able to improve performance for the contralesional high probability region and become faster for targets on the left, previously neglected space, although his performance did not reach the same speed as his RTs for right-sided targets. These data are in agreement with the studies of Geng and Behrmann (2002; 2006). Although their protocol had a reduced number of positions and could have suffered from the confound of position priming, their patients with neglect were sensitive to the probability of the stimulus location, and this acted as a cue for directing attention.

We demonstrated (Shaqiri and Anderson, 2012, 2013) that neglect patients have a preserved but attenuated priming effect, but are also sensitive to some extent to probability distributions, although a longer exposure duration is needed to demonstrate this sensitivity.

Taken together, these data could have important implications for the rehabilitation of neglect patients. First, the non-spatial features of neglect must be understood to be important contributors to the nature and recalcitrance of the clinical symptoms. Second, deficits in domains such as priming, temporal processing, and working memory may underlie deficits that can have pervasive effects on daily behavior and limit the benefits due to conventional rehabilitation. Our data also suggest that if given enough time and experience, neglect patients can benefit from regularities of their environment, as we have shown by training a neglect patient over three days (Chapter 2; Shaqiri and Anderson, 2012). If considered when designing and testing rehabilitation techniques for neglect, the observations suggest new domains for intervention and emphasize that constant, regular biases with training over multiple sessions may help patients to develop the intrinsic biases that will improve performance across multiple tasks, and in activities of daily life.

6.4 Conclusion

In the present thesis, a number of different studies were presented, that demonstrate that beyond the spatial aspect of neglect, the disorder is linked with a range of other deficits, including working memory, temporal processing, motor imagery, statistical learning and priming impairments. Taken together, this range of impairments makes it extremely difficult for neglect patients to build accurate mental models of the environment and to update those models when contingencies change. In essence, neglect patients have difficulty using incoming information from the environment in order to create and then adapt to changes in the environment. It is a difficulty that most rehabilitation techniques available have not succeeded in overcoming. A possible suggestion is that with enough time and information, some neglect patients might be amenable to training. As such, the deficits outlined in this thesis should be targets of new research and considered when for developing new rehabilitative techniques for what has proven to be an extremely difficult disorder to treat.

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