BRAIN RESEARCH REVIEWS

Review

A review of lateralization of spatial functioning in nonhuman primates

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ABSTRACT

The majority of research on functional cerebral lateralization in primates revolves around vocal abilities, addressing the evolutionary origin of the human language faculty and its predominance in the left hemisphere of the brain. Right hemisphere specialization in spatial cognition is commonly reported in humans. This functional asymmetry is especially evident in the context of the unilateral neglect, a deficit in attention to and awareness of one side of space, that more frequently occurs after right-side rather than left-side brain damage. Since most of the research efforts are concentrated on vocalization in primates, much less is known about the presence or absence of spatial functions lateralization. Obtaining this knowledge can provide insight into the evolutionary aspect of the functionally lateralized brain of *Homo sapiens* and deliver refinement and validation of the nonhuman primate unilateral neglect model. This paper reviews the literature on functional brain asymmetries in processing spatial information, limiting the search to nonhuman primates, and concludes there is no clear evidence that monkeys process spatial information with different efficiency in the two hemispheres. We suggest that lateralization of spatial cognition in humans represents a relatively new feature on the evolutionary time scale, possibly developed as a by-product of the left hemisphere intrusion of language competence. Further, we argue that the monkey model of hemispatial neglect requires reconsideration.

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1. Introduction

In this review we address the question of whether nonhuman primates display a similar right hemisphere functional specialisation as humans when processing spatial information. First, we introduce the idea of cerebral lateralization, the possible ways it could have emerged within the evolutionary history and its advantages and disadvantages. Second, we explore the lateralization phenomena in the spatial cognition and language domains. Third, we elaborate on unilateral neglect, a syndrome with a strong lateralization component in humans. Fourth, we recount the results of relevant monkey studies and re-examine the available evidence on functional cerebral asymmetries for processing spatial information in monkeys. Finally, the reviewed literature is briefly summarized and a conclusion formulated with a short discussion of the consequences of the findings and possible future research directions.

1.1. Cerebral lateralization

Cerebral lateralization of the brain has received considerable theoretical and experimental attention where it is commonly suggested that hemispheric asymmetries ensure more efficient employment of neuronal processing space, paralleled by a reduction of possible interference between concurrent processes (Bradshaw, 2001; Levy, 1977). Behavioural lateralization also occurs at a population level, where it can yield survival benefits through a coordination of individual behaviour with a group of asymmetrically behaving members (Vallortigara and Rogers, 2005; Vallortigara et al., 1999). The ubiquity of neural and behavioural asymmetries found in the animal kingdom (Bisazza et al., 1998; Vallortigara, 2000, 2006; Vauclair et al., 1999, 2006) advocates that the advantages of lateralization outweigh the possible disadvantages as in, for instance, a predator being able to predict a prey's actions or the detrimental impact of unilateral brain injuries on an animal's functions (Corballis et al., 2000; Vallortigara and Rogers, 2005; Vallortigara et al., 1999).

From an evolutionary point of view, the occurrence of relatively independent operating cerebral hemispheres most likely resulted from an increase in absolute brain size, coupled with a relatively lower increase rate of the number of callosal axons (Aboitiz et al., 2003; Olivares et al., 2000, 2001; Rilling and Insel, 1999; Striedter, 2006). Logically, interhemispheric communication in larger brains is compromised both by less dense callosal connections and longer transmission delays due to an increased distance between the hemispheres (Olivares et al., 2000, 2001; Ringo et al., 1994). Collectively, these anatomical changes that occurred in larger brains might have scaled down the amount of cooperation between the two hemispheres that promoted an increase in interhemispheric asymmetries (Gannon et al., 1998; Hopkins and Rilling, 2000; Rilling and Insel, 1999; Ringo et al., 1994). Importantly, the above scenario holds true mainly for the prefrontal and temporo-parietal visual areas that execute higher cognitive functions and are interhemispherically connected by slow-conducting, weakly myelinated fibres (Aboitiz, 1992; Aboitiz et al., 1992, 2003; Lamantia and Rakic, 1990; see for a review, Schuz and Preissl, 1996). This independency of brain areas contrasts with to the primary and secondary somatosensory cortices, where proper functioning requires efficient interhemispheric integration. In particular, for these sensory brain areas, the effect of greater interhemispheric distances is counterbalanced by fast-conducting, highly myelinated callosal projections (Aboitiz, 1992; Aboitiz et al., 1992, 2003; Lamantia and Rakic, 1990).

1.2. Spatial cognition and language

Systematic analyses of possible functional differences between the two hemispheres of the nonhuman primate brain can shed further light on the puzzling cognitive advance of

Homo sapiens with language faculty as a hallmark. A simplified traditional view underscores the functional dichotomy of the human brain with the left hemisphere yielding a relative specialization in language processing and the right hemisphere showing superiority in spatial cognition (Flöel et al., 2005; Hugdahl, 2000; Smith et al., 1996; Stephan et al., 2003; Vogel et al., 2003; Walter et al., 2003).

One of the critical issues of brain asymmetries concerns the evolutionary sequence of events that occurred to form the functionally lateralized human brain, as we currently know it. Did the spatial cognition resources that originally were symmetrical begin to "occupy" the right hemisphere as a consequence of the left-hemisphere "intrusion" by language and praxis? Alternatively, is the concentration of spatial cognition processes in the right hemisphere phylogenetically ancient (Bradshaw, 2001; Corballis et al., 2000; LeDoux, 1982)? Here we can formulate two potential scenarios: (1) the two hemispheres in our ancestors' brains were functionally equivalent with respect to their spatial cognition processes, before the emergence of left hemisphere language-adeptness; and (2) the right hemisphere was already more proficient in processing spatially directed interactions with the environment before the language faculty began to emerge in humans.

To this point then, the majority of comparative research on nonhuman primates has been focused on finding functional and neuroanatomical asymmetries for vocal communication and auditory processes. These communication abilities are often believed to have some degree of continuity with respect to certain components of human language (e.g., Beecher et al., 1979; Belin, 2006; May et al., 1989; Petersen et al., 1978, 1984; Poremba, 2006; Poremba et al., 2004; Poremba and Mishkin, 2007; Zoloth and Green, 1979). Much less is known about the possible nonhuman primate brain lateralization of spatial cognition, which may represent a more ancient cognitive capability. Although, it is often assumed that cerebral asymmetry does not underlie spatially directed behaviour in nonhuman primates (Husain and Nachev, 2007; Husain and Rorden, 2003; Karnath, 2001; Karnath et al., 2001; Milner, 1987; Payne and Rushmore, 2003), no systematic evaluation of this hypothesis has been undertaken as yet. This lack of systematic evaluation is especially remarkable in light of the fact that the spatial information processing capacity of nonhuman primates resembles that of humans, and any such comparison would be both fairer and more controllable. In the vocalization domain, for instance, there is a continuous debate with respect to the question of how many and which language sub-processes are species- or language-specific (cf. Fisher and Marcus, 2006; Hauser et al., 2002; Pinker and Jackendoff, 2005). It is particularly hard to determine to what degree both verbal signals and the calls of particular primate species are homologous and/or analogous to human language.

1.3. Unilateral spatial neglect

The knowledge of hemispheric asymmetries underlying space perception and spatially directed action is not just relevant to the evolutionary theory of cerebral lateralization. Considering the deficits in spatial functioning in humans that result predominantly from right hemisphere damage, research on hemispheric specialization of spatial cognition in monkeys gains more importance, as these species might serve as an appropriate animal model of such dysfunctions.

Unilateral or hemispatial neglect is an umbrella term that refers to a heterogeneous neuropsychological disorder of spatial cognition, which is a common clinical manifestation after a stroke (Ferro, 2001). The occurrence of hemineglect is frequently associated with damage to the inferior and superior parietal lobes, some parts of the frontal lobe (Husain et al., 2000; Ringman et al., 2004) and white matter connecting these parietal and prefrontal regions (Bartolomeo et al., 2007; Doricchi et al., 2008; but see Karnath et al., 2001). The possible symptoms of neglect comprise, independently or in combination, the loss of conscious representations in the contralesional space (Driver and Mattingley, 1998; Rafal, 1994), defective orientation of spatial attention toward the contralesional side that controls motor programs (Husain and Kennard, 1996) or the egocentric reference frame rotation or translation in the direction of the ipsilesional side (Kerkhoff et al., 2006; Richard et al., 2005 but see Chokron, 2003). Apart from these representational distortions, hemineglect patients typically demonstrate a deficiency in initiation eye or limb movements towards the contralesional side as well (Heilman et al., 1985; Husain et al., 2000; Mattingley et al., 1998).

Recent studies have also revealed that spatial working memory across saccades is dysfunctional in unilateral parietal hemineglect patients, as demonstrated by patients' persistent revisiting of locations in the ipsilesional visual field (Husain et al., 2001; Mannan et al., 2005; Parton et al., 2006; Sprenger et al., 2002). Such spatial working memory impairment seems to contribute to the severity of the contralesional side neglect by exacerbating the attentional bias toward the ipsilesional visual field. Also performance in non-lateralized tasks that require sustained attention and spatial working memory demonstrate a negative correlation with the severity of spatial neglect and a positive relation to spontaneous recovery (Buxbaum et al., 2004; Husain et al., 2001; Malhotra et al., 2005, 2009).

Another phenomenon known as visual extinction is often associated with neglect by some researchers and considered a milder form of neglect (Heilman and Watson, 1977), while others emphasise the distinction between the two disorders (Cocchini et al., 1999; Hier et al., 1983). Counter to spatial neglect, visual extinction is manifested as a failure to detect a contralesional target only in the simultaneous presence of an ipsilesional distracter and thus is only apparent in the presence of a competing stimulus.

Notwithstanding the causes and particular manifestations of neglect, right hemisphere dominance is clearly present. This dominance can be seen in a significantly higher incidence of hemineglect after right than after left cerebral hemisphere damage (for a meta-analysis see Bowen et al., 1999). The occurrence and severity of spatial neglect disorders are predominantly associated with right-hemisphere damage with a frequency ratio of at least 2:1 (Beis et al., 2004; Ringman et al., 2004), which is very similar to the occurrence contingency found for visual extinction by Becker and Karnath (2007). Moreover, the restoration of affected functions in the acute phase of neglect is more complete and rapid in individuals with left hemisphere stroke compared with right-sided brain damage (Denes et al.,

1982; Ringman et al., 2004; Stone et al., 1992, 1993). For these reasons, we emphasise once again that it is important to establish whether the animal species used as models of hemispatial neglect demonstrate a similar to human hemispheric asymmetry.

1.4. Scope of the reviewed literature

The previous subsection can be aptly summarized by Husain and Rorden's (2003) remark that damage of the corresponding perisylvian regions in the two cerebral hemispheres in humans frequently results in different deficits: Language disorders for the left hemisphere impairment and a more severe spatial neglect for right hemisphere injury. Some authors consider this functional asymmetry of the perisylvian regions an evolutionary development characteristic that is exclusive to humans (Husain and Rorden, 2003; Milner, 1987; Payne and Rushmore, 2003). This notion is then argued as a potential explanation for the lack in monkey studies of unambiguous evidence for similarly profound and enduring hemispatial neglect as is found in humans (Husain and Rorden, 2003; Milner, 1987; Payne and Rushmore, 2003). To evaluate this last statement, we recount in the following section the experiments that investigated lateralization of spatial cognition in monkeys and those that aimed at producing a nonhuman primate model of hemispatial neglect. Because the number of reports that systematically investigated cerebral lateralization of spatial functions in monkeys is scarce, we also consider studies that indirectly yielded important clues about potential hemispheric specialization in the nonhuman primate brain.

The spatial information processes under scrutiny here represent phenomena that in human subjects seem to be handled with different efficiency by the two hemispheres, i.e., some of these neural processes are classically compromised in hemispatial neglect. First, we recount studies that examined animals' performance in visuospatial discrimination tasks with a working memory component. The core of these tasks is the comparison of a spatial aspect of a stimulus (orientation or relative position) with a test target or a mental reference. Secondly, we consider a number of experiments investigating oculomotor behaviour, namely, both visually- and memory-guided saccades, that in neglect patients are significantly decreased in accuracy and latency (e.g., Husain et al., 2001; Mannan et al., 2005; Parton et al., 2006; Sprenger et al., 2002). Finally, we refer to a series of studies in which an experimentally induced stroke in monkeys served as a model of the human condition. Since stroke is one of the main causes of unilateral spatial neglect in humans, the animals in these experiments were tested with a battery of tests that assessed the degree of their hemineglect. This set of stroke studies, together with the experiments involving focal brain lesions, are relevant to our discussion in the light of the concept that neglect patients have more enduring neglect symptoms than do monkeys. This non-equivalence is commonly explained by the human right hemisphere specialization in spatially directed behaviour, which cannot be easily compensated for by the left hemisphere. Our primary aim here is to systematically evaluate the nature and magnitude of neglect manifestations in nonhuman primates.

2. The evidence on spatial cognition lateralization in nonhuman primates

A number of studies with human subjects have demonstrated right hemisphere superiority in tasks entailing a comparison of visuospatial attributes of two stimuli (Kessels et al., 2000; Ng et al., 2000). A lateralization pattern has been noted primarily for the versions of a visuospatial discrimination task that additionally engaged working memory (Corballis et al., 2002); a brain function often compromised in hemispatial neglect patients (Malhotra et al., 2005, 2009; Mannan et al., 2005; Parton et al., 2006). In the following subsection we discuss research carried out on monkeys that were trained to perform visuospatial discrimination tasks.

2.1. Visuospatial discrimination tasks

2.1.1. Orientation discrimination
One of the ways to investigate hemispheric asymmetries when processing a particular type of representation is to use a split-brain animal. In such an animal, cerebral hemispheres are disconnected, which ensures independent processing of input within each hemisphere. A number of possible tract sections of the early visual pathway can be performed in a monkey brain to guarantee circumscribed visual input. The visual tract sections are often combined with medial disconnection of the whole or different parts of the corpus callosum in order to preclude interhemispheric transfer between certain brain areas. The subsequent behavioural tests applied separately to the left and the right visual field and thereby to the corresponding hemispheres, allow a direct comparison examination of the equivalence of function.

An early study on a group of seven monkeys (5 *Macaca mulatta* and 2 *Macaca nemestrina*) demonstrated a quite consistent left hemispheric dominance in a working memory task with a spatial aspect, that is line orientation discrimination (Hamilton et al., 1974). Prior to the training the animals underwent optical chiasm, corpus callosum, anterior commissure and hippocampal commissure section ensuring the possibility to train in the tasks independently in each hemisphere. The sequential orientation discrimination task yielded results where one monkey learned the task equally well with both hemispheres while the remaining six macaques showed a left-sided advantage. A later study from this research group, utilising a better-counterbalanced design, confirmed a left-hemisphere dominance in a task that combines orientation discrimination with response mapping in a small group of rhesus macaques. The same animals did not show a consistent hemispheric asymmetry as a group in an analogous pattern discrimination task (Hamilton, 1983). Moreover, Hamilton and Vermeire (1988) reproduced this finding with a larger group of 25 split-brain rhesus monkeys (*Macaca mulatta*). It is intriguing that this group of monkeys displayed a right-hemisphere advantage for face discrimination learning and in 15 subjects it was accompanied by left hemisphere specialization for orientation discrimination. However, this opponent laterality of face and orientation discriminations was independent (not correlated), which indicates a lack of causality in the evolution/development of this complementary functional asymmetry.

Final confirmation of the left hemisphere superiority in orientation discrimination comes from a study by Vogels et al. (1994). Two split-brain rhesus monkeys (*Macaca mulatta*) with heads fixed during the experimental task stared at the fixation spot in the middle of the screen to ensure that laterally presented oriented bars stimulated only the contralateral hemisphere (Vogels et al., 1994; see also Orban and Vogels, 1998; Vogels et al., 1997). The monkeys displayed performance asymmetry, but this effect was only obvious when the to-be-compared oriented bars were presented sequentially and not during the task where the two stimuli were shown simultaneously. This between-tasks difference related to the working memory component. The different outcome suggests an involvement of higher brain areas in functional lateralization and not simply dissociation at the visuosensory level.

2.1.2. Relative position judgment

Traditionally, lateralization studies on animals also have reported on the effects of experimentally induced unilateral brain lesions, either independently or in combination with callosal sectioning. In this way, apart from an assessment of lateralization of brain functions, cortical regions crucial for processes compromised in the examined dysfunction can be investigated. Animal brain lesion studies that correlate cognitive deficits with neural substrates are of great importance since they control the range of damaged neural tissue and allow behavioural testing before and after surgical intervention within the same subjects.

In a visuospatial comparison task, rhesus monkeys with a unilateral occipital lobectomy combined with splenial transection had to judge two simultaneously presented stimuli comprised of a square with a dot inside, which could be placed either in the centre or off-centre along the vertical meridian (Jason et al., 1984). Monkeys with left-sided lobectomy had significantly higher discrimination thresholds of the dot position than did the right hemisphere lesioned group. Surprisingly, each animal in the right lobectomy group improved its performance post-operatively, but without a sham-operated control group it is not clear whether this lowering of the discrimination threshold reflects extensive practice or a facilitatory effect of the right-sided lesion.

2.1.3. Discussion

When considering these studies on macaques we can conclude that this primate species does manifest functional specialization of the left hemisphere in orientation discrimination, but only when additional stages of short-term storage and representational comparisons with response mapping are required. The direction of hemispheric asymmetry seems to contrast with the right hemisphere dominance found in humans for similar orientation judgments (Benton et al., 1975; Corballis et al., 2002; Dupont et al., 1998; Harris et al., 2008; Orban and Vogels, 1998; Wang et al., 2007; Warrington and Rabin, 1970). Moreover, an impairment of orientation discrimination is apparent in patients with right hemisphere injury as opposed to the left hemisphere (Benton et al., 1975), and in left hemineglect individuals (Harvey et al., 2007; Wilkinson et al., 2008). In contrast to the right hemisphere advantage in humans performing positional judgments (Taylor and Warrington, 1973; Warrington and Rabin, 1970), rhesus monkeys have been observed to be more impaired in judging dot locations after a left-sided lesion (Jason et al., 1984). Taken as a whole, the opposite pattern of lateralization in these experiments reflects either genuine inter-species differences in hemispheric lateralization of the same cognitive processes or inter-species difference of the implemented strategy.

2.2. Eye movements and goal-directed orienting

Systematically evidence accumulates on the inherent interactions between spatial attention mechanisms and eye movement control (see for a review, Van der Stigchel et al., 2006). The discovery of interactions between oculomotor and attentional circuits resulted in a theory of premotor origin of attention suggesting a common mechanism underlying programming of saccadic eye movements and directing attention to spatial locations (Rizzolatti et al., 1987; Sheliga et al., 1994). The premotor theory of attention was further refined by the findings that the shift of spatial attention precedes the eye movement latency to that saccadic goal (e.g., Kowler et al., 1995; Shepherd et al., 1986; Van der Stigchel and Theeuwes, 2005).

Similarly intertwined mechanisms have been proposed for attention and spatial working memory processes (Awh and Jonides, 2001) and for spatial working memory and eye movements (Theeuwes et al., 2005). The interactions between attention and spatial working memory have been exposed by a facilitated visual performance at the location kept in working memory as compared with any other tested location (Awh and Jonides, 2001). The influence of the memorized location on saccades executed during the retention phase of the task was demonstrated by the trajectories of these eye movements that diverted away from the memorized location (Theeuwes et al., 2005).

The motor theory of attention and the numerous demonstrations of close interactions between goal directed attention and spatial working memory as well as spatial working memory and oculomotor programming are in line with the common co-occurrence of deficits of theses processes in hemispatial neglect patients (e.g., Heilman et al., 1985; Husain and Kennard, 1996; Husain et al., 2000, 2001; Malhotra et al., 2005, 2009; Mannan et al., 2005; Mattingley et al., 1998). In the following sub-sections we discuss monkey studies that tested attentional processing, spatial working memory or saccadic performance. In line with the revealed mutual relations between these functions, many tasks involve at least two of these processes.

2.2.1. Visually- and memory-guided saccades

Reversible deactivation of predetermined brain regions by cooling or muscimol (GABA$_A$ agonist) application can be an important alternative to surgical lesions. Complementarily to the permanent lesion studies, reversible deactivation techniques examine interference with the circuitry on a short time scale and a small spatial extent. A disadvantage of this method, however, is that short-term effects of neural dysfunction might diverge from processes in chronic states where idiosyncratic solutions develop in response to permanent neuronal tissue damage.

Visually- and memory-guided saccades were measured in rhesus monkeys before and after muscimol injections that

reversibly suppressed activity of the frontal eye fields (Dias and Segraves, 1999). The inactivation was performed in the left and right cerebral hemisphere in the two animals. For saccades toward the retinotopic representation of the injected site, latencies and targeting errors were increased, and velocities were decreased. Moreover, an impaired performance of memory-guided saccades was manifested by occurrence of premature eye movements to targets in the ipsilateral field pointing to a lack of inhibitory control. The effects were comparable in both monkeys thus indicating no hemispheric dominance.

In a similar way, reversible inactivation of the lateral intraparietal area in macaque monkeys influenced memory and visually guided saccades (Li et al., 1999). One monkey was subjected to muscimol injections in the right lateral intraparietal area while the other monkey was injected in the right and the left hemisphere. A general detrimental effect of muscimol on performance (error rates and misses) was demonstrated for the memory-guided saccades directed into the contralesional visual field. Moreover, saccades to remembered locations in the contralesional field were hypometric with lower peak velocity. Latencies of both visually and memory guided saccades after reversible inactivation of lateral intraparietal cortex (LIP) significantly increased with a larger effect for those saccades directed to the contralesional field. Notably, the authors noted no interhemispheric differences in effects of the muscimol-induced lesions.

2.3. Spatial oculomotor updating

A similar reversible lesion study examined the influence of a unilateral injection of muscimol that inactivated the area LIP on a double-saccade task (Li and Andersen, 2001). This classical task requires that the planning and execution of the second saccade take into account occurrence of the first eye movement. One of the macaques used in this experiment had inactivation performed on both left (2 sessions) and right LIP (4 sessions). Although, the authors did not analyse the behavioural results from the point of view of hemispheric lateralization, in Table 1 (p. 50) it is apparent that the effect of muscimol on the latency of the second saccade (with working memory component) was more prominent for the left hemisphere. Unfortunately, without a concrete statistical test and such bi-hemispheric measurements taken in more animals, this finding can only be described as anecdotal evidence.

Berman and her co-workers (2005) examined further spatial updating across saccades with special attention paid to the eye movements that cross visual hemifields and thus involve interhemispheric communication. The two rhesus macaques that took part in this study underwent forebrain commissurotomy to preclude interhemispheric information exchange. While the main finding was that direct cortico-cortical communication is very important for across-hemifield updating, it is not the only route of updating. For our discussion a more pertinent finding is that even as the performance differed depending of the hemifield toward which the second saccade was directed, it was not consistent in the two animals. One monkey demonstrated worse performance in the left visual field where the updated

position of the target depended on information transfer from left to right hemisphere, whereas the other animal showed a clear deficit only in the upper right quadrant of the visual field with an opposite direction of interhemispheric communication. Because the performance differences were so idiosyncratic and in some conditions the monkeys exhibited rapid changes in behaviour, the researchers ascribed the results partially to learning and the subsequent generalization of the learned behaviour to other parts of the visual field.

2.3.1. Visuospatial orienting

Functional cerebral lateralization can be also investigated with the use of an imaging technique such as functional magnetic resonance imaging (fMRI). With fMRI one can indirectly trace neuronal activation changes within the entire brain of behaving individuals by measuring a signal that is based on the local blood oxygen level in the brain (active neurons require more oxygen than silent ones). This way, a network of cooperating brain areas involved in a particular task can be assessed, as well as any likely differences in activation distributions between the two hemispheres.

Another advantage of using this whole brain imaging technique is its application in describing the neural processing of a healthy brain. To this end, a considerable amount of data has been generated with regard to the functional lateralization of the human brain (e.g., Flöel et al., 2005; Siman-Tov et al., 2007; van der Ham et al., 2007, 2009). Due to technical difficulties, the implementation of fMRI in studies with behaving monkeys has a much shorter history and accordingly less data is available. However, because of the importance of generalizing the results of single cell recordings from macaque to the human brain, this bridging method is beginning to be more often also in animals (Orban et al., 2006; Vanduffel et al., 2002), indeed a trend in neuroscience research that is steadily growing.

Among the sparse imaging studies in animals there is a noteworthy fMRI experiment on two cynomolgus monkeys (*Macaca fascicularis*) that revealed an intriguing asymmetric activation (Baker et al., 2006). Monkeys were required to execute rapid saccades to visual cues that activated a widely distributed oculomotor network underlying goal-oriented processing. Apart from classical activation of the LIP, the frontal eye fields (FEF), the supplementary eye fields and the superior colliculus, the researchers came across right unilateral pulvinar activation that was clearly present in both animals. The lateral pulvinar was previously found to contribute to visuospatial attention and orienting (Andersen, 1989; Karnath et al., 2002; Petersen et al., 1987) and the human fMRI data also shows a strong functional rightward lateralization of this structure (Fischer and Whitney, 2009). This commonality in human and nonhuman primate lateralized processing may provide cues for the evolutionary origin of the asymmetry.

Some hemispheric asymmetries might be characterized by subtle temporal dynamics, which can be easily obscured by the time-averaged signal obtained with the fMRI technique. Complementary information with a high temporal resolution can be acquired with electrophysiological methods, like e.g., electroencephalography (EEG). The disadvantage of EEG

Table 1 – Summary of hemispheric lateralization studies in nonhuman primates.				
Study	Species (No. subjects)	Task	Superior hemisphere	Comments
fMRI				
Baker et al. (2006)	*Macaca fascicularis* (2)	Saccades to visual cues	Right	Intact brain (magnetic resonance imaging MRI); lateralization found in the pulvinar
Kagan et al. (2010)	*Macaca mulatta* (2)	Working memory oculomotor task	Right	Right hemisphere showed a slightly weaker contralaterality of fronto-parietal regions than the left hemisphere (this effect was much greater in humans)
Reversible lesions				
Dias and Segraves (1999)	*Macaca mulatta* (3)	Visually- and memory-guided saccades	None	Reversible inactivation of the frontal eye field (1 left and 2 right)
Li and Andersen (2001)	Macaque monkeys (not specified) (2)	Double saccade task	Left (trend)	Reversible inactivation of the lateral intraparietal cortex (in one animal 2 left and 4 right injections)
Li et al. (1999)	Macaque monkeys (not specified) (2)	Memory- and visually-guided saccades	None	Reversible inactivation of the lateral intraparietal cortex (in total 6 left and 10 right injections)
Split-brain and/or lessions				
Berman et al. (2005)	*Macaca mulatta* (2)	Double-saccade task	Subject dependent	Forebrain commissurotomy
Crowne et al. (1989)	*Macaca irus* (4)	Visual stimuli detection	None	Arcuate (1 left and 1 right) or posterior parietal (1 left and 1 right) cortex removal
Deuel and Farrar (1993)	*Macaca fascicularis* (30)	Unilateral and bilateral visual or somatosensory stimulation, stimulus array cancellation	None	Frontal periarcuate (6 left and 10 right) or inferior parietal cortex (6 left and 8 right) lesions
Deuel and Regan (1985)	*Macaca fascicularis* (9)	Dexterity, strength, tactile reaching, somatic sensation, gesture task	None	Polysensory inferior parietal lobule and adjacent superior temporal sulcus lesions (3 right and 6 left)
Faugier-Grimaud et al. (1985)	*Macaca fascicularis* (5)	Visually-guided hand usage in shifting a vertical rod	None	Area 7 of parietal cortex removal (first lesions: 1 right and 2 left)
Faugier-Grimaud et al. (1978)	*Macaca fascicularis* (5)	Visually-guided hand movements	None	Posterior parietal removals (first lesions: 3 left and 2 right)
Gaffan and Hornak (1997)	*Macaca mulatta* (8) and *Macaca fascicularis* (7)	Visual search	None	Unilateral optic tract section (3 left and 3 right)+frontal commissurotomy
Hamilton (1983)	*Macaca mulatta* (8)	Sequential orientation discrimination	Left	Split-brain
Hamilton et al. (1974)	*Macaca mulatta* (5) and *Macaca nemestrina* (2)	Sequential orientation discrimination	Left	Split-brain
		Sequential motion direction discrimination	Left (trend)	
Hamilton and Vermeire (1988)	*Macaca mulatta* (25)	Sequential orientation discrimination	Left	Split-brain
Heilman et al. (1995)	*Macaca speciosa* (2)	Visually-guided hand movements	None	Frontal arcuate cortex damage (1 left and 1 right)
Jason et al. (1984)	*Macaca mulatta* (9)	On-off centre dot position discrimination	Left	Unilateral occipital lobectomy (5 right and 4 left) and splenial transection
Vogels et al. (1994)	*Macaca mulatta* (2)	Perceptual orientation discrimination	None	Split-brain
		Sequential orientation discrimination	Left	
Warren and Nonneman (1976)	*Macaca mulatta* (12)	Delayed response	None	Frontal (3 right and 1 left) or posterior foveal prestriate cortex (4 right and 4 left) ablations

measurements is their relatively law spatial resolution. Due to various trade-offs associated with different methods, it is greatly important to collect data on the same topic using diverse, complementary techniques that jointly offer a more global and more comprehensive description of the processes taking place in the brain.

The summed activity of many neurons creates field potentials that collectively constitute the macro-potentials (EEG signal) that can be recorded via surface electrodes. In animals, the electrodes can be chronically implanted to improve signal-to-noise ratio. The recorded macro-potentials can be used to directly compare the electrophysiological responses of the two hemispheres during the performance of a cognitive task (Stamm et al., 1977). Using this method Stamm et al. (1977) recorded responses in the prefrontal, precentral and occipital cortex of stumptail monkeys (*Macaca speciosa*). In a delayed response task that required remembering the position of a cue (left or right) a slow surface-negative steady-potential (SP) shift during the delay period over the prefrontal area was consistently present and dominant in one of the hemispheres.

The side on which the SP shift was greater depended on the hand that the animal was trained to use to give a response. In particular, in the four monkeys that were over-trained with the right hand, the dominant SP shift was localized over the left prefrontal cortex, while in the one monkey that was trained to give the response with the left hand, the SP shift was larger over the right hemisphere. Importantly, inter-manual transfer (sessions with the non-trained hand responses) did not significantly change the prefrontal SP shift in the two hemispheres, still yielding higher shifts in the hemisphere contralateral to the trained hand. Moreover, the two animals that were taught to give a response with both hands in alternating sessions displayed substantial SP shifts over both hemispheres; however, after substantial training with one of the hands, the result was an increase of potential in the contralateral prefrontal region and a decrease in the ipsilateral prefrontal SP shift.

Overall, however, these two monkeys showed greater magnitude SP shifts on the right side, which correlated with their orientation bias toward the left side of the display. While tempting to draw a parallel of such left-sided attentional bias to the phenomenon observed in healthy humans known as pseudo-neglect (Nicholls and Roberts, 2002; Siman-Tov et al., 2007), the interactions between attentional and trained hand-dominance biases that were observed in these monkeys were far from being clear. Taken together, the findings by Stamm et al. (1977) point to the importance of ontogenetic experience (training of unilateral actions) and spatial orientation biases that can greatly influence future studies on functional hemispheric lateralization in animals, which in most cases are over-trained in particular tasks and manual actions.

2.3.2. Discussion

In the above-described studies the most convincing results on functional lateralization in monkeys seems gained form the fMRI experiment by Baker et al. (2006). As an evolutionary old brain structure the subcortical pulvinar is more likely to show a similar functional asymmetry in humans and nonhuman primates than the more advanced cortical regions. This notion is further confirmed by a recent fMRI study that directly compared cortical activation in humans and rhesus monkeys during a working memory oculomotor task (Kagan et al., 2010). Importantly, the researchers teased apart the contralaterality of spatial cue and memory representations from inter-hemispheric asymmetries of the activation patterns. The results revealed that the contralateral tuning of cue and memory delay in dorsolateral prefrontal cortex, FEF and LIP was much stronger in

monkeys than in humans. In contrast, these fronto-parietal areas showed much greater hemispheric asymmetry of contraversive selectivity in humans than in monkeys (Kagan et al., 2010). This lateralization pattern in human participants matched the previous proposal suggesting that the left hemisphere predominantly encodes the right space, while the right hemisphere represents both hemifields (Mesulam, 1999). Given the findings reported by Kagan et al. (2010) it is tempting to speculate that the difference in the degree of contralateral organization among primate species is related to the evolution of hemispheric lateralization.

3. The monkey model of neglect

We could distinguish two main techniques in producing animal models of the neglect syndrome. On the one hand, efforts were undertaken to induce stroke in monkeys and to test the possible protective effects of drugs on the affected animals. This approach has direct application for further clinical trials on active compounds. On top of these pharmacological applications, the brain damage evoked by artery occlusion in monkeys directly corresponds with the most commonly found brain lesions in human stroke patients. On the other hand, numerous studies employ localized uni- or bilateral brain lesions that can be carried out in either single or multiple stages. The advantage of this latter method is the control of the position and the size of the removed neuronal tissue that allows accurate testing of hypotheses, thereby advancing greater understanding of the neuronal mechanisms underlying neglect.

3.1. Stroke studies

As mentioned previously, in a number of earlier papers the possibility of functional lateralization of spatial cognition in nonhuman primates is discarded without extensive references or analysis of the available evidence (Husain and Nachev, 2007; Milner, 1987; Payne and Rushmore, 2003). The main argument offered is that in monkeys spatial neglect is never as severe and persistent as observed in patients; hence, the spatial functions that are crucially affected in this syndrome are not lateralized in monkeys. In the next few paragraphs we evaluate whether the above statement is indeed justified. Since neglect very frequently occurs after a stroke we turn to the animal model of ischemic brain insult and the resulting neglect. These animal models of disease offer the sole opportunity not only to test possible treatment or prophylactic drugs, but also to learn more about the mechanisms of a given syndrome and brain function.

New World common marmosets (*Callithrix jacchus*) were used to develop a primate model of ischemic insult by occluding the middle cerebral artery (MCA) through the application of electrocoagulation (Marshall and Ridley, 1996). Behavioural assessment on the animals was carried out pre-operatively, and at different times post-operatively. The motor and spatial deficits were dissociated by requiring from the monkeys a retrieval of food pieces with a pre-determined hand, controlled through the spatial layout of the set-up (Hill and Valley staircase tasks). The greatest impairment was that of a motor-intentional nature, which in humans is more often related to damage in the frontal cortex (Binder et al., 1992; Bisiach et al., 1990; Ghacibeh et al.,

2007; Liu et al., 1992) although the parietal cortex was also indicated in a patient study (Mattingley et al., 1998). Two of the monkeys that had more extensive cortical damage manifested a transient visuospatial neglect as revealed by their failure to retrieve food items from the contralateral side even with their ipsilesional, unaffected forelimb. Overall, neglect of a visuospatial nature was detected only in two monkeys during the brief acute stage with a somewhat longer lasting visual extinction, i.e., a failure to detect a contralateral stimulus only when it was presented concurrently with the ipsilesional stimulus.

In the later studies that tested the neuro-protective effects of certain drugs the researchers occluded a more proximal region of the MCA and produced infarcts in the frontal, temporal and parietal cortices, the underlying white matter and the subcortical structures (Marshall et al., 1999, 2000, 2001, 2003a,b,c). This procedure generated more consistent behavioural outcomes with the monkeys no longer being able to use their contralesional arm properly, which proved to be a long-lasting dysfunction. The animals initially were also unable to act with their ipsilesional healthy arm toward the contralateral compromised visual field, thus exhibiting a lateralized perceptual–attentional deficit and a strong bias to act within the ipsilesional hemifield—a purer form of spatial neglect.

Marmosets also showed extinction when they were presented with two choice alternatives, and this inability to process information in parallel persisted longer than 9–10 weeks. In general, the spatial attentional bias was completely absent after 20 weeks and frequently much earlier, while motor impairment was virtually not improved after that time (Marshall et al., 2003c). Extinction, unfortunately, was tested in the marmosets only up to 9–10 weeks, and although recovery was observed, it is still detectable after that period (Marshall et al., 1999, 2000, 2001, 2002, 2003a,b). It is important then to include a longer-term evaluation of extinction because in patients this cognitive complication is very often present even in the chronic stage of neglect (Farnè et al., 2004). Regrettably, we cannot communicate here anything about possible predominance of one of the hemispheres in displaying neglect syndrome in common marmosets since the surgery in these monkeys was performed only on the right hemisphere. This right-sided stroke applies to all experiments conducted by Marshall's research group (Marshall et al., 1999, 2000, 2001, 2002, 2003a,b,c). Nonetheless, it is clear that in these New World monkeys the spontaneous restitution of attentional and perceptual processes that biased actions toward the ipsilesional side is more rapid and complete compared to the recovery in humans. In neglect patients, for instance, only 43 % show signs of spontaneous recovery in the acute phase and complete recovery can be observed only in 9 % of convalescing persons (Farnè et al., 2004) although higher complete recovery rates were also reported (Cassidy et al., 1998). The prompt recuperation from spatial neglect in monkeys suggests neuronal compensation for a rather functionally symmetric brain though in some cases there was a demonstrated presence of intra-hemispheric recovery process as well. For example, a group of monkeys with ablated frontal arcuate gyrus and the sectioned callosum recovered at a similar tempo and to a similar extent as did the monkeys with the same frontal damage but intact interhemispheric communication (Watson et al., 1984).

3.2.   Brain lesions

A number of lesion experiments that probed neural correlates of unilateral neglect in monkeys yielded a neglect model not related to stroke. In particular, eight cynomolgus monkeys (*Macaca fascicularis*) underwent right frontal "association" cortex aspiration (both banks of the arcuate sulcus and the posterior third of sulcus principalis) that resulted in a clear extinction of the contralesional visual and somatosensory stimuli when presented with a simultaneous target on the ipsilesional side (Deuel and Collins, 1984). Besides that perceptual–attentional deficit, all the monkeys displayed a much lower probability of detecting individually presented items in the contralesional side although the effect was transient, and the animals spontaneously recovered after 8–10 weeks post-operatively (Deuel and Collins, 1984). Somewhat more variable recoveries were obtained in Deuel and Collin's earlier experiment, where three animals spontaneously improved behaviourally after 28 to 42 days, whereas seven monkeys needed a longer period of recovery with additional training (Deuel and Collins, 1983).

A classic ablation study by Gaffan and Hornak (1997) explicitly evaluated the severity of neglect in monkeys compared to the human condition. The researchers looked at the effects of posterior parietal removals on visual search performance in seven cynomolgus (*Macaca fascicularis*) and eight rhesus monkeys (*Macaca mulatta*), which were subsequently combined with frontal eye field ablation. Importantly, optic tract section causing hemianopia (blindness to the half of the visual field) without neglect served as a quantitative reference for the task performance in order so as to assess whether the severity of deficits in these Old World monkeys was comparable to humans. In patients, visual neglect is not simply a consequence of hemianopia (the loss of vision in one half of the field); the deficits are always more severe in neglect.

Eventually, posterior parietal cortex (PPC) or FEF unilateral removals in this group of macaques did not produce visual neglect analogous to that observed in humans, given that the associated deficiencies were not more pronounced than hemianopia induced by optic tract section. However, visual neglect equivalent to human impairments was achieved in the group of monkeys subjected to optic tract section combined with frontal commissurotomy. Then again, such a pattern of brain damage, here evoked experimentally, is very rare in the neglect patients population, which somewhat reduces any practical application of these results. Relevant to our argumentation is the fact that no unambiguous functional cerebral asymmetries were found, as the side of unilateral lesions had little effect on the decrease in performance of the visual search task (Gaffan and Hornak, 1997).

Unilateral lesions of the inferior parietal and the periarcuate cortex in long-tailed macaques (*Macaca fascicularis*) resulted in overall behavioural deficits that did not differ quantitatively, but did produce subtle qualitative differences that could be discerned (Deuel and Farrar, 1993). Because the animals' performance was evaluated only during the acute post-operative phase, we were not able to assess the spontaneous recovery rate or deficits perseverance. Likewise, in the study of Gaffan and Hornak (1997), the severity of motor and perceptual effects was similar for left (12) and right (18) injured hemispheres (Deuel and Farrar, 1993). Removal of the lateral portion of the precentral

gyrus and the superior temporal sulcus in the same monkey species also did not result in any apparent differential hemispheric distribution of unilateral neglect, although the small number of subjects addressed has to be considered (3 right and 6 left hemispheres) (Deuel and Regan, 1985). Earlier studies on rhesus monkeys (*Macaca mulatta*) also did not demonstrate any differences in a delayed response task after left or right unilateral dorsolateral frontal or inferior-temporal ablations (Warren and Nonneman, 1976). Given the foregoing studies it is not surprising that one other monkey species, *Macaca irus*, displayed only a short-lasting contralesional neglect of visual stimuli after arcuate or PPC removal without any evident effect of the lesion side (Crowne et al., 1989).

In line with the foregoing, two-stage bilateral lesions of area 7 of the parietal cortex in long-tailed macaques (*Macaca fascicularis*) also did not reveal any obvious hemispheric biases; actually, the effects of the first unilateral surgery were very quickly ameliorated (Faugier-Grimaud et al., 1978). The consequences of the second lesion required only a slightly longer recovery period, indicating that area 7 is not crucial for visually guided hand movements as was tested here (Faugier-Grimaud et al., 1978). In a later study from the same lab, monkeys were trained to shift a vertical rod with their hand and place it in front of an illuminated target (Faugier-Grimaud et al., 1985). Latencies of the responses mainly showed an increase for the arm contralateral to the lesion with no obvious differences between the left and right posterior parietal animals after the first operation.

After the second lesion, movement accuracy was affected in a similar way; that is, a decrease in performance was demonstrated with the contralesional hand with a larger effect in the contralateral working space. Once again, there was no indication that the left or right hemisphere was more specialized in performing this task accurately. The effects of the area 7 lesions on visually guided hand movements were clearly very mild. Nevertheless, one cannot discard the possibility on the basis of these two studies that other, perceptual–attentional deficits emerged post-operatively since these were not tested here. A comparable contralesional motor effect was observed in two *Macaca speciosa* monkeys that underwent unilateral subpial suction of the frontal arcuate cortex (Heilman et al., 1995). Regardless, the very rapid post-operative recovery difference in this respect was observed between the two animals. Namely, the monkey with the lesion in the left hemisphere recovered more quickly than the right hemisphere damaged animal. Then again, the very small number of animals involved and the subjective scoring of post-lesioned restitution does limit the significance of this observation.

3.3. Discussion

From the studies discussed above a clear picture emerges with regard to spatial neglect in several macaque monkey species. The experimentally induced neglect in monkeys had a milder form than that observed in humans. It is also evident that recovery from the deficits occurred very rapidly without any specific treatment. At the end of these studies, most of the affected macaques showed complete recovery, while in humans, neglect deficits can be detected even after tens of months. With regard to possible hemispheric differences, the

studies recounted here unambiguously support the notion that the monkey brain is symmetrical in processing spatially directed behaviour. However, the young age of the laboratory animals might have confounded the results to some degree and, consequently, the conclusions. In humans, neglect occurs most often in older individuals who inherently have a higher risk of stroke and related to that occurrence of brain damage (Ringman et al., 2004; Becker and Karnath, 2007). These are conceivably persons with diminished neuronal plasticity and, therefore, a lower capacity for restoration after neuronal tissue damage. The juvenile monkeys could have shown a more rapid recovery due to their younger age. Moreover, it is widely accepted that there is a considerable interplay of ontogenetic and environmental factors in the development of hemispheric asymmetries (Corballis, 2009; Gil-da-Costa and Hauser, 2006; Grabowska et al., 1994; Sun et al., 2005, 2006; Sun and Walsh, 2006). Hence, lateralization of brain functions can be more prominent in older and more experienced individuals than in youngsters.

One other concern is that the experiments were not explicitly designed to test the presence or absence of functional lateralization in processing spatial information or/and the authors did not statistically compare the performance of the right- and left-sided lesion groups. Finally, it might be said that the lateralized defects in spatial neglect, like an increased detection threshold for contralesional visual stimuli or slower and inaccurate motor action toward the compromised visual space irrespective of the hand used (directional hypokinesia), do not depend on the brain damage side. Specifically, it has been shown that certain brain areas in the inferior parietal cortex that are crucial for spatially directed (oculo)motor actions (lateral intraparietal cortex LIP and area 7a) heavily over-represent contralateral space (rhesus monkeys: Barash et al., 1991; Battaglia-Mayer et al., 2005; Blatt et al., 1990; Crowe et al., 2004; Lynch et al., 1977; humans: Schluppeck et al., 2006; Swisher et al., 2007).

4. Evolution and spatial cognition lateralization

The overview provided in the preceding sections raises a number of important issues with regard to the possibility of hemispheric lateralization of spatial functions in nonhuman primates. First, there is no single monkey study that clearly shows a more severe neglect or a longer recovery after experimentally induced right- as opposed to left-hemisphere damage. Second, the spontaneous recovery in macaque monkeys is very rapid and almost complete after 2–3 months, while in humans recovery can last tens of months, and it is not uncommon that these patients show persistent deficits even after years. Third, we did not find any apparent lateralized distribution of spatial working memory in monkeys, which also differs from an observed human right hemisphere superiority (cf. Table 1). Finally, left-hemisphere dominance in sequential orientation discrimination, a task possibly engaging some aspects of spatial working memory, has consistently been observed in split-brain macaques across a number of behavioural studies (cf. Table 1). The intriguing part here is that human subjects performing similar orientation discrimination tasks show a right hemisphere advantage. As

suggested earlier, such a remarkable dissociation can reflect on species differences either in lateralization direction of the same underlying neuronal process or in a task solving strategy taxing somewhat distinct processes.

In total we found only two studies, both using magnetic resonance imaging, where nonhuman primates displayed a similar to human asymmetrical hemispheric advantage in a visuospatial task (Baker et al., 2006; Kagan et al., 2010). The study by Baker et al. (2006) on two cynomolgus monkeys revealed a clearly higher right hemisphere activation of an evolutionary old subcortical structure, the pulvinar, thereby replicating the results from human subjects (Fischer and Whitney, 2009) and yielding additional evidence for homology between human and monkey (Desimone et al., 1990; Snow et al., 2009). The combination of the results from the monkey and human studies yields an interesting possibility that phylogenetically ancient subcortical brain structures are asymmetric, and in monkeys, such a hemispheric lateralization resembles the functional pattern reported in humans. The strong point of this notion is that monkey subcortical brain regions should have clear homologues in *Homo sapiens*' brain assuring straightforward inter-species comparisons. Related, Kagan et al. (2010) demonstrate that the more evolutionarily advanced fronto-parietal cortex in humans is to a much greater degree asymmetric with respect to contraversive selectivity. That is, the right fronto-parietal areas in rhesus monkeys processes mainly visuospatial information from the contralateral field and, to a very limited extent, from the ipsilateral side, whereas in humans, this brain region is involved in analysing input from both visual half-fields. In contrast, the left hemisphere fronto-parietal regions in both species represent predominantly the right visual field. The remaining bulk of these negative or inconclusive studies most likely reflect the hemispheric symmetry of species like macaques that are more phylogenetically distant from humans.

To conclude, in light of the existing evidence, we are inclined to confirm the idea that monkeys do not process spatial information differentially in either the left or right hemisphere. There is currently no reason to assume that a parieto-frontal network subserving spatial cognition is asymmetrically distributed in the monkey brain. It seems therefore very plausible that in the course of evolution, the human right-hemisphere superiority in spatial cognition arose later than, or in parallel with an emerging language faculty.

In contrast to the spatial cognition findings, there is much clearer evidence for functional brain lateralization in monkeys concerning left hemisphere species-specific vocalization processing (e.g., Beecher et al., 1979; Belin, 2006; Hauser and Andersson, 1994; Heffner and Heffner, 1984; May et al., 1989; Petersen et al., 1978, 1984; Poremba, 2006; Poremba et al., 2004; Poremba and Mishkin, 2007; Zoloth and Green, 1979). Such vocalizations are often perceived to be analogous to some aspects of human language. Further, a similarity to human right-hemisphere advantage in discriminating faces is also frequently reported for monkeys (Hamilton and Vermeire, 1988; Hauser, 1993; Vermeire et al., 1998). When we combine these findings, a picture emerges where humans inherited right hemispheric dominance in the processing of faces and very likely relative specialization of the left hemisphere when handling meaningful vocalizations.

We further venture the argument here that such vocalizations represent one of the multiple prerequisites of contemporary human language. At the same time, visual working memory that is not asymmetrically processed in our phylogenetic ancestors became lateralized in humans in a way that dissociated spatial and verbal processes to the right and left hemispheres, respectively. Actually, verbal and spatial working memory in humans was reported by some researchers to recruit partially overlapping neural networks that were at least quantitatively asymmetrically distributed in the left and right hemispheres (Walter et al., 2003). However, a more likely picture is that the two circuits highly overlap with some left prefrontal areas showing verbal specificity and bilateral parietal regions that are engaged in both working memory types with a somewhat higher left sided activity in the verbal tasks (Cabeza and Nyberg, 2000; Gruber and von Cramon, 2003; Ray et al., 2008). Such a pattern of results gives support to the proposal that spatial working memory is phylogenetically older than its verbal counterpart and probably served as the basis for verbal working memory and language acquisition in the course of evolution (Aboitiz, 1995; Aboitiz and Garcia, 1997; Aboitiz et al., 2006; Ray et al., 2008).

With respect to the nonhuman primate model of hemispatial neglect, the results of this literature evaluation point to important and potentially problematic issues. On the one hand, it remains to be seen whether the brain areas affected by experimentally evoked stroke or disabled by ir(reversible) lesions in monkeys represent functional homologues of the regions damaged in human neglect patients. On the other hand, the right hemisphere specialization in spatial cognition commonly encountered in humans inherently establishes differences between humans and monkeys for the severity of the neglect syndrome. Thus, the animal models of neglect might fail to equal the human condition because the effects of unilateral neuronal tissue damage were assessed from a symmetrical nonhuman primate brain. While it remains a valuable source of diverse dysfunctions that are in one or another way related to the human condition and which can be used to test protective compounds for a number of these ailments, the full scenario of the consequences of hemispatial neglect cannot be determined in monkeys.

5.   Future directions

Even though we are inclined to confirm the lack of hemispheric lateralization of spatial working memory and attention in our primate ancestors, some issues still leave a few grains of uncertainty until future experiments resolve them. To begin with, the monkeys with surgically induced neglect underwent a somewhat simplified behavioural testing that might have overlooked more subtle deficits apparent in humans, such as extinction. Any future studies should implement additional tests that will explicitly evaluate possible spatial working memory dysfunctions. Systematic investigations of hemispheric differences in the severity of neglect deficits and the long-term recovery profile are also vital, not only for clinical purposes, but also for the advancement of brain evolution theory. In animal studies of neglect it is crucial in the future to consider the subjects' age

and thereby control possible ontogenetic differences in brain lateralization.

From an evolutionary perspective, further experimental demonstration is needed to confirm that lateralized structural characteristics and cognitive processes represent complementary asymmetric patterns that evolved independently through natural selection and less so by exerting reciprocal pressures (Dien, 2008). If this thesis is proven, one should accept that each hemisphere adaptively developed different roles. While the cerebral hemispheres would seemingly influence one another due to their complementarity, essentially there would be no relationship between them at the individual level, but only if we consider population means (Dien, 2008).

Equally relevant are investigations of interhemispheric connectivity. For instance, valuable results were obtained in another study that combined the positron emission tomography (PET) data correlation analysis with structural equation modelling (introducing information of directional relationships in an anatomical network). The researchers demonstrated remarkable interhemispheric differences of functional connectivity in humans (McIntosh et al., 1994). A visual object and spatial tasks were used to tap ventral and dorsal visual pathways. While both tasks (face and dot-location matching) exhibited right hemisphere dominance in exerting an influence on the contralateral homologous areas, for our purposes we will concentrate on the spatial task. Specifically, the dorsal occipito-parietal region exercised a much stronger positive effect on posterior parietal area 7 in the right than in the left hemisphere. Further, area 7 positively influenced area 46 of the frontal cortex, which subsequently, as a feedback path, interacted with the ventral occipito-parietal cortex. Conversely, such indirect frontal feedback communication was discontinued in the left hemisphere.

In light of the latest advances in understanding left unilateral neglect in humans as well as in the lateralization of functions affected mainly by right-hemisphere damage, the current review may have a great importance. The most recent theory decomposing the mechanism of hemispatial neglect points to the crucial role of long range intrahemispheric white matter connecting PPC with the prefrontal areas that comprise the well-known attentional and spatial working memory cortical network (Doricchi et al., 2008; Thiebaut de Schotten et al., 2005). Such a view corroborates the findings discussed earlier, namely, that the closest resemblance to the human neglect condition in monkeys was evoked only by a section of the white matter that links the posterior and frontal brain regions (Gaffan and Hornak, 1997). The fact that the functional interactions between the parietal and frontal regions are much more evident in the right as compared to the left hemisphere in the tasks requiring spatial cognition advocates the preponderance of neglect in right-brain injured patients due to right-sided asymmetry of parieto-frontal functional interactions. The superiority of the right hemisphere for spatial attention tasks possibly results from a neural connectivity advantage (Thiebaut de Schotten et al., 2005) and high-speed-optimal myelination of axons within the right brain or from the right to the left hemisphere (Barnett and Corballis, 2005). Consequently, if one seeks to understand hemispheric lateraliza-

tion of functions, whether in humans or non-human primates, one should focus future endeavours on analysing functional connectivity of the main nodes that form a larger neuronal network and their possible differences in the two hemispheres.

Finally, we need to consider the evolutionary origins of particular brain areas. It is known, for instance, that some subregions of macaque and human PPC are not homologous, reflecting evolutionary changes. Namely, anterior parts of the intraparietal sulcus (IPS) comprising anterior, medial ventral intraparietal and posterior parietal areas (AIP, MIP, VIP and PPR) are the most likely preserved across the primate species (AIP: Grefkes et al., 2002; MIP: Grefkes et al., 2004; PPR: Hagler et al., 2007; Trillenberg et al., 2007; VIP: Bremmer et al., 2001). With regard to the human homologue of the saccade-related LIP, discrepant results are reported (Koyama et al., 2004; Shikata et al., 2008), whereas caudal intraparietal area (CIP) of the posterior part of the IPS and the V6 complex of the parieto-occipital sulcus are found to be more medially in the human brain (CIP: Shikata et al., 2003; V6: Dechent and Frahm, 2003; for a review, see Grefkes and Fink, 2005). This shift from the lateral to the medial bank of the IPS is attributed to the great expansion of the dorsal visual stream in humans (Grefkes and Fink, 2005). Likewise, a comparative fMRI study by Denys et al. (2004) associated inter-species functional dissimilarities of brain areas with the evolutionary expansion of the dorsal visual stream. Remarkably, shape sensitivity in the monkey was relatively stronger in the intraparietal than in the temporal regions, while the reverse was observed in humans and overall, shape-related activity was more balanced between ventral and dorsal cortex in monkeys. It is therefore important to establish exactly which sub-areas of the PPC show the right-sided functional asymmetry in humans, the evolutionary younger or those that are shared with the non-human primates. The functional magnetic imaging technique currently represents the most practical way to investigate this issue in both humans and animals.

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