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Spatial attention systems in spatial neglect

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ABSTRACT

It has been established that processes relating to 'spatial attention' are implemented at cortical level by goal-directed (top-down) and stimulus-driven (bottom-up) networks. Spatial neglect in brain-damaged individuals has been interpreted as a distinguished exemplar for a disturbance of these processes. The present paper elaborates this assumption. Functioning of the two attentional networks seem to dissociate in spatial neglect; behavioral studies of patients' orienting and exploration behavior point to a disturbed stimulus-driven but preserved goal-directed attention system. When a target suddenly appears somewhere in space, neglect patients demonstrate disturbed detection and orienting if it is located in contralesional direction. In contrast, if neglect patients explore a scene with voluntarily, top-down controlled shifts of spatial attention, they perform movements that are oriented into all spatial directions without any direction-specific disturbances. The paper thus argues that not the top-down control of spatial attention itself, rather a body-related matrix on top of which this process is executed, seems affected. In that sense, the traditional role of spatial neglect as a stroke model for 'spatial attention' requires adjustment. Beyond its insights into the human stimulus-driven attentional system, the disorder most notably provides vistas in how our brain encodes topographical information and organizes spatially oriented action – including the top-down control of spatial attention – in relation to body position.

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1. Introduction

When we look at our environment, the brain identifies the important information in the scene for further examination. This selection of relevant information can be seen a key element of visual perception. Two major forms of selection of sensory signals

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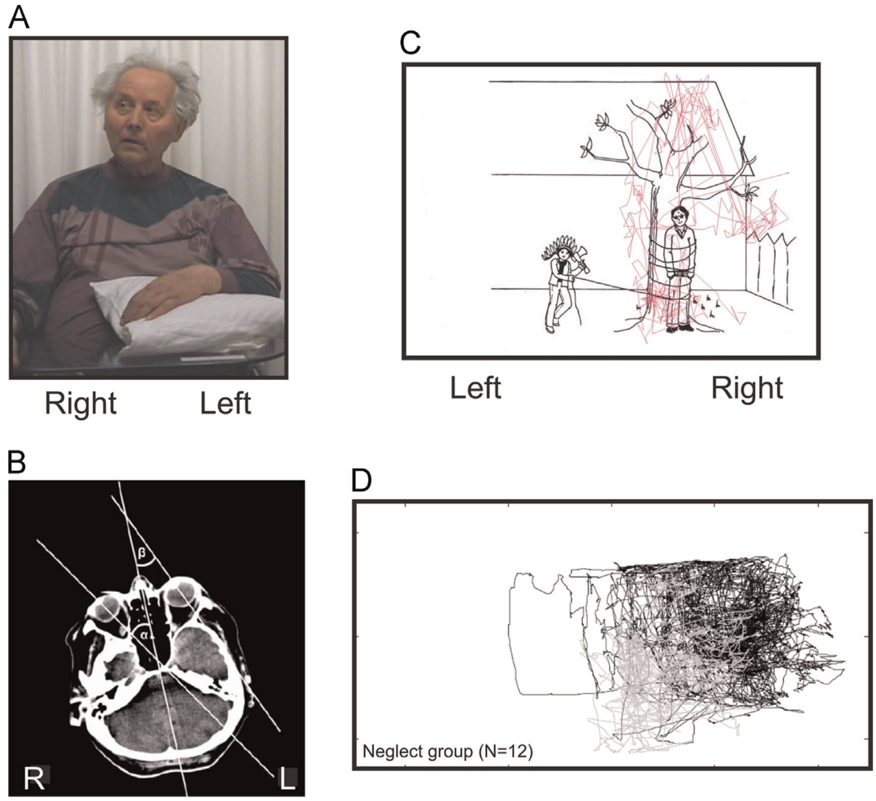

Fig. 1. Spatial neglect behavior following a right hemispheric stroke. (A) Example of the spontaneous eye and head orientation of patients with spatial neglect following a right hemispheric stroke while 'doing nothing', i.e. just sitting and waiting. Eye-in-head and head are tonically oriented towards the ipsilesional, right side. (From Fruhmann-Berger and Karnath (2005)). (B) The eye-in-head deviation is even evident on the clinical brain scans taken at admission where the participant is simply asked to remain still. (Modified from Becker and Karnath (2010)). (C) Scan path (*red*) of a patient with spatial neglect while verbally describing the content of a line drawing (*black*). The little boy on the left is neither visually explored nor verbally mentioned; the quintessence of the displayed story was mistaken. (Modified from Karnath (1994a)). (D) Scan paths (eye and head combined) of a group of 12 patients with spatial neglect during active visual search (*black lines*) as well as at rest (*gray lines*). The patients show a tonic bias of their active and their passive behavior toward the ipsilesional, right side. (Modified from Fruhmann-Berger et al. (2008)). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

have been distinguished: stimulus-driven (bottom-up) and goal-driven (top-down) selection (Müller and Rabbitt, 1989). The final selection of a location for preferential processing based on these processes is commonly termed 'spatial attention'. Two anatomically distinguishable cortical networks have been identified to represent goal-directed versus stimulus-driven attentional processes (Corbetta and Shulman, 2002; Section 2 below). The present paper addresses a behavior in neurological patients that has repeatedly been interpreted as a prime example of a disturbance of these attentional processes (e.g., Kinsbourne, 1970, 1993; Heilman et al., 1987, Mesulam, 1999; Corbetta et al., 2005). After predominantly right hemisphere brain lesions (for review Karnath and Rorden (2012)), patients with so-called 'spatial neglect' no longer orient towards large parts of the scene contralateral to the lesion and thus neglect people or objects located there (Fig. 1). Already at rest, i.e., when doing nothing (just relaxing), the patients deviate head and eyes towards the ipsilesional side (Fig. 1). This paper will discuss which aspects of this behavior can be understood as a dysfunction of 'spatial attention' and which aspects require an alternative explanation.

2. The interhemispheric imbalance model

Kinsbourne (1970) was among the first to suggest a model of disturbed spatial attention in patients with neglect. He hypothesized that neglect patients suffer from an attentional bias with excessive orienting towards the ipsilesional side due to an imbalance of two opponent processors controlled by the right and the left hemispheres respectively, each of which directs attention towards the opposite end of surrounding space. Moreover, he postulated that the competition between both processors is mediated by mutual inhibitions across transverse commissures. An interhemispheric activation imbalance in neglect patients thus biases the vector of attentional orienting and elicits ipsilesional shifts of attention and gaze. A crucial prediction of this model is that orienting is not intact within either hemispace in neglect patients. Rather, a lateral gradient of attention sweeps across both hemispaces, such that attention is always biased into the ipsilesional direction. In the cat model, Payne and Rushmore (2004) have proposed a similar interhemispheric imbalance hypothesis of neglect. Their model suggests that the neglect-inducing cortical lesion or deactivation causes an imbalance in activity between brain hemispheres through imposed disruption of cortical and corticocollicular circuits, leading to imbalance of the orienting system into ipsilesional direction. With respect to the latter it might be objected, however, that the evidence for animal analogues of spatial neglect in rodents and carnivorans is difficult since they often fail to provoke the complex behavioral abnormalities typically seen in humans and/or allow alternative interpretations of the observed impairments (e.g., Milner, 1987).

The advent of fMRI in the last decades of neuroscientific research has established that processes relating to 'spatial attention' are implemented at cortical level by networks linking the posterior parietal cortex, frontal eye fields, ventral frontal cortex, and the right temporo-parietal junction (TPJ) (Corbetta and Shulman, 2002; Petersen and Posner, 2012). Corbetta and colleagues differentiated between a 'dorsal system' underlying the goal-directed top-down stimulus–response selection and a 'ventral system' responsible for the stimulus-driven detection of behaviorally relevant stimuli, especially when unattended (Corbetta and Shulman, 2002; Corbetta et al., 2002). The dorsal network, whose core regions include the intraparietal sulcus and the frontal eye field, generates endogenous signals about likely contingencies and sends out top-down signals to visual areas and to the ventral network, restricting ventral activation to behaviorally important stimuli. On the other hand, the ventral system, which includes the ventral frontal cortex and the TPJ, is involved in detecting new and unexpected stimuli of behavioral relevance. When a salient stimulus occurs outside the current focus, the ventral network sends a reorienting signal to the dorsal network, followed by attentional orienting towards the behaviorally relevant salient event (Corbetta and Shulman, 2002; Corbetta et al., 2008).

Based on this concept Corbetta et al. (2005) hypothesized that spatial neglect in stroke patients arises when structural damage in the ventral attention network causes functional imbalance in the dorsal attention network. In an fMRI experiment, the authors scanned patients with spatial neglect twice, once in the acute and once in the chronic stage of the stroke, while they performed a classical Posner-like attentional orienting task: a central arrow cue covertly directed subjects' attention (75% validly, 25% invalidly) to the left or right and was followed by a target briefly flashed at one of the two locations. In addition to structural damage in the right ventral attention network, they found that the intraparietal sulcus (IPS) and superior parietal lobule (SPL) of the right hemisphere were not active at the acute stage but reactivated at the chronic stage when neglect symptoms had improved. In contrast, the homologous left hemisphere IPS/SPL structures were more strongly activated at the acute stage than at the chronic stage. In other words, the authors observed a functional imbalance in the structurally intact IPS/SPL at the acute stage, manifested as a relative hyperactivation in the left hemisphere and relative deactivation on the right. Consistent with Kinsbourne's (1970, 1993) hypothesis, the authors concluded that this interhemispheric push–pull pattern in the structurally intact dorsal attention system mediates the rightward bias of spatial attention in neglect patients. A problematic aspect of this study, however, is that linking abnormally reduced BOLD signal levels in an infarcted hemisphere to behavioral changes is difficult. In particular, the observation that *non*-neglect stroke patients can also show an fMRI activation pattern comparable to that observed by Corbetta et al. (2005) significantly questions its relationship to spatial neglect. The following section outlines these problems in more detail.

3. Imbalance of BOLD does not necessarily reflect a change in behavior

One attractive feature of the interhemispheric imbalance hypothesis (Kinsbourne, 1970, 1993; Corbetta et al., 2005; Corbetta and Shulman, 2011) is that the pathology observed in neglect patients appears nicely linked to functional imaging results from healthy subjects associated with spatio-attentional orienting (Corbetta and Shulman, 2002; Corbetta et al., 2008). Despite this theoretical elegance, one may ask whether or not functional imaging in stroke patients necessarily provides additional areas of the brain that critically subserve a behavioral deficit beyond structural imaging alone.

In this context, it is important to examine whether an interhemispheric push–pull pattern in BOLD, i.e., a functional imbalance with a relative hyperactivation in the left hemisphere and a relative deactivation on the right is specific for neglect patients (Corbetta et al., 2005), or is also present in stroke patients without neglect. In fact, the latter has been observed in a fMRI study that compared acute right hemispheric stroke patients with and without spatial neglect while these performed a Posner-like spatial attention task (Umarova et al., 2011). The next question that arises is whether an interhemispheric push–pull pattern in BOLD is related to the phenomenon of 'spatial attention' at all or may represent a general phenomenon due to brain damage, not necessarily reflecting a change in behavior.

Observations pointing in the latter direction have recently been reported (de Haan et al., 2013). The authors acquired fMRI data from *non*-neglect stroke patients working on a *non*-spatial attention task (a simple visual orientation judgment task). Despite not showing a behavioral deficit on this task, the non-neglect stroke patients demonstrated an abnormal interhemispheric balance comparable to the one reported by Corbetta et al. (2005) and by Umarova et al. (2011). The abnormal BOLD fMRI signal appeared as a mere function of distance from the acute lesion (Fig. 2). A possible mechanism for these abnormal BOLD effects resulting from stroke lesions is disruption of cerebrovascular reactivity due to the leaking out of vasodilatory substances from the infarct in the context of peri-infarct gliosis (Barreto et al., 2011; D'Esposito et al., 2003; Martin et al., 2001).

The studies of Umarova et al. (2011) and de Haan et al. (2013) suggest that the physiological changes and corresponding interhemispheric imbalance detected by fMRI BOLD in acute stroke close to the lesion border – as, e.g., in the IPS/SPL area of the dorsal goal-directed attention network close to the territory of lesion overlap in the acute stroke patient group studied by Corbetta et al. (2005) – must not necessarily reflect changes in the neural function, nor necessarily influence the individuals' attentional orienting behavior in space.

4. The conceptual problem: tonic interhemispheric imbalance should induce 'circling' behavior

Beyond these physiological concerns there is also a conceptual problem inherent to the model of tonic attentional imbalance resulting from an interhemispheric functional push–pull pattern (Kinsbourne, 1970, 1993; Payne and Rushmore, 2004; Corbetta et al., 2005; Corbetta and Shulman, 2011). A lateral gradient systematically orients attention to the most right-sided of horizontally aligned stimuli. In a natural scene, which typically surrounds the individuum, the model thus predicts that neglect patients continuously turn more and more to the right, when e.g. searching for a particular object. As outlined by Kinsbourne (1993), patients are expected to start 'circling' around their earth-vertical body axis. 'Circling' is indeed observed in animals with experimentally induced unilateral brain lesions (Kennard and Ectors, 1938; Pycock, 1980). A common hypothesis for this behavior is that it results from a hemispheric imbalance of forebrain dopamine systems, particularly an imbalance of nigrostriatal function (Kennard and Ectors, 1938; Pycock, 1980; Willis and Kennedy, 2004). Kinsbourne (1993) took the occurrence of 'circling' behavior in animals as support for his attentional imbalance model. The fact that – other than lesioned animals – human patients with neglect are not observed in such states of rightward circling was not weighted by him as an argument against the interhemispheric imbalance model in humans but rather was attributed to 'associated deficits that limit mobility' (Kinsbourne, 1993, p. 65). In other words, according to Kinsbourne, the fact that stroke patients with neglect often suffer from additional hemiparesis simply prevents them from 'circling' around their earth-vertical body axis.

For several reasons this is not a convincing assumption. Important counter-arguments derive from studies investigating spontaneous exploratory eye movements performed by neglect patients when searching for relevant targets in visual scenes. They

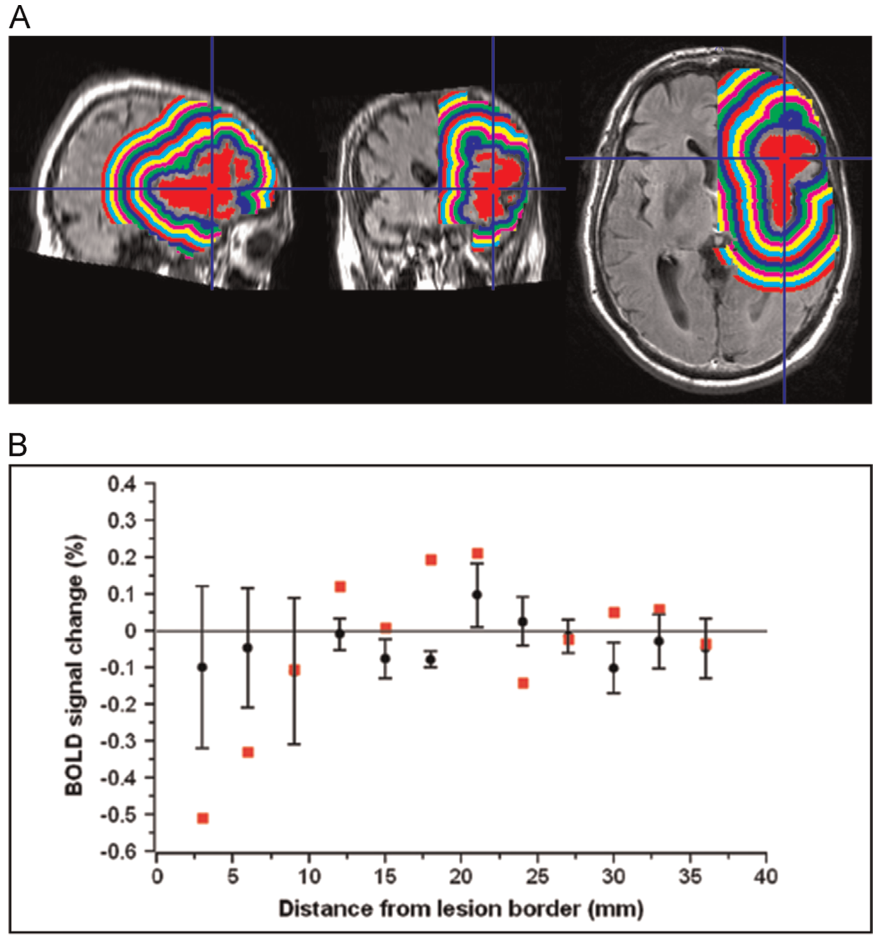

Fig. 2. Abnormal BOLD fMRI signal in stroke patients is a function of distance from the lesion. (A) The lesion (*red*) and the dilation of this lesion into 12 adjacent 3 mm right hemispheric, structurally intact perilesional regions for a non-neglect right hemisphere stroke patient. Lesion shape and perilesional regions are plotted onto the neglect patients' T2-FLAIR image. In each of these 3 mm perilesional regions percent signal change was measured for task responsive voxels in both the intact left and the damaged right hemisphere. (B) The interhemispheric imbalance score in each 3 mm perilesional region for the non-neglect patient (*red squares*) as well as the control group (*black circles*). The non-neglect patient showed abnormal interhemispheric balance: the percent signal change in the (damaged) right hemisphere was lower than in the (intact) left hemisphere, particularly in areas near the lesion border and their homologs. (Modified from de Haan et al. (2013)). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

will be described in the following section. The pattern of such exploratory movements has been taken as a robust and transparent index of the distribution of attention in space (Kowler et al., 1995; Kustov and Robinson, 1996). This comparison seems pertinent, given the fact that overt and covert shifts of attention are tightly coupled and, moreover, are usually assumed to share most if not all of their anatomical substrates (Fischer and Breitmeyer, 1987; Rizzolatti et al., 1987; Corbetta, 1998; de Haan et al., 2008; Buschman and Miller, 2009; Bisley et al., 2011).

5. A (pathological) new center of neglect patients' spatial attention

A central prediction of an attentional gradient model resulting from tonic interhemispheric imbalance (Kinsbourne, 1970, 1993; Payne and Rushmore, 2004; Corbetta et al., 2005; Corbetta and Shulman, 2011) is that neglect patients who search for relevant targets in visual scenes should demonstrate a continuous gradual increase in frequency of fixations from the left to the right. Moreover, the model predicts that this gradual increase in frequency of fixations is independent of the size of the respective search array. A continuous gradient from the left to the right edge should occur with smaller as well as with larger stimulus arrays since a directional imbalance model has no information about (egocentric) positions relative to the subject. The gradient systematically orients attention always towards the most right-sided border.

A first study by Behrmann et al. (1997) recorded eye movements in neglect patients during visual search in an array of randomly presented letters. In line with the prediction of the interhemispheric imbalance model, the authors found a gradient in the patients' eye movement pattern. From the left to the right of the search field, the neglect patients made more fixations and spent more time searching (Fig. 3c). While their experiment covered a search area in front of the patients with a horizontal extension of about $\pm 25°$ left and right of the body's mid-sagittal plane (Fig. 3c), Karnath et al. (1998) subsequently used a much larger stimulus array of $\pm 140°$ that surrounded the patient (Fig. 3d). The latter allowed for unrestricted eye and head movements as in natural situations. Clearly different from the prediction of the interhemispheric imbalance model, they found that the distribution of exploratory movements in patients with spatial neglect did not follow a lateral gradient of attention; the patients did not orient their attention towards the extreme ipsilesional, right side, nor even close to it. Rather, the patients' distribution of combined eye and head movements was roughly bell-shaped along the horizontal axis with a center of exploration situated on the ipsilesional right (Fig. 3d). Interestingly, the neglect patients' distribution of search movements surrounding this 'new' center largely

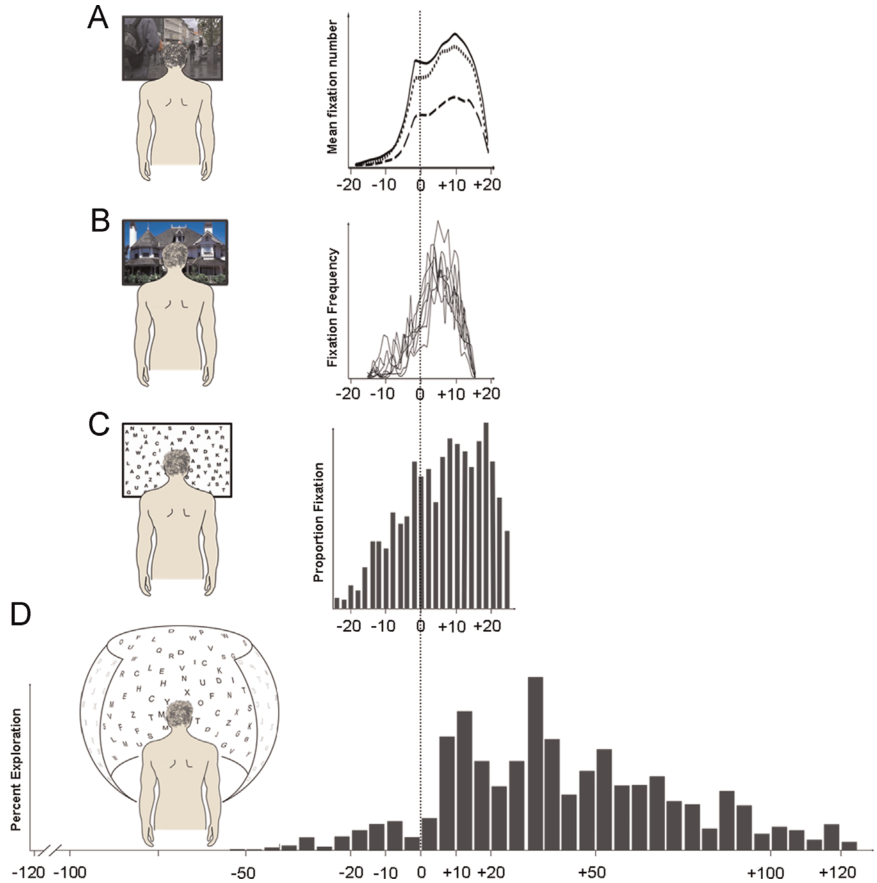

Fig. 3. Spatial distribution of goal-directed exploratory behavior of neglect patients. In stimulus arrays of different horizontal extensions, neglect patients explored (A) color photographs and videos (Machner et al., 2012), (B) color photographs (Ptak et al., 2009), or randomly distributed letters; the latter either (C) in a restricted search area in front of the subjects (Behrmann et al., 1997) or (D) in an area that entirely surrounded the subjects (Karnath et al., 1998). The studies consistently observed a continuous *in*crease of the distribution of attentional orienting from left to right up to a maximum on the neglect patients' right. The maximum was not at the right edge of the respective search array nor corresponded to the anatomical limits of maximally displaced horizontal eye, head, or arm movements. Rather, the maximum was regularly followed by a continuous *de*crease towards more eccentric positions on the right. The latter became particularly obvious if the search field was widened such that it surrounded the individuum (D). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

resembled the pattern typically observed in healthy subjects while orienting to eccentric visual targets; neglect patients oriented their attention symmetrically and with decreasing frequencies towards more eccentric positions on the right and the left side. It is important to note that the new center was located far away from the anatomical limits of horizontal gaze, head, and eye-in-head movements. The decrease of exploration towards more eccentric locations right of the new center thus could not be explained by anatomical restrictions.

The findings of Karnath et al. (1998) were not in contrast with the results reported by Behrmann et al. (1997). Rather, they showed that the continuous *in*crease of ocular exploration that these authors observed from the left side of the search field up to about $+20°$ on the right of the patient's sagittal midline, is followed by a continuous *de*crease towards more eccentric positions on the right if the search field is widened towards scenes surrounding the individuum.

Meanwhile several exploratory eye movement experiments have been conducted using search displays of similar size to the one used by Behrmann et al. (1997). The displays had horizontal extensions of $\pm 16°$ (Sprenger et al., 2002; Ptak et al., 2009), of $\pm 20.5°$ (Bays et al., 2010), and of $\pm 24°$ (Machner et al., 2012) to the left and right of the body's mid-sagittal plane. These studies presented geometrical figures, letters as well as colored photographs and movies from everyday scenes, the latter in order to represent more realistic search situations. The experiments consistently revealed a continuous *in*crease of the distribution of fixation frequency from left to right up to a maximum on the neglect patients' right. However, in contrast to the predictions of the interhemispheric imbalance model and in line with the observations by Karnath et al. (1998), this maximum was not at the right edge of the search stimulus. On average, it already occurred at about $+7°$ (Ptak et al., 2009; Machner et al., 2012), $+13°$ (Sprenger et al., 2002), or at $+5°$ and $+11°$ – the latter in two single cases (Bays et al., 2010) – on the right, consistently followed by a *de*crease towards more eccentric positions on the right (Fig. 3a and b). A close inspection of the data by Behrmann et al. (1997) reveals that even in this original data set one can vaguely discern a beginning *de*crease of fixation frequency right of the maximum at about $+19°$ (Fig. 3c).

As for the visual modality comparable observations have been reported concerning the tactile modality in patients with spatial neglect. Karnath and Perenin (1998) found the distribution of patients' exploratory hand movements shifted towards the right. The median activity lay right of the body's midsagittal plane but the frequency of tactile exploration decreased towards the periphery of peripersonal space on the right and the left side. A direct comparison of neglect patients' visual and tactile search in the same workspace revealed that the center of exploration activity in both modalities was substantially shifted towards the ipsilesional right, with a clear linear relationship between the visual and tactile search biases (Schindler et al., 2006). Like the data obtained for the visual modality (Fig. 3), these findings were in clear contrast to the predictions of the attentional imbalance model of neglect

(Kinsbourne, 1970, 1993; Payne and Rushmore, 2004; Corbetta et al., 2005; Corbetta and Shulman, 2011); they revealed a *de*crease – instead of a continuous gradual *in*crease – of attentional orienting towards the right.

The consistent and theoretically important observation of these studies is the *de*crease of neglect patients' distribution of voluntary attention in space towards more eccentric positions on the right of this center, although these locations are *far away from the anatomical limits* of horizontal eye, head, and arm movements. Thus, an explanation for this exploratory pattern based on simple physiological feedback signals evoked by maximally displaced lateral eyes-in-orbit, head-on-trunk, and/or arm-to-trunk positions appears implausible. Rather, it seems that neglect patients – like healthy subjects – decreasingly orient voluntary attention towards more and more eccentric positions on the right of the exploration center when searching the surroundings space.

5.1. The exact position of the biased exploration center is influenced by various factors

The magnitude of the rightward bias of spatial orienting in neglect, i.e. the rightward position of the center of the bell-shaped distribution of exploratory movements, is, of course, not invariant, but depends on various factors. If neglect patients are at rest, i.e. are in a situation without any specific requirements (just relaxing), the rightward bias of exploratory eye movements is less pronounced than the one observed if the patients actively search for a target in a scene (Fruhmann-Berger et al., 2008). The rightward bias also increases with the load of information within a scene (Machner et al., 2012), or with the working memory load of the search task (Sprenger et al., 2002). Further, the bias de- or increases with a left- or rightward skewed luminance distribution within the search array (Bays et al., 2010), and generally decreases during the time course of neglect recovery (Fruhmann-Berger et al., 2008). Further task demands influencing the quantity of attentional resources available for performance and thus determining the presence and magnitude of the rightward bias have recently reviewed by Bonato (2012). To conclude, though all factors listed in this section have an impact on the exact position of the new (pathological) center on the patients' right, the overarching observation is that the patients' distribution of voluntary attention in space show no continuous gradual increase but rather a continuous *de*crease towards more eccentric positions on the right of this center.

6. Disturbed stimulus-driven but preserved goal-directed attention system in neglect

Using a search array of $\pm 20.5°$ situated in front of the subjects, Bays et al. (2010) demonstrated that the failure of neglect patients to orient their attention towards contralesionally located stimuli voluntarily was statistically indistinguishable from the failure to orient if stimuli occurred unexpectedly at these contralesional locations. Beginning at a position of about $+15°$ on the right they observed a continuous decrease of target fixations towards the patients' contralesional left regardless of whether attention was top-down goal-driven or bottom-up stimulus-driven. Their observation of disturbed stimulus-driven spatial attention in neglect patients is consistent with the repeatedly reported finding that neglect patients' saccades to suddenly flashed targets left of fixation are disturbed; if initiated at all, such leftward saccades are hypometric, increased in number (due to more corrective saccades) and delayed relative to saccades directed towards the ipsilesional side (Girotti et al., 1983; Karnath et al., 1991; Walker and Findlay, 1996; Behrmann et al., 2001–2002). The question thus arises whether or not a parallel (dys)functioning of the two attentional networks – top-down goal-driven and bottom-up stimulus-driven – is to be understood as a general principle underlying spatial neglect. To determine whether this is the case, it is important to assess whether this parallel dysfunction within neglected parts of the visual scene (see Bays et al. (2010)), likewise exists in the spontaneously attended parts of the visual scene, i.e. in those parts of space that neglect patients spontaneously orient to and explore when searching for a particular item. Interestingly, studies have demonstrated that the latter does not appear to be the case.

Niemeier and Karnath (2000) examined neglect patients' voluntary exploratory behavior during visual search in a large array that surrounded the individuum, extending $\pm 140°$ to the right and left of the body's mid-sagittal plane. In light as well as in darkness, the patients' distribution of attention, as measured by the combined eye/head movements, was roughly bell-shaped along the horizontal axis with the center of exploration situated on the ipsilesional right. Within that spontaneously explored area, however, movements were directed in all spatial directions, i.e. leftward, rightward, upward, downward. Moreover, when explicitly tested whether eye movements into the contralesional direction differed from eye movements into any other direction, no significant differences were found, neither for the number of saccades executed, nor for saccade amplitude, nor for the disengagement, i.e. the duration of fixation preceding a saccade in one of the directions. Neglect patients' voluntary saccades differed from those of control subjects only in reduced amplitudes. However, the amplitudes were generally reduced for saccades executed into all four directions; no direction-specific deficit was observed in neglect patients. This finding has been replicated in group studies using photographs and movies of everyday situations (Ptak et al., 2009; Machner et al., 2012) as well as in a study of a single neglect case (Husain et al., 2001). These results argue against an interpretation of spatial neglect as a *general* deficit to plan and execute saccades into contralesional direction: within the spontaneously attended parts of the visual scene, there was no direction-specific deficit in neglect patients' top-down control of spatial attention.

In a second experiment (Niemeier and Karnath, 2003), the authors now directly contrasted ‘top-down’ control with ‘stimulus-driven’ control of spatial attention in neglect patients. They compared identical saccades performed towards identical target locations that were either voluntarily selected or stimulus-driven (Fig. 4). In the first part of the experiment (Fig. 4a), in which neglect patients voluntarily searched for visual targets, the typical rightward bias of the distribution of goal-driven exploratory eye movements occurred. Within that spontaneously explored area, however, voluntary eye movements directed into the contralesional leftward direction did not differ significantly from voluntary eye movements directed into any other direction. In contrast, in the second part of the experiment, in which the patient repeated his/her own eye movement scanpath from the first part but now with stimulus-driven saccades (Fig. 4b), the same neglect patients displayed a prominent direction-specific saccade deficit. When tracking the jumping target in the contralateral leftward direction, neglect patients performed significantly more saccades and showed smaller saccade amplitudes than when tracking the target in any other direction, despite the fact that these patients had been able to perform the same leftward eye movements in the first part of the experiment without deficits.

The results argue for dissociated functioning of the two spatial attention systems within the spontaneously attended parts of the surroundings. Specifically, they suggest a disturbed stimulus-driven, but a preserved goal-directed attentional system in spatial neglect. When a target suddenly appears somewhere in space,

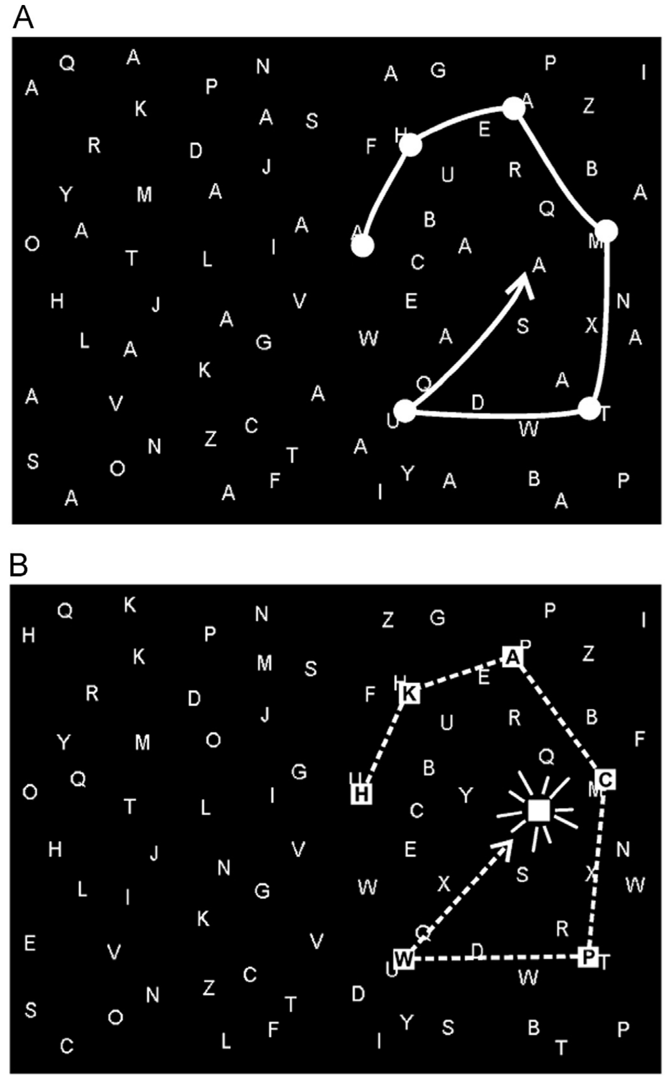

Fig. 4. Experimental paradigma contrasting directly 'top-down' control with 'stimulus-driven' control of spatial attention in neglect patients (Niemeier and Karnath, 2003). In two experimental conditions, patients performed identical saccades towards identical target locations that were either voluntarily selected or stimulus-driven. (A) Task 1 ('top-down' control): while the 'scanpath' was recorded the subject voluntarily explored arrays of white letters on a black background and indicated each detected target letter 'A' with a mouse click. Superimposed onto the display is a schematic of a short piece of a subject's scan path consisting of fixations (white circles) and saccades (lines connecting the circles). (B) Task 2 ('stimulus-driven' control): Individual scanpath from task 1 was taken and underlayed the presentation of a red square-shaped target window. The window should be visually tracked while it jumped across the letter arrays. Every 3 s the window jumped to a new position. The displacements of the target window matched exactly the metrics of the scanpaths the subject had used during the searches in Task 1. Thus, the patient repeated his/her own eye movement scanpath from Task 1, not with voluntary saccades but now with stimulus-driven saccades. The target window was visible at one position at a time (here depicted as a white square with 'light beams'). But for comparisons with (A), the graph also shows previous window positions. For the first 1.5 s the red window remained blank (to encourage maintained fixation) and then revealed randomly selected letters, one at a time (the probability of A's matched that of task 1). As in Task 1 'A's detected within the target window were indicated by a mouse click.

neglect patients demonstrate a direction-specific failure to detect and orient attention if the target is located contralesionally of the current point of fixation. The latter is observed if targets are flashed in the neglected (Girotti et al., 1983; Karnath et al., 1991; Walker and Findlay, 1996; Behrmann et al., 2001–2002; Bays et al., 2010) as well as in the spontaneously attended (Niemeier and Karnath, 2003) parts in space and thus argues for a general deficit of the stimulus-driven attention system. A possible consequence of a disturbance of this system could be the direction-specific disengagement deficit described by Posner et al. (1984, 1987). The authors have demonstrated posterior parietal lesions to result in a disruption of attentional disengaging and thus in a failure of or in increased latencies before contralesional shifts of attention to suddenly flashed visual targets. In contrast, if neglect patients explore a scene with voluntarily, top-down controlled shifts of spatial attention, they perform movements that are oriented into all spatial directions without any direction-specific disturbances (Niemeier and Karnath, 2000, 2003; Husain et al., 2001; Ptak et al., 2009; Machner et al., 2012). The goal-directed system underlying the top-down control of spatial attention thus appears to function well in neglect patients. A preserved goal-directed but disturbed stimulus-driven attention system also fits with the location of brain damage observed in spatial neglect (for review Karnath and Rorden (2012)); stroke lesions of neglect patients typically include those territories constituting the 'ventral attention network' responsible for the stimulus-driven detection of relevant targets and typically spare those of the 'dorsal attention network' underlying goal-directed target selection (Corbetta and Shulman, 2002; Corbetta et al., 2002, 2008).

Nonetheless there is a marked behavioral difference to healthy subjects also for the top-down control of spatial attention: the neglect patients' distribution of voluntarily executed search behavior is no longer symmetrically bell-shaped to the left and right in reference to their trunk midline, but is symmetrically bell-shaped to the left and right with respect to a 'new' center located on the ipsilesional right (cf. Fig. 3). The following section will provide a possible explanation for this difference.

7. Spatial bias despite an undisturbed goal-directed attention system

It is proposed that the 'new' center of the distribution of goal-directed spatial attention in neglect results from an altered neural representation of egocentric space. This neural representation allows us to reconstruct the position of external objects with respect to our body (Ventre et al., 1984; Karnath, 1994b). The assumption is that any spatially oriented action – including the voluntary control of spatial attention in form of exploratory eye/head/hand movements – is organized in relation to such a body reference (Fig. 5a). To obtain body-related internal representations of the surroundings, input from different peripheral sources needs to be integrated (see Section 7.1 below). In neglect patients, this integration process appears to work with a systematic error, resulting in a rotation of the whole egocentric reference frame around the subject's earth-vertical body axis to a new equilibrium (or 'default position') on the right (Fig. 5b; Karnath, 1997). As in healthy subjects, this position represents the center of exploratory activity in neglect patients. Its position in reference to the body, however, is shifted towards the ipsilesional right side, leading to a biased distribution of spatial attention and a neglect of items situated on the contralesional side (Fig. 5b). The new 'default position' of the egocentric reference frame is also the reason for the biased eye-in-head and head-on-trunk orientation (Fruhmann-Berger and Karnath, 2005; Becker and Karnath, 2010). In conclusion, it is argued that it is not the top-down control of spatial attention itself that is disturbed in patients with spatial neglect. Rather, it is the body-centered matrix (or egocentric reference frame of spatial coordinates) on top of which the voluntarily controlled shifts of spatial attention are executed that is altered.

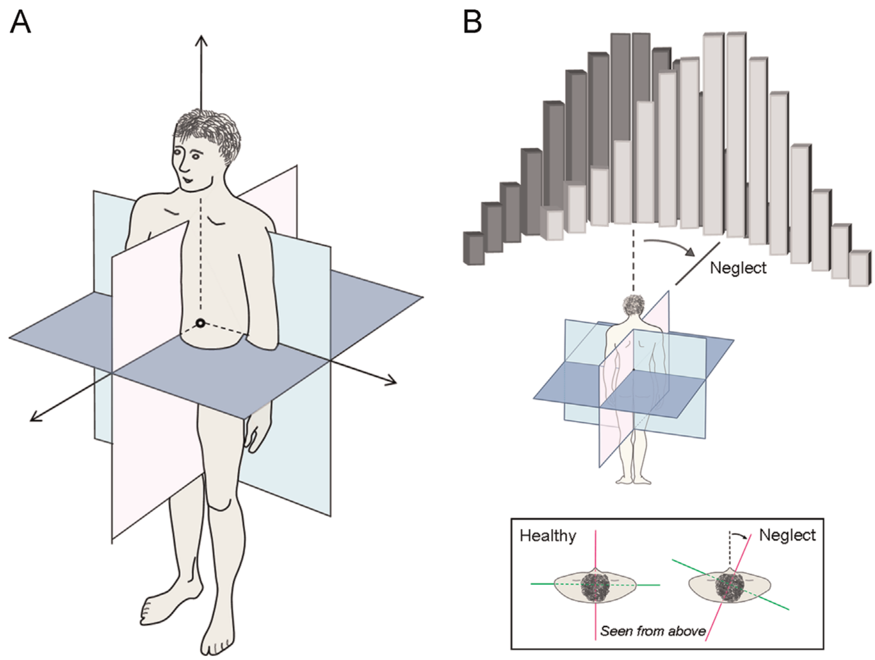

Fig. 5. Body-related internal representation of the surroundings. (A) Egocentric reference frame: Our brain uses internal maps of the visual environment, in which the topographical positions of objects reflect their body-centered position in space (instead of the retinotopic position of their images). Spatially oriented action – including the voluntary control of spatial attention in form of exploratory eye/head/hand movements – is organized in relation to such a body reference. (B) Sketch of the rightward deviation of egocentric space representation in patients with spatial neglect. The whole egocentric reference frame has been assumed to be rotated to a new equilibrium (or 'default position') on the right. As in healthy subjects, this position represents the center of exploratory activity in neglect patients. Its position in reference to the body, however, is shifted towards the ipsilesional right side, leading to a biased distribution of spatial attention and a neglect of items situated on the contralesional side. The dashed line indicates the 'default position' of the egocentric coordinate system in healthy subjects; the *black histogram* their ocular exploration of space along the horizontal dimension of space. The continuous line indicates the 'default position' of the egocentric coordinate system in patients with spatial neglect; the *gray histogram* their ocular exploration of space along the horizontal dimension. (Modified from Karnath (1997)). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

7.1. Coordinate transformations to represent visual space in body-related internal maps

Neurophysiological findings in monkeys as well as functional imaging and psychophysical results in humans have revealed that our brain uses internal maps of the visual environment. These maps contain information concerning the topographical positions of objects in terms of their head- and trunk-centered as well as world-centered position in space, instead of the retinotopic position of their images (Andersen et al., 1993, 1997; Battaglini et al., 1997; Galletti et al., 1993; Brotchie et al., 1995; Snyder et al., 1998; Boussaoud and Bremmer, 1999; Bottini et al., 2001; Frankenstein et al., 2012; Chen et al., 2012; Schindler and Bartels, 2013; Sai et al., 2014; Chen et al. 2014). The cortical regions encoding these body-related maps provide us with redundant information about the position and motion of our body in space and thereby play an essential role in adjusting body position relative to external space.

To obtain a body-related internal representation of the visual surroundings, the input from the retina has to be combined with eye position signals as well as head position information. One

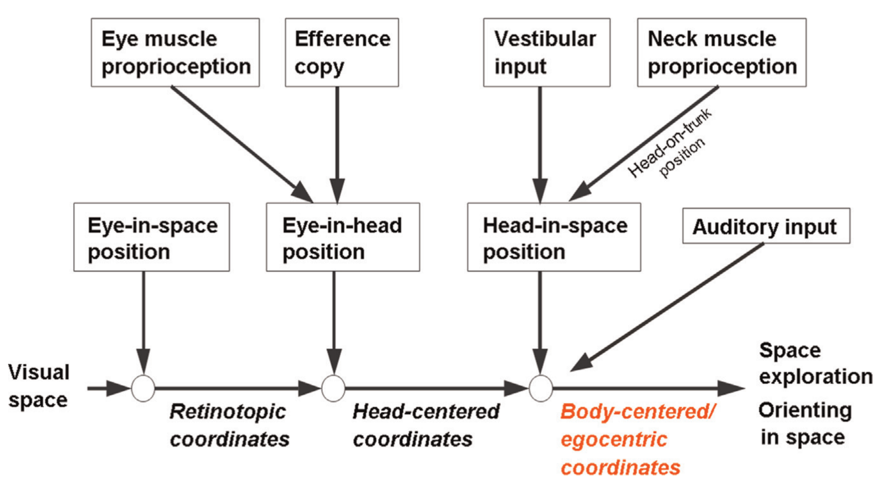

Fig. 6. Sketch of coordinate transformations required for representation of visual space in an egocentric reference frame. The topographical positions of objects in retinotopic coordinates need to be combined at least with the information of eye-in-head, head-in-space and head-on-trunk position. Sources of the head position information is the proprioceptive signals derived from the spindles of the neck muscles as well as the afferent signals from the vestibular system. In neglect patients, these coordinate transformations are working with a systematic error leading to a new equilibrium (or 'default position') of the egocentric reference frame. (Modified from Karnath et al. (1994b)).

source of the head position information is the proprioceptive signals derived from the neck muscle spindles; another source is the afferent signals from the vestibular system (Fig. 6).

The assumption that neglect results from damage to those cortical structures that are crucial for transforming the sensory input from these peripheral sensory organs into body-related internal maps (Karnath, 1994b), predicts that appropriate manipulation of the afferent input should alter the lateral bias of neglect patients. Indeed, the *compensatory effects on spatial neglect* that have been observed with asymmetric vestibular (Silberpfennig, 1941; Rubens, 1985), optokinetic (Pizzamiglio et al., 1990; Kerkhoff et al., 2012), and neck-proprioceptive stimulation (Karnath et al., 1993; Schindler et al., 2002) are in accordance with this view. These types of stimulation reduced or even extinguished the ipsilateral bias of spatial attention and contralateral neglect. Under stimulation, the patients' originally rightward deviated center of distribution of voluntarily executed search behavior moved leftward towards their trunk midline, allowing the patients to detect

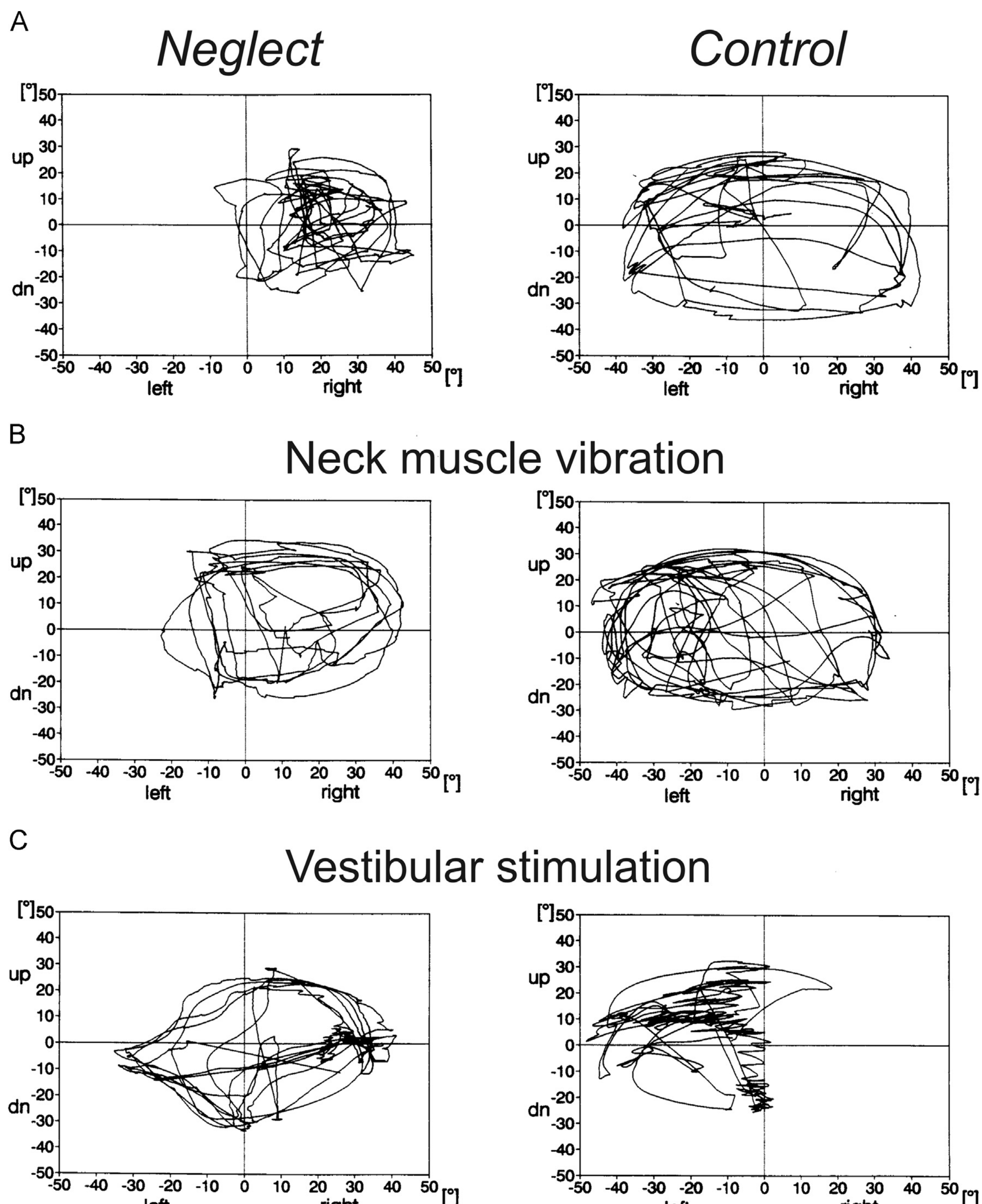

Fig. 7. Behavioral effect of asymmetric vestibular and neck proprioceptive stimulation. Scan path of a neglect patient (left) and a control subject (right) while searching for a target in complete darkness. Position 0°/0° was the body's midsaggital plane at eye level. (A) Spontaneous exploration behavior without stimulation. (B) Exploration with the left posterior neck muscles vibrated. (C) Exploration with left-sided vestibular stimulation (cold water irrigation). Both types of stimulation led to a reduction (B) or even abolition (C) of contalesional neglect; spatial attention was (more) symmetrically distributed left and right of the body's midsaggital plane. Vice versa under stimuluation the control subject showed 'neglect-like' asymmetric exploration behavior. (From Karnath et al. (1996)).

previously neglected items on the contralesional side (Fig. 7). Vice versa, *asymmetric vestibular or neck-proprioceptive stimulation induced 'neglect like' behavior in healthy individuals*; after stimulation, these individuals failed to direct spontaneous search movements towards the side opposite of input stimulation (Fig. 7). The findings demonstrate that the brain uses the input from these afferent channels to elaborate a unitary representation of egocentric space. Integration of the contributing input from the retina, neck muscle spindles and cupulae is used for spatial orientation, space exploration, and determination of egocentric body position in space. In neglect patients, this integration process appears to be disturbed (Fig. 5b).

8. Possible interaction between attentional gradient and altered egocentric reference frame

A natural environment typically consists of several objects that surround the individuum, providing space-related as well as object-related information. The selection of relevant information from such a scene thus evokes attentional processes that are both object- as well as body-related. In fact, neurophysiological as well as neuroimaging studies have revealed that the brain uses both body-centered/egocentric as well as object-centered coordinates to code spatial locations of stimuli (Olson and Gettner, 1995, 1999; Olson, 2003; Galati et al., 2000; Sai et al., 2014; Chen et al. 2014). Egocentric and object-based mechanisms also seem to be inherent to the disturbed orienting behavior of neglect patients (Hornak, 1992; Karnath and Fetter, 1995; Walker and Findlay, 1997; Barton et al., 1998; Karnath et al., 1998; Behrmann et al., 2002).

Recent data argue for a direct interaction of object-based and egocentric aspects in spatial neglect (Karnath et al., 2011). Patients explored single objects presented at five different egocentric positions along the horizontal dimension of space (−80°, −40°, 0°, +40°, +80°) while their eye and head movements were recorded. Most interestingly, data analysis revealed that object-based neglect varied with egocentric position. While neglect of the objects' left side was strong at contralesional egocentric positions, it ameliorated at more ipsilesional egocentric positions of the objects (Fig. 8a). The patients showed steep, ramp shaped patterns of exploration for objects located on the far contralesional side, and a broadening of these patterns as the locations of the objects shifted toward the ipsilesional side (Fig. 8b). These results may indicate that visual input is coded in egocentric and object-based coordinates simultaneously. The data fitted well with the predictions by a computational model of spatial attention that assumed simultaneous coding of visual input in two kinds of coordinates, termed the 'Integrated Space-Object map (ISO-map)' model (Niemeier and Karnath, 2002a). In neglect patients, the salience functions of this model were assumed to show a biased bell-shape for the representation of spatial position in egocentric coordinates (Fig. 9a), while a lateral gradient was proposed for the representation of spatial position in within-object coordinates (Fig. 9b). The final saliency of a target is obtained by the multiplication of a linear gradient on the object-based part and a shifted bell curve on the egocentric part (Fig. 9c).

A central prediction of this direct interaction between object-based and egocentric coordinates is that the left–right asymmetry in neglect should improve with more ipsilesional positions of the objects. The salience imbalance is expected to always favor the right object half, while this imbalance/gradient becomes less steep and the width of the salience distribution expands with more ipsilesional egocentric object positions. Indeed, the data of several studies fitted well with the predictions by the ISO-map model (Niemeier and Karnath, 2002b; Karnath et al., 2011; Li et al., 2014), but are also compatible with other computational models of spatial attention (Pouget and Sejnowski, 1997, 2001; Mozer, 1999, 2002; Deneve and Pouget, 1998, 2003).

9. Concluding remarks

Neglect patients demonstrate a defect of the stimulus-driven attentional system, leading to disturbed bottom-up reactions to behaviorally relevant stimuli. When a target suddenly appears somewhere in space, they show disturbed detection and orienting if the target is located in contralesional direction of the current focus. A possible mechanism underlying this disturbance might be a direction-specific disengagement deficit (Posner et al., 1984, 1987). The authors demonstrated posterior parietal lesions to result in a disruption of attentional disengaging and thus in increased latencies before contralesional shifts of attention.

In contrast to a disturbed stimulus-driven attentional system, the goal-directed attentional system concerned with top-down controlled orienting appears preserved. If neglect patients explore a scene with voluntarily, top-down controlled shifts of spatial attention, they perform movements that are oriented into all spatial directions without any direction-specific disturbances. The

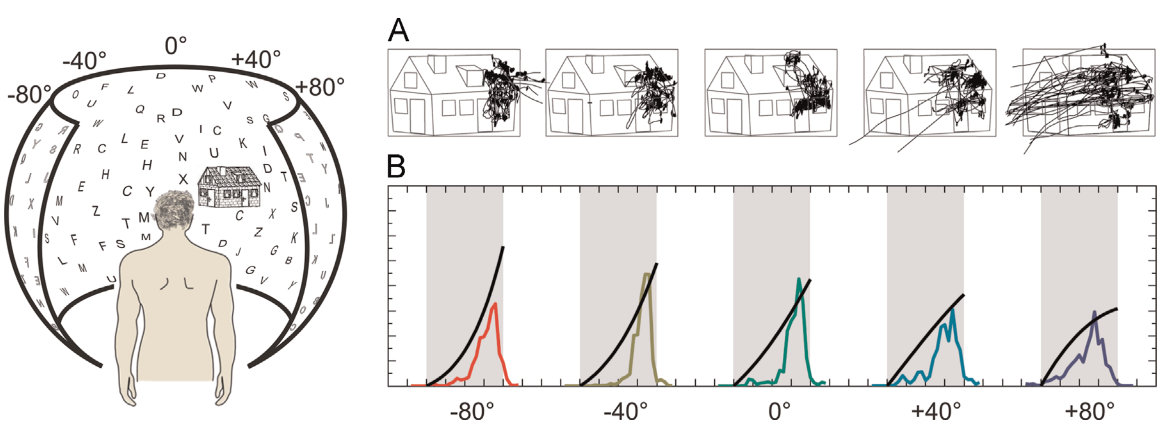

Fig. 8. Direct interaction of object-based and body-centered/egocentric aspects in spatial neglect. (A) Typical scanpaths of a right brain damaged patient with spatial neglect, scanning an object stimulus at each of 5 different egocentric horizontal positions (−80°, −40°, 0°, +40°, +80°). Note that in each experimental trial only one stimulus was present at one of the 5 egocentric positions. (B) Average distribution of exploratory eye movements recorded in a group of neglect patients at the 5 egocentric stimulus positions (illustrated in different colors). The gray area indicates the extension of the object stimuli presented at the 5 egocentric sites. The patients showed steep, ramp shaped patterns of exploration for objects located on the far contralesional side, and a broadening of these patterns as the locations of the objects shifted more to the ipsilesional side. The black lines illustrate the predicted saliency curves according to the Integrated Space-Object map (ISO-map) model (see manuscript text). Scaling in percent exploration time. (From Karnath et al. (2011)). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

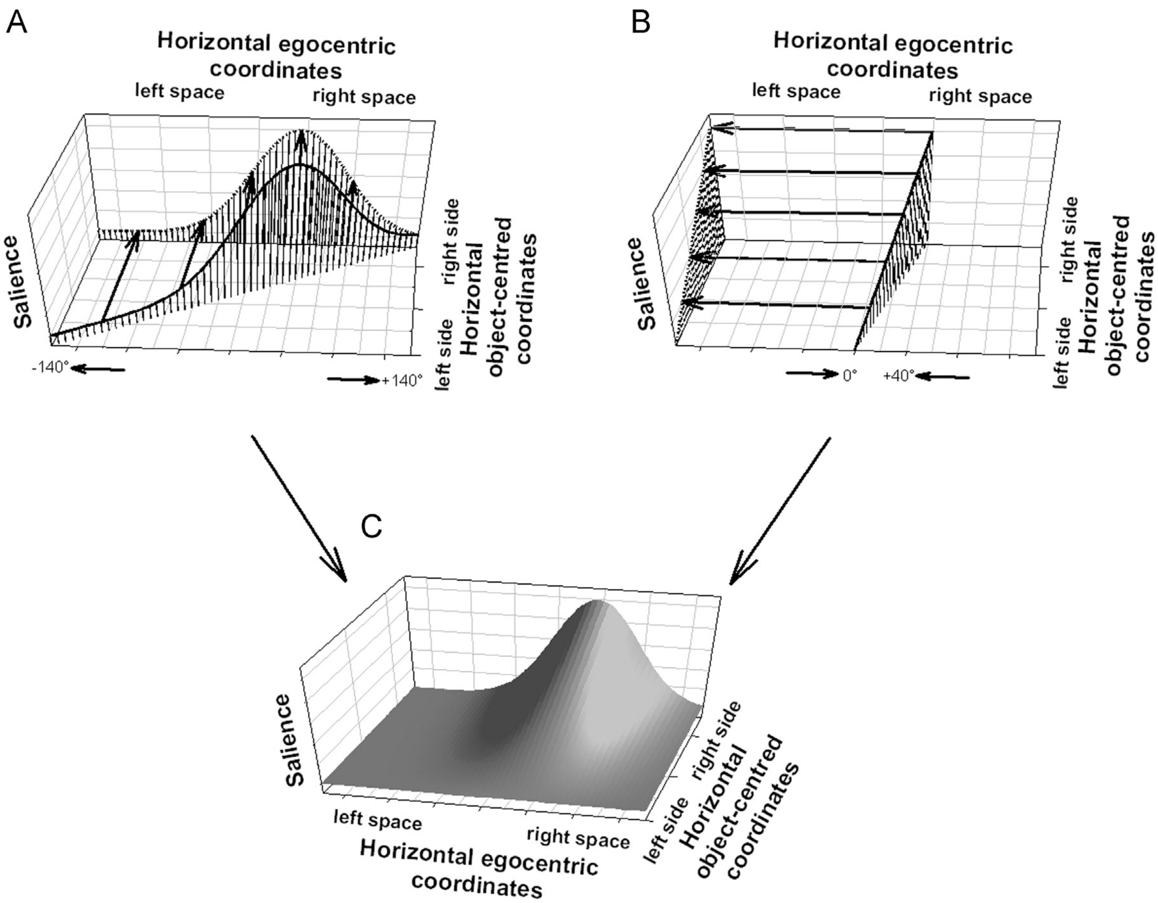

Fig. 9. The 'Integrated Space-Object map (ISO-map)' model of spatial attention in neglect. (A) The disturbed salience function is assumed bell-shaped along its horizontal egocentric dimension, and (B) is supposed to be ramp-shaped along its horizontal object-centered axis. (C) The 3D salience function resulting from the multiplication of these two 2D curves. A central prediction of the direct interaction between object-based and egocentric coordinates (C) is that the left–right asymmetry in neglect should improve with more ipsilesional positions. (From Niemeier and Karnath (2002a)).

distribution of these exploratory movements is biased but exhibits an 'equilibrium' on the right, far away from any anatomical limits of horizontal eye, head, or arm movements. Like healthy subjects, neglect patients do not orient their attention always towards the extreme ipsilesional side nor start 'circling' around their earth-vertical body axis. Rather, the patients' distribution of voluntary attention shows a symmetrical, roughly bell-shaped *de*crease towards the left and the right of the 'equilibrium'. The bias of the distribution is assumed to result from an altered representation of own body position with respect to external objects, while the voluntary (top-down) guidance of spatial attention itself – executed on top of this body-related matrix – appears undisturbed.

An interhemispheric imbalance model resulting in an attentional left-to-right gradient (Kinsbourne, 1970, 1993; Payne and Rushmore, 2004; Corbetta et al., 2005; Corbetta and Shulman, 2011) in which the 'relative position of a stimulus is a major determinant of its standing on the attentional hierarchy, its absolute location is not (Kinsbourne, 1993)' does not explain the observed equilibrium of goal-directed top-down control of spatial attention in neglect. The neglect patients' voluntary allocation of attention in space rather documents that the 'attentional hierarchy' of stimuli located along the horizontal dimension of space is influenced by the position of these stimuli relative to the patient's body, i.e. by their egocentric coordinates. To obtain an equilibrium reliably occurring in a certain range of egocentric positions in clear distance of anatomical limits by maximally displaced horizontal eye, head, or arm movements, it is necessary to supply the system with information allowing the reconstruction of own body position with respect to external objects. This body-centered matrix (or egocentric reference frame of spatial coordinates) appears to be altered in spatial neglect – not the voluntarily controlled shifts of spatial attention executed on top it.

One could speculate about a modified version of the interhemispheric imbalance model in which eye-in-head and head-in-space information – conveyed by proprioceptive and visuo-vestibular input – is fed in. Spatial neglect could be regarded to result from a tradeoff between (i) an attentional left-to-right gradient and (ii) altered processing of afferent information serving to reconstruct own body position with respect to external objects (see Section 8 above). However, such modified versions would require a new label – e.g., 'integrative models of spatial neglect' – since they dissolve the decisive aspect of the original concept of an interhemispheric imbalance model, namely that neglect is assumed to be a directional – not a body-centered – phenomenon.

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