The Role of Temporo-parietal Cortex in Subcortical Visual Extinction

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Abstract

■ Visual extinction is an intriguing defect of awareness in stroke patients, referring to the unsuccessful perception of contralesional events under conditions of competition. Previous studies have investigated the cortical and subcortical brain structures that, when damaged or inactivated, provoke visual extinction. The present experiment asked how lesions of subcortical structures may contribute to the appearance of visual extinction. We investigated whether lesions centering on right basal ganglia may induce dysfunction in distant, structurally intact cortical structures. Normalized perfusion-weighted MRI was used to identify structurally intact but abnormally perfused brain tissue, that is, zones that are receiving enough blood supply to remain structurally intact but not enough to function normally. We compared patients with right basal ganglia lesions showing versus not showing visual extinction. In the extinction patients, the contrast revealed cortical malperfusion that clustered around the right TPJ. It seems as if malfunction of this area is a critical aspect in visual extinction not only after cortical lesion but also in the case of subcortical basal ganglia damage. Our results support the idea that a normally functioning TPJ area plays a decisive role for the attentional network involved in detecting of visual stimuli under conditions of competition. ■

INTRODUCTION

Extinction is an intriguing defect of awareness in stroke patients, referring to the unsuccessful perception of a contralesional event when a competing stimulus appears simultaneously on the ipsilesional side (Driver, Mattingley, Rorden, & Davis, 1997). Extinction is not restricted to the visual domain. It can occur within as well as between different sensory modalities (e.g., Rapp & Hendel, 2003; Ladavas, Pavani, & & Farne, 2001; Vaishnavi, Calhoun, & Chatterjee, 2001; Deouell & Soroker, 2000; Maravita, Spence, Clarke, Husain, & Driver, 2000). The disorder is as asymmetrically associated with the human right hemisphere as is spatial neglect (Becker & Karnath, 2007). However, extinction and neglect show obvious differences and may dissociate (Vallar et al., 1994). This could point to anatomically related but (partly) separated neural representations (Karnath, Himmelbach, & Küker, 2003).

So far, a number of studies have been conducted to identify those areas in the human right hemisphere that induce visual extinction when injured. Early lesion studies in neurological patients (Vallar, Rusconi, Bignamini, Geminiani, & Perani, 1994; Heilman & Valenstein, 1972; Critchley, 1949) and temporary inactivation by TMS in healthy subjects (Battelli, Alvarez, Carlson, & Pascual-Leone, 2008; Dambeck et al., 2006; Hilgetag, Theoret, & Pascual-Leone, 2001; Pascual-Leone et al., 1994) suggested a relationship of extinction to posterior parietal lobe areas. Modern lesion analysis techniques (see, for a review, Rorden & Karnath, 2004) have been applied to narrow the cortical site typically associated with visual extinction. It seemed as if the region at the intersection of right ventral inferior parietal lobule, caudal superior and middle temporal cortex, and lateral occipital cortex—broadly defined as TPJ—is a crucial area for provoking the disorder (Karnath et al., 2003). Support to this observation has been given by recent TMS findings in healthy volunteers. Meister et al. (2006) observed that single-pulse TMS over right TPJ caused extinction-like performance in a detection task of unilaterally versus bilaterally presented visual stimuli, whereas more rostral application of TMS over superior temporal gyrus (STG) had no such extinction effects. Further, a recent study by Grandjean, Sander, Lucas, Scherer, and Vuilleumier (2008) has revealed that damage to area TPJ is correlated with the extinction of auditory stimuli.

Beyond cortical injury, visual extinction also has been observed after damage of subcortical structures, namely, basal ganglia, thalamus, internal capsule, and periventricular white matter (Vallar et al., 1994). To date, it is still uncertain how these subcortical structures contribute to the disorder. Is it the neuronal loss in these subcortical structures or do these lesions induce functional changes in distant, structurally intact cortical structures as this has been observed for other cognitive disorders (Hillis et al., 2001, 2002, 2005; Karnath et al., 2005; Demeurisse, Hublet,

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Paternot, Colson, & Serniclaes, 1997; Weiller, Ramsay, Wise, Friston, & Frackowiak, 1993)? To investigate this question, the present study used perfusion-weighted MRI (PWI) in patients with subcortical strokes centering on right basal ganglia. PWI allows identifying structurally intact but abnormally perfused brain tissue, that is, zones that are receiving enough blood supply to remain structurally intact but not enough to function normally. In contrast to previous TMS (Battelli et al., 2008; Dambeck et al., 2006; Meister et al., 2006; Hilgetag et al., 2001; Pascual-Leone et al., 1994) and PWI (Hillis et al., 2006) studies on extinction, the present experiment did not use a priori definitions of discrete ROIs for anatomical analyses. Instead, we used spatial normalization to analyze the PWI data. This technique allows us to investigate the entire area of abnormal perfusion in each individual by transforming the subjects' brains and respective PWI data to a common stereotaxic space so that they become comparable between subjects (cf. Karnath et al., 2005). Moreover, we used voxelwise interhemispheric comparisons to take into account existing regional differences of perfusion characteristics within each hemisphere.

METHODS

Subjects

Thirteen patients with first-ever subcortical stroke centering on basal ganglia consecutively admitted to the Centre of Neurology in Tübingen were included in the study. Because stenoses are known to produce false-positive depictions of perfusion deficits, especially in time-to-peak perfusion images (Yamada et al., 2002), we excluded those patients with a hemodynamically relevant extracranial stenosis in the internal carotid arteries, that is, ≥70%, demonstrated by Doppler sonography. Due to the use of contrast agent, the number of potential participants had to be further limited with respect to their kidney functions. Following standardized clinical testing (see below), the patients were divided into two groups. One group suffered from visual extinction (with or without additional auditory and/or tactile extinction) as well as from spatial neglect (n = 8), whereas the other group had spatial neglect but no extinction (n = 5). All patients gave their informed consent to participate in the study, which has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. Clinical and demographic data of all patients are given in Table 1.

Clinical Investigation

The patients were clinically tested for visual, auditory, and tactile extinction. For each modality, 10 unilateral stimuli on either side and 10 bilateral stimuli were presented in a pseudorandom order. Visual extinction was tested by the usual clinical confrontation technique. Movements of the examiner's left and/or right index finger were presented in the patient's left and/or right visual half field. One of the 13 investigated patients had additional left inferior quadrantanopia. In this subject, visual stimuli were presented in the intact visual field. Auditory and tactile stimulation were conducted with the patient's eyes closed. The auditory modality was tested by rustling with a small piece of paper near the patient's left and/or right ear. Tactile extinction was investigated by applying short fingertips on the dorsal surface of the patient's left and/or right hand while the patient's arms lay in front of them. If the patient was not able to report this gentle unilateral tactile stimulation at the contralateral hand due to left-sided sensory loss, the examination was repeated with softly twitching at the left and/or right shoulder. Patients were classified as showing extinction when they reported at least 90% of the unilateral stimuli on each side correctly, but failed to perceive the left stimulus during bilateral stimulation in >50% of the trials.

Spatial neglect was diagnosed when the patients showed the typical clinical behavior, such as spontaneous eye and head orientation toward the ipsilesional side (Fruhmann-Berger & Karnath, 2005), orienting toward the ipsilesional side when addressed from the front or the left, and ignoring contralesionally located people or objects. In addition, all patients were further assessed with the following clinical tests: the "letter cancellation" task (Weintraub & Mesulam, 1985), the "bells test" (Gauthier, Dehaut, & Joanette, 1989), and a copying task (Johannsen & Karnath, 2004). Not all subjects could be investigated with all three tests due to different clinical constraints (cf. Table 1). Nevertheless, neglect patients had to fulfill the criterion for spatial neglect in at least two of the three tests. Full details about the test procedure and criteria are described elsewhere (Fruhmann-Berger & Karnath, 2005).

Magnetic Resonance Imaging and Analysis

For the depiction of structurally lesioned brain tissue, we used diffusion-weighted imaging (DWI) imaging within the first 48 hr post-stroke and T2-weighted fluid-attenuated inversion-recovery (FLAIR) sequences when imaging was conducted 48 hr or later after stroke onset (Schaefer et al., 2002; Ricci, Burdette, Elster, & Reboussin, 1999; Noguchi et al., 1997; Brant-Zawadzki, Atkinson, Detrick, Bradley, & Scidmore, 1996). The mean time between stroke and imaging as well as the clinical investigation was 4.9 days (SD = 3.8) in the group with visual extinction and spatial neglect and 4.5 days (SD = 5.4) in the group with spatial neglect only (t = 0.14, p = .891, two-tailed). Scans were obtained on a 1.5-T MR system (Magnetom Sonata; Siemens, Erlangen, Germany). The FLAIR sequence was acquired with 72 axial slices (thickness = 1 mm, interslice gap = 1 mm), a field of view (FOV) of 192 × 256 mm^2, matrix 192 × 256 pixels, repetition time (TR) of 9310 msec, and an echo time (TE) of 122 msec. DWI was performed with

Table 1. Demographic and Clinical Data of the Patients with and without Visual Extinction following Lesions Centering on Right Basal Ganglia

			Extinction						*Spatial Neglect*				
			Visual[a]		*Tactile*[a]		*Auditory*[a]		*Letter Cancellation (Hits)*		*Bells Test (Hits)*		*Copying*
Patient	*Sex*	*Age*	*Left*	*Right*	*Left*	*Right*	*Left*	*Right*	*Left*	*Right*	*Left*	*Right*	*(% Omitted)*
E1	F	48	0	10	10	10	10	10	8	29	0	14	25
E2[b]	M	66	0	10	0	10	0	10	4	24	2	4	50
E3	F	46	2	10	8	10	8	10	20	27	8	15	0
E4	F	78	0	10	0	10	0	10	–	–	2	11	62.5
E5	M	65	0	10	0	10	0	10	10	26	1	13	37.5
E6	M	53	0	10	0	10	0	10	0	14	0	6	87.5
E7	F	68	0	10	0	10	0	10	1	27	0	15	37.5
E8	F	68	0[c]	10	–	–	0	10	0	3	0	4	87.5
N1[b]	M	71	10	10	10	10	10	10	–[d]	–[d]	–[d]	–[d]	87.5
N2	F	46	10	10	10	10	10	10	24	30	–	–	25
N3	M	75	9	10	8	10	8	10	0	23	0	10	–
N4	F	39	9	10	0	10	10	10	18	28	2	14	12.5
N5	M	52	8	10	8	10	8	10	0	13	1	15	0

E = patients with visual extinction and spatial neglect; N = patients with spatial neglect only; F = female; M = male; – = not tested.

[a]Number of detected stimuli under bilateral simultaneous stimulation (all patients detected all unilaterally presented left- and right-sided stimuli correctly).

[b]Patients with hemorrhagic stroke (all other subjects suffered from ischemia).

[c]Patient with additional left inferior quadrantanopia (tested for visual extinction in the preserved visual field).

[d]In this patient, the Albert's (1973) test could be applied revealing 0 hits on the left and 13 on the right.

a single-shot EPI spin-echo sequence (TR = 3200 msec; TE = 87 msec; FOV = 230 × 230 mm^2; matrix = 128 × 128 pixels; slice thickness = 5 mm; gap = 1 mm; *b* values of 0, 500, and 1000 sec/mm^2). The boundary of the lesion was delineated directly on the individual MRI image for every single transverse slice using MRIcron software (www.mricro.com/mricron; Rorden, Karnath, & Bonilha, 2007). In order to illustrate the common region of structurally lesioned brain tissue per group, both the scan and lesion shape were then transferred into stereotaxic space using the spatial normalization algorithm provided by SPM2 (www.fil.ion.ucl.ac.uk/spm/). For determination of the transformation parameters, cost–function masking was employed (Brett, Leff, Rorden, & Ashburner, 2001).

Dysfunctional brain tissue due to abnormal perfusion was visualized using PWI (Belliveau et al., 1990), performed in the same scanning session as the structural scans. Fifty repetitions of perfusion-weighted EPI sequences (TR = 1440 msec; TE = 47 msec; FOV = 230 × 230 mm^2; matrix = 128 × 128; 12 axial slices; slice thickness = 5 mm; gap = 1 mm) were obtained with gadolinium diethyl triamineene pentaacetic acid (Gd-DTPA) bolus power injected at a rate of 3–5 ml/s. The amount of bolus used depended on the body weight of the subject. Time-to-peak (TTP) maps were calculated to detect possible brain areas of dysfunction. TTP represents the time at which the largest signal drop occurs in the signal intensity curve with respect to the first image. TTP maps are generated directly from the signal intensity curves and do not rely on deconvoluting algorithms or the choice of adequate input functions (Thijs et al., 2004; Calamante, Gadian, & Connelly, 2002). In order to identify common regions of perfusion abnormality in the two groups of patients, the PWI volumes were spatially realigned and then transferred into stereotaxic space using the spatial normalization algorithm provided by SPM2. The normalized TTP maps were spatially smoothed with a Gaussian filter of 2 mm. For SPM normalization, we used a template featuring symmetrical left–right hemispheres (cf. Aubert-Broche et al., 2003). Subsequently voxelwise interhemispheric comparisons were performed for each individual before extracting perfusion deficit volumes. This method takes regional biases for perfusion parameters into account, as each region is compared voxel by voxel to its mirrored region in the unaffected hemisphere, thereby comparing homologous regions and avoiding a region-specific bias (cf.

Karnath et al., 2005). For each voxel of the affected right hemisphere, the TTP value of its mirrored voxel in the unaffected left hemisphere was subtracted, resulting in the "TTP delay." For the determination of volumes with perfusion abnormalities, we defined the threshold for TTP delays ≥3.0 sec. The resulting maps are denoted "TTP delay maps" in the following. The TTP delay threshold was based on previous observations that TTP delays >2.5 sec in Wernicke's area were associated with language dysfunction (Hillis et al., 2001), and that the general functional impairment of stroke patients correlated best with the volume of PWI abnormality for TTP delays ≥4 sec (Neumann-Haefelin et al., 1999). The area of mismatch between DWI/FLAIR and PWI abnormalities, that is, the zones of structurally intact but dysfunctional neural tissue, was determined by subtracting for each subject the normalized DWI/FLAIR map from the normalized TTP delay map. Finally, we performed two analyses to compare perfusion abnormalities in the patient groups with and without visual extinction. In the first analysis, the superimposed mismatch images of the group without visual extinction were subtracted from the overlap mismatch images of the group with visual extinction. Details concerning the subtraction technique were given elsewhere (Rorden & Karnath, 2004). In a second analysis, we used the nonparametric Brunner and Munzel test as implemented in the MRIcron toolset (Rorden et al., 2007) to statistically compare, on a voxel-by-voxel basis, the TTP delays within the area of mismatch between the group with visual extinction and the group without visual extinction.

RESULTS

Figure 1 shows the overlay plots of the normalized DWI/FLAIR data for the patient group with visual extinction plus spatial neglect and for the group with spatial neglect only. In both groups, the subcortical lesions centered on right basal ganglia. The comparison of lesion volumes between the patients with visual extinction (mean: 17% of right hemisphere volume; *SD* = 10.2) and controls (9.9%; *SD* 8.7) revealed a numerical nonsignificant difference ($U = 12, Z = -1.17, p = .242$). The correlation between the behavioral measure of visual extinction and lesion volume in basal ganglia was likewise not significant ($\rho = -.165, p = .591, n = 13$).

The spatially normalized perfusion abnormalities accompanying these lesions, that is, the zones of mismatch between DWI/FLAIR and PWI abnormalities, are illustrated in Figure 2. The mismatch images of all individuals in a group were superimposed, creating an overlap image showing the common regions of structurally intact (no DWI/FLAIR abnormalities) but abnormally perfused tissue in each group. To illustrate the common area of hypoperfusion in the patients with visual extinction in direct contrast to those areas abnormally perfused in the patients who did not show this disorder, we subtracted the overlay mismatch images of the latter group from the overlap mismatch images of the extinction group. The resulting subtraction images highlight structurally intact regions that were both typically hypoperfused in patients with visual extinction as well as typically spared in patients without this

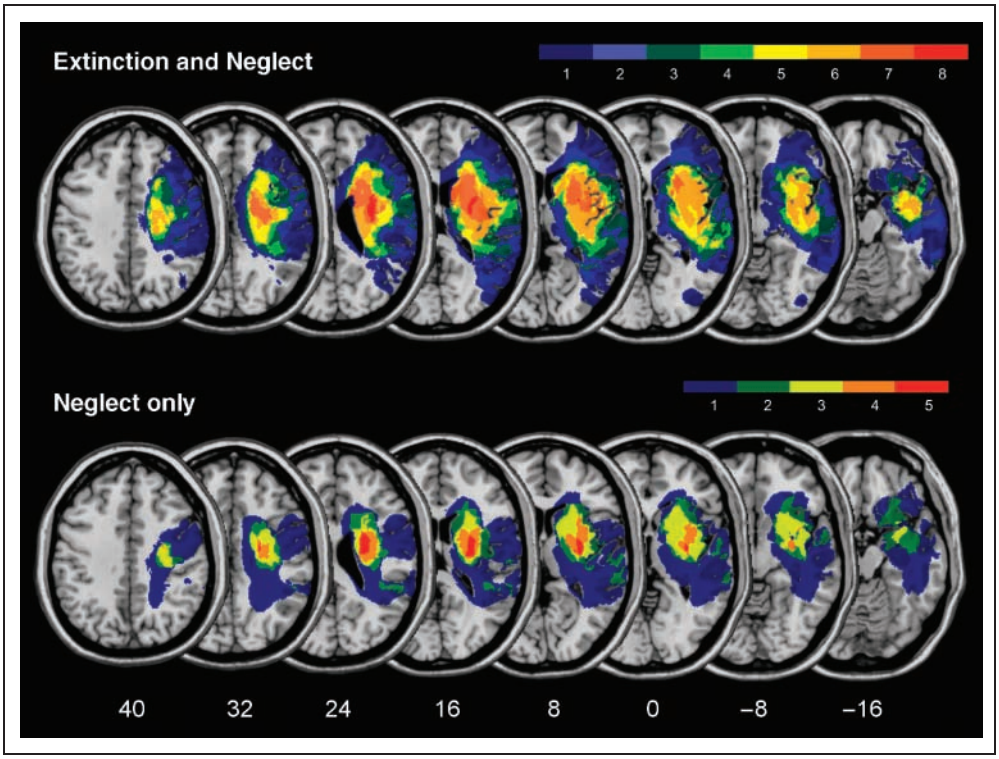

Figure 1. Overlay plots of the normalized structural lesions (based on normalized DWI/FLAIR MR images) for the groups of patients with and without visual extinction. The number of overlapping areas is illustrated by different colors, coding increasing frequencies from dark blue ($n = 1$) to red (n = max). MNI *z*-coordinates of the transverse sections are given.

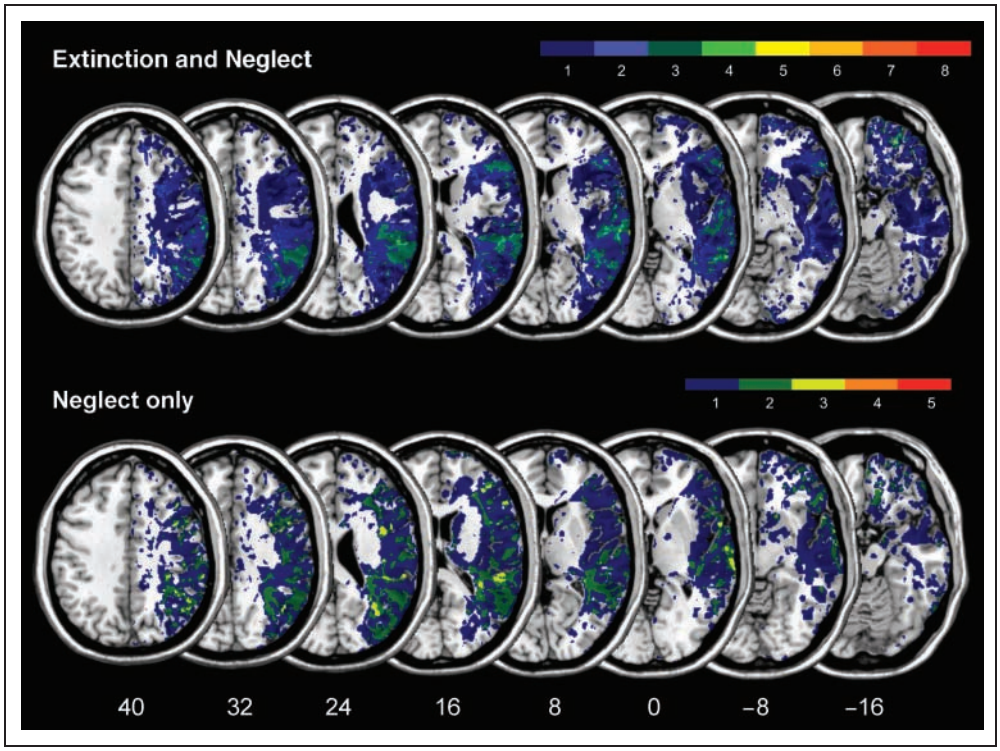

Figure 2. Overlay plots of the normalized TTP delay maps showing the common regions of mismatch between DWI/FLAIR and PWI abnormalities, that is, of structurally intact but abnormally perfused tissue, for the groups of patients with and without visual extinction. The number of overlapping areas showing abnormal perfusion is illustrated by different colors, coding increasing frequencies from dark blue (n = 1) to red (n = max.). MNI z-coordinates of the transverse sections are given.

disorder (Figure 3A). By using the anatomical parcellation of the MNI single-subject brain by Tzourio-Mazoyer et al. (2002) implemented in MRIcron software (Rorden et al., 2007), we found the center of abnormal perfusion in right TPJ (Figure 3A). The hypoperfused area clustered around MNI coordinates ($x = 58, y = -38, z = 24$ and $x = 62, y = -26, z = 11$) in the posterior part of STG, the posterior part of MTG (around $x = 50, y = -61, z = 4$ and $x = 62, y = -48, z = 0$), angular gyrus (around $x = 46, y = -44, z = 32$ and $x = 48, y = -45, z = 30$ and $x = 38, y = -57, z = 38$), and supramarginal gyrus ($x = 60, y = -37, z = 26$). Small clusters within inferior frontal cortex were also observed.

The results of the voxelwise statistical analysis of the TTP delays pointed in the same direction. The uncorrected statistical map illustrated in Figure 3B revealed differences in the same areas as indicated by the subtraction analysis. However, due to the small number of patients in the present study inherent to the methodology (exclusion of patients with either stenosis in the internal carotid arteries, insufficient kidney function, inability to tolerate the MR environment, older additional lesions, or inability to give informed consent), only few voxels of this statistical map survived the adjustment for multiple comparisons. Nevertheless, despite not reaching statistical significance after correction for the overall alpha level, the difference in TTP delay between the two patient groups around TPJ was considerably larger than the difference in TTP delay between the two patient groups in the rest of the brain.

DISCUSSION

The present study used PWI to examine the structurally intact cortical tissue in a continuous series of 13 patients showing versus not showing visual extinction subsequent to subcortical strokes centering on right basal ganglia. In the extinction patients, we found dysfunctional (although structurally intact) cortical brain tissue that clustered around right TPJ. The area of malfunction included caudal parts of right superior and middle temporal gyri as well as parts of supramarginal and angular gyri.

What could be the physiological mechanisms linking the structural damage in the present patients with basal ganglia lesions and the dysfunction in area TPJ? Different mechanisms have discussed how damage to subcortical structures may cause functional or metabolic abnormalities in cortical areas. One concept is "diaschisis." Diaschisis is believed to be a result of reduction of neuronal activity from axonal damage leading to brain dysfunction distant from the stroke (Stirling Meyer, Obara, & Muramatsu, 1993; Feeney & Baron, 1986). In the present case, such a pathomechanism could have affected the striato-cortical projections linking putamen and caudate nucleus with the cortical TPJ region (Yeterian & Pandya, 1993, 1995, 1998). Also, vascular disorders such as a loss of autoregulation, release of vasoactive substances, and/or abnormally vasoconstricted arterioles and stenosis have been suggested occurring with hypoperfusion (Takano et al., 1988; Slater, Reivich, Goldberg, Banka, & Greenberg, 1977). PWI does not provide the possibility to differentiate between

etiologies. It only allows us to identify zones that are receiving enough blood supply to remain structurally intact, but not enough to function normally. Nevertheless, several studies have demonstrated that it is, indeed, the cortical abnormalities rather than the neuronal loss in the subcortical structures that provoke the cognitive disturbance. By using PWI, as well as single-photon emission computed tomography, it has been shown that left- or right-sided subcortical lesions cause cognitive deficits (such as spatial neglect or aphasia) only if the subcortical damage provokes additional malperfusion of cortical gray matter structures in the ipsilesional hemisphere (Hillis et al., 2002, 2005; Demeurisse et al., 1997; Weiller, Willmes, et al., 1993; Weiller, Ringelstein, Reiche, Thron, & Buell, 1990). Without this malfunction of cortical structures, subcortical brain lesions did not provoke the disturbances. Thus, it seems that damage of subcortical structures alone does not provoke these cognitive disorders but rather requires additional malfunction of cortical gray matter structures. Following these previous studies on aphasia and/or spatial neglect, we expect a similar mechanism also for visual extinction after subcortical stroke. We assume that visual extinction after a basal ganglia lesion results from the malfunction of cortical brain tissue rather than from the neuronal loss in basal ganglia itself.

Our finding of dysfunctional cortical brain tissue around right TPJ in extinction patients is consistent with previous observations demonstrating that cortical stroke lesions or application of TMS at right TPJ may cause a functional breakdown of those processes that give rise to visual extinction (Meister et al., 2006; Karnath et al., 2003). What

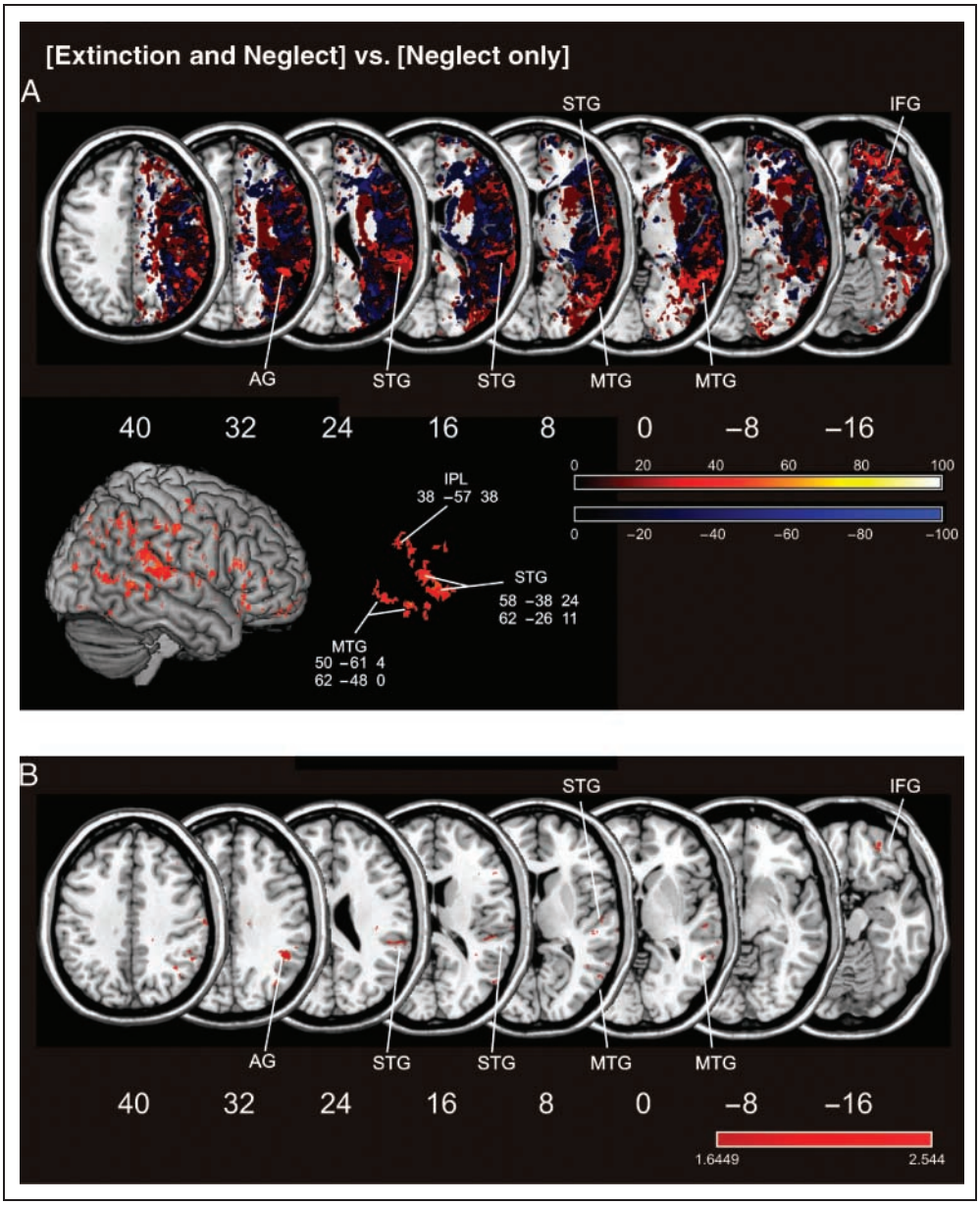

Figure 3. (A) Overlay plot of the subtracted superimposed mismatch images of the visual extinction group with additional neglect minus the mismatch images of the group with neglect but no extinction. The percentage of overlapping areas of structurally intact but abnormally perfused tissue in the visual extinction group after subtraction is illustrated by different colors, coding increasing frequencies from dark red to white. The different colors from dark blue to lighter blue indicate regions abnormally perfused more frequently in controls than in extinction patients. MNI *z*-coordinates of the transverse sections are given. The surface view of the center of overlap represents cortical regions that were damaged >30% more frequently in extinction patients than in patients who had no extinction. MNI *z*-coordinates of the locations marked are given. (B) Statistical map resulting from the voxelwise analysis of the TTP delays within the area of mismatch using the nonparametric Brunner and Munzel test as implemented in the MRIcron toolset (Rorden et al., 2007). The data are not adjusted for multiple comparisons (uncorrected data). Color bar indicates *Z*-scores. IPL = inferior parietal lobule; AG = angular gyrus; STG = superior temporal gyrus; MTG = middle temporal gyrus; IFG = inferior frontal gyrus.

do we know about the cognitive functions implemented in the right TPJ region? The right TPJ area has been suggested to play a critical role in a ventral fronto-parietal attention network (Corbetta, Patel, & Shulman, 2008; Corbetta & Shulman, 2002). Corbetta et al. differentiated between two fronto-parietal network systems of attentional processing—anatomically and functionally segregated into a dorsal and a ventral system. The dorsal fronto-parietal network, whose core regions include dorsal parietal and frontal cortices, embodies top–down control mechanisms that generate endogenous signals about likely contingencies and send out signals that bias the processing of appropriate stimulus features and locations in sensory cortex. In contrast, the ventral fronto-parietal network represents bottom–up control mechanism for the detection of behaviorally relevant stimuli. It has been suggested that the latter works as a "circuit breaker" for the dorsal system, directing attention to salient events (Corbetta & Shulman, 2002). The ventral network is largely lateralized to the right hemisphere and includes area TPJ as well as ventral frontal cortex. Enhanced activation of this system is observed in functional imaging studies when subjects are cued to expect a target at one location but it unexpectedly appears at another in the Posner spatial cueing paradigm (Macaluso, Frith, & Driver, 2002; Arrington, Carr, Mayer, & Rao, 2000; Corbetta, Kincade, Ollinger, McAvoy, & Shulman, 2000), in the presence of distracters that share the critical features with the target stimulus (Serences et al., 2005), in target detection when the objective is embedded among other stimuli (Serences et al., 2005; Downar, Crawley, Mikulis, & Davis, 2000, 2001), or in active execution of voluntary search-related visual orienting and exploration (Himmelbach, Erb, & Karnath, 2006; Nobre, Sebestyen, Gitelman, Frith, & Mesulam, 2002; Hopfinger, Buonocore, & Mangun, 2000).

On this background, it seems reasonable that a lesion or dysfunction due to malperfusion of right TPJ area may evoke disturbed detection of distinct events in a stimulus-driven fashion as it is typical for visual extinction. Extinction has been hypothesized to be the result of biased competitive interactions between the ipsilesional and contralesional sensory input (Desimone, 1998; Duncan, 1998; Duncan, Humphreys, & Ward, 1997; Desimone & Duncan, 1995). The idea is that although the brain can process many stimuli simultaneously, ultimately, only one action can be performed at a time. This leads to a selection process where the multiple sensory inputs compete for selective attention. When a stimulus loses the competition for attention, it is not available for consciousness. In extinction patients, unilateral damage to an area of the brain involved with target detection thus might bias this competition by weakening the mental representation associated with the contralesional input, leading to a failure to gain access to selective attention under competitive conditions. This weakened representation would then still be able to gain access to selective attention when presented in isolation (Duncan, 1998; Duncan et al., 1997; Desimone & Duncan, 1995).

In healthy volunteers, processes of spatial attention act in a supramodal context (Macaluso et al., 2002; Driver & Spence, 1998). For the ventral attention system, neuroimaging studies have shown the involvement of area TPJ and IFG in processing salient multimodal visual, tactile, and auditory events (Corbetta & Shulman, 2002; Downar et al., 2000). In correspondence with these findings, the unsuccessful perception of contralesional events in patients with extinction may affect more than only the visual modality (Hillis et al., 2006; Karnath et al., 2003; Stone, Halligan, & Greenwood, 1993). Likewise, our present data indicate an involvement of area TPJ in processing stimuli from different modalities. Five out of eight (62.5%) of our extinction patients had concurrent visual and tactile extinction, and six out of eight (75%) had concurrent visual and auditory extinction. A previous study by Hillis et al. (2006) revealed multimodal extinction, that is, visual and tactile extinction (the authors did not test for auditory extinction), in 23% of their right-hemisphere stroke patients. In this group, visual extinction was associated with dysfunction, that is, with structural or perfusion abnormalities, in right visual association cortex (right Brodmann's area [BA] 19). Tactile extinction was associated with dysfunction in right inferior parietal lobule, including angular and supramarginal gyri (BA 39/40). The combination of visual and tactile extinction was strongly associated with diffusion and/or perfusion abnormalities in both BA 19 and BA 39/40.

Surprisingly, Hillis and coworkers found visual extinction correlated neither with a dysfunctional TPJ nor with any of the deep brain areas reported in previous studies (Manes, Paradiso, Springer, Lamberty, & Robinson, 1999; Vallar et al., 1994). A possible explanation for this discrepancy could be related to the time between imaging, clinical examination, and stroke onset. Hillis et al. (2006) included stroke patients that underwent MRI within 24 hr postonset, whereas Vallar et al. (1994) examined patients up to 30 days post-stroke, Manes et al. (1999) between 4 and 8 weeks after stroke, and Karnath et al. (2003) between 3 and 9 days post-stroke on average. Hillis et al. speculated that patients with small strokes may have initially showed extinction and neglect but recovered in the first few days after stroke, whereas patients with larger lesions may have failed to recover, thus giving a preference toward an association of visual extinction with larger lesions covering also TPJ. The present study cannot clarify this issue. The present patients could not be examined within 24 hr after stroke onset; imaging and clinical examination were performed 4.5 and 4.9 days post-stroke on average.

To conclude, previous studies have suggested that (real/virtual) lesions centering on the cortical area TPJ (Grandjean et al., 2008; Meister et al., 2006; Karnath et al., 2003) or subcortical lesions of basal ganglia, thalamus, internal capsule, and periventricular white matter (Vallar et al., 1994), as well as insula (Manes et al., 1999) may provoke left-sided extinction. The present data suggest that a subcortical lesion of right basal ganglia may not determine

left-sided visual extinction per se. When we compared patients with right basal ganglia lesions showing versus not showing visual extinction, we observed in the extinction patients cortical malperfusion that clustered around right TPJ. Thus, it appears as if malfunction of this area is a critical aspect in visual extinction not only after cortical lesion but also in the case of subcortical basal ganglia damage. Our results support the idea that a normally functioning TPJ area plays a decisive role for the attentional network involved in detecting of visual stimuli under conditions of competition.

Acknowledgments

This work was supported by the Bundesministerium für Bildung und Forschung (BMBF-Verbund 01GW0641 "Räumliche Orientierung"), the Deutsche Forschungsgemeinschaft (SFB 550-A4), and the European Union (PERACT-Marie Curie Early Stage Training MEST-CT-2004-504321). We thank the team from the Section of Neuropsychology at the Center of Neurology in Tübingen for their help with data acquisition and clinical testing.

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