BRAIN COMMUNICATIONS

The anatomy of spatial neglect after posterior cerebral artery stroke

Christoph Sperber,[1] Jacob Clausen,[1] Thomas Benke[2] and Hans-Otto Karnath[1,3]

Spatial neglect is a common consequence of stroke in the territory of the right middle cerebral artery. Damage to a perisylvian fronto-temporo-parietal network has been demonstrated to underlie this disorder. Less common, stroke to the posterior cerebral artery territory may also lead to spatial neglect. This study aimed to uncover the anatomical underpinnings of spatial neglect after posterior cerebral artery infarction. A sample of 50 posterior cerebral artery infarct patients was screened for spatial neglect. Neural correlates of neglect were investigated both with voxel-based lesion behaviour mapping and with region-of-interest analyses. Brain damage neither to the splenium, nor to the parahippocampal gyrus, nor to the thalamus was predictive of spatial neglect. Only damage to the perisylvian fronto-temporo-parietal network of spatial neglect was significantly associated with neglect severity. We conclude that both posterior and middle cerebral artery stroke induce spatial neglect after damage to the same perisylvian brain network. The findings contradict previous theories that postulated neural correlates of spatial neglect specifically supplied by the posterior cerebral artery. In posterior cerebral artery stroke patients, affected parts of this network are located at the border zone between the posterior and middle cerebral artery territories. Inter-individual variability in the localization of the border between both artery territories appears to mediate the occurrence of spatial neglect after posterior cerebral artery stroke.

1 Division of Neuropsychology, Hertie-Institute for Clinical Brain Research, Centre of Neurology, University of Tübingen, 72076 Tübingen, Germany
2 Department of Neurology, Medical University Innsbruck, A - 6020 Innsbruck, Austria
3 Department of Psychology, University of South Carolina, Columbia, SC 29208, USA

Correspondence to: Christoph Sperber, PhD
Centre of Neurology, University of Tübingen, 72076
Tübingen, Germany
E-mail: christoph.sperber@klinikum.uni-tuebingen.de

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Abbreviations: CoC = centre of cancellation; MCA = middle cerebral artery; PCA = posterior cerebral artery; ROI = region-of-interest

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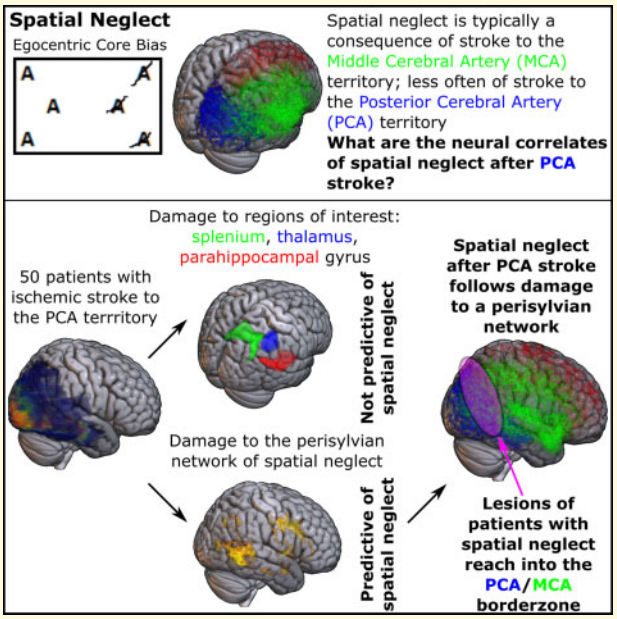
Graphical Abstract



Introduction

One typical sign of acute right hemisphere stroke is spatial neglect. Patients with this deficit consistently deviate towards the ipsilesional side and neglect stimuli on the contralesional side (Heilman *et al.*, 1987; Karnath and Rorden, 2012). The neural correlates of this disorder have been subject of various studies, revealing mostly anatomical correlates in the middle cerebral artery (MCA) territory. It has been suggested that these structures form a perisylvian fronto-temporo-parietal network involved in spatial orienting and neglect (Karnath, 2009), a theory recently supported by using machine learning-based multivariate lesion-behaviour mapping (Wiesen *et al.*, 2019).

Spatial neglect has also occasionally been reported after damage to the posterior cerebral artery (PCA) territory (Vallar and Perani, 1986; Cals *et al.*, 2002; Mort *et al.*, 2003; Bird *et al.*, 2006; Park *et al.*, 2006). Cals and colleagues examined 117 patients with PCA stroke and reported that most patients with spatial neglect presented damage that reached into temporal or parietal lobes, i.e. into regions well known to be associated with spatial neglect after MCA stroke. In contrast to this study, other groups concluded that specific structures within the PCA territory are associated with neglect. Mort *et al.* (2003) found that the inferior medial temporal lobe, and especially the parahippocampal gyrus, was associated with spatial neglect. Bird *et al.* (2006) found critical areas in the posterior white matter. They also investigated the role of damage to the thalamus, a region known to be a critical for spatial neglect (Watson *et al.*, 1981; Karnath *et al.*, 2002). However, this analysis did not yield any positive findings. A further study by Park *et al.* (2006) highlighted the role of splenial damage for the occurrence of spatial neglect after PCA lesions, which was further supported by studies based on tractography (Umarova *et al.*, 2014; Lunven *et al.*, 2015) and single cases (Tomaiuolo *et al.*, 2010).

In the light of these controversial findings, this study aimed to re-address the question of the neural correlates of spatial neglect after PCA stroke. In particular, we aimed to investigate if its neural correlates constitute an anatomical entity separate from the known perisylvian fronto-temporo-parietal network or if spatial neglect after PCA stroke follows damage to the same network.

Materials and methods

Patient recruitment

Patients admitted to the Centres of Neurology at Tübingen University Hospital or at the Medical University Innsbruck with a first unilateral right, acute ischaemic stroke in the territory of the PCA were recruited. Diagnosis was confirmed by either MRI or CT; only patients with clearly demarcated lesions were included. We recruited 50 patients without regard to presence of spatial neglect (see Table 1 for demographics). The study was approved by the local ethical committee and all patients provided written consent to participate in our study.

Neuropsychological examination

Spatial neglect was assessed with different cancellation tasks: letter cancellation (Weintraub and Mesulam, 1985), bells cancellation (Gauthier *et al.*, 1989), star cancellation

Table 1 Demographic data

	All patients	Neglect present	No neglect
Number	$N = 50$	$N = 8$	$N = 42$
Age (years)	64.7 ± 13.8	67.4 ± 9.3	64.1 ± 14.6
Sex (f/m)	14/36	3/5	11/31
Time since stroke (d)	2.1 ± 3.2	3.8 ± 5.7	1.9 ± 2.8
Visual field defect (yes/no/unknown)	38/5/7	7/1/0	31/4/7
Lesion type (C/CC)	36/14	5/3	31/11
Lesion size (cm^2)	31.5 ± 24.9	63.6 ± 32.9	25.4 ± 17.8

Demographic data for all patients, as well as for patients diagnosed with spatial neglect versus patients without spatial neglect. For descriptive information about the constitution of our sample, we determined whether the mean CoC score was or was not in the pathological range; cut-offs were set at >0.082 (Rorden and Karnath, 2010). Data are represented as mean and standard deviation. In seven patients, the method to assess visual field defects was not sufficient to provide a definite diagnosis or data were missing; these are listed as 'unknown'. Lesion type was visually classified into cortical (C) and cortical + central/choroidal (CC) PCA stroke. Lesion type and presence of neglect were not associated [χ^2 (1, $N = 50$) = 0.426, $P = 0.67$].

(Halligan *et al.*, 1991) and the Ota task (Ota *et al.*, 2001). All tasks were administered as paper and pencil tests on 21.0 cm × 29.7 cm sheets, horizontally placed and centred on the patient's sagittal midline. No time limit was set and tests were administered until the patient confirmed completion. Letter, bells and star cancellation consist of target and distractor items randomly placed on the sheet. The patient's task was to mark all targets (either letter 'A', or black solid objects in the shape of bells or stars). The Ota task consists of circles that are either closed or open on the left or the right side. Patients were instructed to mark closed circles by crossing them out and open circles by encircling them. To establish comparability of the outcome from the Ota task with the other three cancellation tasks, only marked items versus missed items were compared. Fifteen patients were tested on the star cancellation and Ota tasks, while 35 patients were tested on letter and bells cancellation. For each test performance, we calculated the Centre of Cancellation (CoC; Rorden and Karnath, 2010) and computed an averaged CoC per subject. This continuous score is 0 if targets are marked perfectly symmetrical, and ranges up to −1 for maximal neglect of items on the right. Visual field defects were assessed using the conventional neurological confrontation method or a PC-based visual field screening (Zimmermann and Fimm, 2009).

Imaging and lesion mapping

Structural scans were acquired on average 2.1 ± 3.2 days after stroke onset by either MR ($n = 20$) or CT ($n = 30$) imaging. If both imaging modalities were available, MR was preferred. For subjects with MR available, we used diffusion-weighted imaging if scans were acquired up to 48 h after stroke onset, and T_2 fluid attenuated inversion recovery imaging afterwards. Lesions were semi-automatically delineated on axial slices of the MR or CT scans using the algorithm provided by the Clusterize Toolbox (De Haan *et al.*, 2015). Scans were then warped into 1 mm × 1 mm × 1 mm resolution MNI space with the Clinical Toolbox (Rorden *et al.*, 2012), which normalizes scans of lesioned brains using default SPM algorithms (www.fil.ion.ucl.ac.uk/spm, last accessed 24 September 2020) and age-specific brain templates for both MR and CT. If available, MR scans were co-registered with high-resolution T_1 images for normalization.

Lesion analysis and statistical analysis

Voxel-based lesion-behaviour mapping of the averaged CoC score was performed using *t*-test statistics implemented in NPM software (Rorden *et al.*, 2007). Correction for multiple comparisons was carried out using voxel-wise permutation thresholding, which is considered an optimal solution to thresholding (Karnath *et al.*, 2018), with 4000 permutations at $P < 0.05$. Only voxels affected in at least five patients were tested.

In addition to the hypothesis-free, voxel-wise analysis, we performed hypothesis-driven region-of-interest (ROI) analyses to investigate the possible role of specific regions. A first analysis identified for each normalized lesion the overlap with those brain regions that had been associated with spatial neglect after PCA stroke in previous studies (see the Introduction section). The following ROIs were tested: (i) the splenium of the corpus callosum, as defined by the JHU ICBM DTI atlas (Mori *et al.*, 2008), (ii) the parahippocampal gyrus, as defined by the Automatic Anatomical Labelling atlas (Tzourio-Mazoyer *et al.*, 2002) and (iii) the thalamus, as defined by the Automatic Anatomical Labelling atlas.

A second ROI analysis addressed the question if spatial neglect after PCA stroke can be explained by damage to the known perisylvian network associated with spatial neglect after stroke in the MCA territory, or if it constitutes a separate anatomical entity. The ROI was defined by consulting a recently published topography of spatial neglect using multivariate lesion behaviour mapping (Wiesen *et al.*, 2019). This study, however, included 18 patients that were also part of this study. We thus recomputed the multivariate lesion behaviour mapping analysis by Wiesen and co-workers by excluding these 18 patients. In short, CoC scores of 185 right brain damaged patients were mapped by multivariate

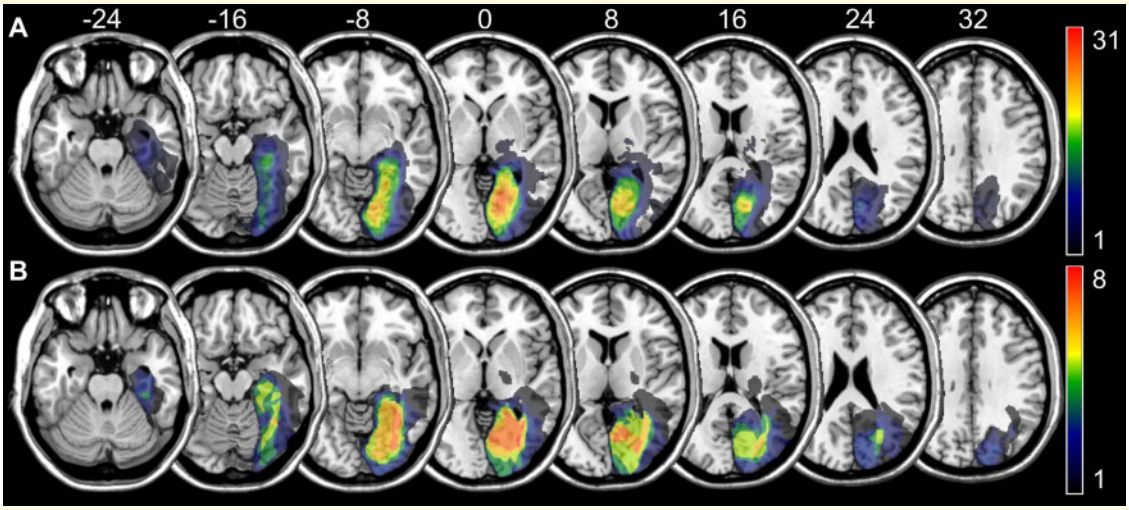


Figure 1 Overlap topographies of lesions. Simple lesion overlap topographies of (**A**) 42 patients without spatial neglect and (**B**) eight patients with spatial neglect after PCA territory stroke. Colour-coding depicts the number of overlaying lesions per voxel. Numbers above slices indicate *Z*-coordinates in MNI space; the right in depicted images is the right hemisphere of patients.

lesion-behaviour mapping based on support vector regression. Hyperparameters $C = 30$ and $\gamma = 4$ were chosen to compute a model using an epsilon-support vector regression with non-linear radial basis function kernel. Final thresholding of the β-map was carried out by permutation testing with 4000 permutations and subsequent false discovery rate correction at $q = 0.05$. For more details, see other studies (Zhang *et al.*, 2014; Sperber *et al.*, 2018; Wiesen *et al.*, 2019). The resulting map for this study (Fig. 1C) only marginally differed from the map reported by Wiesen *et al.*; exclusion of 18 subjects did not markedly affect the anatomy of spatial neglect as identified by multivariate lesion behaviour mapping. Again, large significant clusters covered posterior parts of temporal and parietal lobe, reaching into the border areas between posterior and MCA.

All ROI analyses were performed using MATLAB 2017 and IBM SPSS Statistics 25. Due to skewed data and uneven groups, statistical comparisons were performed using non-parametric, two-tailed Mann–Whitney tests at $P < 0.05$. Data for regression analyses were de-skewed by log-transformation. Note that regression analyses were additionally conducted with non-de-skewed data, and both regression analyses and group comparisons were additionally conducted with one neglect patient removed, who was an outlier in regards to time between stroke and behavioural assessment. Results in these additional analyses did not differ from the analyses presented in the paper (see online materials at http://dx.doi.org/10.17632/zrg3c45h2j.2, last accessed 24/09/2020). References to grey matter regions in the data interpretation were made according to the Automatic Anatomical Labelling atlas (Tzourio-Mazoyer *et al.*, 2002) and to white matter regions with a tractography-based fibre tract atlas (Mori *et al.*, 2008). Probabilistic maps of the fibre tract atlas were thresholded at $P \geq 0.3$ to obtain binary maps.

Data availability statement

All topographies and data underlying the main analyses, including results of additional analyses, are publicly available at Mendeley data (http://dx.doi.org/10.17632/zrg3c45h2j.2). The datasets generated and analyzed during this study are protected by the data protection agreement of the Center of Neurology at Tübingen University, as approved by the local ethics committee and signed by the participants. The agreement covers data storage for 10 years at the Centre of Neurology at Tübingen University. They are available from H.-O.K. and T. B., as well as the local ethics committee (ethik.kommission@med.uni-tuebingen.de) on reasonable request.

Results

We identified eight patients with spatial neglect after infarction of the PCA territory, equivalent to 16.0% of the total sample (see Supplementary Table 1 for additional demographic data). They showed mild to severe neglect and suffered from larger lesions than subjects without spatial neglect ($U = 49$, $P < 0.01$). Topographies of all lesions are depicted in Fig. 1.

Voxel-based whole-brain analysis

Statistical voxel-wise lesion behaviour mapping in all 93 949 voxels affected in at least 5 patients identified 20 voxels significantly associated with spatial neglect (see online materials at http://dx.doi.org/10.17632/zrg3c45h2j.2

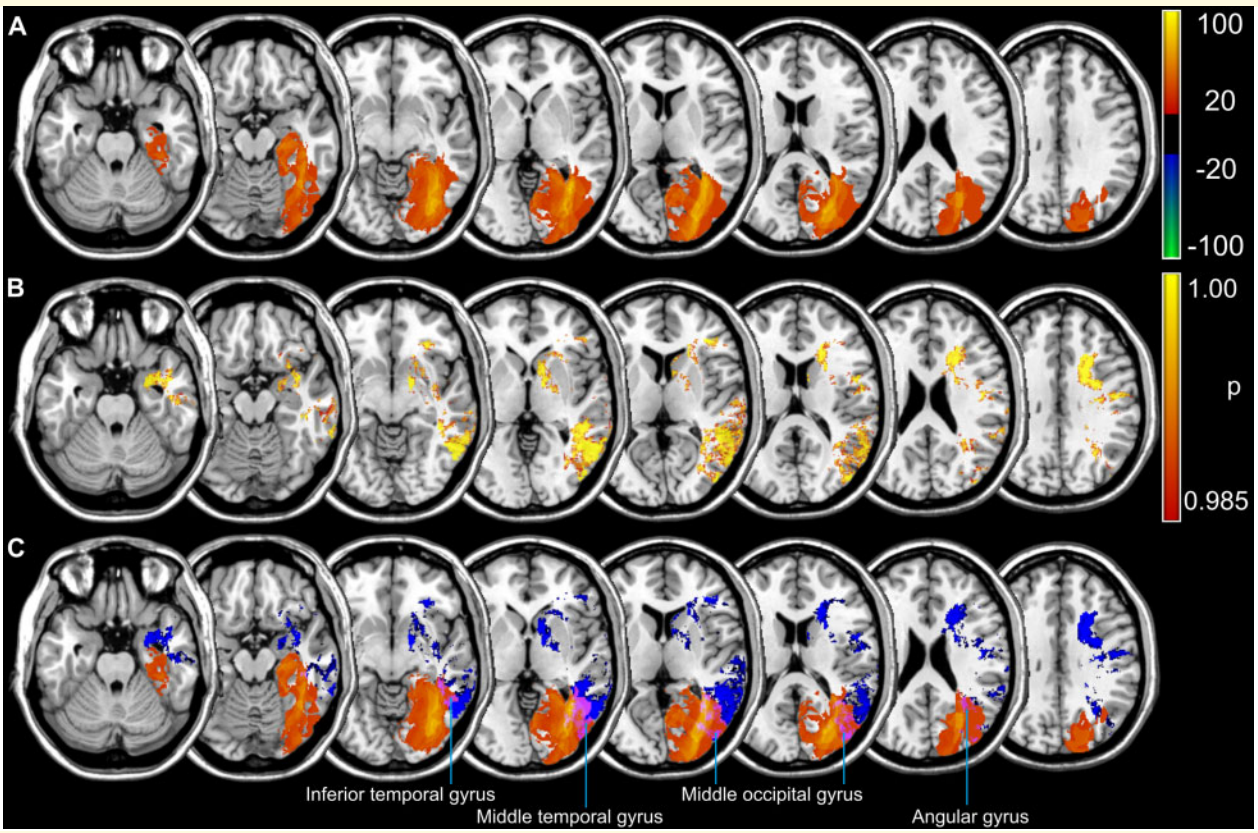


Figure 2 Relationship between spatial neglect after PCA stroke and the perisylvian network of spatial neglect. (**A**) Lesion subtraction plot contrasting areas more frequently damaged in PCA stroke patients with versus without spatial neglect (red–yellow). In this plot, a value of e.g. 20 reflects that the voxel is damaged 20% more frequently in patients with neglect than in patients without neglect (for more details on the method see Rorden and Karnath, 2004). Note that negative values were rare and no voxel below −20% is visible on slices depicted in the figure. (**B**) Voxel-wise multivariate lesion behaviour mapping in a sub-sample of 185 right brain damaged patients with and without spatial neglect from a Wiesen *et al.* (2019). All these subjects were not part of this study. The topography is thresholded at a false discovery rate correction at $q = 0.05$, equivalent to $P < 0.0152$. Results did not reveal notable differences to the perisylvian network of spatial neglect from this previous study. (**C**) Subtraction plot as in **A**, overlapped with the topography of the perisylvian network of spatial neglect (blue; data as in **B**).

for the full topography). These voxels were located in the middle occipital gyrus, yet the small cluster size effectively provided non-interpretable results. For comparison with previous studies, we also computed a lesion subtraction plot. On a descriptive level, it highlights those voxels more frequently affected in patients with spatial neglect than in patients without neglect (Fig. 2A). Peak voxels (probability ≥50%) in this plot were located in posterior white matter, fusiform gyrus, inferior and middle occipital gyrus, inferior and middle temporal gyrus and parahippocampal gyrus.

ROI analysis: candidate regions in the PCA territory found in previous studies

The volumetric overlap between individual PCA lesions and ROIs was statistically compared between patients with spatial neglect versus patients without spatial neglect. We found no significant differences for the splenium (Neg+ mean = 0.8 cm^2; Neg− mean = 0.5 cm^2; U = 125.5, P = 0.26), the parahippocampal gyrus (Neg+ mean = 2.1 cm^2; Neg− mean = 1.1 cm^2; U = 94.5, P = 0.05) or the thalamus (Neg+ mean = 0.1 cm^2; Neg− mean = 0.1 cm^2; U = 163.5, P = 0.91). Next, we applied simple linear regression to investigate if the overlap could predict spatial neglect (i.e. mean CoC scores as the continuous dependent variable). Neither damage to the splenium [$F(1,49)$ = 0.194; P = 0.66], nor to the parahippocampal gyrus [$F(1,49)$ = 0.98; P = 0.33], nor to the thalamus [$F(1,49)$ = 0.014; P = 0.91] was predictive of spatial neglect.

ROI analysis: right perisylvian fronto-temporo-parietal network of spatial neglect

Figure 2B illustrates the perisylvian network topography revealed by re-computing a previous multivariate lesion

behaviour mapping analysis (Wiesen *et al.*, 2019) but with 18 patients excluded (see Materials and methods section). All nine patients with spatial neglect demonstrated an overlap between the individual PCA lesion and the perisylvian network topography thresholded at false discovery rate $q = 0.05$, equal to $P < 0.0152$; the volumetric overlap varied between 0.4 and 20.5 cm^2. This overlap was significantly larger in patients with spatial neglect than in patients without spatial neglect (Neg+ mean = 4.7 cm^2; Neg− mean = 0.4 cm^2; $U = 36$, $P < 0.001$). Furthermore, simple linear regression to predict spatial neglect (i.e. mean CoC scores as the continuous dependent variable) based on the overlap was significant [$F(1,49) = 8.45$; $P < 0.01$; $\beta = 0.39$; $R^2 = 0.15$].

In Fig. 2C, the perisylvian network map is related to the lesion subtraction plot highlighting those voxels more frequently affected in patients with versus without spatial neglect after PCA stroke. Grey matter areas where the multivariate lesion behaviour mapping topography overlapped were found in inferior and middle temporal gyrus, middle occipital gyrus and angular gyrus. However, the largest overlap was found in white matter areas. These included the superior longitudinal fascicle and the inferior fronto-occipital fascicle.

Discussion

We investigated a sample of 50 patients with PCA infarction to determine the neural correlates of spatial neglect after PCA stroke. Hypothesis-free voxel-based lesion behaviour mapping revealed no areas significantly associated with spatial neglect. The ROI analysis offered more statistical power. Interestingly, brain damage to PCA territory regions-of-interest defined in reference to previous studies did not yield significant results. Neither damage to the splenium, nor to the parahippocampal gyrus, nor to the thalamus was predictive of spatial neglect in PCA stroke. In contrast, patients with spatial neglect after PCA stroke demonstrated a significantly larger overlap with the right perisylvian network found to underlie spatial neglect (Wiesen *et al.*, 2019). The network comprises superior/middle temporal, inferior parietal and ventrolateral frontal cortices, as well as long white matter association fibres connecting these regions. The structures where the lesions of our PCA neglect patients more frequently overlapped with this network than those of the PCA patients without neglect were grey matter areas in the middle and inferior temporal gyri as well as the inferior fronto-occipital fascicle and the superior longitudinal fascicle in white matter. Spatial neglect after PCA stroke thus appears to be due to damage to the same network observed with spatial neglect after MCA stroke.

The area of overlap in our PCA neglect patients affected the perisylvian network at its most caudal parts, namely those parts located at the border zone between MCA and the PCA territories. This border zone shows a high inter-individual variability (van der Zwan *et al.*, 1993; Phan *et al.*, 2007; Tatu *et al.* 2012) and different variants of PCA vasculature exist (Shaban *et al.*, 2013). For example, parts of middle temporal cortex and inferior parietal lobule can be supplied by either of the two territories (Tatu *et al.*, 2012). The reason that PCA stroke damages the perisylvian network only in some patients (and thus causes spatial neglect) while it does not in other PCA stroke patients may be rooted in this inter-individual variability in the localization of MCA and PCA territories.

The question remains what may have led to different results between the present analysis and previous studies that have reported anatomical correlates of neglect in PCA stroke patients outside of the perisylvian fronto-temporo-parietal network of spatial neglect (cf. Karnath, 2009; Karnath and Rorden, 2012; Wiesen *et al.*, 2019). As introduced above, two previous studies applied lesion subtraction analysis on small PCA stroke patient samples (Mort *et al.*, 2003; Bird *et al.*, 2006). In correspondence with the study by Mort *et al.* (2003) the lesion subtraction plot in this study also found a few voxels in the parahippocampal gyrus more frequently affected in PCA patients with versus without neglect. Using similar methods, Bird *et al.* (2006) investigated eight subjects with spatial neglect and found critical areas in the posterior white matter, similar to this study. In an additional diffusion tensor imaging analysis, they revealed that a fibre tract connecting parahippocampal gyrus and angular gyrus runs through the critical white matter areas, and thus might be relevant for spatial neglect. However, lesion subtraction analyses only provide a descriptive anatomical analysis, lacking statistical inference. When specifically tested in a ROI analysis, the present analysis did not confirm a crucial role of the parahippocampal gyrus in spatial neglect. Park *et al.* (2006) investigated a group of 45 PCA stroke patients, including 26 patients showing signs of spatial neglect, by visually inspecting the scans. They found that only damage to both the splenium of the corpus callosum and the occipital lobe induced spatial neglect. This study did not observe evidence for such an association. Several possible reasons for this discrepancy exist. First, Park and colleagues only qualitatively assessed lesion sites and additionally separated splenial lesions into 'complete' and 'incomplete' lesions. Contrary, this study objectively assessed brain damage in normalized lesion masks obtained from high-resolution clinical imaging. Second, Park *et al.* (2006), as well as several other previous studies on spatial neglect after PCA stroke (Mort *et al.*, 2003; Bird *et al.*, 2006; Park *et al.*, 2006; Tomaiuolo *et al.*, 2010), assessed spatial neglect with multiple different clinical tests, including the line bisection task. This measure dissociates from the egocentric bias in spatial neglect as assessed by cancellation tasks both behaviourally (Binder *et al.*, 1992; Ferber and Karnath, 2001; Sperber and Karnath, 2016; McIntosh *et al.*, 2017) and anatomically (Binder *et al.*,

1992; Rorden *et al.*, 2006; Verdon *et al.*, 2010). Thus, previous studies might have found specific critical areas in the PCA territory that are not necessarily related to the egocentric bias in spatial neglect, as investigated in this study.

The latter question can also be understood as a limitation of the present investigation. This study investigated the pathological egocentric bias of neurological patients after right hemisphere stroke. Neurologists often diagnose this deficit instinctively in acute stroke with neurological signs such as ignoring contralesional stimuli, and spontaneous and sustained ipsilesional deviation of eye and head position (Karnath and Rorden, 2012). Corbetta and Shulman (2011) and Karnath and Rorden (2012) defined these symptoms as so-called 'core symptoms' of spatial neglect. Instead, other scientists defined 'neglect' as a heterogeneous and multifactorial disorder (Halligan *et al.*, 2003; Verdon *et al.*, 2010), measurable by a multitude of behavioural tasks including cancellation tasks, line bisection, reading tasks and more. Based on such a multifactorial definition of 'neglect', the investigated behaviour might represent several dissociating deficits of spatial attention and orientation at once (Verdon *et al.*, 2010; Sperber and Karnath, 2016). How these deficits relate to the egocentric core symptoms of spatial neglect is still under discussion (Corbetta and Shulman, 2011; Karnath and Rorden, 2012; Yue *et al.*, 2012; McIntosh *et al.*, 2017; Turgut *et al.*, 2017). While this study argues that the egocentric core deficit of spatial neglect is not associated with damage to areas specifically damaged by stroke to the PCA, this might still be the case for the other deficits, i.e. deficits beyond the 'core deficits' as defined by Corbetta and Shulman (2011) and Karnath and Rorden (2012). For example, defective line bisection has been shown to be associated with damage to brain areas located more posteriorly than the commonly assumed neural correlates of the egocentric core symptom of spatial neglect (Binder *et al.*, 1992; Rorden *et al.*, 2006; Verdon *et al.*, 2010). Thus, it can be the case that the conclusions of this study do not apply to neurological patients selected on the basis of defective line bisection [if not measured as described by McIntosh *et al.* (2017)].

Conclusion and perspective

The results of this study argue that both PCA and MCA stroke can induce spatial neglect after damage to the same perisylvian brain network. Contrary to previous studies, these results argue that there are no neural correlates of spatial neglect specifically supplied by the PCA. Clinical neurologists should be aware that spatial neglect may be caused by stroke to parts of the perisylvian network, which follows ischaemia in the PCA borderline territory. This finding may be particularly important when attempts are made to differentiate hemianopia from neglect, and also in the rehabilitation setting because both syndromes differ grossly as to their treatment approaches.

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Supplementary material

Supplementary material is available at *Brain Communications* online.

Competing interests

The authors report no competing interests.

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