Functional topography of early periventricular brain lesions in relation to cytoarchitectonic probabilistic maps

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Abstract

Early periventricular brain lesions can not only cause cerebral palsy, but can also induce a reorganization of language. Here, we asked whether these different functional consequences can be attributed to topographically distinct portions of the periventricular white matter damage. Eight patients with pre- and perinatally acquired left-sided periventricular brain lesions underwent focal transcranial magnetic stimulation to assess the integrity of cortico-spinal hand motor projections, and functional MRI to determine the hemispheric organization of language production. MRI lesion-symptom mapping revealed that two distinct portions of the periventricular lesions were critically involved in the disruption of cortico-spinal hand motor projections on the one hand and in the induction of language reorganization into the contra-lesional right hemisphere on the other hand. Both regions are located in a position compatible with the course of cortico-spinal/cortico-nuclear projections of the primary motor cortex in the periventricular white matter, as determined by the stereotaxic probabilistic cytoarchitectonic atlas developed by the Jülich group.

1. Introduction

Periventricular brain lesions are among the most frequent causes for cerebral palsy (Ashwal et al., 2004). This type of lesion typically occurs during the early 3rd trimester of pregnancy, either as intrauterine insults or as complications of premature birth (Krägeloh-Mann, 2004; Staudt et al., 2004). The motor dysfunction of patients with such lesions is commonly believed to result from structural damage to cortico-spinal projections in the periventricular white matter (Banker & Larroche, 1962). Indeed, several transcranial magnetic stimulation (TMS) studies could show that in patients with large unilateral periventricular lesions, TMS of the affected hemisphere did not elicit motor responses in target muscles of the (contralateral) paretic hand, indicating that the lesion had disrupted the normal crossed cortico-spinal projections from the affected hemisphere (Carr, Harrison, Evans, & Stephens, 1993; Maegaki et al., 1997; Nezu, Kimura, Takeshita, & Tanaka, 1999; Staudt et al., 2002a).

Periventricular lesions, however, do not only affect the motor system, but can—in the case of left-sided lesions—also induce a reorganization of productive language functions into the contralesional, right hemisphere (Carr, Harrison, Evans, & Stephens, 1993; Maegaki et al., 1997; Nezu, Kimura, Takeshita, & Tanaka, 1999; Staudt et al., 2002a). Right-hemispheric language organization induced by early left-sided brain lesions typically achieves normal language functions (Table 1; Muter, Taylor, & Vargha-Khadem, 1997; Staudt et al., 2002b), but can compromise right-hemispheric functions such as visuo-spatial abilities (Lidzba, Staudt, Wilke, & Krägeloh-Mann, 2006). To observe right-hemispheric organization in our...
patients with periventricular lesions was unexpected insofar as these lesions typically leave cortical language zones—at least macroscopically—intact. As a possible explanation for this phenomenon, we suggested that structural damage to facial motor projections of the left hemisphere, with their well-known relevance for articulation (Wildgruber, Ackermann, Klose, Kardatzki, & Grodd, 1996), might induce this reorganization of language.

In the current study, we addressed this issue by asking whether specific, topographically distinct locations of periventricular lesions are critical for (a) the disruption of hand motor projections of the cortico-spinal tract and (b) the induction of language reorganization. We did this by taking advantage of previously collected and published data on this well-described sample of patients (Staudt et al., 2001, 2002a).

2. Materials and methods

2.1. Subjects

Eight patients (4 women; age range, 17–25 years) with congenital right hemiparesis due to left-sided periventricular brain lesions were included (Table 1). Informed written consent and approval from the local ethics committee were obtained.

In a previous study (Staudt et al., 2002a), seven of these patients had undergone focal TMS to determine whether the affected hemisphere still possessed crossed cortico-spinal projections to the paretic hand. Four patients showed preserved crossed projections to the paretic hand, three did not. No TMS data were available for patient #4 (Table 1); the subject thus was excluded from the analysis on cortico-spinal projections (see below).

In a further study (Staudt et al., 2001), all but one patient (#8) from the current sample were examined with respect to right- and left-hemisphere activation during speech by functional MRI during silent word generation: The subjects were instructed to silently generate word chains, the first word starting with a letter given by the examiner, the next word starting with the last letter of the previous word, and so on. The procedure, which was applied in an identical manner in patient #8, is described in detail in Staudt et al. (2001). The lateralization of language production in this group of patients was found to be highly variable (Table 1)—in contrast to healthy right-handed controls, who showed a consistent and strong leftward asymmetry of activation. Due to the overall sample size, we dichotomized the patient group into those presenting a higher number of fMRI activated voxels in the left versus the right hemisphere (L > R; n = 3), and those with a higher number in the right versus the left hemisphere (R > L; n = 5; Table 1).

2.2. Lesion analysis

The brain lesions of the patients were demonstrated by structural MRI (Fig. 1). Anatomical 3D data sets were
obtained on a 1.5 Tesla Siemens Vision system (MPRAGE, 128 contiguous sagittal slices, TR [repetition time] = 9.7 ms, TI [inversion time] = 300 ms, TE [echo time] = 4 ms, voxel size 1 x 1 x 1.5 mm³). Mapping of lesions was carried out by one experimenter without knowledge of test results and clinical features of the patients. The boundary of the lesion (including periventricular white matter loss and ventricular enlargement) was delineated manually on every single transversal slice of the individual MRI using MRicro software (Rorden & Brett, 2000) (http://www.mricro.com). Periventricular white matter loss was determined by delineating the enlarged portion of the left ventricle through direct comparison with the unaffected right ventricle shape on the same transversal slice. Both the scan and lesion shape were then transformed into stereotaxic space using the spatial normalisation algorithm provided by SPM2 (http://www.fil.ion.ucl.ac.uk/spm/), using default settings. For determination of the transformation parameters, cost-function masking was employed (Brett, Leff, Rorden, & Ashburner, 2001). None of the patients showed a midline shift, neither before nor after normalisation (Fig. 1).

To investigate whether topographically different portions of a periventricular lesion are responsible for a disruption of cortico-spinal hand motor projections and for the reorganization of language into the contra-lesional right hemisphere, we classified the patients into different groups and performed group contrasts using lesion subtraction analysis (Rorden & Karnath, 2004). To identify the white matter structures that are commonly damaged in patients who develop language representation predominantly in the right hemisphere but are typically spared in those with language representation predominantly in the left hemisphere, a first contrast was performed. We subtracted the superimposed lesions of those patients with predominant left hemisphere language representation (L > R) (Fig. 2A, 2nd row) from the overlap images of those with predominant language representation in the right hemisphere (R > L) (Fig. 2A, 1st row). Moreover, to identify the white matter structures that are commonly damaged in patients with disrupted crossed cortico-spinal projections to the paretic hand but are typically spared in patients with preserved hand motor projections, in a second contrast we subtracted the patients with preserved cortico-spinal hand motor projections (Fig. 2A, 4th row) from the patients with disrupted cortico-spinal projections (Fig. 2A, 3rd row). For both contrasts, an arbitrarily chosen threshold of 70% difference between groups was applied to define voxels that are “critically involved”, so that all voxels were marked with Groups A and B being either patients with disrupted (A) versus preserved (B) hand motor projections, or with predominantly right-hemispheric (A) versus predominantly left-hemispheric (B) language activation.

In our sample, this meant that, for the language contrast, all voxels were marked in which a lesion was present in 4/5 (80%) or 5/5 (100%) patients with right-hemispheric language organization (Group A), but in 0/3 (0%) of the patients with predominantly left-hemispheric language activation (Group B)—resulting in suprathreshold differences of (80% - 0% = 80%) or (100% - 0% = 100%), respectively. For the hand motor contrast, all voxels were marked in which a lesion was present in 3/3 patients (100%) with disrupted hand motor projections (Group A'), but in 0/4 (0%) or only 1/4 patients (25%) with preserved hand motor projections (Group B')—resulting in suprathreshold differences of (100% - 0% = 100%) or (100% - 25% = 75%), respectively (Fig. 2B).

To identify the anatomical relation of the affected white matter structures to the anatomical position of cortico-spinal/cortico-nuclear projections1 originating in the primary motor cortex, we here used the new strategy of lesion analysis suggested by Papageorgiou and co-workers (in press). These authors combined established lesion subtraction techniques with the stereotaxic probabilistic cytoarchitectonic atlas, the latter developed by the Jülich group (Amunts & Zilles, 2001). In Fig. 3, we thus plotted the resulting subtraction images onto the stereotaxic probabilistic cytoarchitectonic map of the cortico-spinal/cortico-nuclear tract by Bürgel et al. (2006). This map illustrates the relative frequency with which the cortico-spinal/cortico-nuclear tract of ten normal human brains was present on a MNI reference brain in a voxel (e.g., a 50% value of the cortico-spinal tract in a certain voxel of the reference brain indicates that the fiber tract was present in that voxel in five out of ten brains). The probabilistic cytoarchitectonic map thus serves as a measure of intersubject variability for each voxel of the reference space.

3. Results

We found the two centers of overlap in the white matter close to the left ventricle and clearly separated (Fig. 2). Plotting these centers onto the Jülich stereotaxic probabilistic cytoarchitectonic map revealed that both centers clearly affected the cortico-spinal/cortico-nuclear projection (Fig. 3). The area typically damaged in patients with disrupted cortico-spinal projections to the paretic hand (red area in Fig. 2B; pink contour in Fig. 3) extended from

Number of patients in Group A with voxel lesioned

\[ \text{Total number of patients in Group A} - \text{Number of patients in Group B with voxel lesioned} \]

\[ \text{Total number of patients in Group B} > 70\% \]

1 In the paper by Bürgel and coworkers (Bürgel et al, 2006), all descending projections originating from primary motor cortex (M1) were identified as “cortico-spinal” projections. This nomenclature is somewhat misleading, since the approach these authors used also labelled motor projections from the M1 face representation (K. Amunts, personal communication). Since these fibers do not project to the spinal cord, but to the facial nerve nuclei, we used the term “cortico-spinal/cortico-nuclear tract” to refer to this structure.
MNI coordinates \((x, y, z)\) over \((-21; -23; 31)\) to \((-20; -17; 35)\). In contrast, the white matter structure that was commonly damaged in patients who developed language representation predominantly in

Fig. 1. Coronal reconstructions of the normalized 3D data sets depicting the extent of the lesion in each individual patient. MNI y-coordinates of the coronal sections are given.
the contralesional right hemisphere (green area in Fig. 2B; white contour in Fig. 3) was located more inferiorly (z-direction) and more anteriorly (y-direction). The area extended from MNI coordinates \((x, -18; y, -22; z, 21)\) over \((x, -17; y, -18; z, 21)\) and \((x, -18; y, -13; z, 22)\) to \((x, -8; y, -4; z, 16)\).

Neither of the reverse contrasts, i.e., the contrast searching for brain areas typically damaged in patients with...
preserved cortico-spinal hand motor tracts but not in patients with disrupted tracts, nor the contrast searching for brain areas typically damaged in patients with predominantly left-hemispheric language but not in patients with predominantly right-hemispheric language yielded any voxels fulfilling this condition.

4. Discussion

Our present analysis revealed that topographically separate locations of early left periventricular brain lesions are critical for the disruption of cortico-spinal hand motor projections and for the induction of language reorganization in the contralesional right hemisphere.

The congruency of the critical region for the integrity or disruption of hand motor projections with cytoarchitectonic probabilistic maps of the cortico-spinal tract suggest that the cortico-spinal system had already been established at the time of the insult (the early 3rd trimester of pregnancy; Krägeloh-Mann, 2004). This is consistent with observations by Eyre and colleagues (2000), who reported that, in the human fetus, outgrowing cortico-spinal projections have already reached their spinal target zones at the beginning of the 3rd trimester of pregnancy. In contrast, in the somatosensory system, we could recently demonstrate that outgrowing thalamo-cortical somatosensory projections can bypass a periventricular lesion along alternative routes, so that the new position of such pathways is no longer compatible with predictions from “adult” anatomy (Staudt et al., 2006).

The white matter locus critically involved in inducing reorganization of language production in the contralesional right hemisphere is—at least partially—also located in the course of motor projections originating in the primary motor cortex, as determined from the present analysis combining lesion subtraction techniques with the Jülich stereotaxic probabilistic cytoarchitectonic atlas. Furthermore, this region is located anterior and inferior to the region critically involved in the integrity or disruption of hand motor projections, which is compatible with the position of facial motor projections relative to hand motor projections in the periventricular white matter: According to the homuncular organization of the primary motor cortex (Fig. 2b, left), the face is represented inferior and, due to the oblique course of the precentral gyrus, also anterior to the hand. In addition, in the somatotopic organization of the internal capsule, the facial motor projections pass through the genu and, thus, again anterior to the hand motor projections passing through the posterior limb. Together, these findings corroborate our previously published hypothesis (Staudt et al., 2001) that structural damage to facial motor projections plays an important role in inducing right-hemispheric language organization in such patients. This hypothesis is also in accordance with recent reports on a relevance of speech-related cortical motor areas already during the early phases of normal language development during the first year of life (Imada et al, 2006).

One could further confirm this finding by testing the integrity or disruption of facial motor tracts in such patients using TMS. We refrained, however, from performing such measurements in our patients, since TMS of the face motor region often implies painful stimulation of temporal muscles. Future research on periventricular lesions might also include diffusion tensor imaging, to further enhance our understanding of the functional consequences of such lesions on specific white matter tracts.

The observations of this study should not be mistaken as claiming that damage to facial motor projections is the
only possible mechanism responsible for right-hemispheric organization of language in patients with left-sided periventricular lesions. Especially in the patients with larger lesions, it is quite evident that other white matter structures involved in language processing (e.g., the arcuate fasciculus) as well as subcortical grey matter structures such as the basal ganglia are at least partially damaged; furthermore, the periventricular lesions might also have had a negative influence on the microanatomical integrity of cortical language areas, even if this was not evident on structural MRI. Finally, all our patients were left-handed (most likely due to their right-sided hemiparesis), so that a potential influence of this “pathological left-handedness” on the organization of language cannot be excluded either.

In conclusion, this study demonstrates that different functional consequences of early periventricular brain lesions can be attributed to topographically distinct loci of the white matter damage.

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