Review

(Re-)organization of the developing human brain following periventricular white matter lesions

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Abstract

Unilateral periventricular brain lesions served as a model for the investigation of (re-)organization following insults to the developing human brain. In both the motor and the language systems (re-)organization was observed in the contra-lesional hemisphere. In the motor system, the contra-lesional hemisphere can develop (or maintain) ipsilateral cortico-spinal projections to the paretic hand; in the language system, left-sided lesions can induce (re-)organization of speech production in the right hemisphere. This interhemispheric (re-)organization can achieve normal language functions, whereas the hand contra-lateral to the lesion always remains markedly impaired. Despite these functional differences, the two systems share common principles concerning their reorganizational mechanisms:

1. Interhemispheric (re-)organization always occurred in areas homotopic to the “original” areas in the affected hemisphere, (2) the degree of interhemispheric (re-)organization correlated with structural damage to hand or facial motor tracts, and (3) afferent functions (the somatosensory hand representation, the perception of speech) did not follow their efferent counterparts (the motor hand representation, and the production of speech), but remained in the affected hemisphere.

Keywords: Early periventricular brain lesions; Cerebral palsy; Reorganization; Developmental plasticity; Congenital hemiparesis; Language; Sensorimotor

1. Introduction

The developing central nervous system (CNS) possesses greater capacities of post-lesional compensation than the mature adult brain. This observation is known as the “Kennard principle”, referring to a study of motor outcome following experimental lesions to the motor cortex of monkeys at different ages (Kennard, 1936).

In the human brain, this principle has first been confirmed clinically, concerning both motor and language functions: Gardner et al., 1955 reported that hemispherectomies in patients suffering from a hemiparesis due to a brain lesion acquired before or around birth (“congenital hemiparesis”) seldomly led to a deterioration in hand motor functions, whereas hemispherectomies performed in patients without such pre-existing early lesions (e.g. for brain tumors...
abolished active motor functions of the contra-lateral hand almost completely. This difference indicates that, in the patients with congenital hemiparesis, the initial “developmental” lesion had induced a (re-)organization of hand motor functions into the contra-lesional hemisphere, whereas this was no longer possible in the adult brain. In the language domain, the reorganizational potential of the developing brain is even more obvious. Children with pre-or perinatally acquired left-hemispheric lesions can reach normal levels of language abilities even in cases with extensive brain damage (Muter et al., 1997).

With the advent of modern neurophysiological and neuroimaging techniques, it has become possible to study the mechanisms by which this compensation is achieved. In the language domain, patients with early left-hemispheric lesions have repeatedly been reported to show an increased participation of brain areas in the contra-lesional right hemisphere during various language tasks (Booth et al., 1999; Hertz-Pannier et al., 1997; Lehe´ricy et al., 2000; Liegeois et al., 2004). In the sensorimotor domain, children with extensive unilateral early brain lesions but relatively preserved hand functions consistently showed evidence for ipsilateral, fast-conducting cortico-spinal pathways allowing the contra-lesional hemisphere to exert motor control over the paretic hand (Benecke et al., 1991; Carr et al., 1993; Eyre et al., 2001; Farmer et al., 1991; Jang et al., 2001; Kastrup et al., 2000; Macdonell et al., 1999; Maegaki et al., 1997; Nezu et al., 1999; Nirkko et al., 1997; Shimizu et al., 2000; Staudt et al., 2002a, 2004a, b; Thickbroom et al., 2001; Vandermeeren et al., 2003). This type of cortico-spinal reorganization is possible throughout the pre- and perinatal period, and even during the first months of life; it has, however, never been reported for lesions acquired after the age of 2 years (Maegaki et al., 1997), or for adult hemiparetic stroke (Cramer and Bastings, 2000; Turton et al., 1996). Such pathways, however, do not develop in all patients with congenital hemiparesis, and even those in which such pathways had developed still show a broad range of residual hand functions (Staudt et al., 2004a).

This variability in the types and efficacies of CNS (re-)organization following early lesions has been attributed to several factors influencing the process of (re-)organization. Important factors are the extent and location of the lesion, the presence or absence of epilepsy, and the maturational stage of the CNS at the time when the insult occurred (Carr et al., 1993; Maegaki et al., 1997; Müller et al., 1997; Nezu et al., 1999; Thickbroom et al., 2001; Woods and Teuber, 1978). In addition to its likely influence on (re-)organization, the maturational stage of the brain at the time of the insult also determines the type of structural pathology, with a certain but not prominent overlap between the lesion types and the timing periods (Evrard, 2001; Krägeloh-Mann, 2004; Uvebrant, 1988; Volpe, 1995; Fig. 1).

Adverse events occurring during the period of cerebral morphogenesis and neuronal migration (i.e., the 1st and 2nd trimester of pregnancy) typically result in brain malformations, whereas insults acquired beyond this period (i.e., during the 3rd trimester of pregnancy) typically lead to gliotic and/or cystic defects. Such defects can be further subdivided into those affecting the periventricular white matter (e.g., periventricular leukomalacia or periventricular hemorrhages), which originate mainly during the “early” 3rd trimester, and those affecting mostly gray matter structures (e.g., cortico-subcortical infarctions, parasagittal “watershed” lesions, or basal ganglia/thalamic lesions), which originate mainly during the “late” 3rd trimester of pregnancy or perinatally.

For a number of reasons, periventricular lesions are an ideal model for a systematic investigation of the mechanisms of CNS (re-)organization in the developing human brain. First, periventricular lesions are known to arise during a narrowly defined period of brain development of 24–36 weeks of gestation. Second, these lesions do not cause direct cortical damage. This facilitates the data analysis during functional imaging experiments; in addition, absence of cortical damage often also means absence of epilepsy. And third, due to the vulnerability of long descending projections, especially of cortico-spinal motor tracts, in the periventricular white matter, such lesions often imply a well-defined structural damage to these fiber tracts. This facilitates the investigation of relationships between their structural properties and their consequences, both in terms of impairment and of the (re-)organization induced.

The purpose of this article is to review and summarize our previous publications on (re-)organization after periventricular brain lesions, with studies covering the sensorimotor system (Staudt et al., 2000, 2002a, 2003, 2006) as well as the language system (Staudt et al., 2001a, 2002b), and to compare the obtained results between the two domains.

Note: Whether lesions to a developing CNS induce actual “reorganization” (i.e., changes of an already existing organization), or whether they primarily cause abnormalities of organization can often not be decided. Therefore, the term “reorganization” might often be inappropriate in
patients with developmental lesions. In order to express this uncertainty, the term (re-)organization is used.

2. (Re-)organization in the sensorimotor system

The first topic we addressed in the sensorimotor system was the relationship between the topography (e.g., location and extent) of periventricular lesions and the resulting impairment of motor functions.

We hypothesized that motor impairment in patients with periventricular lesions is caused, at least in part, by compromising descending cortico-spinal motor tracts in the periventricular white matter (Banker and Larroche, 1962). To test this hypothesis, a technique was developed to quantify the severity of structural damage to cortico-spinal pathways in the periventricular white matter (Staudt et al., 2000). This technique makes use of anatomical landmarks of pyramidal tract somatotopy to reconstruct semi-coronal planes from 3D MRI data sets.

For the upper extremity semi-coronal plane, the “hand-knob” (Yousry et al., 1997) with its characteristic omega or epsilon shape on axial images is sought in the central sulcus. On the corresponding sagittal images, the lateral part of this knob looks like a hook with its tip pointing backwards into the central sulcus; the central sulcus in the depth of this hook was used as the upper landmark. According to the somatotopic organization in the internal capsule, the second landmark was the anterior third of the posterior limb of the internal capsule. For the lower extremity semi-coronal plane, the very top of the central sulcus was used as the upper landmark. The second landmark was again determined in the internal capsule, now in the middle of the posterior limb. On the basis of these landmarks, the relevance of a periventricular lesion for upper and lower limb cortico-spinal projections can be assessed and quantified by measuring its lateral extent.

Both for patients with unilateral and with bilateral periventricular lesions, we found that this lateral extent of the lesion correlated significantly with the impairment of upper and lower limb motor dysfunction (Staudt et al., 2000, 2003). This result confirmed our initial hypothesis. Motor impairment in patients with periventricular lesions is—at least in part—related to structural damage to cortico-spinal (“pyramidal”) motor projections in the periventricular white matter.

In the next step, we validated this approach using focal transcranial magnetic stimulation (TMS), the “golden standard” for the identification of cortico-spinal pathways: When TMS elicits short-latency motor-evoked potentials (MEP) in a target muscle, this demonstrates that mono-synaptic fast-conducting cortico-spinal fibers to the motoneurones of this target muscle originate from the stimulation site. Thus, the stimulated cortical area is identified as the primary motor representation (M1) of this muscle. The usefulness of this technique in the investigation of patients with congenital hemiparesis has repeatedly been demonstrated, both for the documentation of the integrity or disruption of crossed cortico-spinal pathways and for the detection of ipsilateral pathways originating from the contra-lesional hemisphere (Benecke et al., 1991; Carr et al., 1993; Eyre et al., 2001; Farmer et al., 1991; Jang et al., 2001; Kastrup et al., 2000; Macdonell et al., 1999; Maegaki et al., 1997; Nezu et al., 1999; Nirkko et al., 1997; Shimizu et al., 2000; Staudt et al., 2002a, 2004a,b; Thickbroom et al., 2001; Vandermeeren et al., 2003).

We detected a strikingly clear relationship between the lateral extent of the periventricular lesion determined on semi-coronal MRI planes (see above) and not only the aspect of disruption versus integrity but also that of the reorganization of cortico-spinal hand motor projections (Staudt et al., 2002a; Fig. 2): All patients with “small lesions” (SL) showed preserved contra-lateral cortico-spinal projections to the paretic hand, whereas such contra-lateral projections were absent in the patients with “large lesions” (LL). Instead, all these patients with LL possessed fast-conducting ipsilateral cortico-spinal pathways originating in the contra-lesional hemisphere. Two patients in the overlapping zone (“intermediate”) showed both types of projections (Staudt et al., 2002a). Thus, three groups of patients could be identified, according to the type of cortico-spinal organization: group SL with only contra-lateral projections, group LL with only ipsilateral projections, and a small “intermediate group” showing both contra- and ipsilateral projections.

In order to visualize cortical activation during movements of the paretic hand associated with these different types of cortico-spinal (re-)organization, we also performed fMRI experiments in these patients. Both in Group SL and Group LL, we detected an increased participation of the contra-lesional hemisphere. In group LL, the “hand-knob” area of the contra-lesional hemisphere was consistently activated, demonstrating that both hands shared a common cortical motor representation. In Group SL, the ipsilateral activation during paretic hand movement was typically located in multiple areas of the contra-lesional hemisphere. In a voxelwise group analysis (“random effects”; Friston et al., 1999), systematic topographical differences between the two groups were observed. Compared with activation of the ipsilateral hemisphere in healthy controls, the patients in Group LL showed

![Fig. 2. (Modified from Staudt et al., 2002a): schematic illustration of cortico-spinal tract (re-)organization in the three subgroups of patients (P = paretic hand). SL = “small lesion”, LL = “large lesion”. Reprinted with permission from Oxford University Press, Copyright (2002).]
significantly stronger activation in the ipsilateral “hand knob” area, whereas in Group SL, an area in the inferior precentral sulcus (corresponding to Brodmann area 6 = premotor cortex) was more strongly activated than in controls.

Both groups also showed activation in the affected (= contra-lateral) hemisphere during movements of the paretic hand, which was always located in the central (Rolandic) area. In Group SL, this activation corresponded to the unchanged primary motor (M1) representation of the paretic hand in the affected hemisphere, as determined by TMS. In Group LL, the functional relevance of this contra-lateral activation first remained unclear, since TMS detected no cortico-spinal pathways originating from these sites. To clarify the functional role of this contra-lateral activation in group LL, additional experiments focussing on the sensory representation of the paretic hand were performed. Here, we had in mind the hypothesis put forward by Thickbroom et al. (2001), suggesting that this contra-lateral activation of such patients might reflect sensory processing of the moving paretic hand. Indeed, the contra-lateral activation during active movements of the paretic hand in such patients could also be evoked during passive movements of the paretic hand, and magnetoencephalography (MEG) demonstrated that the first cortical response to a tactile stimulation of the paretic thumb was located in the Rolandic cortex of the affected hemisphere, with a normal latency of approximately 20 ms. This demonstrates that the primary somatosensory representation (S1) of the paretic hand was preserved in its original topography in the Rolandic region of the affected hemisphere, which means that afferent thalamo-cortical somatosensory projections had apparently “bypassed” the lesion to reach their original cortical destination area in the postcentral gyrus. Such axonal “bypasses” of somatosensory afferent projections could be directly visualized using MR diffusion tensor tractography (Fig. 3).

Functionally, these patients display a “hemispheric dissociation” between a (contra-laterally preserved) primary somatosensory (S1) and an (ipsilaterally reorganized) primary motor (M1) representation of the paretic hand. This dissociation easily explains the bilateral activation during active movements of the paretic hand, with motor commands being generated in the ipsilateral (contra-lesional) hemisphere, and sensory feedback from the moving hand being processed in the contra-lateral (affected) hemisphere.

3. (Re-)organization of language

The (re-)organization of language functions was studied only in patients with left-sided lesions, since in patients with right-sided lesions, no interhemispheric shift of language functions was to be expected.

During fMRI of speech production (silent generation of word chains), all patients showed an increased participation of their contra-lesional (right) hemisphere, as compared with healthy right-handed controls. This indicated that, despite the absence of structural damage to cortical language areas (e.g., Broca’s area), the periventricular lesions had induced an interhemispheric (re-)organization of language functions—without affecting the quality of language abilities, as documented by normal verbal IQs in these patients (Staudt et al., 2001a, 2002b).

Since the degree of right-hemispheric participation in speech production correlated significantly with the severity of structural damage to facial motor projections (assessed with a technique equivalent to that described for upper and lower extremity projections; Staudt et al., 2000), we concluded that an impairment of speech motor output from the left hemisphere had contributed to induce this interhemispheric “shift” of productive language functions (Staudt et al., 2001a). Accordingly, no such shift was observed for the activation during perception of speech (as assessed using a story-listening task)—a function which does not depend on motor output. Thus, the patients with large left-hemispheric lesions showing a predominantly right-hemispheric activation during speech production display a hemispheric dissociation between a (left hemispherically preserved) perception and a (right hemispherically reorganized) production of speech. This parallels the findings in the sensorimotor system, where
such patients also showed a hemispheric dissociation between a (contra-laterally preserved) “perception” and an (ipsilaterally reorganized) “production” of paretic hand movements.

Finally, patients with a predominantly right-hemispheric activation during speech production were used to investigate the topography of right-hemispheric language organization as a consequence of early left-sided brain damage. These patients with left periventricular lesions present an ideal model for this question, because (a) cortical structures are (at least macroscopically) intact, which facilitates the processing of fMRI data, (b) none of them showed epilepsies (as an additional confounding factor), and (c) their cognitive functions were intact.

When the patients’ right-hemispheric activation patterns during speech production were compared with the left-hemispheric activation patterns of healthy right-handed controls, no significant difference was detected for the topographies of activation (Fig. 4). Thus, when an early left-sided brain lesion induces right-hemispheric organization of speech, areas homotopic to the original left-hemispheric language zones are recruited for the processing of language (Staudt et al., 2002b).

In summary, these studies on language organization in patients with left-sided periventricular lesions demonstrated that right-hemispheric organization of language occurs (a) even in the absence of direct cortical damage, (b) maybe as a consequence of structural damage to facial motor tracts, and (c) in areas homotopic to the “original” language zones in the left hemisphere.

4. Discussion

Unilateral periventricular brain lesions served as a model for the investigation of cortical and cortico-spinal (re-)organization following insults to the developing human brain. Since both sensorimotor and language functions were studied, we can now look at the similarities of and the differences between these two domains, concerning the potential and limitations of (re-)organization after early lesions.

The limitations of (re-)organization after early lesions are quite apparent in the motor system: First, even small periventricular lesions in a “strategic” position can cause major hand motor dysfunction, and this dysfunction can be predicted using normal anatomical landmarks of pyramidal tract somatotopy. This argues against the possibility for an effective “peri-lesional” reorganization of this function. And second, although all patients with group LL possessed ipsilateral cortico-spinal projections allowing the contra-lesional hemisphere to exert motor control over the paretic hand, this type of cortico-spinal (re-)organization never achieved a really good hand function (with well-preserved individual finger movements). This contrasts strongly with the superior efficacy of (re-)organization in the language system, in which all patients, even those with maximum extent of their left-sided periventricular lesion, showed normal verbal IQ scores. This observation is in accordance with a bulk of clinical experience describing the phenomenon of impaired motor versus intact cognitive functions in many children with early unilateral brain lesions (Cioni et al., 1999).

But despite the apparent differences in the efficacy of (re-)organization between the two systems, striking parallels concerning the mechanisms involved were detected. In both systems, major (re-)organization was observed for the “productive” aspects (i.e., for the motor representation of the paretic hand, and for the production of speech). This (re-)organization consisted always of a take over of functions by the contra-lesional hemisphere, and it occurred always in cortical areas homotopic to the areas harboring the respective functions in the healthy brain. Thus, in our data, no evidence for non-homotopic (re-)organization was observed, neither in the affected hemisphere (“peri-lesional”), nor in the contra-lesional hemisphere.

In addition, in both systems, no interhemispheric (re-)organization was observed for the perceptive aspects (i.e., for the somatosensory representation of the paretic hand and for the perception of speech). Thus, the patients with large lesions showed hemispheric dissociations between (interhemispherically reorganized) motor/productive functions in the contra-lesional hemisphere and (preserved) sensory/perceptive functions in the affected hemisphere. This phenomenon might indicate a general difference in the (re-)organizational properties of afferent versus efferent functions in the developing human brain, which could be related to different time tables of maturation between afferent versus efferent projections: At the beginning of the 3rd trimester of pregnancy, cortico-spinal motor projections have already reached their spinal target areas (Eyre et al., 2000); thus, these pathways will be directly damaged by a large periventricular lesion. In contrast, thalamo-cortical projections have not yet been fully established (Kostovic and Judas, 2002), so that afferent pathways can still show...
adaptive changes in response to a periventricular lesion—as demonstrated by the detection of “axonal bypasses” in our study (Staudt et al., 2006).

The maturational stage of the CNS determines not only which mechanisms are available for post-lesional reorganization, but also influences the efficacy of these mechanisms. This was shown for reorganization with ipsilateral corticospinal pathways. The earlier during development a unilateral lesion occurred (1st and 2nd trimester versus early 3rd trimester versus late 3rd trimester), the better was the motor function of the paretic hand depending on such ipsilateral tracts (Staudt et al., 2004a). Thus, it is tempting to speculate that the exact timing of the lesion might also be relevant for the efficacy of reorganization within the group of patients with periventricular lesions, and maybe not only concerning motor functions, but also concerning the quality of somatosensory functions mediated by “axonal bypasses” as described above. Unfortunately, this question cannot be answered with the cohort of the studies reviewed here, since most of our patients were born at term after apparently uneventful pregnancies, so that no precise information as to the exact timing of their unnoticed intrauterine lesions could be obtained. This interesting topic can only be addressed in future studies recruiting patients in whom the exact time of the insult is known, either from prenatal imaging, or in pretermers with cerebral complications.

In conclusion, the studies reviewed here allowed detailed insights into the mechanisms involved in the (re-)organization of somatosensorimotor and language functions following lesions to the developing human brain. Such knowledge is necessary to develop and evaluate strategies of therapeutic intervention in children with early brain lesions. In addition, the methodologies and results of these studies contribute to improve the non-invasive “mapping” of cortical functions in individual children with early brain lesions when epilepsy surgery is considered for the relief of pharmaco-refractory seizures (Staudt et al., 2001b, 2004a).

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References


