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Early Determination of Somatosensory Cortex in the Human Brain

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The developing brain possesses a high potential for neuroplasticity. Yet, this remarkable potential of (re-)organization is not a general principle. It seems to vary among different functional systems. Here, we show that distinct brain structures involved in somatosensory processing are already prenatally determined so that a pre- or perinatally acquired (congenital) brain damage of such structures results in a persistent somatosensory deficit. Eleven patients with hemiparesis due to congenital cortico-subcortical unilateral stroke who showed versus not showed a somatosensory deficit were contrasted with magnetic resonance imaging lesion–behavior mapping. The brain areas which were typically damaged in patients with a somatosensory deficit but typically spared in patients without a somatosensory deficit were located in the primary and secondary somatosensory cortex (S1, S2) as well as the inferior parietal cortex directly neighboring S1 and S2. The results argue for an early functional determination of primary and secondary somatosensory cortex, without substantial capacities for (re-)organization. They demonstrate that cortical damage of these areas cannot be compensated by shifting the functional representation to undamaged parts of the cortex.

Keywords: brain development, human, plasticity, somatosensory cortex, stroke

Introduction

Early brain lesions often cause less severe functional deficits than similar lesions to the mature brain (Payne and Lomber 2001). If a lesion occurs before the topographical specificity for a respective brain function is fully determined, cortical representations can primarily develop in brain regions different to the usual adult topography. However, the availability of such compensational mechanisms as well as their efficacy varies with regard to the affected brain region or functional system (Krägeloh-Mann 2004).

For language functions, such mechanisms are of superior efficacy: Even children with extensive damage to the left hemisphere can acquire normal language proficiency (Eisele and Aram 1995). This is possible because homotopic areas of the right hemisphere are able to take over functions which originally would have developed in the left hemisphere (Staudt, Lidzba et al. 2002, 2008).

In the motor system, interhemispheric (re-)organization has also been demonstrated (Carr et al. 1993; Eyre et al. 2001; Staudt, Grodd, et al. 2002, 2004, 2008). In patients with severe unilateral lesions disrupting the corticospinal projections, normally transient ipsilateral projections from the fetal period can be maintained, connecting the precentral gyrus and central sulcus of the contralesional hemisphere with the paretic hand (Eyre et al. 2001). However, in such cases of motor system (re-)organization, hand function is always impaired, that is, mechanisms of (re-)organization are incomplete in terms of functional compensation (Staudt et al. 2004).

In contrast, in the somatosensory system, a bilateral organization of the spino-thalamo-cortical projections to the primary somatosensory cortex (S1) has never been observed, neither transitory during development nor in the mature brain, neither in humans nor in other mammals (except for the hedgehog; Regidor 1992). Thus, in the somatosensory system, a developmental ipsilateral "alternative" to the normal contralateral organization does apparently not exist so that the development of an ipsilateral S1 hand representation as a compensatory mechanism after early unilateral brain damage seems unlikely. Accordingly, in the literature, we did not find any clear evidence for an interhemispheric (re-)organization of S1 in children with early brain lesions. When electrical median nerve stimulation of the paretic hand was used to elicit somatosensory-evoked potentials (SEPs) in congenitally hemiparetic patients with extended lesions (Ragazzoni et al. 2002) or posthemispherectomy (Bernasconi et al. 2000; Holloway et al. 2000), all ipsilateral cortical responses showed prolonged latencies (39–65 ms) and abnormal topographies. This was interpreted as evidence for ipsilateral reorganization via non-lemniscal sensory fibers (Ragazzoni et al. 2002). Maegaki et al. (1995) reported on a child with a large unilateral malformation, in whom median nerve stimulation of the paretic hand evoked an atypically configured early cortical SEP in the contralateral (malformed) hemisphere and an additional early negative component (N20) in the contralesional hemisphere. The presence of the contralateral SEP in the malformation, although atypically configured, raised some doubt, however, whether their finding really indicated an ipsilateral S1 representation (Maegaki et al. 1995). When functional imaging techniques were applied in patients with congenital hemiparesis, tactile stimulation or passive movement of the paretic hand typically elicited ipsilateral cortical activation in nonprimary sensory areas, especially in the S2 region (Bernasconi et al. 2000; Bittar et al. 2000; Chu et al. 2000). Activation in the ipsilateral "rolandic" cortex during sensory stimulation has only been observed twice (Holloway et al. 2000; Janszky et al. 2003); nevertheless, SEPs were prolonged in one of these cases (Holloway et al. 2000), and no neurophysiological information concerning the latency was available in the other patient (Janszky et al. 2003). All these data indicate that mechanisms of cortical (re-)organization within the somatosensory system are

restricted compared with both language and motor system. The observed ipsilateral (re-)organization within the somatosensory system cannot be considered as (re-)organization of the primary somatosensory cortex (S1)—however, the detected (re-)organization within the ipsilateral hemisphere might contribute to a better functional outcome after unilateral brain damage as well, yet unclear to what extent.

Concerning intrahemispheric (re-)organization, Wilke et al. (2008) reported the topography of S1 to be slightly more variable in the lesioned compared with the contralesional hemisphere in patients with cortical lesions—therefore, the possibility of some degree of intrahemispheric (re-)organization of S1 can neither be excluded nor confirmed.

In contrast to the limited capacity for cortical (re-)organization in the somatosensory system, this system possesses an exceptional degree of "axonal plasticity" after early subcortical lesions: Ascending thalamocortical somatosensory projections possess the remarkable ability to bypass even large pre- and perinatally acquired white matter lesions in order to reach their original cortical destination in the postcentral gyrus (although other cortical areas would be much closer) (Staudt et al. 2006). These large "detours" already point to an early regional specification of the postcentral gyrus as the primary somatosensory cortex.

Taken together, these data suggest an early determination of the human somatosensory cortex, even before thalamocortical connections have been established.

Recently, animal research reported a similar observation of developing thalamocortical projections finding alternative routes to their original cortical destination (Little et al. 2009). In Sema6A mutant mice lacking the guidance molecule Semaphorin-6A, developing thalamocortical axons growing out from the visual part of the thalamus (the dorsal lateral geniculate nucleus) are initially misrouted in the ventral telencephalon. Nevertheless, these misrouted axons are able to find their way to the visual cortex via alternate routes and reestablish a normal pattern of thalamocortical connectivity.

Such results from both human and animal research argue for an early regional specialization that already exists before the ingrowth of specific thalamic afferents. Yet, there are other animal studies suggesting that specific thalamic input does indeed play a major role in cortical field generation. One impressive example is the observation that the removal of the caudal parts of the cortical neuroepithelial sheet unilaterally at an early stage of development in marsupials does not abolish cortical fields that normally reside in the removed cortex. Rather, in this reduced cortical sheet, normal spatial relationships between visual, somatosensory, and auditory cortical fields are established. This implies that cortical fields can apparently form in a new location on portions of the cortical sheet that would normally be occupied by a different sensory modality (Huffman et al. 1999).

Thus, 2 opposing hypothesis are currently under discussion-early regional specification on the one hand and specific thalamic afferent contribution determining cortical field development on the other hand.

As mentioned above, our previous data argue in favor of an early determination of the somatosensory cortex in the human brain. This would also explain the clinical observation that a somatosensory deficit can be pronounced in patients with cortical lesions, whereas even large white matter lesions often only result in a mild deficit (Wilke et al. 2008).

In order to test this hypothesis, we recruited a sample of patients with early cortical lesions, that is, pre- and perinatally acquired stroke of the middle cerebral artery (MCA), with and without a somatosensory deficit. According to our hypothesis, we expected 1) to be able to identify a "critical" cortical area, lesions of which would result in a somatosensory deficit and 2) this "critical" area to be located in the postcentral gyrus. If these 2 criteria were to be met, our hypothesis of an early determination of somatosensory cortex would be confirmed.

Subjects and Methods

Subjects

Eleven children and young adults (age range: 10–30 years; mean: 14.2 years; 6 females) with congenital hemiparesis due to a unilateral MCA stroke (late third trimester lesion; Krägeloh-Mann 2004) were recruited. MCA stroke usually occurs during the late third trimester of pregnancy or "perinatally" (Krägeloh-Mann 2004); however, determining the exact timing of the lesion was not possible in our patients as lesions were only diagnosed after appearance of clinical symptoms during the first months of life. The lesions seen in our patients were of variable extent—however, none of them involved the thalamus directly. All patients with evidence of bilateral pathology on magnetic resonance imaging (MRI), as well as patients with brain malformations or periventricular lesions, were excluded. Further exclusion criteria were mental retardation, pregnancy, epilepsy, or contraindications to MRI (including orthodontic braces). All patients had a preserved contralateral motor representation with crossed corticospinal projections from the affected hemisphere to target muscles of the paretic hand, as documented by focal transcranial magnetic stimulation.

Informed written consent and approval from the Ethik Kommission der Medizinischen Fakultät, Eberhardt-Karls-Universität, Tübingen, were obtained.

Clinical Characteristics

With regard to somatosensory functions, different tests were used: 1) touch perception sensitivity: sensory threshold was measured by Semmes–Weinstein monofilament diameter size (minimal size of a filament whose touch to the distal thumb phalanx palmarly could be perceived in 3 of 4 trials; the diameters provide a logarithmic scale of force exerted, and thus, a linear and interval scale of perceived intensity; Semmes–Weinstein Von Frey Monofilaments; Stoelting Co.); 2) two-point discrimination (2-pd: the minimal distance of 2 points of tactile stimulation which could not be distinguished (in mm)); 3) vibratory sense (the threshold for detecting vibration stemming from a standard tuning fork was assessed upon placing the tuning fork on the radial epicondylus [Pestronk et al. 2004]. Subjects had to report when they ceased to feel the vibration, measured on a scale from 0 to 8 as inscribed on the tuning fork. In this case, higher values therefore indicate a higher sensitivity to vibration and lower values indicate stronger impairment); and 4) sense of position (the minimal angle of passive thumb movement for whom the direction (flexion/extension) could not be perceived).

On the basis of performance on the "touch perception sensitivity test," the patient group was dichotomized in a group of patients with a clear somatosensory deficit (Group 2) and a group of patients with absent or mild somatosensory deficit (Group 1): In 4 patients (Group 1), touch perception sensitivity in the paretic hand was as good as in the nonparetic hand (quotient $\text{score}_{\text{nonparetic hand}}/\text{score}_{\text{paretic hand}} \geq 1$), whereas in the remaining 7 patients (Group 2), the touch perception sensitivity of the paretic hand was worse compared with their nonparetic hand (quotient $\text{score}_{\text{nonparetic hand}}/\text{score}_{\text{paretic hand}} < 0.8$).

With regard to motor function (classified as described in Staudt, Grodd, et al. 2002; Staudt et al. 2004), all subjects had at least a preserved grasp function (score 3) and some were even able to perform some independent finger movements (score 2) (see Table 1).

Table 1
Results of somatosensory tests

Patient		2-point-discrimination nonparetic	2-point-discrimination paretic	Vibratory sense nonparetic	Vibratory sense paretic	Sense of position nonparetic	Sense of position paretic	Touch perception sensitivity nonparetic	Touch perception sensitivity paretic	Motor dysfunction [0–4]
Group 1	1	0.5	0.5	6	2	3	3	2.8	2.8	2
	2	0.2	5.6	8	8	3	3	3.36	3.2	3
	3	0.7	2	8	8	3	3	2.36	2.36	3
	4	0.2	1.2	8	8	5	5	2.36	2.36	2
Group 2	5	0.15	2.5	8	8	3	3	3.22	4.17	2
	6	0.2	4.4	8	6	3	10	3.22	4.31	3
	7	0.1	8.5	8	4	3	3	3.22	4.46	2
	8	0.4	4.3	6	4	3	20	3.22	4.17	3
	9	0.5	6	8	4	5	10	2.44	3.22	2
	10	0.3	2.2	8	4	3	3	1.6	2.38	3
	11	4	3.5	8	6	3	10	2.83	4.56	2

Results of 4 different somatosensory tests for both the paretic and the nonparetic hand are displayed for each patient of "Group 1" (without somatosensory deficit) and "Group 2" (with somatosensory deficit). For 2-pd, sense of position and touch perception, higher values reflect stronger functional impairment. Only for vibratory sense, lower values reflect stronger functional impairment. In the right column, the motor score of each patient is indicated. For further details on the measurements, see Subjects and Methods.

Lesion Analysis

For each patient, a high-resolution whole-brain T_1-weighted anatomical volume was sagittally acquired on a 1.5T Siemens Avanto MR scanner using a 3D gradient echo protocol, with a flip angle of 15°, a time echo of 4.94 ms, and a time repetition of 11 ms. Each slice had a thickness of 1 mm with an in-plane resolution of 1 × 1 mm^2. Mapping of lesions was carried out without knowledge of test results and clinical features of the patients. The boundary of the lesion was manually delineated directly on the individual MRI image for every single transversal slice using MRIcron software (Rorden et al. 2007) (http://www.sph.sc.edu/comd/rorden/mricron/). All lesions were plotted onto the right hemisphere. Both the scan and lesion shape were then mapped into stereotaxic space using the spatial normalization algorithm provided by SPM5 (http://www.fil.ion.ucl.ac.uk/spm/). For determination of the transformation parameters, cost function masking was employed (Brett et al. 2001).

To identify the anatomical structures commonly damaged in patients with a somatosensory deficit but typically spared in patients without a somatosensory deficit, a subtraction analysis was performed (Rorden and Karnath 2004). Considering the low number of subjects that were available for this study, a conservative threshold of 60% was used, meaning those areas of the brain that were damaged at least 60% more frequently in patients with a somatosensory deficit than in patients without a somatosensory deficit were identified. The results of this analysis were anatomically interpreted with the aid of the stereotaxic probabilistic cytoarchitectonic atlas (Schleicher et al. 2000; Amunts and Zilles 2001), analogous to the approach described by Papageorgiou et al. (2008). This atlas illustrates the relative frequency with which a certain cytoarchitectonically defined area of 10 normal human brains was present on an MNI reference brain in a voxel (e.g., a 50% value of an area in a certain voxel of the reference brain indicates that the area was histologically present in that voxel in 5 of 10 postmortem brains). The probabilistic cytoarchitectonic atlas thus serves as a measure of intersubject variability for each voxel of the reference space.

Results

Lesion Analysis

Lesion overlap plots were calculated demonstrating the anatomical overlap of the individual normalized lesion images, one for the group of 7 patients with a somatosensory deficit and one for the group of 4 patients without a somatosensory deficit (Fig. 1). In order to identify the structures in which lesions were typically associated with the presence of a somatosensory deficit, but which were typically spared in those patients without such a deficit, we subtracted the lesion overlap plot of the group of patients without a somatosensory deficit from the lesion overlap plot of patients with this deficit. This subtraction analysis revealed 784 voxels that were typically damaged in patients with a somatosensory deficit and typically spared in patients without such a deficit (i.e., damaged at least 60% more frequently in the group of patients with a deficit than in the group without a deficit; Fig. 2). The voxels were located in the primary somatosensory cortex (S1), the secondary somatosensory cortex (S2), and the inferior parietal cortex (IPC). Since the stereotaxic probabilistic cytoarchitectonic atlas divides S1, S2, and IPC into several smaller overlapping subareas (Geyer et al. 1999, 2000; Grefkes et al. 2001; Caspers et al. 2006; Eickhoff et al. 2006), a weighted mean probabilistic map was calculated for these areas by dividing the sum of the probabilistic maps of the subareas by the map that describes the amount of overlap of these subareas per voxel. 47.96% of the subtraction analysis results could be assigned to S1, 34.06% to S2, and 96.94% to the IPC. The reason the sum of these percentage values was higher than 100% is that the probabilistic maps of S1, S2, and IPC partly overlap at their borders (see Fig. 2). In other words, a given voxel from

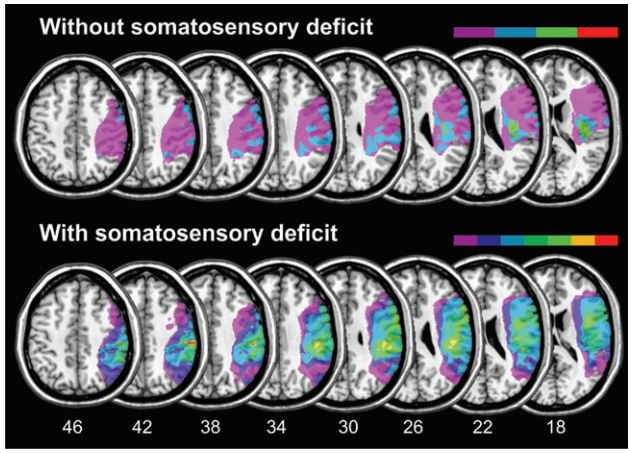

Figure 1. Lesion overlap plots: lesion overlap plots for the group of patients without a somatosensory deficit ($n = 4$) and the group of patients with a somatosensory deficit ($n = 7$). The number of overlapping lesions is illustrated by different colors, coding increasing frequencies from violet ($n = 1$) to red (n = max. number of subjects in the respective group). Montreal Neurological Institute z-coordinates of each transverse section are given.

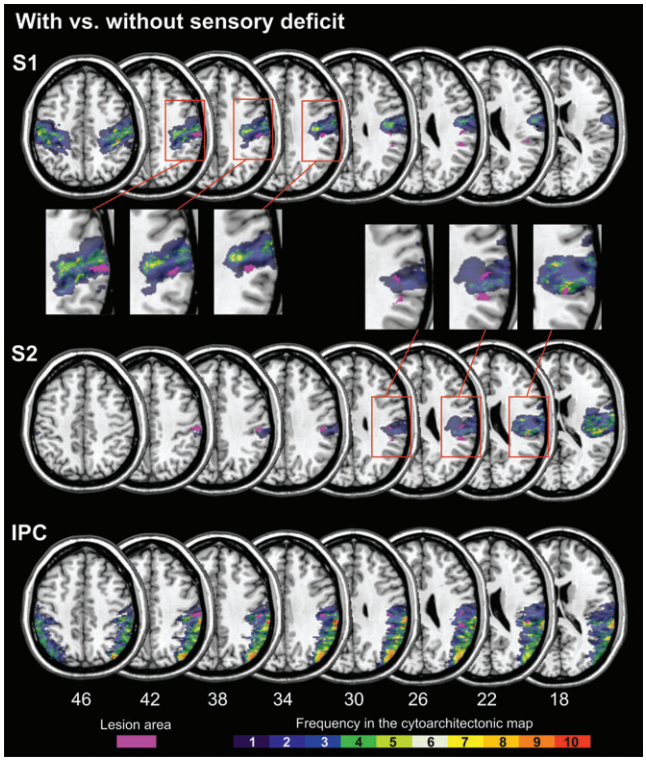

Figure 2. Lesion subtraction analysis: the results of the lesion subtraction analysis in relation to the weighted mean stereotaxic probabilistic cytoarchitectonic maps of the primary somatosensory cortex (S1, top row), the secondary somatosensory cortex (S2, middle row) and the IPC (bottom row). The color coding of the cytoarchitectonic map from 1 (dark blue, observed in 1 postmortem brain) to 10 (red, overlap in all 10 postmortem brains) represents the mean frequency for which in each voxel of the atlas the S1, S2, or IPC, respectively, was histologically present (e.g., yellow color in the top row indicates that the primary somatosensory cortex was on average present in that voxel in 7 of 10 postmortem brains). The pink outline represents the brain areas commonly damaged in patients with a somatosensory deficit and typically spared in patients without a somatosensory deficit. Montreal Neurological Institute *z*-coordinates of each transverse section are given.

the subtraction analysis results could be assigned to more than one area.

Discussion

In the present study, somatosensory deficits in patients with pre- or perinatally acquired (congenital) MCA stroke could be attributed to the involvement of distinct cortical areas. Thus, our hypothesis (a) about the existence of a common anatomical substrate for a somatosensory deficit in patients with early brain lesions could be confirmed. The present findings thus support the assumption of a limited potential for cortical plasticity within the somatosensory system: Lesions located in these areas can apparently not be compensated by cortical (re-)organization. Thus, our findings indicate an already early determination of such brain regions to somatosensory processing.

Concerning our hypothesis (b), the critical brain region uncovered in the present study could be assigned to the primary somatosensory cortex (S1, 48% of the subtraction analysis results), the secondary somatosensory cortex (S2, 34% of the subtraction analysis results), and the IPC (97% of the subtraction analysis results), directly neighboring S1 and S2. Thus, our findings corroborate also our hypothesis (b) that the "critical" cortical area affects the postcentral gyrus, and thus a region which is attributed to somatosensory processing in the adult brain.

The current findings contribute to a better understanding of clinical observations in patients with early brain lesions. Patients with cortical lesions to the postcentral gyrus show variable, however, often severe functional deficits. In contrast, in the case of subcortical lesions with a preserved postcentral gyrus, functional deficits are mostly absent or mild (Wilke et al. 2008). The latter can be explained by the observation that even large white matter lesions can be bypassed by developing thalamocortical axons, finally reaching an intact postcentral gyrus (Staudt et al. 2006). This exceptional degree of axonal plasticity and an undamaged somatosensory cortex are considered to be the precondition for the good functional outcome in this patient group (Staudt et al. 2006). With regard to patients with cortical lesions, the clinical observation of a variable and often severe functional deficit finds an explanation with the variable anatomy of underlying lesions, that is, the variable degree of involvement of S1/S2, which can be spared by the lesion or not. If these areas are lesioned, neighboring cortical areas within the lesioned hemisphere are apparently not capable to overtake somatosensory functions and thereby compensate a functional deficit. This is compatible with functional MRI studies in patients with early cortical and subcortical brain lesions, in which no evidence for "intrahemispheric (re-)organization," that is, a shift of activation toward adjacent cortical regions was found (Guzzetta et al. 2007; Wilke et al. 2008).

The results of this study also contribute to a more fundamental developmental neurobiological controversy about the mechanisms of regional specialization in the developing brain. Creutzfeldt et al. (1977) proposed that the developing cortex would initially lack region-specific differences and that only selective input from the thalamus would determine the formation of the different cytoarchitectonic areas. This so-called "tabula rasa" hypothesis was contrasted by Rakic (1988) with what he termed the "protomap hypothesis." In this theory, regional specialization of the cortex is determined genetically and develops independently from thalamic input so that outgrowing thalamic afferents are attracted in a region-specific manner. This "protomap hypothesis," which was substantiated by a number of genetic studies in experimental animal data, receives further support from our human lesion studies: In a previous study, we could demonstrate that, in the case of large periventricular white matter lesions, developing thalamocortical somatosensory projections take long and curved detours around the lesion to reach the postcentral gyrus (Staudt et al. 2006). This observation is not compatible with the tabula rasa hypothesis, according to which these outgrowing somatosensory axons could have induced the formation of primary somatosensory cortex in any cortical area; long and curved detours to reach the postcentral gyrus would not have been be necessary.

Such trajectories indeed strongly argue in favor of the existence of an intrinsic and specific attraction of these outgrowing somatosensory thalamic projections by the postcentral gyrus. Therefore, some regional specialization must have occurred before the advent of thalamic input—which contradicts the tabula rasa hypothesis. Our new data presented here can be understood as a consequence of this early functional determination: We demonstrate that cortical damage

to such areas with early specialization cannot be compensated simply by shifting the functional representation to undamaged parts of the cortex but results in a region-specific functional deficit. A potential topic for further research that could provide additional support for this conclusion would be the investigation of the connectivity of the lesioned and nonlesioned cortices in our patients with diffusion tensor imaging.

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Notes

Conflict of Interest : None declared.

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