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Cerebral and cerebellar language organization in a right-handed subject with a left temporal porencephalic cyst: An fMRI study

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ABSTRACT

To test the hypothesis of crossed cerebro-cerebellar language dominance (Mariën, Engelborghs, Fabbro, & De Deyn, 2001) in atypical populations, the pattern of cerebral and cerebellar language organization in a right-handed woman with a large porencephalic cyst in the left temporal lobe with no secondary clinical neurological symptoms was studied by means of an fMRI-language paradigm. Extensive neuropsychological examinations were performed to formally rule out cognitive dysfunctions. The fMRI task, consisting of a covert controlled oral word generation task, disclosed a pattern of bilateral activity in the frontal language areas, slightly more pronounced in the left hemisphere, and unilateral activation of the left inferior and superior temporal and supramarginal gyrus. This pattern of supratentorial activations was reflected at the infratentorial level by bilateral activations in the posterior lobe of the cerebellum with slightly more activity located in the right cerebellar hemisphere. This pattern of bilateral cerebral and cerebellar activation seems to confirm that the distribution of supratentorial language dominance is intrinsically reflected at the level of the cerebellum. Bilateral frontal language representation might be the consequence of neurofunctional compensation for the structural anomaly affecting eloquent brain regions resulting in an operational inefficiency of the neural network subserving language in the left hemisphere.

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1. Introduction

A number of recent clinical and neuroimaging studies has indicated that the typical patterns of unilateral cerebral language organization are reflected at the infratentorial level by a lateralized involvement of the cerebellum (Jansen et al., 2005; Price, 2000; Stoodley, Valera, & Schmahmann, 2010). In addition to the view that the speech centre of right-handers is located in the anterior left hemisphere, Broca already postulated that in right-handers, a hemispherical transposition of the seat of vocal linguistic ability can occur as a consequence of congenital or early brain injury impeding the development of the speech centre at the foot of the third frontal convolution of the left hemisphere (Mariën, Paquier, Cassenaer, & De Deyn, 2002). A unique possibility to enrich current insights in the lateralization and organization of language functions and the recently acknowledged role of the cerebellum in linguistic processing (Jansen et al., 2005; Stoodley et al., 2010) is to investigate individuals in whom an anomalous organization of brain functions is clinically evident or might be theoretically expected. An intriguing group of patients with congenital neurological lesions are subjects with *porencephalic cysts* (PCs) that replace brain tissue. Porencephaly is a cystic defect in the cerebrum communicating with the ventricle or the subarachnoid space (or with both), due to a developmental malformation or destructive lesion (Naef, 1958). The neuropsychological and neuroimaging findings of a left-handed man with a PC replacing a large part of the left parietal, temporal and occipital lobe suggested that intrahemispheric reorganization may take place in the presence of a PC and that language, motor and somatosensory functions are not necessarily transferred to the undamaged, contralateral hemisphere (Danckert et al., 2004). An interview with 32 PC-patients revealed that in 91% neurological deficits similar to those of a focal unilateral cerebral lesion appear, spastic weakness and seizures accounted for respectively 44% and 41% of the initial symptoms (Naef, 1958). These findings show that PC may be associated with clinical conditions, researchers have not been able to find a causal relation between the location of the cyst and the symptoms: seizures (Ho et al., 1998), psychosis (Alexander, Lapointe, Flynn, & Honer, 1997; Douzenis, Rizos, Papadopoulou, Papathanasiou, & Lykouras, 2010), schizophrenia (Boyer, Dassa, & Lancon, 2011), and bipolar disorders (Arora, Sinha, & Sarkar, 2009; Relan, Chaturvedi, & Shetty, 2002).

The hypothesis of a lateralized linguistic cerebellum (Mariën, Engelborghs, Fabbro, & De Deyn, 2001), i.e. the pattern of lateralized dominance for language at the cortical level is crosswise reflected at the level of the cerebellum, has not been investigated in a subject with a congenital brain lesion without secondary neurological, neuropsychological or neurodevelopmental symptoms. The Word Generation task used in this study was chosen because studies showed that this task consistently activates the inferior frontal gyrus of the language dominant hemisphere (Cai, Paulignan, Brysbaert, Ibarrola, & Nazir, 2010; Jansen et al., 2005), and lobule VI and CrusI/II of the contralateral cerebellum (Jansen et al., 2005; Stoodley & Schmahmann, 2009; Stoodley et al., 2010). In contrast to a semantic fluency task in which the initial stimulus triggers a related semantic network, the participant has to initiate a new search at the phonological level, which is a demanding process relying on executive, frontal lobe functions. Lesions in the frontal cortex (Baldo, Schwartz, Wilkins, & Dronkers, 2006; Robinson, Shallice, Bozzali, & Cipolotti, 2012), but also at the cerebellar level often result in verbal fluency deficits. Patients with focal cerebellar lesions produce significantly fewer words during a phonological verbal fluency task, while the semantic fluency was unaffected, as compared to age- and education-matched controls (Leggio, Silveri, Petrosini, & Molinari, 2000). Leggio et al. (2000) assigned this deficit in cerebellar patients to difficulties in acquiring a novel searching strategy. Stoodley and Schmahmann (2009) concluded that the disconnection of the cerebral-prefrontal system offers an explanation for the perceived deficits in verbal fluency, since the inferotemporal structure responsible for the semantic fluency capabilities is not innervated by the cerebellum.

2. Material & methods

2.1. Participant

After an extensive manual search of two MRI databases (ZNA Middelheim n > 10,000, Antwerp University Hospital entire database) only one out of 30 individuals identified with a PC matched the stringent selection criterion of a clinically neurologically and psychiatrically healthy subject with an isolated, congenital PC in the left hemisphere. Healthy was defined as a lack of secondary neurological symptoms originating from the PC. This native Flemish-speaking, 50-year-old, right-handed (Edinburgh Handedness Inventory = +100) woman had an unremarkable medical history and normal developmental milestones. Family history was negative for developmental disorders and learning disabilities. A large PC in the left temporal lobe was detected on a CT scan after she had sustained a minor head trauma in a traffic accident. The clinical neurological examination and EEG were normal. She had normal hearing and normal visual acuity.

2.2. Design

The study was conducted according to the revised Declaration of Helsinki (1998) and approved by the Medical Ethics Committee of the University of Ghent. The patient signed an informed consent and gave her approval for the use of the data.

2.2.1. Neuropsychological assessment

Extensive neuropsychological investigations were performed by means of standard psychometric tests to assess a variety of cognitive functions including intelligence (Wechsler Adult Intelligence Scale-III, *WAIS-III*), learning and memory (the

Wechsler Memory Scale-Revised, *WMS-R*), attention and concentration (Trailmaking Test, D2 Test of Attention, Stroop Colour-Word Test), and language (Boston Naming Test, *BNT*; Semantic Word Fluency Task).

2.2.2. fMRI paradigm

The Word Generation Task used in this study was previously described in more detail (Cai et al., 2010; Hunter & Brysbaert, 2008). The paradigm included an activation and control task of 15 s each, both separated by a rest period of 15 s. The patient was instructed to think of as many words as possible beginning with a visually presented letter (letters: b, d, k, l, m, n, p, r, s or t), which was back-projected on a flat screen in the scanner. As a control condition, silent repetition of the meaningless letter string "baba" was used. Each cycle consisting of an activation task (15 s), rest (15 s), a control task (15 s) and rest (15 s) was repeated ten times, resulting in a total duration of 10 min. Both tasks were performed in silence to avoid head movement activation and artefacts.

2.3. Imaging

A Siemens Trio 3.0-Tesla scanner (Siemens Medical Solutions, Germany) was used for anatomical and functional imaging. The scan was equipped with an eight-channel head coil. Functional images were obtained using a T2*-weighted gradient-echo planar imaging sequence [TR = 2630, TE = 35 ms, image matrix = 64*64, FOV = 224 mm, flip angle = 80°, slice thickness = 3.0 mm, distance factor = 17%, voxel size = 3.5*3.5*3 mm^3]. Forty axial slices covering the whole cerebrum and cerebellum were obtained. A high-resolution T1-weighted anatomical scan was obtained using a MPRAGE sequence [TR = 1550 ms; TE = 2.39 ms; flip angle = 9°; matrix = 256*256; FOV = 220 mm; voxel size = 0.9*0.9*0.9 mm^3].

2.4. Data analysis

fMRI data were analysed using SPM8 software (www.fil.ion.ucl.ac.uk/spm). After motion and slice timing correction, all functional images were registered to the T1-weighted data set. The non-rigid transformation of the anatomical T1-weighted image to MNI space was then applied to all fMRI data. A visual quality inspection was performed to ensure that the registration was performed adequately. The registered functional data were then smoothed spatially with a Gaussian kernel with a full width at half maximum of $6 \times 6 \times 6$ mm^3. Based on the timings of the experiment, the following contrast was generated: word generation > repetition of baba. An FWE-corrected α-value for multiple comparisons of 0.05 is reported. The LI-toolbox for SPM8 was used to calculate laterality indices. Because the LI is strongly dependent on the threshold used for the images in the analysis, a bootstrapping approach was applied (Wilke & Schmithorst, 2006) to create threshold-dependent laterality curves as to avoid a fixed and arbitrary threshold, which can obscure laterality findings (Wilke & Lidzba, 2007). Taking equally spaced t-thresholds into account, an overall weighted bootstrapped LI is calculated. Indices range from −1 to +1, with extremes representing a strong lateralization to the right and left, respectively. Using the AAL template (Tzourio-Mazoyer et al., 2002), the weighted LI was calculated for the pars triangularis, pars opercularis, and cerebellum, respectively.

3. Results

3.1. Neuropsychological assessment

As reflected by a significant discrepancy of 17 IQ-points between the normal verbal IQ (=108, +0.50 SD) and the superior performance IQ (=125, +1.60 SD) the intelligence profile was characterized by an asymmetrical distribution of the IQ-levels. On the WMS-R, she obtained index scores within the superior range for working memory (index = 134, +2.26 SD), as well as for delayed recall (index = 133, +2.20 SD). A consistent and symmetrical distribution of visual (index = 138, +2.53 SD) and verbal memory (index = 126, +1.73 SD) indices was found. The subject obtained normal to superior scores for general attentional skills, as measured by the WMS-R attention index (=101, +0.06 SD), visual search and sequencing skills (Trail Making Test), sustained visuo-motor attention (D2 Test of Attention), inhibition of a competing and more automatic response set (Stroop Colour-Word Test), digit span and symbol substitution (WAIS-III). Visual recognition and naming, as measured by the BNT, was normal. Word fluency and the verbal subtests of the WAIS-III scored within the normal range.

3.2. fMRI results

fMRI activations included in Table 1 are part of a significantly activated cluster and represent the highest activity peaks of a particular cluster. As a result, not all areas mentioned in the text are included in the table, although they are visible in Fig. 1. For example, the activation of the right inferior frontal gyrus resulted in a significant cluster of 5 active voxels (Table 1), but is in fact part of four clusters ranging from 5 to 366 active voxels for this particular region.

The Word Generation task resulted in an atypical pattern of bilateral supratentorial activity involving both supplementary motor areas, the precentral frontal gyri, left and right insula and visual association cortices. Even activation of the inferior frontal gyrus was found in both hemispheres, but more pronounced on the left side (Table 1). Significant activation was also observed in the superior and inferior temporal gyrus, the supramarginal gyrus, the putamen, the cuneus, the inferior parietal

Table 1
Significant fMRI activations.

|	Left hemisphere			Right hemisphere		
	XYZ	Z	CS	XYZ	Z	CS
Cerebrum						
Precentral gyrus	−46 −2 40	>8.00	3210	46 4 40	>8.00	676
	−28 −14 54	5.92	84			
Middle frontal gyrus				36 36 24	>8.00	1945
Medial frontal gyrus				68 −38 −14	7.24	130
				14 62 −4	5.68	25
Inferior frontal gyrus	−44 42 8	>8.00	516	54 28 8	4.98	5
Supplementary Motor Area	0 8 62	>8.00	3046	24 2 62	7.12	154
Insula	−28 22 10	>8.00	230	38 20 4	7.40	227
Superior temporal gyrus	−60 −44 10	7.61	61			
Inferior temporal gyrus	−52 −56 −12	>8.00	470			
Superior parietal lobe				36 −76 44	>8.00	596
Inferior parietal lobe	−42 −46 44	>8.00	448			
Supramarginal gyrus	−58 −46 28	7.29	119			
Visual association cortex	−30 −98 −12	6.36	140	26 −102 −10	6.01	212
Cuneus	−26 −78 32	>8.00	1094			
Calcarine	0 −84 −2	6.34	133			
Putamen	−26 −4 8	5.82	50			
Cerebellum						
Lobules IV–V	−40 −48 −28	5.56	57			
Lobule VI				34 −64 −26	7.44	270
				12 −76 −28	5.60	31

XYZ = MNI coordinates; Z = Z-score; CS = Cluster Size, Cerebellar nomenclature based on Schmahmann, Doyon, Toga, Petrides, and Evans (2000). Family wise error correction: p < 0.05.

lobe and the calcarine fissure of the left hemisphere. The superior parietal lobe, middle and medial frontal gyri were activated in the right hemisphere.

At the cerebellar level, bilateral activation was found in Crus I (Schmahmann et al., 2000) of the posterior lobe (Fig. 1), but more pronounced in the right than in the left hemisphere. The activation in Crus I of the right cerebellum was included in a significant cluster in the lobule VI of the right cerebellum (Table 1), while the activation of Crus I of the left cerebellar hemisphere was found in a significant left lobule IV–V cluster (Table 1).

3.3. Lateralization index

Left cerebral hemisphere lateralization is defined as a value between 0.50 and 1, right cerebral hemisphere dominance has a LI between −1 and −0.50, while a range of −0.50 and 0.50 reflects bilateral activation (Cai et al., 2010). Activation of the
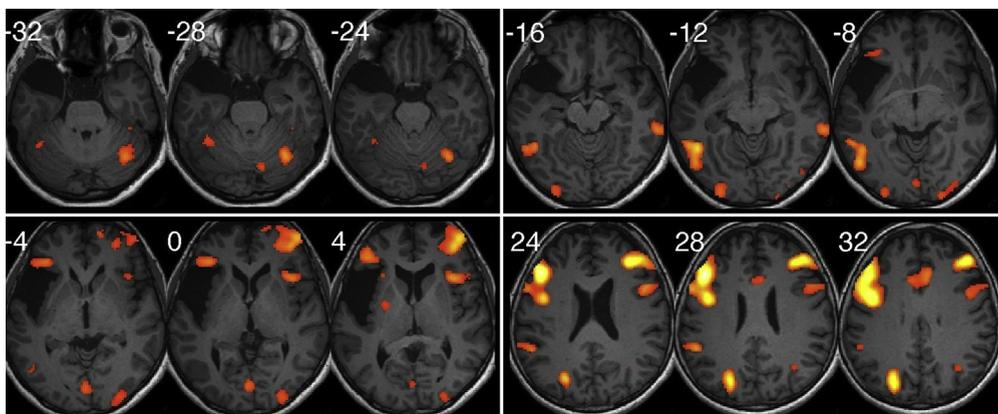
Fig. 1. Significant fMRI activations. Values represent MNI Z-coordinates; −32 until 4: extent of the porencephalic cyst in the left temporal lobe; −32, −28 & −24: bilateral cerebellar activation; −16, −12 & −8: left visual association cortex activation, −4, 0, 4 & 24, 28, 32: bilateral frontal activation. Orientation of the images according to the neurological convention: left = left; right = right.

inferior frontal gyrus resulted in an atypical bilateral cerebral language pattern (mean LI = 0.42). A similar LI is found for the activations at the level of the cerebellum, a LI of −0.31 indicates bilateral cerebellar language organization.

4. Discussion

The pattern of cerebral and cerebellar language organization was studied in a right-handed subject with a large PC in the left temporal lobe by means of an fMRI-language task. Except for a significant difference between verbal and non-verbal intelligence levels, the neuropsychological test results were homogeneously distributed.

The Word Generation task used in this study is an example of phonemic fluency and is typically associated with a consistent pattern of strong unilateral activations in the language dominant hemisphere: the inferior frontal gyrus and the prefrontal area, the supplementary motor area, superior temporal gyrus (BA22 & BA38) and the supramarginal gyrus (BA40), the bilateral thalamus, basal ganglia and midbrain (Cai et al., 2010; Jansen et al., 2005). A significant activity pattern is found as well in lobule VI and CrusI/II of the contralateral cerebellum (Jansen et al., 2005; Stoodley & Schmahmann, 2009; Stoodley et al., 2010). Although slightly more pronounced in the left cerebral hemisphere, bilateral activations were found in the frontal language areas, while unilateral activation of the inferior and superior temporal gyrus and supramarginal gyrus was found in the left cerebral hemisphere. The atypical pattern of neuronal activity at the supratentorial level was reflected at the cerebellar level by bilateral activations of Crus I, with a slightly more prominent activation in the right cerebellar hemisphere. The LI, a degree of lateralization in a particular brain region, confirms this atypical bilateral involvement of cerebral and cerebellar structures in controlled oral word production.

These results add to the theory that the cerebro-cerebellar network plays a crucial role in linguistic processing: lesions in the frontal cortex (Baldo et al., 2006; Robinson et al., 2012), but also at the cerebellar level often may induce verbal fluency deficits. Patients with focal cerebellar lesions produced significantly fewer words during a verbal fluency task, while semantic fluency is unaffected. This finding is assigned to the difficulties in acquiring a novel searching strategy (Leggio et al., 2000) due to the disconnection of the cerebral-prefrontal system (Stoodley & Schmahmann, 2009). The linguistic deficits following pure cerebellar damage are attributed to the pathophysiological mechanism of *crossed cerebello-cerebral diaschisis*: a lesion in the cerebellum might be responsible for a distant functional depression of the supratentorial association areas following a loss of transmission of excitatory impulses through the cerebello-cerebral pathways (Mariën et al., 2001).

In accordance with our findings, congenital lesions located in the left temporal lobe often occur with atypical language organization reflected by means of a (different) word generation task. A pattern of crossed cerebro-cerebellar activation was observed in a population with normal to average verbal intelligence and a functional language shift to the right hemisphere after congenital periventricular lesions in the left hemisphere (Lidzba, Wilke, Staudt, Krageloh-Mann, & Grodd, 2008). Staudt et al. (2001) correlated the size and lateral extent of a left congenital periventricular brain lesion with the rightward asymmetry: less fMRI activity was observed in the right hemisphere when the total lesion volume was smaller, sometimes resulting in bilateral activation. Since the cortical temporal language zones in the left hemisphere were intact, the authors held white matter destruction responsible for the shift (Staudt et al., 2001). Based on the theory of near-equipotentiality, the authors concluded that: "… different severities of early left hemisphere lesions can cause different degrees of participation of homologous areas in the two hemispheres" (p. 964) (Staudt et al., 2002).

In a patient with a large PC located in the left temporo-occipito-parietal lobe and normal language performance on different cognitive tests, receptive speech representation was located in the right hemisphere, while expressive speech was subserved by the left frontal lobe (Danckert et al., 2004), a pattern that was also observed in 11 healthy subjects, out of 47 with speech production located in the left hemisphere, participating in a combined fMRI and a dichotic listening task (Van der Haegen, Westerhausen, Hugdahl, & Brysbaert, 2013). The bilateral pattern of cerebral and cerebellar activity in our subject adds to the theory of near-equipotentiality because (1) the cyst is smaller than the cyst described in Danckert et al. (2004), (2) the location is closer to the posterior part of the frontal lobe, and (3) Wernicke's area is intact. A bilateral organization of expressive language is probably the result of a compensatory mechanism and might reflect operational inefficiency of the neural network subserving language in the left hemisphere (Deary & Caryl, 1997). An illustration of this inefficiency might be found in the significantly lower VIQ level.

The MNI template enables the conversion of the brain into a stereotaxic space and automatically identify the different cerebral and cerebellar structures. This standard spatial normalization technique is applied in this subject to identify the structures of the right hemisphere, although a comparison at the level of the cyst is difficult. Nevertheless, the cyst has no effect on the normal anatomical architecture of the frontal lobes, resulting in a reliable analysis of the bilateral frontal activity pattern and associated LI. The functional repercussions of the location of the cyst are not quite clear due to the nature of the word-generation task since temporal language organization was not investigated. However, it can be hypothesised that during language development the presence of the cyst resulted in an atypical frontal language organization with associated bilateral cerebellar involvement.

The LI value may depend on several data acquisition and analysis factors (Seghier, 2008). The results presented in this work should therefore be interpreted in light of the selected task and regions of interest. As it has been demonstrated that a regional LI analysis can be more specific as compared to the whole hemisphere evaluation. For this, specific ROIs (the pars triangularis, pars opercularis, and cerebellum) were used to evaluate expressive language functions and therefore our results should be interpreted in the context of this ROI selection. In addition, it is known that LI values depend on the statistical threshold that is

used. In this context, we adopted a bootstrap analysis that generates threshold-independent LI values (Wilke & Schmithorst, 2006).

Summing-up, in this study functional language organization at the supra- and infratentorial level is investigated in a right-hander with early destruction of a large part of the left temporal lobe and subsequent atypical expressive language organization. The findings of a bilateral cerebellar involvement confirms that the pattern of bifrontal representation of expressive language function is intrinsically reflected at the level of the cerebellum and may serve as a compensatory mechanism for the lesion.

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