Modality specific activations in working memory in children treated for cerebellar medulloblastoma: an fMRI study

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Purpose

Medulloblastomas, the most common primitive malignant tumors in children, are mainly located in cerebellum and classically treated by a combination of surgery, radiotherapy and/or chemotherapy [1]. After treatment, survivors have a progressive neurocognitive impairment, especially working memory, because of many factors, probably including pre-treatment factors (hydrocephalus, tumor invasions and compressions) and the multimodal treatment [2]. Working memory (WM) is a system of short-term information processing and storage involving an essential cognitive function in everyday life like thought, learning, and communication. In recent study, two components of working memory including phonological loop and visuo-spatial sketchpad were of particular interest and several tasks for assessing each domain in children have been established. The cerebellum has traditionally played a role in motor control, physical coordination and balance but it has been also recently considered to contribute to cognitive, emotional and language processing [3]. However, role of the cerebellum in visuo-spatial sketchpad has been rarely described. The number of medulloblastoma survivors has been increased by treatment advances requiring more the rehabilitation. We benefited the advantages of functional MRI to study the contribution in WM disorders in children who had been treated for medulloblastomas.
Methods and materials

Participants

9 patients and 12 healthy controls were included over 3 years. Among these subjects, 4 patients and 3 healthy controls were excluded: excessive movement (n=3), left-handedness (n=1), anxiety (n=2), lack of task performance (n=1), leaving 9 healthy children volunteers (5 boys, 4 girls, mean of age 11.1y (SD = 2.2y) and 5 patients (5 boys, mean of age 12.1y (SD = 0.6y) suitable for analysis. The patients were treated with surgery and radiotherapy (5/5), +/- chemotherapy (3/5) in Grenoble, Lyon and St-Etienne Pediatric oncology Hospital units with at least 6 months interval after end of treatment. The handedness was determined by means of Delattolas laterality test [4]. The study has been approved by the local SUD EST V Ethic Committee and by the DGS (National Health authorities). All of the children’s parents/legal guardians provided written informed consent.

Inclusion criteria: the participants must be native French speakers; right-handed; age of 8 to 12 years 11 months; the overall IQ from 70 to 130; having a good performance in the previous fMRI training; without any traditional contra-indications of MRI. The healthy subjects have not any history of psychiatric, neurological or other major medical disorder. The patients who treated for medulloblastoma after age of 6 years (homogeneous population in terms of brain maturation) and at least six months after the end of all treatments.

Imaging

Task and Stimuli

The participants were instructed to perform four classical n-back tasks (1-back tasks) according to modality of presentation (visual vs. auditory presentation) and nature of displayed information (verbal vs. non-verbal) (fig. 1). Four experimental tasks have been tested: auditory verbal task (AUVE), auditory non-verbal (AUNV), visual verbal (VIVE) and visual non-verbal (VINV). Each task was presented once during the experimental paradigm. The task included 28 stimuli, pseudo-randomly presented. Visual tasks: each stimulus (word or spatial pattern) was centered on the middle of a black screen. All tasks were presented by using the E-prime software (E-prime Psychology Software Tools Inc., Pittsburgh, USA).
Fig. 1: Un exemple d'un modèle de bloc pour tâche visuelle non verbale (4 blocs au total). Temps de présentation d'un stimulus: 2000 ms, temps entre deux stimuli pour la réponse de l'objet: 3000 ms. Temps de repos initial: 30000 ms. Le temps de repos entre les essais: 25 000 ms.

References: Grenoble institute of neuroscience, Grenoble university - Grenoble/FR

MR acquisition

The experiment was performed on a 1.5 T MR scanner with 30 mT/m gradient strength and a standard Philips head coil.

Functional image acquisition: fMRI scanning was performed with a gradient-echo/T2* weighted EPI method. Thirty-two adjacent axial slices parallel to the bi-commissural plane were acquired in interleaved mode. Slice thickness was 4 mm. The voxel size was 4×4×4 mm; 256 mm field of view. The main sequence parameters were: TR=5 s, TE=50 ms, flip angle=77°, 56 dynamics. Images were acquired during 3 first seconds of each TR, 2 extant seconds for auditory and visual cues exposure. A "block" design has been used during the fMRI session. Four runs have been measured during the fMRI session corresponding to each task. Tasks were randomly presented across subjects. The total duration of each run was 4 min 40. During each run, we measured the whole brain volume 56 times. The field map was subsequently used during data processing.

Anatomical image acquisition: Finally, a T1-weighted high-resolution three-dimensional anatomical volume was acquired, by using a 3D gradient echo inversion recovery sequence (field of view=256 mm; resolution: 1×1×1 mm; 128 axial spiral slices).

Data analysis

Data analysis was performed by using the general linear model as implemented in SPM8 where each event is modeled using a hemodynamic function model. The modality of presentation (visual, auditory) and the nature of information (verbal, non-verbal)
in four experimental conditions: VIVE, VINV, AUVE and AUNV were defined and a flexible design analysis on the contrast images derived from individual analyses in healthy participants was performed. Subsequently, two types of main effects have been calculated:

**Main effect of modality of presentation:** The contrast \([AU(VE+NV) vs. VI(VE+NV)]\) was calculated in order to identify modality specific activations in healthy children. The opposite contrast \([VI(Ve+NV) vs. AU(Ve+NV)]\) was also calculated.

**Main effect of nature of information:** The contrast \([VE(AU+VI) vs. NV(AU+VI)]\) was calculated in order to explore the cerebral regions required in WM processing according to the nature of information and similar calculation for the opposite contrast \([NV(AU+VI) vs. VE(AU+VI)]\).

The anatomical location of the activated regions revealed by the main effects was determined by using the xjview toolbox, MRICron and the spatially unbiased atlas template (SUIT).

The variables did not have a Gaussian distribution and they were not all parametric. Therefore, Mann-Whitney U test was chosen for analyzing neuropsychological and behavioral data.
Results

Working memory test

In the tests involving the visuospatial sketchpad or nonverbal working memory, Mann-Whitney U test found a significant difference in pattern test that the patient group has performance significantly lower than the control group (U=11, Z=2, p=0.04). Behavioral results also showed a significant difference in reaction time for two condition VINV (U=3343, Z= -2, p= 0.04) and AUNV (U=3327, Z= -2, p= 0.04) means that the reaction time to perform the nonverbal condition in patient group was significantly longer than the control group.

Cerebellum is involved in working memory

Cerebellar lesion topography for 5 patients is shown in fig. 2. In the patient group, all 4 patients with principal resected lesions in left inferior cerebellar lobe (lobule VIIB/VIII,IX and Crus I/II) had WM impairment. The patient with only inferior vermis resection was the only one without WM deficit. The activations maps showed a reduction of cluster size in the patients group vs. healthy children group in all tasks and contrasts.
Fig. 2: Anatomical lesion mapping of patient group with lobules labeled from the spatially unbiased infratentorial template (SUIT) of the cerebellum and brainstem by Diedrichsen and colleagues [5] and being visualized on MRICroN software.

References: Grenoble institut of neuroscience, Grenoble university - Grenoble/FR

In healthy subject group, analyzing the contrast for both effects of presentation modality and nature of information, it was found that the left posterior cerebellar lobe was activated for visual vs. auditory contrast and nonverbal vs. verbal contrast (fig. 3). This is consistent with other outcomes that the verbal working memory activated predominantly the right side while the nonverbal WM activated the left side of posterior cerebellar lobe [6-9], demonstrating the involvement of the posterior cerebellar lobe in working memory and the left-right lateralization of this region in verbal and nonverbal WM. Schmahmann and Sherman [10] found that cerebellar cognitive affective syndrome with visuospatial disorganization and impaired visuospatial memory was seen in patients with posterior cerebellar lobe lesion. Moreover, Hokkanen et al. [11] found that patients with left cerebellar lesion performed slowly in a visuospatial task and Wallesch & Horn [12] reported that an excision of the left cerebellar hemisphere tumors evoked visual spatial deficits. Medulloblastoma survivors with WM disorders were due to a combination of several risk factors that cerebellar damage was an important factor. Due to ethical constraints, the assessment of WM disorders caused by each specific factor is difficult to perform. The rehabilitation for this population therefore also needs to calculate all possible risk factors.

Fig. 3: Overlaps on MRICroN of resected lesion area (yellow), activations observed in nonverbal vs. verbal tasks contrast (purple clusters) and in visual vs. auditory contrast (green clusters), with threshold (p = 0.05, cluster voxels > 4).

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BOLD activation patterns within the brain
During these visual tasks, the greater activations were found bilaterally in the inferior frontal gyrus (IFG) (BA45/47), middle frontal gyrus (MFG) (BA46), inferior parietal lobule (IPL) (BA40) and the fusiform gyrus (BA17/18). The auditory tasks activated bilateral temporo-frontal regions, particular in the superior temporal gyrus (STG) (BA 21/22), IFG (BA 47) and IPL (BA 40), predominantly in the left side for AUVE tasks and in the right side for AUNV tasks.

Compared to auditory tasks, visual tasks produced greater BOLD signals in bilateral parieto-occipital areas (BA17/18/19), especially the bilateral primary visual cortex, bilateral superior and inferior frontal gyrus, bilateral fusiform gyrus and left MFG. On the other hand, auditory vs. visual contrast evoked prominent activations in bilateral parieto-temporal areas, especially the bilateral primary auditory cortex (BA41/42), Wernicke's area (BA22) as well as bilateral STG (BA21/22). Compared to nonverbal tasks, common activations by verbal tasks were bilaterally observed in the MTG (BA 21/22), supramarginal gyrus (BA 40) with left-sided predominance whereas nonverbal vs. verbal contrast activated predominately the right middle occipital gyrus (BA18/19), right fusiform gyrus and right lingual gyrus (BA17). These results were comparable with those in literature [13-16]. The verbal presentation predominated on the left side hemisphere whereas the nonverbal presentation predominated on the right side of brain. This result showed a left-right lateralization in the verbal and nonverbal WM, which agrees well with other studies [15-19].
Conclusion

The present study provides further evidence of the view that the cerebellum plays a role in working memory in children similar to that already described for adults in literature.

Damage to the left posterior cerebellar lobe may impair nonverbal working memory performance and children with cerebellar lesions should routinely undergo long-term monitoring of their intellectual development.

In addition, our results reinforce the existence of functional cerebro-cerebellar networks during WM tasks.
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References


