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Assessing language and visuospatial functions with one task: A "dual use" approach to performing fMRI in children

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ABSTRACT

In order to increase the rate of successful functional MR studies in children it is helpful to shorten the time spent in the scanner. To this effect, assessing two cognitive functions with one task seems to be a promising approach. The hypothesis of this study was that the control condition of an established language task (vowel identification task, VIT) requires visuospatial processing and that the control condition (VIT_{CC}) therefore may also be applicable to localize visuospatial functions. As a reference task, a visual search task (VST, previously established for use in children) was employed. To test this hypothesis, 43 children (19 f, 24 m; 12.0 ± 2.6, range 7.9 to 17.8 years) were recruited and scanned using both tasks.

Second-level random effects group analyses showed activation of left inferior-frontal cortex in the active condition of the VIT, as in previous studies. Additionally, analysis of the VIT_{CC} demonstrated activation in right-dominant superior parietal and high-frontal brain regions, classically associated with visuospatial functions; activation seen in the VST was similar with a substantial overlap. However, lateralization in the parietal lobe was significantly more bilateral in the VST than in the VIT_{CC}.

This suggests that the VIT can not only be applied to assess language functions (using the active>control contrast), but also that the control>active condition is useful for assessing visuospatial functions. Future task design may benefit from such a "dual use" approach to performing fMRI not only, but also particularly in children.

Introduction

Functional magnetic resonance imaging (fMRI) has become an important research tool for assessing normal and abnormal functional development of the brain (Berl et al., 2006; Durston and Casey, 2006; Johnson, 2001). Its lack of harmful radiation makes it an important non-invasive approach; as such, fMRI can be used to further investigate several questions of great interest, such as language organization and development (e.g. Holland et al., 2001), functional development of the healthy brain (e.g. Durston and Casey, 2006), or the neural basis of neurobehavioral disorders (e.g. Bird et al., 2006).

However, researchers using fMRI to investigate children are facing several challenges (Byars et al., 2002; Freilich and Gaillard, 2010; O'Shaughnessy et al., 2008; Wilke et al., 2003). Excessive head motion, lack of compliance once inside the scanner, inattentiveness, and refusal to enter the scanner in the first place are among the main reasons for unsuccessful studies (O'Shaughnessy et al., 2008; Yerys et al., 2009; Yuan et al., 2009). Task duration and time spent in the scanner is one of the most limiting factors for successfully acquiring functional images in children (Yerys et al., 2009). Therefore, shorter task batteries may be helpful in increasing success rates when performing fMRI in children.

To this end, using a single task to examine two different cognitive domains may constitute an interesting approach. Two similar cognitive functions (response inhibition and suppression) have been examined in one task using a single (third) control condition (Bunge et al., 2002) before, and a motor and a cognitive task have been successfully combined, with one condition serving as a control for the other one (Holland et al., 2001). However, the examination of two different cognitive functions within one task using one condition as a contrast for the other one (and vice versa) seems to be novel. Such a "dual use" of the information gained in one task would have several advantages: the time saved by running one instead of two paradigms must be expected to yield a higher success rate, particularly in younger children (Yerys et al., 2009); alternatively, more robust information could be obtained in the same time by examining one function with two different tasks (the relevance of which was shown by DeGuibert et al. (2010), Gaillard et al. (2004), and Wilke et al. (2010) for language functions).

In previous studies, we have addressed neural plasticity and reorganization following early brain lesions (Everts et al., 2010; Lidzba

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et al., 2006b; 2008; Staudt et al., 2002). In this context, language and visuospatial functions are of particular interest (as both domains seem to interact; Lidzba et al., 2006a), and we successfully established several tasks for assessing either domain in children (Lidzba et al., 2006b; Wilke et al., 2005, 2006). However, as time constraints are even more pressing in pediatric patients (Yerys et al., 2009), the aim of combining the assessment of these two functions in one task was the main motivation for this study.

When designing the vowel identification task (VIT; Wilke et al., 2006), we used two complex graphical patterns that subjects were required to match in the control condition. We hypothesized that this pattern matching in the control condition (VIT_{CC}) requires visuospatial functions and that this, when contrasted with the active condition (VIT_{AC}) (phonological processing; see Fig. 1), would reveal a typical visuospatial activation pattern. While the VIT_{AC} has successfully been applied to assess language producing brain regions (Everts et al., 2009; Ressel et al., 2006; Wilke et al., 2006, 2010), the VIT_{CC} was as yet not systematically studied. In order to test our hypothesis, we aimed at comparing the brain regions activated in the VIT_{CC} with those activated in the well-established visual search task (VST; Lidzba et al., 2006b), in the same group of children. In previous studies, the VST has successfully been used to assess visuospatial functions (Everts et al., 2009; Lidzba et al., 2006b); it was therefore used as a reference task. The observation of similar activation patterns in the VIT_{CC} and the VST would confirm our hypothesis that the VIT_{CC} does indeed require visuospatial functions and that the VIT can be used to assess both language and visuospatial functions.

Subjects and methods

Participants

Overall, 43 healthy children (24 males and 19 females) aged 7.9 to 17.8 years (mean age 12.0 ± 2.6 years) were included in this study. Participants were recruited through public announcements and newspaper articles. Interested parents underwent telephone screening with the study coordinator. General MR contraindications applied; study specific exclusion criteria were the presence of neurological or psychiatric disorders, hearing deficits, cognitive impairment, or prematurity(<37 weeks gestational age). All children were native German speakers and had normal or corrected-to-normal vision. At this stage, 4 children had to be excluded because of a metal implant (1), neuropsychiatric disorders (1), or prematurity (2). One child did not show up for scanning.

Handedness was assessed using the Edinburgh Handedness Inventory (EHI; Oldfield, 1971). On a separate appointment children underwent neuropsychological testing, consisting of the HAWIK IV, a German version of the Wechsler Intelligence Scale for children (Petermann and Petermann, 2007), which yields a full-scale IQ as well as standard scores for verbal comprehension, perceptual reasoning, working memory, and processing speed. All procedures were approved by the local institutional review board. All parents gave written informed consent and all children gave assent. Children were compensated for their participation. Anatomical images were screened for structural abnormalities by an experienced neuroradiologist.

Tasks

Children performed two functional MRI tasks, the vowel identification task (VIT; Wilke et al., 2006) and the visual search task (VST; Lidzba et al., 2006b).

The VIT was originally designed to assess predominantly left-hemispheric language functions in children. The task was implemented as a block-design with two conditions. The active condition (VIT_{AC}) was aimed at inducing phonological processing: here, the picture of a concrete object was presented and children were required to decide whether the vowel “i” (always pronounced /i:/ in German) was present in the name of the object (see Fig. 1). If so, a button press was required. Children were specifically instructed not to spell the word but instead to judge “what it sounds like”. Images were presented for 4 s each with a pause of 1 s (when only the fixation cross and the reminders were shown), such that each block contained 6 images, half of which were shown on the right and half on the left part of the screen. The VIT_{CC} was aimed at avoiding phonological processing while still requiring a matching (of sorts) and a decision making process. To this effect, abstract images were generated by employing the concept of mathematical fractals, resulting in complex and colorful, but completely unnameable images. In order to balance the decision making component, subjects were presented with two images, a bigger and a smaller one, and were required to decide whether the smaller one fits into the larger one “like the piece of a puzzle” (see Fig. 1). If so, they were again required to push a button. The timing was identical to the one used in the VIT_{AC}. The whole task was completed within 5 min 30 s, containing 6 control and 5 active blocks. Between conditions the screen turned green for 1 s to indicate the beginning of the other condition.

The VST was originally designed to assess predominantly right-hemispheric visuospatial functions in children. The active condition consisted of two complex figures (Rey-Osterrieth figure; Rey, 1941) that were shown on the screen and children had to decide whether they were completely identical or whether a small part was missing in one of them. If so, a button press was required. Children were specifically instructed to “try to find the errors”, but not to worry should they not have been done in time before the next images appeared. The control condition again showed two versions of the complex figure, but in this case, the orientation (identical or different) needed to be assessed; if the orientation was different, a button press was required. In order to make sure the children knew when to do which part of the task, the background was shown in blue in the control condition. As in the VIT the screen turned green for 0.5 s between conditions to

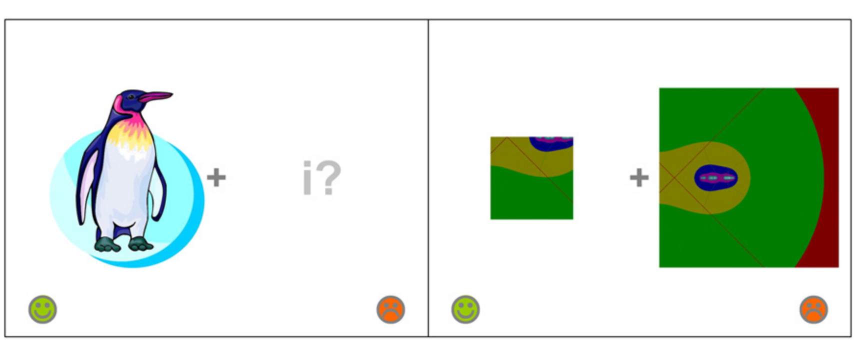

Fig. 1. Stimulation material of the vowel identification task (VIT): in the active condition (VIT_{AC}; left) children are required to decide whether “there is an “i” in the name of the object”, in the control condition (VIT_{CC}; right) children are required to decide whether “the small pattern fits into the larger one like the piece of a puzzle”.

indicate the beginning of the other condition. Again a block design was used with 6 blocks of the control and 5 blocks of the active condition. Each block contained 5 images that were presented in randomized order for 5.5 s each with a pause of 0.5 s (when only the fixation cross and the reminders were shown).

Preparation of participants

Children were prepared extensively prior to entering the scanner (Wilke et al., 2003). The whole procedure was explained to them and their parents; the tasks were practiced outside the scanner room until the children were sure to have understood them and did not have any further questions. They were shown around the scanner room and if they wanted to one parent (who also underwent screening for MR contraindications) was allowed to accompany them. Before starting the next task, the task was again explained to them in the form of an audio-visual animation. To help the children lying still, especially when not performing the tasks, they were shown a film as long as the anatomical series was recorded.

Data acquisition and processing

Data was acquired in 2010 on a 1.5-T whole body MR scanner (Avanto, Siemens Medizintechnik, Erlangen, Germany), using a 12-channel head coil. A T2-weightened echo-planar imaging (EPI) sequence was used to acquire functional images with the following parameters: TR = 3000 ms, TE = 40 ms, matrix = 64×64, 40 slices, covering the whole brain, yielding a voxel size of $3 \times 3 \times 3$ mm^3. For each task, 110 images were acquired. Additionally, a gradient-echo B0 fieldmap was acquired with TR = 546 ms, TE = 5.19/9.95 ms, with the same slice prescription as the functional series. An anatomical T1-weightened 3D-data set with TR = 1300 ms, TE = 2.92 ms was also acquired, yielding 176 contiguous slices with an in-plane matrix of 256×256, resulting in a voxel size of $1 \times 1 \times 1$ mm^3. Care was taken to ensure comfortable placement of children, and a foam cushion was used to minimize head movement.

Visual stimulus delivery was achieved by screen projection, using a custom-made MR compatible setup. A single MR-compatible push button (Current Design Inc. Philadelphia, PA, USA) was used to report their decisions. Task adherence was monitored visually during scanning and analyzed retrospectively by assessing the expected button presses in the control conditions of the two tasks as these are both less difficult and less ambiguous (for example, the child may think of a synonym of the presented object in the VIT_{AC} that does not contain an “i”; Wilke et al., 2006).

Datasets were processed using SPM8 software (Wellcome Trust Centre for Neuroimaging, London, UK), running in Matlab (MathWorks, Natick, MA, USA). The first 10 scans of each functional series (corresponding to the first block of the control condition) were rejected to allow for the stabilization of longitudinal magnetization, leaving 100 scans per series (5 blocks each of the active and the control condition) to be analyzed. Functional images were realigned and unwarped using the individually-acquired B0 fieldmap, correcting for both EPI and motion × B0 distortions (Andersson et al., 2001). Functional series with motion exceeding one voxel size (3 mm) in any direction were rejected. In order to achieve spatial normalization, the anatomical dataset was segmented using unified segmentation (Ashburner and Friston, 2005), based on custom-generated pediatric reference data (Wilke et al., 2008), which was also used to overlay results on. Following coregistration, global signal trends were removed (Macey et al., 2004) and the functional images were smoothed with a 9 mm full width at half maximum (FWHM) Gaussian filter.

First level analyses were done using the General Linear Model (Friston et al., 1995), contrasting the active condition with the control condition (both tasks) and the control condition with the active condition (VIT). The resulting contrast images were entered into a random-effect second level analysis, applying a one-sample *t*-test on a voxel-by-voxel basis. Gender, age (in months) and handedness (EHI-score) were used as co-variables of no interest (Hahn et al., 2010; Rubia et al., 2010; Schapiro et al., 2004; Szaflarski et al., 2002). Significance was assumed at $p \leq .01$, FWE-corrected for multiple comparisons. Results are overlaid on a custom-made gray matter prior, using functionality available within MRIcron (www.mricron.com). While minimizing the amount of deformation a pediatric brain undergoes during spatial normalization (Wilke et al., 2002, 2008), it should be noted that the use of a customized pediatric template precludes using or reporting standard MNI coordinates of activation foci. Lateralization of activation was assessed in the individual t-maps, using functionality available within a designated toolbox (Wilke and Lidzba, 2007). Based on previous studies (Lidzba et al., 2006b; Wilke et al., 2006, 2010), we expected left-lateralized frontal activation in the VIT_{AC}, and right-lateralized parietal activation in the VST as well as in the VIT_{CC}; therefore, lateralization in the frontal as well as the parietal lobe was assessed using a bootstrapping approach (Wilke and Schmithorst, 2006). Here, a positive lateralization index (LI) indicates left-dominance, while a negative LI indicates right-dominance. Values of $-.2 < \mathrm{LI} < .2$ are considered bilateral (Wilke et al., 2006). A one-sample non-parametrical Wilcoxon signed-rank test was used to assess whether lateralization in either task (VIT_{AC}, VIT_{CC}, and VST) differed from zero, and differences between lateralization indices (VIT_{CC} versus VST) were assessed using the two sample non-parametrical Mann–Whitney-*U*-Test. For all tests, significance was assumed at $p \leq .05$.

In order to assess the extent of overlapping activation, activated voxels and their overlap were assessed for the VIT_{CC} and the VST in the frontal, the parietal, and the occipital lobes, as defined by the respective masks also used for the assessment of lateralization.

Results

Subjects

Imaging data from all children could be used (see Task adherence, below). According to the EHI, 37 children were right-handed, 4 left-handed and 2 ambidextrous. According to the HAWIK IV the mean full-scale IQ of the participating children was 109.7 ± 8.6 (range 91–128), verbal comprehension was 110.6 ± 9.9 (range 88–136), perceptual reasoning 109.8 ± 9.8 (range 81–131), working memory 108.0 ± 12.8 (range 82–144), and processing speed 100.5 ± 13.4 (range 79–126). Upon reviewing the images, no structural brain abnormalities were detected.

Task adherence

All 43 children successfully completed the VST, and all but one child successfully completed the VIT. Data from 3 children performing the VIT had to be discarded due to excessive motion.

In the VIT_{CC} children showed $98.4 \pm 3.2\%$ (range 89.5–100%) of the expected correct button presses, indicating constant task adherence. Two children were below chance level in either condition of the VST (6.7/23.3% in the VST_{CC} and 50/16.7% in the VST_{AC}, respectively) and were therefore removed from all further analyses. The remaining 41 children showed $89.2 \pm 22.6\%$ (range 0–100%) of the expected correct button presses in the VST_{CC}, again indicating constant task adherence. Three of these children were below chance level (0/10/45.8%) in the VST_{CC} but performed well above chance level in the much more complex VST_{AC} (66.7/75/66.7%), so that task adherence can be assumed.

Activation patterns

Activation in the VIT_{AC} was seen primarily in the left inferior frontal and temporal regions (see Fig. 2).

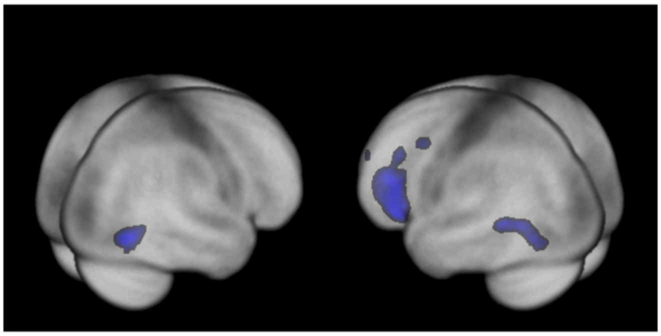

Fig. 2. Group activation map of the active condition of the vowel identification task (VIT_{AC}): random effects analyses (n = 39); p<.01, FWE-corrected. Note activation in the left inferior frontal and temporal regions, classically associated with language functions. Results are rendered on the custom-made gray matter template.

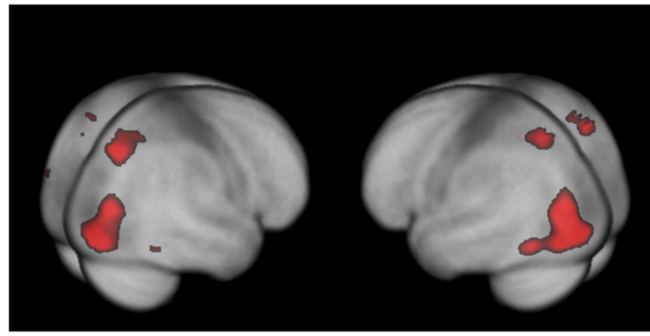

Fig. 4. Group activation map of the active condition of the visual search task (VST); random effects analyses (n = 41); p<.01, FWE-corrected. Note activation in bilateral occipital and posterior parietal regions, classically associated with visual and visuospatial functions. Results are rendered on the custom-made gray matter template.

Activation in VIT_{CC} was seen in bilateral posterior parietal regions, with right hemispheric dominance (see Fig. 3). Activation in the VST (active > control) was seen in posterior parietal and occipital regions (see Fig. 4). Both tasks also activated high-frontal regions (including parts of the precentral gyrus and the superior frontal gyrus), right-dominant in the VIT_{CC} and more bilateral in the VST (see Fig. 5).

Lateralization in the frontal lobe during the VIT_{AC} was left-dominant (LI = .59 ± .37), while it showed a tendency towards right-dominance in the parietal lobe during the VIT_{CC} (LI = − .17 ± .40; see Fig. 6). Lateralization in the VST task was bilateral in the parietal lobe (LI = .03 ± .45; see Fig. 6). Lateralization indices for VIT_{AC} and VIT_{CC} differed significantly from 0 (p<.0001; p = .0173, respectively) while the LI of the VST did not (p = .8307). Activation in parietal cortex was slightly more right lateralized in the VIT_{CC} than in the VST (p = .0433).

In the parietal lobe, there were 2126 activated voxels in the VIT_{CC} and 772 activated voxels in the VST, of which 585 voxels overlapped (75.78%). In the occipital lobe, there were 1357 activated voxels in the VIT_{CC} and 2497 activated voxels in the VST, of which 439 voxels overlapped (17.58%). In the frontal lobe, there were 139 activated voxels in the VIT_{CC} and 70 active voxels in the VST, of which 8 voxels overlapped (11.42%).

Discussion

Minimizing scanning time is an important aspect when performing pediatric neuroimaging as time spent in the scanner is one of the most limiting factors for yielding successful functional series (Yerys et al., 2009). Therefore, the idea of this study was that being able to use *one* task to examine *two* different cognitive functions, namely language and visuospatial functions, would help to reach this objective. To this effect, we hypothesized that the control condition of the vowel identification task (VIT_{CC}) would require visuospatial skills and therefore reveal similar activation patterns as the visual search task (VST), which is known to induce visuospatial processing and was thus used as a reference task (Lidzba et al., 2006b).

Vowel identification task

In the active > control condition of the vowel identification task (VIT_{AC}) activation could be observed in well-known language areas in the left inferior frontal cortex (traditionally known as “Broca's area”; Price, 2010; see Fig. 2). This confirms and extends previous studies using this task (Everts et al., 2009; Ressel et al., 2006; Wilke et al., 2006). The current study therefore replicated this activation pattern in language producing areas in the dominant hemisphere in another large cohort of children. Due to the moderate degree of difficulty and the absence of the need to read, the VIT can, in contrast to more difficult language tasks (e.g. Demb et al., 1995; Gaillard et al., 2001), be performed correctly by normally developed preschool children or handicapped older children (Wilke et al., 2006, in press). The button presses used by the children to report their decisions allow to monitor task adherence online, enabling the researcher to repeat the task immediately if necessary. These advantages make the task a valuable tool for language studies in children.

The matching of two visually complex patterns in the VIT_{CC} requires visuospatial functions. In the current study we investigated the activation pattern in the VIT_{CC} for the first time and observed activation in brain regions classically associated with visuospatial functions: bilateral posterior parietal regions with right-hemispheric

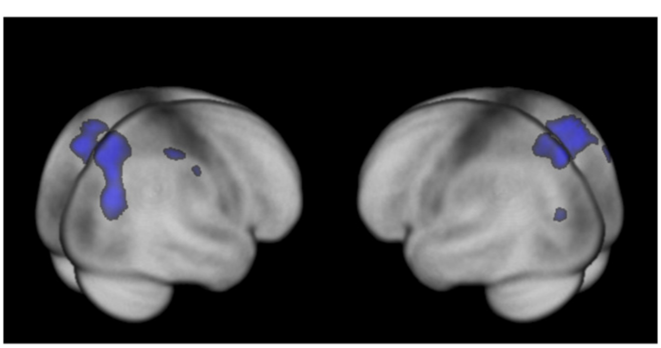

Fig. 3. Group activation map of the control condition of the vowel identification task (VIT_{CC}); random effects analyses (n = 39); p<.01, FWE-corrected. Note activation in bilateral, right-dominant posterior parietal regions, classically associated with visuospatial functions. Results are rendered on the custom-made gray matter template.

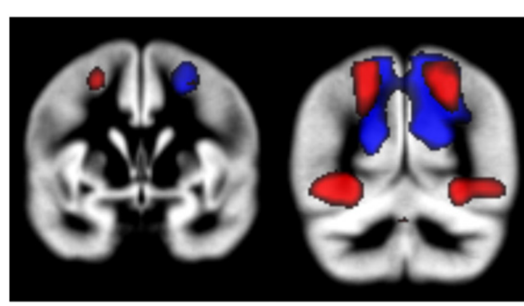

Fig. 5. Activation overlay maps (VIT_{CC}, blue and VST, red); random effects analyses (n = 39/41); p<.01, FWE-corrected. Note overlap of activation in frontal (left panel) brain regions, corresponding to the frontal eye field, and in posterior parietal regions (right panel), classically associated with visuospatial functions. Results are overlaid on the custom-made T1 template; orientation is neurological, i.e., left = left.

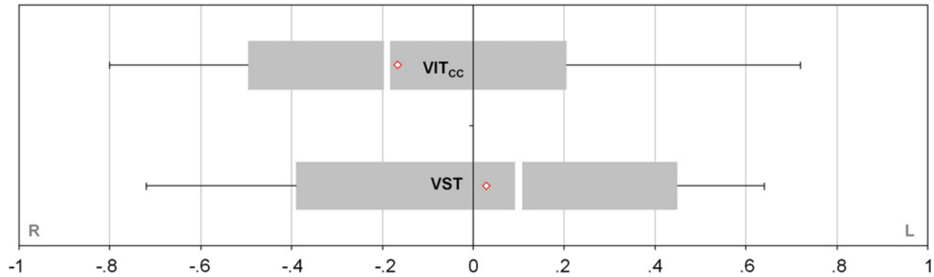

Fig. 6. Lateralization: box–whisker-plots of the lateralization in parietal cortex (VIT$_{CC}$, top, and VST, bottom). Note slightly right-lateralized activation in the VIT$_{CC}$ as opposed to the more bilateral activation in the VST; $p<.05$, Mann–Whitney-*U*-Test.

dominance (see Figs. 3 and 5) and the (predominantly right) frontal eye field (the border territory of the precentral gyrus and the superior frontal gyrus, Pierrot-Deseilligny et al., 2004; see Fig. 5). As in the active condition of the VIT, the pattern matching in the VIT$_{CC}$ can easily be performed by young children, and similarly, online monitoring of task adherence is possible, which is of particular importance especially in children (Church et al., 2010).

Comparison to the visual search task and tasks in literature

The VST revealed activation in bilateral occipital and parietal regions (see Fig. 4) as well as in bilateral frontal eye fields (see Fig. 5) as expected and previously observed (Everts et al., 2009; Lidzba et al., 2006b).

In several studies, superior parietal cortex together with the frontal eye field, has been associated with solving visuospatial problems. Superior parietal regions are thought to be associated with spatial and color encoding as well as the allocation of attention (Carpenter et al., 1999; Claeys et al., 2004; Cohen et al., 1996). The unique contributions of frontal brain regions to visuospatial processing, above and beyond oculomotor control (Cohen et al., 1996), are still controversial (Carpenter et al., 1999; Harris et al., 2000).

Besides some visual search tasks (e.g.; Makino et al., 2004; Nobre et al., 2003), different approaches to map visuospatial functions have been published, with mental rotation (e.g.; Alivisatos and Petrides, 1997; Booth et al., 2000; Carpenter et al., 1999; Clements-Stephens et al., 2009; Cohen et al., 1996; 1997; Ng et al., 2001) and judgment of line orientation (e.g. Clements-Stephens et al., 2008; Ng et al., 2001) being the most common tasks. As hypothesized, there is great overlap between the activation in the VST and the one in the pattern matching in the VIT$_{CC}$; particularly in superior parietal brain regions (see Fig. 5). This overlap of activation in areas associated with visuospatial functions indicates that these functions are required in both of our tasks.

With regard to the more prominent activation in the occipital lobe in the VST, we believe these can be ascribed to lower-level visual processing. For example, Vannini et al. (2004) observed no signal change with increased task demand in an angle discrimination task in occipital regions whereas such signal change was observed in parietal cortex, indicating that occipital areas are not involved in the specific solving of complex visuospatial problems. As the complex stimuli in the VST require more intensive visual scanning, we believe that this explains the stronger occipital activation seen in the VST when compared with the VIT$_{CC}$. This is in line with previous studies observing strong occipital activation when using visually complex stimulus material (Makino et al., 2004; Nobre et al., 2003).

A difference in task complexity is also reflected in the dropout rate in the current study, where data from 2 children performing the VST had to be discarded due to lack of task adherence, while this was not a problem for the VIT$_{CC}$. While the current group is too small to suggest a lower age limit for either task, the VST is, in our experience, more demanding and thus more difficult to solve for younger children.

Visuospatial deficits are the hallmark of, for example, neuropsychological impairment following prematurity (Baron et al., 2009; Isaacs et al., 2003; Marlow et al., 2007; Pavlova et al., 2006), therefore tools to assess these functions using non-invasive neuroimaging approaches in children are of particular interest. The easy-to-do VIT$_{CC}$ is a promising supplementation to existing, more complex visuospatial tasks (e.g. mental rotation tasks, judgment of line orientation, and visual search) that are currently being used in the challenging but highly interesting population of young children (Booth et al., 2000; Clements-Stephens et al., 2008, 2009; Everts et al., 2009; Lidzba et al., 2006b). We therefore suggest that approaches such as the one implemented in the VIT$_{CC}$ are worthy of further investigations regarding their applicability in this context.

Lateralization

Activation in fronto-parietal brain networks has been shown to be crucial for visuospatial problem solving in both lesion (e.g.; Ditunno and Mann, 1990; Newcombe et al., 1987) and functional imaging studies using PET or fMRI (e.g.; Alivisatos and Petrides, 1997; Cohen et al., 1996; Ng et al., 2001). The issue of lateralization of visuospatial functions however is still unresolved: several authors argued for right lateralization or at least predominance (e.g.; Clements-Stephens et al., 2008; Everts et al., 2009; Harris et al., 2000; for review see Vogel et al., 2003), some for left (e.g. Alivisatos and Petrides, 1997), and still others for bilateral involvement (e.g. Booth et al., 2000; Clements-Stephens et al., 2009; Cohen et al., 1996; Jordan et al., 2001). Ng et al. (2000) had proposed right hemispheric "leading" and "kick-starting" but bilateral contribution to visuospatial processing, while Carpenter et al. (1999) and Corballis (1997) had proposed increasing bilaterality with higher task demand. In this context, it seems interesting to remark that changes in the activation pattern with age were seen in visuospatial tasks; however, the available studies are inconclusive, suggesting either a more (Booth et al., 2000) or a less lateralized pattern of activation (Everts et al., 2009) in children when compared with adults. As age effects were not the focus of this study, age was used as a covariate of no interest in our analyses.

In our tasks, a slight right hemispheric dominance of visuospatial functions is seen in the VIT$_{CC}$, while a significantly more bilateral involvement is observable in the VST (see Fig. 6). The rightward dominance is in line with previous studies in healthy children (e.g.; Clements-Stephens et al., 2008; Everts et al., 2009), and we suggest that the more bilateral involvement in the VST might be due to increased task demand in this more complex task. If bilaterality indeed increases with higher task demands (Carpenter et al., 1999; Corballis, 1997), this again argues for using a less complex task when assessing the lateralization of visuospatial functions, particularly when examining children (Schweinsburg et al., 2005). On the other hand, more refined analyses aimed at investigating performance would suffer from the ceiling effect in easier tasks (Berl et al., 2006; Church et al., 2010), suggesting that the choice of the task will heavily depend on the particular aspect under study.

Possible contribution of saccadic eye movement

Saccadic eye movement has been shown to also activate both frontal eye field and parietal cortex (Anderson et al., 1994; Nobre et al., 2000). Saccadic eye movement is required especially to compare the two complex figures in the VST, and here was required in both conditions, while it was only necessary in the VIT_{CC}, not the VIT_{AC} (which may explain the more unilateral activation in the VIT; see Fig. 5). As eye movement was not monitored in our study, we can only speculate about this point. However, Carpenter et al. (1999) for example showed that the level of activity in parietal regions was significantly higher in a mental rotation task than in a task designed to induce saccadic eye movement. Gitelman et al. (2002) and Nobre et al. (2003) compared the activation in a visual search task with activation in a saccadic eye movement task and showed that the main part of activation in the visuospatial task was due to task engagement. Moreover, Loayza et al. (2011) recently observed activation in fronto-parietal networks, similar to those seen in our study, in a spatial processing task not requiring saccadic eye movements. For these reasons, we believe that the activation seen in our tasks is primarily induced by core visuospatial functions, instead of being driven by saccadic eye movements.

"Dual use"

The novel idea of a "dual use" task seems to be an interesting approach for pediatric fMRI task design. It has to be distinguished from dual task studies as recently reviewed by Szameitat et al. (2011). Dual task studies aim at identifying brain regions jointly activated by two different tasks, while the idea of "dual use" task is to assess two functions within one task. While the investigation of two similar functions (Bunge et al., 2002) or a cognitive and a motor task (Holland et al., 2001) have already been combined, the idea to combine tasks from two cognitive domains in one paradigm seems to be novel.

To design a task in a way that the one condition, aimed at localizing a certain cognitive function, can serve as a control condition for the second condition, aimed at localizing another cognitive function and vice versa, is promising. However, it requires careful attention to details above and beyond that already required when designing pediatric fMRI tasks (Church et al., 2010; Freilich and Gaillard, 2010). As with any other fMRI design, functions of interest need to be isolated while functions of no interest need to be balanced between conditions (Church et al., 2010). In our VIT, visual attention, visual perception of objects, matching (of sorts), decision-making, and pressing a button are functions required in both conditions. On the other hand, phonological analysis is only required in the active condition and pattern matching is only required in the control condition, allowing to assess both.

Compared to the conventional approach of using two tasks to examine two cognitive functions, either scanning time can be minimized or more data can be acquired in the same time when using a "dual use" task. As such, the approach may be most beneficial when examining children, or even more so, in pediatric patients (Yerys et al., 2009), but is in no way limited to this group. Future task design especially, but not only, for children in the research and the clinical field may therefore benefit from the idea of the "dual use" of a task.

Limitations

The pattern matching in the VIT_{CC} has the advantage that even younger children have few difficulties in solving the task. While our current group was not designed to be balanced and large enough to assess this aspect, there certainly is a ceiling effect that could become a constraint in future studies in which performance is of relevance. For these reasons, it can currently not be answered if the task is equally useful in adults. In future studies, monitoring eye movements would allow separating the influence of activation due to eye movements from activation due to visuospatial processing. The decision to use a custom template will always have to weigh data processing requirements versus comparability with results from other studies. For the current study, exploring and comparing the effects of these tasks in children for the first time, we decided to give preference to minimizing deformation during spatial normalization (Wilke et al., 2002). While our sample was population-based and as such an appropriate representation of the overall population with regard to the presence of left-handed subjects (about 10%; Oldfield, 1971), the absolute numbers are too small to allow meaningful explorations with regard to possible differences in their lateralization of either function.

Conclusion

This study confirms that the VIT_{AC} is able to assess productive language functions, and that the VST is able to assess visuospatial functions. In addition, we could show that (1) the VIT_{CC} is also useful for assessing visuospatial functions, and (2) both the language and the visuospatial domain can successfully be examined using one, "dual use" fMRI task in healthy children. This approach therefore seems to be promising in the research and the clinical field not only, but also particularly, when examining children.

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References

Alivisatos, B., Petrides, M., 1997. Functional activation of the human brain during mental rotation. Neuropsychologia 35, 111–118.

Anderson, T.J., Jenkins, I.H., Brooks, D.J., Hawken, M.B., Frackowiak, R.S., Kennard, C., 1994. Cortical control of saccades and fixation in man. A PET study. Brain 117, 1073–1084.

Andersson, J.L., Hutton, C., Ashburner, J., Turner, R., Friston, K., 2001. Modeling geometric deformations in EPI time series. Neuroimage 13, 903–919.

Ashburner, J., Friston, K.J., 2005. Unified segmentation. Neuroimage 26, 839–851.

Baron, I.S., Erickson, K., Ahronovich, M.D., Coulehan, K., Baker, R., Litman, F.R., 2009. Visuospatial and verbal fluency relative deficits in 'complicated' late-preterm preschool children. Early Hum. Dev. 85, 751–754.

Berl, M.M., Vaidya, C.J., Gaillard, W.D., 2006. Functional imaging of developmental and adaptive changes in neurocognition. Neuroimage 30, 679–691.

Bird, G., Catmur, C., Silani, G., Frith, C., Frith, U., 2006. Attention does not modulate neural responses to social stimuli in autism spectrum disorders. Neuroimage 31, 1614–1624.

Booth, J.R., MacWhinney, B., Thulborn, K.R., Sacco, K., Voyvodic, J.T., Feldman, H.M., 2000. Developmental and lesion effects in brain activation during sentence comprehension and mental rotation. Dev. Neuropsychol. 18, 139–169.

Bunge, S.A., Dudukovic, N.M., Thomason, M.E., Vaidya, C.J., Gabrieli, J.D., 2002. Immature frontal lobe contributions to cognitive control in children: evidence from fMRI. Neuron 33, 301–311.

Byars, A.W., Holland, S.K., Strawsburg, R.H., Bommer, W., Dunn, R.S., Schmithorst, V.J., Plante, E., 2002. Practical aspects of conducting large-scale functional magnetic resonance imaging studies in children. J. Child Neurol. 17, 885–890.

Carpenter, P.A., Just, M.A., Keller, T.A., Eddy, W., Thulborn, K., 1999. Graded functional activation in the visuospatial system with the amount of task demand. J. Cogn. Neurosci. 11, 9–24.

Church, J.A., Petersen, S.E., Schlagger, B.L., 2010. The "Task B problem" and other considerations in developmental functional neuroimaging. Hum. Brain Mapp. 31, 852–862.

Claeys, K.G., Dupont, P., Cornette, L., Sunaert, S., Van Hecke, P., De Schutter, E., Orban, G.A., 2004. Color discrimination involves ventral and dorsal stream visual areas. Cereb. Cortex 14, 803–822.

Clements-Stephens, A.M., Rimrodt, S.L., Gaur, P., Cutting, L.E., 2008. Visuospatial processing in children with neurofibromatosis type 1. Neuropsychologia 46, 690–697.

Clements-Stephens, A.M., Rimrodt, S.L., Cutting, L.E., 2009. Developmental sex differences in basic visuospatial processing: differences in strategy use? Neurosci. Lett. 449, 155–160.

Cohen, M.S., Kosslyn, S.M., Breiter, H.C., DiGirolamo, G.J., Thompson, W.L., Anderson, A.K., Brookheimer, S.Y., Rosen, B.R., Belliveau, J.W., 1996. Changes in cortical activity during mental rotation. A mapping study using functional MRI. Brain 119, 89–100.
Corballis, M., 1997. Mental rotation and the right hemisphere. Brain Lang. 57, 100–121.
DeGuibert, C., Maumet, C., Ferré, J.-C., Jannin, P., Biraben, A., Allaire, C., Barillot, C., Le Rumeur, E., 2010. FMRI language mapping in children: a panel of language tasks using visual and auditory stimulation without reading or metalinguistic requirements. Neuroimage 51, 897–909.
Demb, J.B., Desmond, J.E., Wagner, A.D., Vaidya, C.J., Glover, G.H., Gabrieli, J.D., 1995. Semantic encoding and retrieval in the left inferior prefrontal cortex: a functional MRI study of task difficulty and process specificity. J. Neurosci. 15, 5870–5878.
Ditunno, P.L., Mann, V.A., 1990. Right hemisphere specialization for mental rotation in normals and brain damaged subjects. Cortex 26, 177–188.
Durston, S., Casey, B.J., 2006. What have we learned about cognitive development from neuroimaging? Neuropsychologia 44, 2149–2157.
Everts, R., Lidzba, K., Wilke, M., Kiefer, C., Mordasini, M., Schroth, G., Perrig, W., Steinlin, M., 2009. Strengthening of laterality of verbal and visuospatial functions during childhood and adolescence. Hum. Brain Mapp. 30, 473–483.
Everts, R., Lidzba, K., Wilke, M., Kiefer, C., Wingeier, K., Schroth, G., Perrig, W., Steinlin, M., 2010. Lateralization of cognitive functions after stroke in childhood. Brain Inj. 24, 859–870.
Freilich, E.R., Gaillard, W.D., 2010. Utility of functional MRI in pediatric neurology. Curr. Neurol. Neurosci. Rep. 10, 40–46.
Friston, K.J., Holmes, A.P., Worsley, K.J., Poline, J.B., Frith, C.D., Frackowiack, R.S., 1995. Statistical parametric maps in functional imaging: a general linear approach. Hum. Brain Mapp. 2, 189–210.
Gaillard, W.D., Pugliese, M., Grandin, C.B., Braniecki, S.H., Kondapaneni, P., Hunter, K., Xu, B., Petrella, J.R., Balsamo, L., Basso, G., 2001. Cortical localization of reading in normal children: an fMRI language study. Neurology 57, 47–54.
Gaillard, W.D., Balsamo, L., Xu, B., McKinney, C., Papero, P.H., Weinstein, S., Conry, J., Pearl, P.L., Sachs, B., Sato, S., Vezina, L.G., Frattali, C., Theodore, W.H., 2004. fMRI language task panel improves determination of language dominance. Neurology 63, 1403–1408.
Gitelman, D.R., Parrish, T.B., Friston, K.J., Mesulam, M.M., 2002. Functional anatomy of visual search: regional segregations within the frontal eye fields and effective connectivity of the superior colliculus. Neuroimage 15, 970–982.
Hahn, N., Jansen, P., Heil, M., 2010. Preschoolers' mental rotation: sex differences in hemispheric asymmetry. J. Cogn. Neurosci. 22, 1244–1250.
Harris, I.M., Egan, G.F., Sonkkila, C., Tochon-Danguy, H.J., Paxinos, G., Watson, J.D., 2000. Selective right parietal lobe activation during mental rotation: a parametric PET study. Brain 123, 65–73.
Holland, S.K., Plante, E., Byars, A.W., Strawsburg, R.H., Schmithorst, V.J., Ball, W.S., 2001. Normal fMRI brain activation patterns in children performing a verb generation task. Neuroimage 14, 837–843.
Isaacs, E.B., Edmonds, C.J., Chong, W.K., Lucas, A., Gadian, D.G., 2003. Cortical anomalies associated with visuospatial processing deficits. Ann. Neurol. 53, 768–773.
Johnson, M.H., 2001. Functional brain development in humans. Nat. Rev. Neurosci. 2, 475–483.
Jordan, K., Heinze, H.J., Lutz, K., Kanowski, M., Jäncke, L., 2001. Cortical activations during the mental rotation of different visual objects. Neuroimage 13, 143–152.
Lidzba, K., Staudt, M., Wilke, M., Krägeloh-Mann, I., 2006a. Visuospatial deficits in patients with early left-hemispheric lesions and functional reorganization of language: consequence of lesion or reorganization? Neuropsychologia 44, 1088–1094.
Lidzba, K., Staudt, M., Wilke, M., Grodd, W., Krägeloh-Mann, I., 2006b. Lesion-induced right-hemispheric language and organization of nonverbal functions. Neuroreport 26, 929–933.
Lidzba, K., Wilke, M., Staudt, M., Krägeloh-Mann, I., Grodd, W., 2008. Reorganization of the cerebro-cerebellar network of language production in patients with congenital left-hemispheric brain lesions. Brain Lang. 106, 204–210.
Loayza, F.R., Fernández-Seara, M.A., Aznárez-Sanado, M., Pastor, M.A., 2011. Right parietal dominance in spatial egocentric discrimination. Neuroimage 55, 635–643.
Macey, P.M., Macey, K.E., Kumar, R., Harper, R.M., 2004. A method for removal of global effects from fMRI time series. Neuroimage 22, 360–366.
Makino, Y., Yokosawa, K., Takeda, Y., Kumada, T., 2004. Visual search and memory search engage extensive overlapping cerebral cortices: an fMRI study. Neuroimage 23, 525–533.
Marlow, N., Hennessy, E.M., Bracewell, M.A., Wolke, D., 2007. Motor and executive function at 6 years of age after extremely preterm birth. Pediatrics 120, 793–804.
Newcombe, F., Ratcliff, G., Damasio, H., 1987. Dissociable visual and spatial impairments following right posterior cerebral lesions: clinical, neuropsychological and anatomical evidence. Neuropsychologia 25, 149–161.
Ng, V.W., Eslinger, P.J., Williams, S.C., Brammer, M.J., Bullmore, E.T., Andrew, C.M., Suckling, J., Morris, R.G., Benton, A.L., 2000. Hemispheric preference in visuospatial processing: a complementary approach with fMRI and lesion studies. Hum. Brain Mapp. 10, 80–86.
Ng, V.W., Bullmore, E.T., de Zubicaray, G.I., Cooper, A., Suckling, J., Williams, S.C., 2001. Identifying rate-limiting nodes in large-scale cortical networks for visuospatial processing: an illustration using fMRI. J. Cogn. Neurosci. 13, 537–545.
Nobre, A.C., Gitelman, D.R., Dias, E.C., Mesulam, M.M., 2000. Covert visual spatial orienting and saccades: overlapping neural systems. Neuroimage 11, 210–216.
Nobre, A.C., Coull, J.T., Walsh, V., Frith, C.D., 2003. Brain activations during visual search: contributions of search efficiency versus feature binding. Neuroimage 18, 91–103.
Oldfield, R.C., 1971. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9, 97–113.
O'Shaughnessy, E.S., Berl, M.M., Moore, E.N., Gaillard, W.D., 2008. Pediatric functional magnetic resonance imaging (fMRI): issues and applications. J. Child Neurol. 23, 791–801.
Pavlova, M., Sokolov, A., Krägeloh-Mann, I., 2006. Visual navigation in adolescents with early periventricular lesions: knowing where, but not getting there. Cereb. Cortex 17, 363–369.
Petermann, F., Petermann, U., 2007. Hamburg-Wechsler Intelligenztest für Kinder — IV (HAWIK-IV). Huber, Bern.
Pierrot-Deseilligny, C., Milea, D., Müri, R.M., 2004. Eye movement control by the cerebral cortex. Curr. Opin. Neurol. 17, 17–25.
Price, C.J., 2010. The anatomy of language: a review of 100 fMRI studies published in 2009. Ann. N. Y. Acad. Sci. 1191, 62–88.
Ressel, V., Wilke, M., Lidzba, K., Preissl, H., Krägeloh-Mann, I., Lutzenberger, W., 2006. Language lateralization in magnetoencephalography: two tasks to investigate hemispheric dominance. Neuroreport 17, 1209–1213.
Rey, A., 1941. L'examen psychologique dans les cas d'encephalopathie traumatique (The psychological assessment in the case of traumatic encephalopathy) [in French]. Arch. Psychol. 28, 286–340.
Rubia, K., Hyde, Z., Halari, R., Giampietro, V., Smith, A., 2010. Effects of age and sex on developmental neural networks of visual–spatial attention allocation. Neuroimage 51, 817–827.
Schapiro, M.B., Schmithorst, V.J., Wilke, M., Byars, A.W., Strawsburg, R.H., Holland, S.K., 2004. BOLD fMRI signal increases with age in selected brain regions in children. Neuroreport 15, 2575–2578.
Schweinsburg, A.D., Nagel, B.J., Tapert, S.F., 2005. fMRI reveals alteration of spatial working memory networks across adolescence. J. Int. Neuropsychol. Soc. 11, 631–644.
Staudt, M., Lidzba, K., Grodd, W., Wildgruber, D., Erb, M., Krägeloh-Mann, I., 2002. Right-hemispheric organization of language following early left-sided brain lesions: functional MRI topography. Neuroimage 16, 954–967.
Szaflarski, J.P., Binder, J.R., Possing, E.T., McKiernan, K.A., Ward, B.D., Hammeke, T.A., 2002. Language lateralization in left-handed and ambidextrous people: fMRI data. Neurology 59, 238–244.
Szameitat, A.J., Schubert, T., Müller, H.J., 2011. How to test for dual-task-specific effects in brain imaging studies— an evaluation of potential methods. Neuroimage 54, 1765–1773.
Vannini, P., Almkvist, O., Franck, A., Jonsson, T., Volpe, U., Kristoffersen Wiberg, M., Wahlund, L.O., Dierks, T., 2004. Task demand modulations of visuospatial processing measured with functional magnetic resonance imaging. Neuroimage 21, 58–68.
Vogel, J.J., Bowers, C.A., Vogel, D.S., 2003. Cerebral lateralization of spatial abilities: a meta-analysis. Brain Cogn. 52, 197–204.
Wilke, M., Lidzba, K., 2007. LI-tool: a new toolbox to assess lateralization in functional MR-data. J. Neurosci. Methods 163 (1), 128–136.
Wilke, M., Schmithorst, V.J., 2006. A combined bootstrap/histogram analysis approach for computing a lateralization index from neuroimaging data. Neuroimage 33, 522–530.
Wilke, M., Schmithorst, V.J., Holland, S.K., 2002. Assessment of spatial normalization of whole-brain magnetic resonance images in children. Hum. Brain Mapp. 17, 48–60.
Wilke, M., Holland, S.K., Myseros, J.S., Schmithorst, V.J., Ball, W.S., 2003. Functional magnetic resonance imaging in pediatrics. Neuropediatrics 34, 225–233.
Wilke, M., Lidzba, K., Staudt, M., Buchenau, K., Grodd, W., Krägeloh-Mann, I., 2005. Comprehensive language mapping in children, using functional magnetic resonance imaging: what's missing counts. Neuroreport 16, 915–919.
Wilke, M., Lidzba, K., Staudt, M., Buchenau, K., Grodd, W., Krägeloh-Mann, I., 2006. An fMRI task battery for assessing hemispheric language dominance in children. Neuroimage 32, 400–410.
Wilke, M., Holland, S.K., Altaye, M., Gaser, C., 2008. Template-O-Matic: a toolbox for creating customized pediatric templates. Neuroimage 41, 903–913.
Wilke, M., Pieper, T., Lindner, K., Dushe, T., Holthausen, H., Krägeloh-Mann, I., 2010. Why one task is not enough: functional MRI for atypical language organization in two children. Eur. J. Paediatr. Neurol. 14, 474–478.
Wilke, M., Pieper, T., Lindner, K., Dushe, T., Staudt, M., Grodd, W., Holthausen, H., Krägeloh-Mann, I., in press. Clinical functional MRI of the language domain in children with epilepsy. Hum Brain Mapp. 2010 Dec 22. [Epub ahead of print].
Yerys, B.E., Jankowski, K.F., Shook, D., Rosenberger, L.R., Barnes, K.A., Berl, M.M., Ritzl, E.K., Vanmeter, J., Vaidya, C.J., Gaillard, W.D., 2009. The fMRI success rate of children and adolescents: typical development, epilepsy, attention deficit/hyperactivity disorder, and autism spectrum disorders. Hum. Brain Mapp. 30, 3426–3435.
Yuan, W., Altaye, M., Ret, J., Schmithorst, V., Byars, A.W., Plante, E., Holland, S.K., 2009. Quantification of head motion in children during various fMRI language tasks. Hum. Brain Mapp. 30, 1481–1489.