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ORIGINAL RESEARCH

Assessing motor, visual and language function using a single 5-minute fMRI paradigm: three birds with one stone

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Abstract

Clinical functional Magnetic Resonance Imaging (fMRI) requires inferences on localization of major brain functions at the individual subject level. We hypothesized that a single "triple use" task would satisfy sensitivity and reliability requirements for successfully assessing the motor, visual and language domain in this context. This was tested here by the application in a group of healthy adults, assessing sensitivity and reliability at the individual subject level, separately for each domain. Our "triple use" task consisted of 2 conditions (condition 1, assessing motor and visual domain, and condition 2, assessing the language domain), serving mutually as active/control. We included 20 healthy adult subjects. Random effect analyses showed activation in primary motor, visual and language regions, as expected. Less expected regions were activated both for the motor and visual domains. Further, reliability of primary activation patterns was very high across individual subjects, with activation seen in 70–100% of subjects in primary motor, visual, and left-lateralized language regions.

These findings suggest the "triple use" task to be reliable at the individual subject's level to assess motor, visual and language domains in the clinical fMRI context. Benefits of such an approach include shortening of acquisition time, simplicity of the task for each domain, and using a visual stimulus. Following establishment of reliability in adults, the task may also be a valuable addition in the pediatric clinical fMRI context, where each of these factors is of high relevance.

Keywords Clinical functional MRI · Children · Visual · Motor · Language · Triple use

Introduction

Functional magnetic resonance imaging (fMRI) is a non-invasive tool to investigate and localize brain functions (Gaillard et al. 2004; Khorrami et al. 2011). In a clinical context, the aim is the delineation of eloquent cortex prior to a neurosurgical intervention (e.g., epilepsy surgery or tumor removal; Church et al. 2010; Gaillard et al. 2001; Thulborn et al. 1996). Here, the necessity to draw conclusions from a given session in an individual patient requires a task to be robust, easy enough to perform, and reliable in the induced activation pattern (Thulborn et al. 1996; Gaillard et al. 2001; Wilke et al. 2005, 2006).

In order to be a good target for a clinically-indicated fMRI exam, a given function has to be important in everyday life, has to have a reliable location in the brain, and needs to be readily identifiable; consequently, the majority of such exams will include questions pertaining to the motor, the visual, or the language domain (Zsoter et al. 2012), usually using robust block designs. Several modifications to simple block designs have already been suggested, including mixed block and event-related designs (Petersen and Dubis 2012), block designs with several conditions (Henson 2007), conjunction approaches (Bremmer et al. 2001), or factorial or parametric designs (Amaro and Barker 2006). Another specific aspect of patient studies is statistical rigor: in functional MRI group studies, the necessary correction for multiple

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comparisons can be done in different ways (Church et al. 2010; Nichols et al. 2003), favoring either sensitivity or specificity. On the individual patient level, however, sensitivity and reliability are of utmost concern; therefore, the activation pattern is commonly assessed at different, and usually uncorrected, thresholds (Gaillard et al. 2001; Zsoter et al. 2012).

The situation is complicated further when it comes to investigating pediatric patients, as specific aspects need to be considered in this setting (Church et al. 2010; Khorrami et al. 2011; Oja et al. 1999). For example, including visual stimulation reduces subject movement in the scanner, and shorter scanning sessions are most important to achieve higher success rates (Church et al. 2010; Yerys et al. 2009; Yuan et al. 2009; Zsoter et al. 2012). We have therefore previously developed a "dual use" fMRI paradigm where either of two conditions aims to induce desired activation in specific brain regions while simultaneously serving as the "control condition" for the other one (Ebner et al. 2011). This allows to dramatically shorten the time spent in the scanner, or to invest this time into acquiring more data.

As an extension to this "dual use" task approach (Ebner et al. 2011), we here aimed at assessing multiple domains in one task. To this effect, we modified an established, primarily passive story-listening task (Wilke et al. 2005) already used in clinical fMRI in children (Wilke et al. 2010; Zsoter et al. 2012). In its original version, the beep-story task contained stories which were modified such that a number of meaningful words were omitted and replaced by a beep-sound. This induces a (conscious or unconscious) "filling-the-gap" of missing words, leading to activation not only in primarily receptive (e.g., superior-temporal) but also more productive (e.g., inferior frontal) language regions (Wilke et al. 2005). The aim of the here-described modification was to reliably assess the language, but also the motor and the visual domain, by one single fMRI task (hence constituting a "triple use" task). This was achieved by combining the beep story (language) task with a visually-cued motor task (video-guided repetitive hand opening and closing). We hypothesized that the mutual active/control relationship between the two conditions would show activation for either motor and visual or language regions, according to the direction of the contrast in ensuing statistical analysis.

Materials and methods

Subjects

Twenty healthy adults (12 females) with a mean age of 31.7 ± 6.99 years were recruited for the reliability study. This study was performed in adults instead of in children in accordance with the provisions of the Declaration of Helsinki regarding vulnerable populations (WMA 2013). Contraindications to MRI were considered as exclusion criteria, as were the presence of known neurological or psychiatric diseases, visual or hearing defects, or pregnancy. All subjects were required to be native German speakers, to be in good general health, and right-handed. This was confirmed by an average Edinburgh Handedness Inventory (EHI; Oldfield 1971) score of 0.88 ± 0.1 (range, 0.63-1). Language abilities were assessed using the Peabody Picture Vocabulary test (PPVT; Williams et al. 1977). MR Images were screened for incidental findings by a board-certified neuroradiologist (TKH); no major abnormalities were detected on structural images in any subject.

Task

Subjects performed a modified version of the beep story task (Wilke et al. 2005). In condition 1, the motor and visual domains are assessed. The subject performed a repetitive opening and closing movement of both hands (motor domain), by adapting to the frequency of a dynamic visual stimulation performing the same movement (visual domain) for 30 s. The video shows two repetitively opening and closing hands, illustrating the motor task to be performed, at a frequency of ~1 Hz. Simultaneously, the subject listened to the backward reproduction of a story (see below) which made its meaning incomprehensible while preserving acoustic characteristics. In condition 2, the language domain is assessed. In each block, one of five children's beep-stories (based on Karunanayaka et al. 2007 and novel to the participant) lasting 30 s each is presented. The children's beep-stories were recorded by a professional female speaker. In the forward reproduction of the story, single (5–6) relevant nouns were removed and replaced by a pure tone (200 Hz, 750 ms), forcing the subject to silently interpolate the missing word by the story context (through a mostly unconscious "filling-the-gap" mechanism). During the story, no visual stimuli are provided (except for a central cross-hair), thus focusing attention on the story. Participants were instructed to move their hands (exactly as practiced before the scan) when the video is shown, and to intently listen to the beep-stories (as they would be quizzed afterwards). Such an announcement has been suggested to increase attention to the task (Sun et al. 2013) and also allows for post-hoc performance monitoring (Wilke et al. 2006). The task was arranged in a block design, with 6 blocks of condition 1 and 5 blocks of condition 2, lasting 30 s each.

The task was expected to generate two types of activation patterns after contrasting the two conditions. Condition 1 was expected to induce activation in sensorimotor (activated by the repetitive hand movements) and visual regions (activated by the dynamic visual input). Condition 2 was expected to induce activation in language processing regions (activated by the beep-stories). Auditory input is present in both conditions and its effect on contrasted analysis was thus expected to be null. A schematic representation of condition 1 and 2 and the hypothesized activation pattern is summarized in Table 1.

Data acquisition and processing

Data were acquired on a 1.5-T MR scanner (Avanto, Siemens Medizintechnik, Erlangen, Germany), using a 12-channel birdcage head coil. Functional images were acquired with a T2*-weighted echo-planar imaging (EPI) sequence (TR = 3000 ms, TE = 40 ms, matrix 64 × 64 × 64, voxel size 3 × 3 × 3 mm, 40 slices). A total of 110 images were acquired in 5:30 min. Additionally, a gradient-echo B0 fieldmap (TR = 546 ms, TE = 5.19 / 9.95 ms, 40 slices) and an anatomical T1-weighted 3D-data set (TR = 1300 ms, TE = 2.92 ms, matrix 256 × 256, voxel size 1 × 1 × 1 mm, 176 slices) were acquired.

Visual stimuli were projected onto an MR-compatible screen while auditory stimuli were delivered using dedicated high-fidelity headphones (MR-Confon, Magdeburg, Germany). All subjects confirmed good audio and visual stimulus delivery after the session. Task execution in condition 1 was monitored online by visually observing motor activity. Task execution in condition 2 was monitored post-hoc by asking questions regarding the content of the story (one question for each story, with three options provided); subjects had to perform above chance level in order to be included. This performance check, assessing both attention and memory, has been shown to be well-applicable in children (Wilke et al. 2005).

All data were processed using SPM12 software (Wellcome Department of Imaging Neuroscience, University College London, UK) running in Matlab (Mathworks, Natick, MA, USA). A 7th degree B-spline interpolation (Unser 1999) was used whenever possible. The first ten EPI images (corresponding to the first block of condition 1) were removed to allow for stabilization of longitudinal magnetization, leaving 100 EPI volumes, also ensuring equal power (50 images = 5 blocks) for both conditions. Functional images were realigned and unwarped, removing EPI and B0*movement distortions (Andersson et al. 2001). Images were coregistered and smoothed with a 6 mm full width at half maximum (FWHM) Gaussian Filter. Spatial normalization was achieved by anatomical T1 volume segmentation (Malone et al. 2015); the resulting normalization parameters were written out as inverse deformation fields and were then used to normalize the individual statistical parameter maps (see below), using a pushforward procedure. Voxel size of the normalized volumes was interpolated to 2 × 2 × 2 mm^3.

Statistics

First level statistical analyses were performed using the framework of the General Linear Model, generating individual parameter maps in native space. Motion parameters (3 traces, plus their shifted versions) from the motion fingerprint (Wilke 2012) were included as covariates. Condition 1 was contrasted over condition 2 to reveal the activation corresponding to visual and motor domains. Condition 2 was contrasted over condition 1 to reveal the activation corresponding to the language domain. Following spatial normalization, the resulting two contrast images per subject were included in separate second level random-effect analyses in the form of a one-sample t-test, using gender, age (in months), handedness (EHI score), and PPVT-score as covariates of no interest, due to these factors' known effects on language activation (Allendorfer et al. 2012; Gebauer et al. 2012; Holland et al. 2001; Szaflarski et al. 2012). Due to presumed differences in activation strength, statistical threshold for the activation patterns in each contrast were defined separately for each condition. As activation strength in the visual and motor domain is known to be higher (Drobyshevsky et al. 2006; Karakas et al. 2013), significance was assumed here at $p \leq 0.0005$, FDR (false discovery rate) corrected for multiple comparisons. For language domain activation, significance was assumed at $p \leq 0.05$, FDR-corrected

Table 1 Simplified schematic design of the "Triple Use" task and resulting hypotheses. In condition 1, a video of two repetitively opening and closing hands is shown, accompanied by an incomprehensible (reversed) story. In condition 2, the comprehensible (forward) beep-stories are presented acoustically, accompanied by a black screen with a small crosshair

Triple use task			
Condition 1(Motor/Visual)	Contrast	Condition 2language	Hypothesized activated region
Hearing	=	Hearing	None
Repetitive hand movement	>	N/A	Primary sensorimotor cortex; SMA; cerebellum
Dynamic visual stimulation	>	N/A	Primary visual cortex; visual association cortex
N/A	<	Language comprehension	Bilateral superior temporal, left inferior parietal
N/A	<	Active language processing	Left inferior frontal gyrus

SMA supplementary motor area

for multiple comparisons. For both analyses, an additional cluster-wise FWE-correction at $p \leq 0.05$ was applied.

Group activation vs. individual activation

Random effects analyses represent the average group activation pattern, but not necessarily reliable activation on the individual subject level (Thirion et al. 2007). This is of particular relevance in the clinical setting, where inference needs to be drawn from the individual dataset at hand (Zsoter et al. 2012). In order to estimate how reliably activation was seen at the individual subject level for each domain, we applied a region of interest (ROI) approach. In the statistical parameter map from the group analysis, we identified the local maximum of all major activation clusters, in both contrasts, based on previous studies (Drobyshevsky et al. 2006; Guzzetta et al. 2007; Karakas et al. 2013; Wilke et al. 2005, 2006; Staudt et al. 2002, 2004). A spherical ROI was defined with a radius of 12 mm, centered on each local maximum; thereafter, the number of suprathreshold voxels in each individual t-map within each ROI was determined. The resulting ROIs are illustrated in the bottom row(s) of Figs. 1 and 2, respectively. If only unilateral activation was seen, the ROI was mirrored to the opposite hemisphere to assess a homotopic region, as done before (Broser et al. 2012). For this analysis, we used a (liberal) threshold of $p \leq 0.001$, uncorrected, as typically used in a clinical setting (Gaillard et al. 2001; Zsoter et al. 2012). "Activation" was defined as the presence of suprathreshold voxels within the ROI. An activation was considered "very reliable" if it was present in at least 90% of subjects, and "reliable" if it was present in at least 70% of subjects; any activation present in less than that was deemed "unreliable". Further, "activation strength" was determined by relating the number of activated voxels to the size of the ROI (123 voxels).

Results

Group activation: condition 1 > condition 2

The group activation pattern from this contrast is shown in Fig. 1. Activation was present in several regions, most prominently in bilateral fronto-parietal regions (around the central sulcus, corresponding to S/M1) and bilateral occipital regions (around the calcarine sulcus, corresponding to V1), with further activation in bilateral posterior middle-temporal (corresponding to V5/MT) and in in bilateral anterior middle-frontal regions. Further activation was seen in

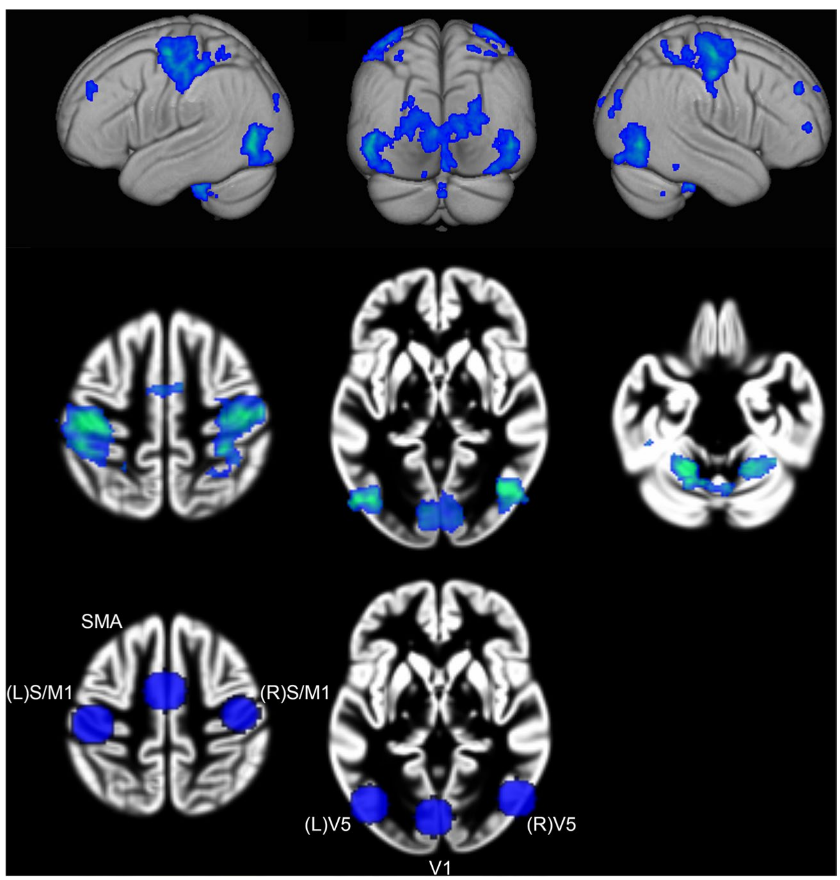

Fig. 1 Activation pattern and region of interest (ROI) from the group-analysis in condition 1 over condition 2 ($p \leq 0.0005$, voxel-wise FDR; $p \leq 0.05$, cluster-wise FWE). Note activation (top and middle rows) of: bilateral fronto-parietal regions (S/M1); bilateral posterior occipital regions corresponding to regions around the calcarine sulcus (V1); bilateral posterior middle temporal regions (V5/MT); supplementary motor area (SMA); anterior middle-frontal regions. Spherical ROIs (bottom row), corresponding to the local maximum of the major activation clusters in rows 1 & 2. Note that no ROI was placed in the cerebellum. Top row: activations are either rendered on the 3D surface (top rows) or overlaid on axial slices (bottom rows) of the gray matter tissue prior used for processing. Middle and bottom rows: activations and ROIs are overlaid on the gray matter tissue prior used for processing

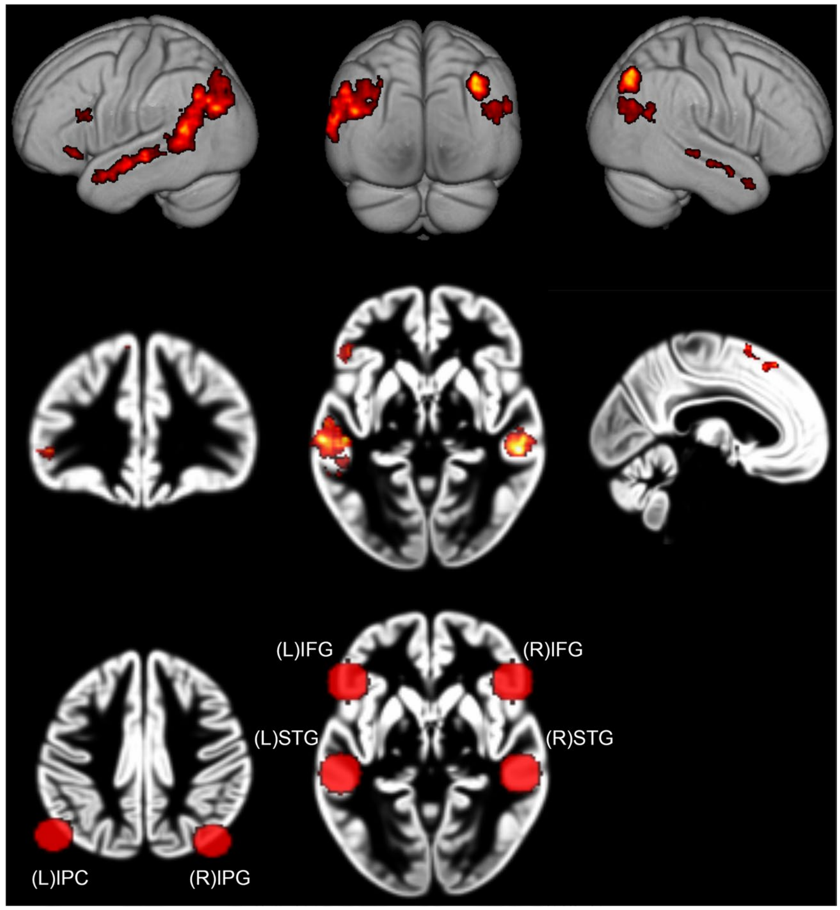

Fig. 2 Activation pattern and region of interest (ROI) from the group-analysis in condition 2 over condition 1 ($p \leq 0.05$, voxel-wise FDR; $p \leq 0.05$, cluster-wise FWE). Note activation (top and middle rows) of: bilateral superior temporal gyrus; posterior temporal and inferior parietal regions, with a leftward dominance (Wernicke); left inferior frontal region (Broca); pre-supplementary motor area (pre-SMA). Spherical ROIs (bottom row), corresponding to the local maximum of the major activation clusters in rows 1 & 2. Note that no ROI was placed in the pre-SMA. Top row: activations are either rendered on the 3D surface (top rows) or overlaid on axial slices (bottom rows) of the gray matter tissue prior used for processing. Middle and bottom rows: activations and ROIs are overlaid on the gray matter tissue prior used for processing

superior frontomesial regions (corresponding to SMA) and in bilateral superior cerebellar regions.

Group activation: condition 2 > condition 1

The group activation pattern from this contrast is shown in Fig. 2. Activation was present in several regions, most prominently in bilateral superior-temporal gyrus, posterior-temporal and inferior-parietal regions, with a leftward dominance, and left inferior-frontal region. Further activation was seen in bilateral dorsomedial frontal regions.

Reliability and activation strength on the individual level

For assessing reliability of individual activation, the following regions were selected from the group activation map: left and right sensorimotor regions (S/M1), supplementary motor region (SMA), primary visual region (V1), left and right middle temporal visual region (V5/MT), left and right superior temporal gyrus (STG), left and right inferior parietal cortex (IPC), and left and right inferior frontal gyrus (IFG). As no significant activation was present on the group level in right IFG and right STG ROIs, the left IFG and the left STG ROIs were mirrored to create these. Due to their midline location, we only used one ROI for V1 and SMA. In summary, we found an activation reliability of 85–100% in the motor domain, of 95–100% in the visual domain, and of 50–95% in the language domain. Reliability of activation and activation strength within each ROI are reported in Table 2 and shown in Fig. 3.

Discussion

The aim of the present study was to investigate the reliability of a "triple use" task approach for robust activation of motor, visual, and primary language regions. The combined mapping of these functions is particularly relevant in the context of parietal, temporal, frontal, or occipital lobe tumors, accounting for a large subset of brain tumors in children (Wells and Packer 2015) and a majority of brain tumors in adults (Zada et al. 2012), and for epilepsy surgery, which is an increasingly-used therapeutic option for drug-resistant structural epilepsy in children and adults (Ryvlin et al. 2014).

Table 2 Overview of the contrast, domains, reliability of activation (i.e., presence of supratheshold activation within the region of interest, in % of subjects), and activation strength (i.e., number of supratheshold voxels within the region of interest, in % of region of interest), expressed as median [interquartile range] for each Region of interest. Cf. Figure 3

Region of interest	Condition	Domain	Activation reliability [% of subjects]	Activation strength [% of VOI]
S/M1 (L)	1 > 2	Motor	100	45.57 [25.89]
S/M1 (R)	1 > 2	Motor	95	54.22 [20.54]
SMA	1 > 2	Motor	85	12.86 [23.19]
V1	1 > 2	Visual	95	74.11 [55.51]
V5 (L)	1 > 2	Visual	95	51.46 [28.05]
V5 (R)	1 > 2	Visual	100	52.7 [24.97]
STG (L)	2 > 1	Language	95	5.68 [8.92]
STG (R)	2 > 1	Language	50	1.14 [4.7]
IPC (L)	2 > 1	Language	80	1.24 [5.78]
IPC (R)	2 > 1	Language	80	1.73 [3.46]
IFG (L)	2 > 1	Language	70	1.14 [4.92]
IFG (R)	2 > 1	Language	50	0.05 [2.1]

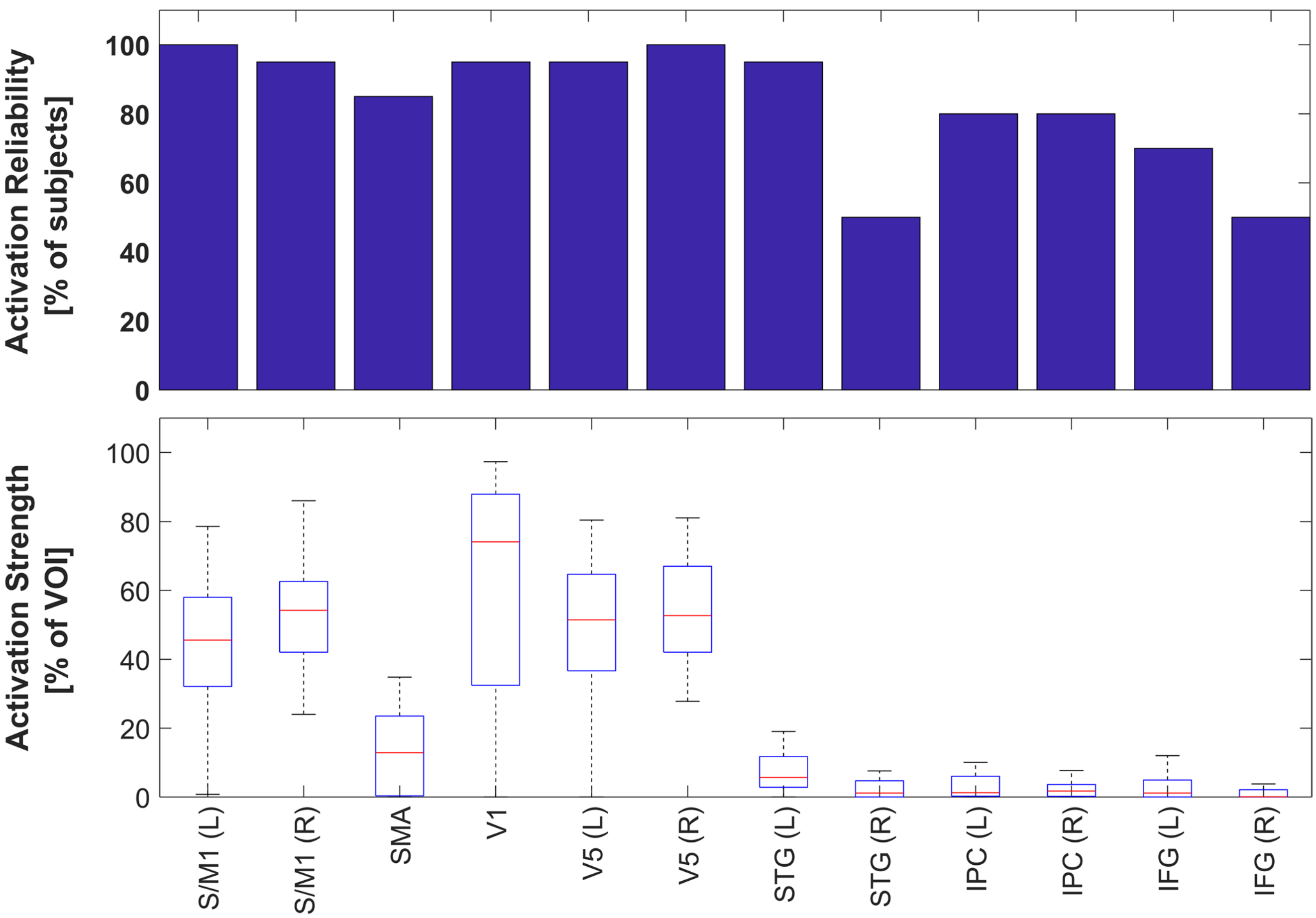

Fig. 3 Reliability of activation (top; percentage of subjects showing activation) and "activation strength" (bottom; percentage of activated voxels within the ROI) within regions selected from the group activation map. Inserts (top): proportion of subjects. For the motor and visual domain: left (L) and right (R) sensorimotor regions (S/M1), supplementary motor region (SMA), primary visual region (V1), left and right middle temporal visual region (V5/MT). For the language domain: left and right superior temporal gyrus (STG), left and right inferior parietal cortex (IPC), and left and right inferior frontal gyrus (IFG). Note activation was "very reliable" in most visual and motor and at least "reliable" in all left-sided language regions (top); also note that the overall level of activation (bottom) was stronger in the motor and visual than in the language domain

Group activation pattern: motor and visual domain

As expected, the activation pattern in condition 1 > condition 2 is characterized by a robust activation in primary sensorimotor and visual regions (Fig. 1).

Activation in S/M1 is in agreement with previous studies in healthy children and adults (Guzzetta et al. 2007; Mall et al. 2005) and in pediatric patients (Staudt et al. 2002, 2004). While bilateral hand movement may not be required in an individual patient, it is easier to perform than unilateral hand movement and provides a reference point in the unaffected hemisphere in case of unilateral pathology. Activation in SMA and cerebellum also agrees with previous studies (Ball et al. 1999; Staudt et al. 2002, 2004; see Fig. 1). The SMA has a role in planning motor tasks (Ball et al. 1999; Nachev et al. 2008) and the cerebellum is important for bimanually-coordinated hand movements (Debaere et al. 2004), likely induced by our subjects paying attention to, and mimicking, the rhythm of the motor activity presented to them visually. Activation in V1 may also be relevant in the clinical context as an individual functional localizer for optic radiation tracking in presurgical mapping (considering V1's high interindividual variability; Amunts et al. 2000).

The distinct (and robust, see below) activation in V5/MT was less expected, but is consistent with previous studies as subjects see a moving stimulus versus a stationary crosshair and V5/MT is involved in visual motion processing (Silvanto et al. 2005; Thakral and Slotnik 2009). Further, there may also be an effect of motor action observation (Buccino et al. 2001; Rumiati et al. 2005). The bilateral activation in anterior middle-frontal regions was unexpected. However, these regions have been implicated in the top-down control of matching visual and motor response (Buccino et al. 2004; Vogt et al. 2007), in line with their role in monitoring action-imitation.

In summary, both primary and secondary motor and visual cortical regions were robustly activated, using one condition only.

Group activation pattern: language domain

The activation pattern in condition 2 > condition 1 shows a robust bilateral activation in classically language-related brain regions (see Fig. 2). This activation of large parts of the language network, including regions traditionally referred to as Wernicke's and Broca's regions, is consistent with the pattern described previously (Wilke et al. 2005). The activation along the superior temporal sulcus was seen before during processing human speech (Tzourio-Mazoyer et al. 2015), and the left posterior-temporal/inferior-parietal activation in Wernicke's region reflects language comprehension (Ahmad et al. 2003; Wilke et al. 2005).

Activation of left Broca's region is in agreement with our previous studies in healthy children (Lidzba et al. 2011; Wilke et al. 2005). Inferior-frontal activation was seen before in passive listening tasks (Lanyon et al. 2009; Suarez et al. 2014), but not consistently (Ahmad et al. 2003). This region seems to activate stronger when active processing of auditory content is required (Lanyon et al. 2009; Vannest et al. 2009; Wilke et al. 2005). This confirms previous studies relating left inferior-frontal regions to semantic and phonologic decision-making, speech planning, and grammatical processing (Ahmad et al. 2003; Lidzba et al. 2011).

Pre-SMA and SMA have been implicated both in motor and cognitive triggering (Nachev et al. 2008), and their activation here likely reflects task switching (Hikosaka and Isoda 2010; Rushworth et al. 2002).

Assessment of laterality of language functions was not the focus of this study. However, the identification of Broca's area using a primarily passive task is a promising alternative to more complicated active task aimed at delineating this region in the presurgical context (Wilke et al. 2006). Caution must be used here, though, as at least in single subjects, this activation was shown to be in disagreement with a more direct assessment of productive language functions (Wilke et al. 2010). We therefore performed post-hoc analyses on the consistency of lateralization in the frontal lobe by applying a threshold-free bootstrapping method (Wilke and Schmithorst 2006; Wilke and Lidzba 2007). This demonstrated left-frontal dominance in 15/20 subjects; when only including subjects with significant left-frontal activation, 14/14 showed a positive lateralization index, indicating bilateral (Wilke et al. 2006) or left-dominant frontal activation (Ebner et al. 2011). This activation may therefore cautiously be considered an additional indicator of frontal dominance, but the relation with lateralization seen in other tasks and in subjects showing atypical language organization remains to be elucidated.

In summary, language regions involved both in comprehension and in production were robustly identified by one condition (Lidzba et al. 2011; Wilke et al. 2005). This activation pattern, together with the motor and visual activation patterns seen in the inverted contrast, confirms our hypothesis that the motor, visual and language domain can successfully be assessed using a single "triple use" task".

Reliability of activation on the individual level

"Very reliable" activation (≥ 90% of subjects) within the ROI was observable for left and right S/M1 and V5/MT, as well as for V1 and left STG. "Reliable" activation with suprathreshold activation in less than 90%, but more than 70% of subjects was observed for SMA, left and right IPC, and left IFG activation. Activation in right STG and right IFG was "unreliable" (Fig. 3, upper plot). This is in line with the left-lateralized activation of language regions in our group, as would be expected from the right-handedness of our subjects (Szaflarski et al. 2012).

Several factors could explain the discrepancy between reliability in the motor/visual and the language domain, including either region-specific biological factors or sub-optimal contrast between conditions. The language-related activation originates from the contrast between forward and backward speech, controlling for voice-selective bi-temporal regions in the brain (Belin et al. 2000). This was suggested to allow isolating regions responsible for auditory semantic processing (such as Wernicke's region; Ahmad et al. 2003). However, the lower activation strength in the language domain observed here may also reflect a lower sensitivity of this particular contrast (Brown et al. 2012). This seems to argue in favor of including a "less matched" acoustic condition for future studies as this would increase the effect size of the contrast (relevant for clinical applications in particular, where sensitivity is favored over specificity; Gaillard et al. 2001; Yerys et al. 2009; Zsoter et al. 2012).

On a side note, it is interesting to note the discrepancy in "activation strength" (at the same threshold) between the motor/visual and the language regions (Fig. 3, lower plot), with much "stronger" activation seen in sensorimotor and visual brain regions. This can be considered a post hoc verification for the presumed different sensitivity of the conditions (Drobyshevsky et al. 2006; Karakas et al. 2013), which lead to our *a priori* choice of a stricter statistical threshold for the motor/visual domain (see methods section).

Benefits of a "triple-use" task and potential applicability in children

The most obvious benefit of a "triple use" task, with respect to traditional "single use" tasks, is in shorter acquisition time. The short duration of 5:30 min is appropriate for children (Byars et al. 2002), and shorter sessions lead to a higher success rate (Vannest et al. 2014; Wilke et al. 2003; Yerys et al. 2009). This "saved time" can then be spent on applying another task (important for the language domain in particular; Gaillard et al. 2004; Wilke et al. 2010).

A second benefit is the simplicity of the task for each domain. While the task may seem complicated at first sight, instructions may be summarized as "move your hands when you see the video; otherwise, listen closely to the stories". This aspect is naturally relevant for children (Church et al. 2010) but also for, e.g., elderly or impaired adults. Also, the inclusion of visual stimulation reduces subject motion (Yuan et al. 2009).

Finally, the "triple use" task allows for monitoring compliance, which is particularly important in children (Church et al. 2010; Vannest et al. 2014; Wilke et al. 2003; Zsoter et al. 2012; Yerys et al. 2009). For condition 1, opening/closing of the hands can be verified visually during the scanning session. In MRI setups including pressure-monitoring squeeze balls, hand motion could also be verified objectively. For condition 2, compliance was assessed post hoc (Wilke et al. 2005) by asking questions about each story's content after the scan. While this approach is inferior to direct and online performance monitoring (Máté et al. 2016), it confirms whether the subject actually completed the task or not, which is most relevant in the clinical setting in particular (Gaillard et al. 2004).

Limitations

This work was meant to demonstrate the reliability of assessing several domains using one fMRI task. Further steps on the way to clinical usability (comparison with existing reference tasks, application in clinical adult and pediatric populations, comparisons with electrophysiological recordings etc.) are still outstanding. Although ultimately, this task is aimed for use in children, its reliability was tested here in adults. However, both conditions were used before in children, including pediatric patients (Holland et al. 2001; Wilke et al. 2005, 2010, 2011; Karunanayaka et al. 2007; Szaflarski et al. 2012; Sroka et al. 2015). We therefore do not believe this to be a major concern. Finally, we do not consider the possibility of a different ceiling effect in the adult group compared to children to be an issue, as the task is very simple to perform.

With regard to our sample size, numbers between 20 and 30 subjects were considered sufficient to ensure reproducibility (Thirion et al. 2007). It was suggested that a significant result in a smaller sample may be actually more convincing, although with a tongue-in-cheek undertone (Friston et al. 2012). In any case, given the very robust results on the group as well as the individual level as described above, we do not believe that sample size is an issue for this study.

While the observed activation pattern described above was very similar to the expected pattern and that observed in previous studies, no formal comparison was made to the same group of subjects performing a "single use task". Hence, slight activation differences as compared to, e.g., simple opening and closing of both hands versus rest, cannot be ruled out. One disadvantage of the stimulation approach taken here (i.e., combine motor and visual stimulation in one condition) is that the ultimate ascription of foci of activation to the one or the other domain may not be possible. For example, the SMA activation may be induced both by action observation and by motor planning. Further, an asynchronous task design (Huang et al. 2009) could potentially be used to better "tease apart" the contribution of either condition to each observable focus of activation.

Finally and as noted before (Dorn et al. 2014), it must be noted that when using a multiple-use task, "activation" may be caused by either activation in condition 2 over condition 1 (language domain) or de-activation in condition 1 over condition 2 (motor/visual domain). For the most part and the expected major activation foci, this will not be an issue, but it theoretically allows for alternative interpretation of less clear-cut findings. Such ambiguities in the interpretation of activation or deactivation could, however, be investigated further using more direct activation measures such as percent signal change (Pernet et al. 2014).

Conclusions

The present study demonstrated that the "triple use" task is able to assess the motor and visual as well as the language domains, without high demands regarding subject cooperation. Most of the major foci of activation identified in the random effect group analysis were demonstrated to also be "very reliably", or at least "reliably" activated on the individual subject level. This suggests that this task is suitable for use in children in general, and in the clinical setting in particular.

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Compliance with ethical standards

Conflict of interest Simona Fiori declares that she has no conflict of interest. Carolin Zendler declares that she has no conflict of interest. Till-Karsten Hauser declares that he has no conflict of interest. Karen Lidzba declares that she has no conflict of interest. Marko Wilke declares that he has no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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