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Original contribution

Targeted brain activation using an MR-compatible wrist torque measurement device and isometric motor tasks during functional magnetic resonance imaging

Martijn P. Vlaar [a,*], Winfred Mugge [a,b], Paul F.C. Groot [c], Sarvi Sharifi [d], Lo J. Bour [d], Frans C.T. van der Helm [a], Anne-Fleur van Rootselaar [d], Alfred C. Schouten [a,e]

[a] Department of BioMechanical Engineering, Faculty of Mechanical, Maritime and Materials Engineering, Delft University of Technology, Delft, The Netherlands
[b] MOVE Research Institute Amsterdam, Faculty of Human Movement Sciences, VU University, Amsterdam, The Netherlands
[c] Department of Radiology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands
[d] Department of Neurology and Clinical Neurophysiology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands
[e] Laboratory of Biomechanical Engineering, MIRA Institute for Biomedical Technology and Technical Medicine, University of Twente, Enschede, The Netherlands

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ABSTRACT

Dedicated pairs of isometric wrist flexion tasks, with and without visual feedback of the exerted torque, were designed to target activation of the CBL and BG in healthy subjects during functional magnetic resonance imaging (fMRI). Selective activation of the cerebellum (CBL) and basal ganglia (BG), often implicated in movement disorders such as tremor and dystonia, may help identify pathological changes and expedite diagnosis. A prototyped MR-compatible wrist torque measurement device, free of magnetic and conductive materials, allowed safe execution of tasks during fMRI without causing artifacts. A significant increase of activity in CBL and BG was found in healthy volunteers during a constant torque task with visual feedback compared to a constant torque task without visual feedback. This study shows that specific pairs of motor tasks using MR-compatible equipment at the wrist allow for targeted activation of CBL and BG, paving a new way for research into the pathophysiology of movement disorders.

1. Introduction

The healthy human body is able to perform fast, accurate and efficient motor actions and is able to correct for perturbations while performing these actions. The central nervous system is responsible for the execution of voluntary as well as involuntary actions like reflexes using a network of multiple interconnected control loops. This network includes the cerebellum (CBL) and basal ganglia (BG) [1]. Part of the role of the CBL is to integrate sensory information and it concerns the unconscious neuromuscular control of a joint [2], which includes correcting for errors [3]. BG is a collective term for a group of brain regions including the caudate nucleus, putamen and globus pallidus. The role of the BG in motor control is less apparent. The BG are supposedly involved in the control of complex patterns of motor activity [1,4].

Movement disorders impair the ability to produce and control bodily movements [5], resulting in immobility and social inconvenience [6]. Over 28% of the population over 50 years old suffers from movement disorders [7]. Many of these disorders have unknown pathophysiology [8–10]. Although specific brain regions, including the CBL and BG, have been implicated in specific movement disorders, still most are being diagnosed by symptoms. Unfortunately, diagnosis of movement disorders can be hindered by the similarity of their symptoms [11]. An incorrect diagnosis could not only lead to ineffective treatment, but also to adverse consequences [12]. Developing tools to aid physicians diagnose patients with movement disorders may facilitate effective treatment by early detection and improved accuracy of the diagnosis.

Functional magnetic resonance imaging (fMRI) is a non-invasive technique for visualizing neural activity, which enables imaging of deep brain structures like the BG. fMRI recordings suffer from image distortions due to movement of the subject's head [16] and to the use of magnetic or conductive materials [17]. Using fMRI to study blood oxygenation level dependent (BOLD) activations in the CBL and BG during the execution of motor tasks and comparing results between

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* Corresponding author at: Department of BioMechanical Engineering, Delft University of Technology, Mekelweg 2, 2628 CD, Delft, The Netherlands. Tel.: +31 152785625.
E-mail address: m.p.vlaar@tudelft.nl (M.P. Vlaar).

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healthy subjects, and patients with certain movement disorders, may help identify pathological changes associated with those movement disorders. The number of studies that investigate brain activation in the CBL and BG during motor tasks with feedback is limited, especially studies that incorporate feedback to enable corrective actions and facilitate the activation of the CBL and BG. Hidler et al. [13] did not find activity in the CBL or BG in an isometric wrist torque task where the subject at 1 Hz interchanged between exerting a certain torque with visual feedback and relaxing compared to a rest task. This finding suggests that a fast switching task is executed using feedforward control. On the other hand, Vaillancourt et al. [14] did find activity in the CBL and BG in healthy subjects when comparing a grip force task with visual feedback to the same task without visual feedback. Visual feedback appears to facilitate adaptation of the subject's motor commands during the task. Klarhöfer et al. [15] found activity in the CBL in healthy subjects when comparing a gripping task with visual feedback to the same task with force perturbations, generated using a haptic manipulator. Hence, increased activation in both CBL and BG, only CBL, and in neither CBL nor BG has been demonstrated using motor tasks during fMRI. However, these activation combinations have been achieved on different joints, areas of focus and experimental setups. This study aims to show these activations on one single joint using an isometric setup.

Creating a paradigm using a pair of subtly different motor tasks and contrasting the recorded fMRI data enable visualization of differences in brain activation between these tasks. Therefore, using fMRI to achieve a better understanding of movement disorders, requires an MR-compatible measurement setup that enables safe execution of motor tasks without causing image artifacts and a measurement paradigm to consistently activate the CBL and BG. Since the wrist is often affected in movement disorders and since it is relatively easily accessible when a subject is in the MR scanner, we aimed for motor tasks using flexion torque of the wrist.

The goal of this research was to selectively evoke brain activity in the CBL or BG using isometric motor tasks during fMRI in healthy subjects. Measurements were performed in an MR scanner using an MR-compatible wrist torque measurement device which was developed specifically for this study.

2. Methods

2.1. Subjects

Ten subjects (5 men), all right-handed with a laterality index greater than 75 according to Edinburgh Handedness Inventory [18] and aged between 25 and 30, were included and provided written informed consent prior to participation in this study, which was approved by the medical ethics committee of the Academic Medical Center Amsterdam (#2011_161). Exclusion criteria were: metal inside the body, claustrophobia, reluctance to be informed about observed abnormalities in MR images, pregnancy, known psychiatric history, known neurological conditions, use of centrally active medication, substantial daily use of alcohol (>2 U per day) or drugs, and use of alcohol or drugs within 24 h before participation in the research.

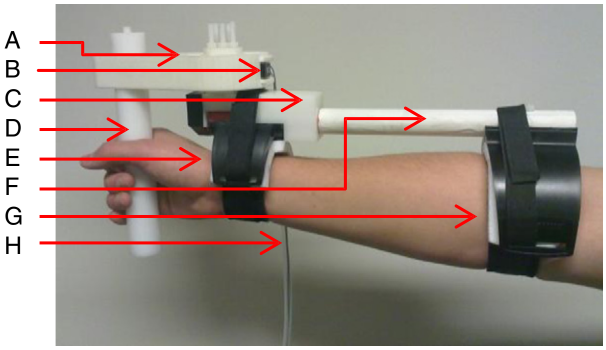

Fig. 1. Isometric wrist torque measurement device with arm support. The device consisted of a polyamide 12 deformable structure [A], light emitter and sensor [B], polyoxymethylene mounting block [C], polyoxymethylene handle [D], plastic armrests [E&G] with moldable foam and Velcro straps, fiberglass rod [F] and 10 m optical fiber [H].

2.2. Equipment

An MR-compatible wrist torque measurement device without magnetic and conductive materials was developed to ensure safety and minimize artifacts (see Fig. 1). Torque was measured (range: ± 1.5 Nm) from deformation of a deformable structure using light intensity measurements (see Fig. 2) (FS-N11MN, Keyence, Osaka, Japan) inside the MR scanner room while all electronics were located in the MR control room. The deformable structure of the wrist torque measurement device was selective laser sintered out of polyamide 12 and was designed to be compliant in one direction with low cross-sensitivity by using a hub-spoke topology. The sensor head (FU-38, Keyence, Osaka, Japan) was made entirely from polymers and was equipped with one emitting and one receiving optical fiber. Torque data were processed in real-time using MATLAB (MathWorks, Natick, MA, USA). The deformable structure was mounted on a lower arm support, which was attached to the right forearm of a subject. The advantages of attaching the wrist torque measurement device to the subject's lower arm instead of to the MR scanner bed were twofold. Firstly, the device could be attached to the subject's arm outside of the MR scanner room thereby saving costly time occupying the MR scanner room. Secondly, subjects did not exert forces on the MR scanner when producing wrist torque, reducing head motion. The right forearm of the subject with attached torque sensor was placed on a sandbag alongside the body without the right forearm touching the hip. A sliding handle and moldable foam allowed for accommodation of a wide range of hand and arm sizes. The 3 T MR scanner (Philips Intera, Best, The Netherlands) was equipped with an eight channel head coil, and a visual information system using a mirror, a projection screen and a beamer, which presented the subject in the MR scanner with task-related information (see Fig. 3). An anatomical scan was acquired using a resolution of 0.875 × 0.875 mm and a slice thickness of 1.2 mm. The functional scans were acquired using: T2* weighted echo planar imaging with an echo time of 30 ms, a repetition time of 2500 ms, a flip angle of 80 , resolution of 2.29 × 2.29 mm and a slice thickness of 3 mm. Each of the 40 slices in a functional scan had a field of view of 220 mm and all 356 functional scans were acquired consecutively. Settings were optimized for fast-paced functional scans of the majority of the brain; however a part of the orbitofrontal cortex was not scanned.

2.3. Hypotheses, contrasts and tasks

Based on the literature the following hypotheses were formulated and pairs of tasks were devised to test these hypotheses.

Hypothesis 1: Comparing a fast switching torque/rest task (1 Hz) with visual feedback to the same task without visual feedback will result in no increased activity in the CBL and the BG since both tasks involve fast movements which entail less error correction. Hypothesis 1 will be evaluated by testing contrast 1: the increase of brain activity during task 1 compared to task 2.

Task 1: Fast switching torque task where the subject was instructed to alternate between relaxing and exerting the amount of torque as indicated by the target on the projection. The exerted torque was also presented on the screen (visual feedback). The target switched from 0 to 0.75 Nm and back at 1 Hz.

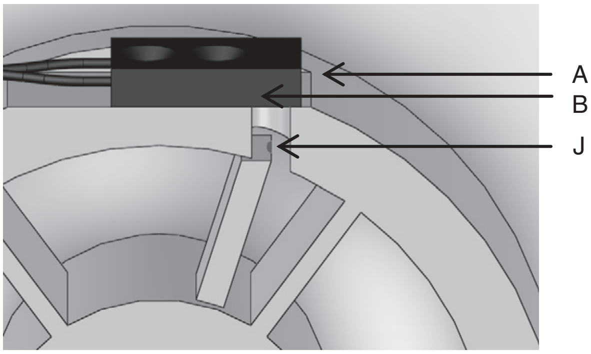

Fig. 2. Simplified representation of the deformable structure [A] and light emitter and sensor [B]. The emitted light is reflected [J] by the reflective surface and registered. When a torque is applied the structure deforms causing a change in the amount of reflected light.

Task 2: Fast switching torque task as in task 1 but without visual feedback. The projection screen showed the switching target torque cueing the subject when to relax and when to exert the flexion torque.

Hypothesis 2a: Comparing a constant torque task with visual feedback to the same task without visual feedback will result in increased activity in the CBL and BG since visual feedback enables error correction. Hypothesis 2a will be evaluated by testing contrast 2a: the increase of brain activity during task 3 compared to task 4.

Task 3: Constant torque task where the subject was instructed to match the target torque of 0.75 Nm on the projection screen with visual feedback.

Task 4: Constant torque task as in task 3 but without visual feedback. The projection screen only showed the target torque.

Hypothesis 2b: Comparing a constant torque task with visual feedback and visual perturbations to the same task without visual feedback will result in increased activity in the CBL and BG since visual feedback enables error correction. Hypothesis 2b will be evaluated by testing contrast 2b: the increase of brain activity during task 5 compared to task 4.

Task 5: Constant torque task as in task 3 but a disturbance signal was added to the visual feedback of the exerted torque, provoking compensatory action from the subject (McRuer and Jex, 1967). The visual disturbance signal was a multisine (Pintelon and Schoukens, 2001) with a maximum amplitude of 0.075 Nm consisting of ten frequencies between 0.1 and 3 Hz and a logarithmically decaying power (−40 dB over the full frequency range).

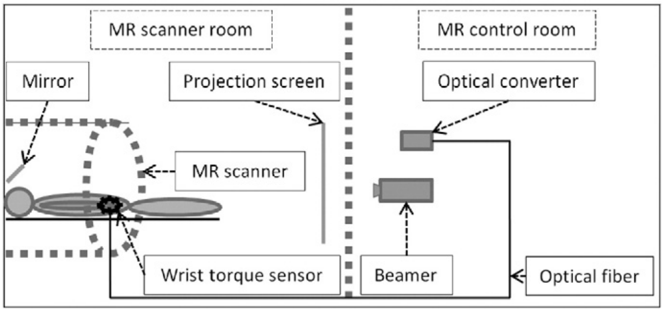

Fig. 3. Schematic representation of the experimental setup. The subject was positioned inside the bore of the MR scanner with the right arm attached to a torque sensor beside the body.

Hypothesis 2c: Adding visual perturbations to the visual feedback during a constant torque task with visual feedback provokes corrective motor actions and will result in further increased activity in the CBL. Hypothesis 2c will be evaluated by testing contrast 2c: the increase of brain activity during task 5 compared to task 3.

Visual input contrast: To account for the absence of visual feedback in task 2 and 4, an additional contrast will be calculated, which tests for the increase of activity in a resting task with visual stimulus (task 7) compared to a resting task with no visual stimulus (task 6).

Task 6: Rest task where the subject was instructed to relax. The projection screen was blank.

Task 7: Rest task where the subject was instructed to watch the projection screen and to exert no torque. The projection screen showed a visual stimulus in the form of a constant target torque and a torque indicator that moved similarly to the torque indicator during constant torque tasks with visual feedback.

The results of contrast 1, 2a and 2b were exclusively masked with the result of the visual input contrast.

Change in activity was not expected to be limited to the CBL and BG. The error corrections from the CBL are processed by the cortical sensorimotor areas [19], therefore increased activity in these areas was expected in contrast 2a, 2b and 2c. Functionally scanning the bulk of the brain allowed for verification of the predicted increases in activation, as well as reviewing unexpected increases in activation throughout the brain.

2.4. Experimental paradigm

Prior to the experiment, subjects received instructions and familiarized themselves with the tasks through practice trials. Each task was performed three times and consisted of 5 s of visual instruction and 35 s of task execution. The visual instruction was a still image (see Fig. 4) that indicated to the subject whether to exert a flexion torque using an arrow and a target torque and whether visual feedback on exerted torque would be provided. A countdown indicated the start of the task at which the arrow disappeared. Each experiment started with a 35 s test run (task 5) of which the data were discarded. The tasks were presented in three consecutive series of seven randomly ordered tasks. The required wrist flexion torque was 0.75 Nm, which roughly corresponds to 5%–10% of the maximum voluntary contraction [20]. To remove passive torque, the torque sensor was calibrated at the start of the experiment while the subject was holding the handle without actively exerting torque. The subjects were instructed to keep their fingers gripped around the handle during all tasks.

2.5. Analysis

The SPM8 (Statistical Parametric Mapping, Wellcome Trust Centre for Neuroimaging, UCL, London, UK, v5236; http://www.fil.ion.ucl.ac.uk/spm) software package was used in combination with Matlab 8.1 (The Mathworks, Inc., Natick, MA, USA) to process the data.

The following preprocessing steps were performed:

1. Anatomical realignment of the functional scans to reduce the effects of head movement.
2. Coregistration of the functional scans to the anatomical scan to achieve alignment.

3. Normalization of functional scans to Montreal Neurological Institute (MNI) template to enable group analysis using a voxel size of 2 × 2 × 2 mm.
4. Smoothing using an 8 mm full width at half maximum (FWHM) kernel of functional scans to account for small anatomical differences between subjects and to improve the signal-to-noise ratio.

The first level analysis consisted of:

1. Specification of the design matrix by entering the onsets and durations of all events (test run, task instructions, and tasks) into the model. To model transient effects of task onset, an extra regressor was included for the first three seconds of each task.
2. Convolving the regressors with the hemodynamic response function. The anatomical realignment parameters are entered as additional regressors.
3. Estimation of the parameters by minimizing the sum of squared residuals.
4. Verification of orthogonality of the regressors of interest.

The second level analysis was performed using the SnPM13 (Statistical nonParametric Mapping, v13.0.11; http://warwick.ac.uk/snpm) toolbox for SPM8. This toolbox uses permutation tests for group analysis with low degrees of freedom ($df = 9$ in this study), where the use of the more common random field theory would yield a too conservative result due to low smoothness of the statistical maps. 1024 permutations per contrast were performed using a variance smoothing with an 8 mm FWHM kernel [21] and provided a distribution of the smoothed variance t statistic (pseudo-t) for each voxel, facilitating statistical tests. The random-effects group analysis was performed on all contrasts ($N = 10$) with a significance level as determined using a False Discovery Rate (FDR) threshold of 5% [22].

Anatomical data were derived from the active voxel coordinates using xjView8 (version 8.12 http://www.alivelearn.net/xjview), which is an SPM8 extension using the MNI single subject anatomical brain map. Subsequently, active voxels were categorized in CBL, BG, temporal and occipital lobes, sensorimotor areas and ‘other brain regions’. Clusters smaller than five voxels were neglected during categorization. All active voxels in the temporal and occipital lobes were assumed to be involved in visual processing, which is a simplification since the temporal lobe is also known to be involved in auditory processing, storing memories and comprehending language [3,4]. Sensorimotor areas comprised, among other related regions, motor cortices, sensory cortices, supplementary motor area, and the premotor cortex.

3. Results

3.1. Activations

Comparing the rest task with and without visual stimulus (task 7 and task 6 respectively) allowed for finding the brain region active when there is a visual stimulus present. However, this visual input contrast did not result in increased activity in brain regions associated with visual processing or any other brain region. Therefore there was no exclusive mask applied to the results of contrasts 1, 2a and 2b.

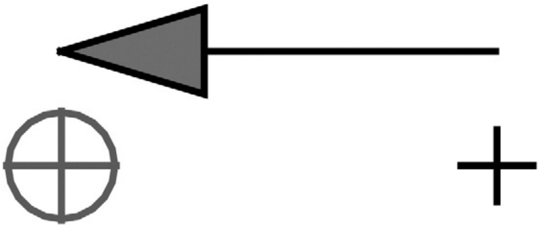

Fig. 4. Visual information as presented to subject. Arrow indicates the desired direction of the exerted torque, the green crosshairs with circle indicate the target torque and the black crosshairs indicate the exerted torque level in tasks with visual feedback.

Contrast 1 did not show any significant increase in activity. On the contrary, contrast 2a (see Table 2, left panel in Fig. 5 and top panel in Fig. 6) showed increased activity in both CBL and BG. Additionally, sensorimotor areas showed increased activity as well as temporal and occipital lobes and other regions (see Table 3 for details). Similarly, in contrast 2b (see Table 2, right panel in Fig. 5 and bottom panel in Fig. 6) increased activity was again found in the CBL and BG. Besides increased activity in the sensorimotor areas and occipital and temporal lobes, additional increased activity was found in other regions (see Table 3 for details). Lastly, contrast 2c did not show any significant increase in activity.

3.2. Movement during functional scans

Translations were smaller than 1.4 mm and rotations were smaller than 2.2 degrees. No data were excluded for analysis. Table 1 shows the maximum inter-scan movement obtained for scans acquired during the rest tasks, the torque tasks and the instruction and transient time. Highest inter-scan movements were found during instruction and transient time, whereas the movement during the torque tasks was generally much lower. The difference in root mean square (rms) movement between tasks was tested for significance using a two factor (task and movement direction) repeated measures ANOVA in SPSS (IBM Corp., Version 20.0, Armonk, NY., USA). Pairwise comparisons revealed that movement during instruction and transient time was significantly higher than during any of the torque tasks (main effects of task $p = 0.008$ and of direction of movement $p = 0.032$). There was no significant difference in movement between the torque tasks or between the torque tasks and rest tasks.

3.3. Task performance

During the constant torque task without visual feedback (task 4), subjects exerted a higher torque than the required torque (0.94 Nm, averaged SD within subject: 0.13 Nm, SD over all tasks and subjects: 0.26 Nm). Likewise, too high torques (1.21 Nm, averaged SD within subject: 0.11 Nm, SD over all tasks and subjects: 0.21 Nm) were exerted during the fast switching torque task without visual feedback (task 2). All subjects reported difficulties with performing these tasks.

3.4. Wrist torque measurement device

The designed wrist torque measurement device did not contain any metal parts, thereby ensuring safety of the subject. The device functioned properly inside the MR scanner environment and was not hindered in any way by the presence of the strong magnetic field. Additionally there was no influence of the presence of the device on the homogeneity of the magnetic field, resulting in undistorted image acquisition. The wrist torque measurement device fitted all subjects due to the moldable foam used for fixation and was not reported to be uncomfortable by any subject. The possibility to attach the device and practice the tasks outside the MR scanner room ensured minimal time spent inside the MR scanner room (approximately 30 min per subject). Most importantly, the wrist torque measurement device allowed us to selectively activate parts of the motor circuit in the brain.

4. Discussion

In this study we used specific motor tasks to successfully demonstrate activation of CBL and BG in isometric motor tasks while head movement was kept to a minimum. The prototyped MR-compatible wrist torque measurement device, free of magnetic and conductive materials, allowed safe execution of tasks during fMRI without causing artifacts.

4.1. Hypotheses

The effect of visual feedback on a task with a fast switching torque level was investigated in contrast 1, where a fast switching torque task with visual feedback (task 1) is compared to a fast switching torque task without visual feedback (task 2). In contrast 1 there was no increased activity in any brain region, which corroborates Hypothesis 1 which stated that adding visual feedback to a fast switching torque task would not increase the ability to perform corrections requiring fine motor control. Yet, possible effects may have been masked due to considerable variation in the exerted torque among subjects.

Contrast 2a investigated the effect of visual feedback on a constant torque task. Confirming Hypothesis 2a and in agreement with Vaillancourt et al. [14], comparing a constant torque task with visual feedback (task 3) to the same task without visual feedback (task 4) resulted in increased activity in the CBL and BG. In contrast 2b a constant torque task with visual feedback and visual perturbations (task 5) was compared to a constant torque task without visual perturbations (task 4), which resulted in further increased activity in the CBL and BG, thereby validating Hypothesis 2b.

The addition of visual perturbations was expected to provoke (more) corrective motor actions, resulting in further increased activity in the CBL (Hypothesis 2c). However, in contrast to Klarhöfer et al. [15] no significant increase of activity was found in contrast 2c, whereas contrast 2b did show more activity in the CBL than contrast 2a (~2900 against ~1600 voxels), indicating that there might be an effect of the added visual perturbation on the CBL, however not strong enough to achieve significance.

4.2. Visual processing

We are interested in the effect of visual feedback on task execution, yet we wanted to exclude activation that is just due to the presence of visual stimuli. Therefore we included the contrast between a resting task with visual stimulus (task 7) and a task without visual stimulus (task 6). This contrast did not result in any active voxels and therefore no exclusive mask was applied to the contrasts 1, 2a and 2b. In contrast 2a (and contrast 2b) the addition of visual feedback did result in an increase of activity in occipital and temporal lobes. A possible explanation for these findings is that during the rest task with visual stimulus there was no direct use of the visual input; this in contrast to the constant torque task with visual feedback where the visual information was used to perform the task.

4.3. Functions of unpredicted active brain regions

The addition of visual feedback to a constant torque task led to unpredicted increased activity in a number of brain regions which will be discussed individually. To the best of our abilities, we identified the functions of the active brain regions presented in Table 2 using literature.

Contrast 2a showed increased activity in the inferior parietal lobule, which integrates sensory information [3,23] and the superior parietal lobule, which is believed to receive considerable visual input as well as somesthetic input of the hand [24]. A subsection of the superior parietal lobule, the precuneus, has been implicated in motor coordination in conjunction with the premotor cortex [25]. Less easily explained activity occurred in the inferior frontal gyrus. This brain region has shown involvement in stopping initiated movements [26], which could be an error correcting mechanism enabled by the visual feedback. Another brain region that showed increase of activity was the anterior cingulate cortex, which has been associated with error detection, integrating input from various sources, and contributing to the modulation of processing in other brain regions [27]. This increased activity is probably explained by the added visual feedback, requiring constant integration of sensory information and modulation of actions. Furthermore the supramarginal gyrus was found to be more active, a region which has been associated with visuospatial activities [4]. Finally, increased activity was found in the thalamus, which acts as the gateway to the cerebral cortex (Hendelman, 2006). Most findings are explainable in the context of the compared tasks.

Contrast 2b showed a further increase of activity in all regions described above which can be explained by the increased difficulty of the task due to the added visual perturbation. Additionally increased activity was found in the pons, an important sensory relay

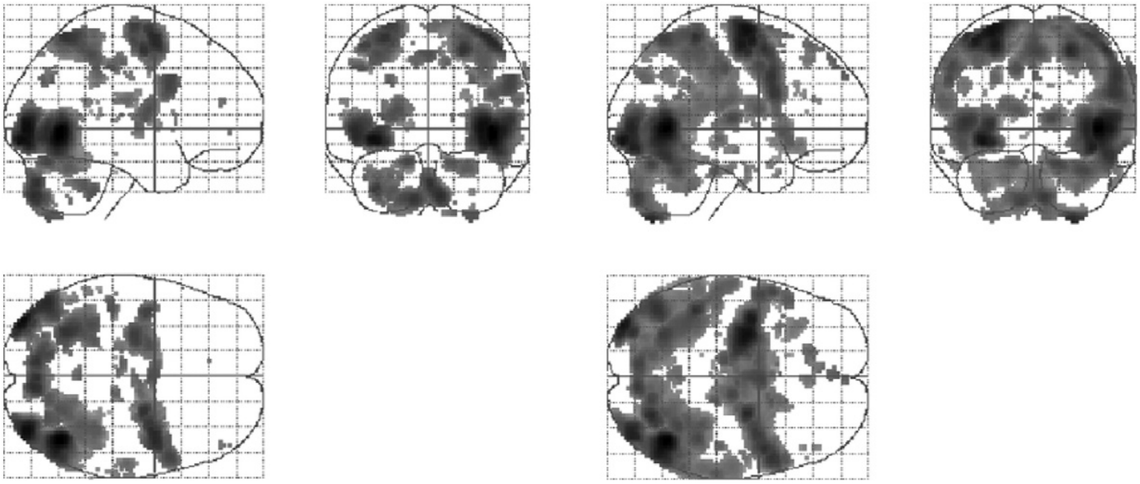

Fig. 5. Significant activation on group level for contrast 2a (left, 9513 voxels, grayscale indicates pseudo-t values ranging from 1.4 to 8.8) and contrast 2b (right, 21,701 voxels, grayscale indicates pseudo-t values ranging from 1.1 to 9.6) presented on a glass brain in side (top left), rear (top right) and top view (bottom). Contrasts 1 and 2c did not show any significant activation.

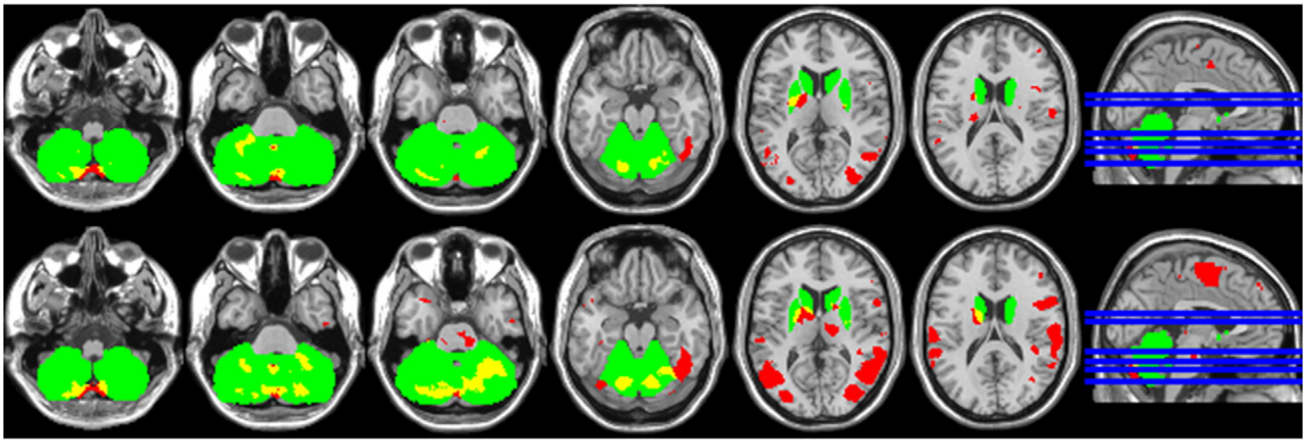

Fig. 6. Significant activation on group level for contrast 2a (top panel) and contrast 2b (bottom panel) for six slices in the axial plane. Green indicates the CBL and BG, red indicates significant activation, and yellow indicates where activation overlaps with the CBL or BG. Blue lines in the rightmost figure indicate where the slices were obtained.

station (Hendelman, 2006), and in the angular gyrus, which besides involvement in language functions [28] has been implicated in saccadic eye movements [3] and visuospatial activities [4] such as orientation [29].

4.4. Reliability

Besides the false discovery rate (FDR) method as described above a more stringent Family Wise Error Correction method (FWE) at $\alpha = 0.05$ was also performed to reassess the significance. The significant effects in contrasts 2a and 2b remained in both CBL and BG when using the FWE with a region of interest analysis (covering the CBL and BG), indicating reasonable robustness of the results.

During the fast switching torque tasks the exerted torque level did not return to zero after a torque was exerted. This effect could be caused, yet not exclusively, by the somewhat sluggish relaxation of the polymer deformable structure of the torque sensor after the load is removed. Both the deactivation dynamics of the muscles and the anticipation of the next contraction are probably also responsible for this effect.

One could argue that it is not so much the maximum translations and rotations, which determine the quality of the fMRI data, but rather the amount of translation and rotation between sequential scans as shown in Table 1. Movement between sequential scans can be corrected by anatomically aligning the separate scans; however movement during the acquisition of one scan cannot be corrected. Therefore it is probably better to regard scans that had excessive inter-scan (hence probably also intra-scan) movements as compromised. In this study the largest translations and rotations between sequential functional scans were found during rest and instruction and transient time, suggesting that subjects tried to reposition themselves between performing motor tasks, perhaps to assume a more comfortable position. These movements affect the maximum translations, whereas they do not necessarily corrupt the fMRI results as they do not occur during tasks of interest. The used wrist torque measurement device has shown to result in little head movement during the motor tasks, which is likely to be a virtue of the fixation of the device to the arm instead of to the MR scanner.

4.5. Overestimation of the required torque level

Overestimation of the required torque level when there is no visual feedback is a common finding [30,31]. In both tasks without visual feedback, the exerted torque was higher than the required 0.75 Nm. An increase of exerted torque has been associated with an increase of fMRI intensity in active voxels [32] or with an increased number of activated voxels in the region [33]. Effects can extend to the primary motor cortex, sensory regions, supplementary motor area, premotor, prefrontal, parietal and cingulate cortices, and cerebellum [32]. The results from contrasts 1, 2a and 2b are likely conservative as they present the increased activity in respect to tasks without visual feedback where the exerted torque levels were higher. More extensive training or intermittent feedback could be employed to attain the correct torque level in the absence of visual feedback.

Table 1
Maximum absolute inter-scan movement (between scans) during different tasks in the experiment (averaged over subjects). Movement is reported for the three translation directions (x-direction: lateral, y-direction: posterior to anterior, z-direction: inferior to superior) and the three rotations (pitch: rotation about x-axis (nodding yes), roll: rotation about y-axis, and yaw: rotation about z-axis (shaking no)).

#	Task	Maximum inter-scan translation [mm/scan]			Maximum inter-scan rotation [°/scan]		
		x	y	z	pitch	roll	yaw
1	Fast switching, feedback	0.04	0.12	0.12	0.11	0.05	0.04
2	Fast switching, no feedback	0.03	0.13	0.10	0.08	0.04	0.04
3	Constant, feedback	0.03	0.13	0.10	0.09	0.05	0.03
4	Constant, no feedback	0.03	0.11	0.11	0.09	0.05	0.04
5	Constant, disturbance	0.03	0.12	0.12	0.09	0.05	0.03
6	Rest	0.04	0.22	0.20	0.18	0.06	0.04
7	Rest with visual stimulus	0.04	0.18	0.15	0.17	0.05	0.05
-	Instruction and transient time	0.09	0.22	0.27	0.30	0.14	0.11

Table 2
Numbers of voxels (rounded to nearest hundred) in brain regions showing increased activity in contrast 2a and contrast 2b.

	Contrast 1 [#]	Contrast 2a [#]	Contrast 2b [#]	Contrast 2c [#]
CBL	–	1.6×10^3	2.9×10^3	–
BG	–	0.4×10^3	0.4×10^3	–
Sensorimotor areas	–	2.6×10^3	7.4×10^3	–
Occipital and temporal lobes	–	3.3×10^3	6.4×10^3	–
Other brain regions	–	1.7×10^3	4.8×10^3	–

4.6. Patient studies

Movement disorders often involve impaired functioning of the CBL or BG, which can be hypo- or hyperactive compared to healthy functioning [34–36]. Abnormal activation of CBL and BG in for example Parkinson's disease and dystonia has been established; however pathophysiologies are not well understood. This study demonstrates that selective activation of CBL and BG can be achieved using an MR-compatible torque measurement device and specific pairs of isometric motor tasks at torque levels that are sufficiently low to be attainable by patients. A study on a larger group of healthy subjects and on patients is warranted to further investigate the feasibility of developing a diagnostic tool based on a comparison of CBL and BG activation between healthy subjects and patients.

4.7. Added value

The motor circuits involved in corrective motor actions have been previously studied using fMRI. Some studies resolved motion of the head by presenting the subject with visual feedback of the head position, requiring the subject to self-stabilize [14,34]. This method of head motion reduction was demonstrated by Thulborn [16]; however it was only validated for eye movement paradigms. Our torque measurement device minimized head movements as it was only attached to the subject's lower arm; by exerting wrist torque the subject did not exert forces on the MR scanner. Many studies used conductive materials in their setup for force measurement, structures and data transfer [13,15,37,38]. The designed torque measurement device was built entirely out of metal-free components, thereby ensuring safety and keeping artifacts to a minimum. Coombes et al. [39] amplified visual feedback of the subject's own force error to provoke corrective action in an isometric grip force task, inducing inter-subject variability of the disturbance signal. In this study we used a visual perturbation signal, which was added to the feedback and was the same for all subjects.

The current study combined various force tasks from literature into one experiment, all on a single joint. The MR-compatible equipment realized unambiguous motor task execution, through conditioning the motor task and subsequent feedback, while limiting head motion.

Table 3
Numbers of voxels (rounded to nearest hundred) in other brain regions showing increased activity in contrast 2a and contrast 2b.

	Contrast 2a [#]	Contrast 2b [#]
Inferior parietal lobule	0.6×10^3	1.1×10^3
Superior parietal lobule	0.4×10^3	0.7×10^3
Precuneus	0.3×10^3	0.5×10^3
Inferior frontal gyrus	0.2×10^3	1.0×10^3
Anterior cingulate cortex	0.1×10^3	0.3×10^3
Supramarginal gyrus	0.1×10^3	0.8×10^3
Thalamus	0.0×10^3	0.3×10^3
Pons	0.0×10^3	0.1×10^3
Angular gyrus	0.0×10^3	0.1×10^3

5. Conclusions

1. Providing visual feedback during an isometric constant torque task activates the CBL and BG.
2. The prototyped metal-free torque sensor, attached to the arm of the subject, allows for safe measurements in the MR scanner room and results in acceptable head displacement during isometric motor tasks.

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