Cortical and Subcortical Correlates of Functional Electrical Stimulation of Wrist Extensor and Flexor Muscles Revealed by fMRI

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Abstract: The main scope of this study was to test the feasibility and reliability of FES in a MR-environment. Functional Electrical Stimulation (FES) is used in the rehabilitation therapy of patients after stroke or spinal cord injury to improve their motor abilities. Its principle lies in applying repeated electrical stimulation to the relevant nerves or muscles for eliciting either isometric or concentric contractions of the treated muscles. In this study we report cerebral activation patterns in healthy subjects undergoing fMRI during FES stimulation. We stimulated the wrist extensor and flexor muscles in an alternating pattern while BOLD-fMRI was recorded. We used both block and event-related designs to demonstrate their feasibility for recording FES activation in the same cortical and subcortical areas. Six out of fifteen subjects repeated the experiment three times within the same session to control intraindividual variance. In both block and event-related design, the analysis revealed an activation pattern comprising the contralateral primary motor cortex, primary somatosensory cortex and premotor cortex; the ipsilateral cerebellum; bilateral secondary somatosensory cortex, the supplementary motor area and anterior cingulate cortex. Within the same subjects we observed a consistent replication of the activation pattern shown in overlapping regions centered on the peak of activation. Similar time course within these regions were demonstrated in the event-related design. Thus, both techniques demonstrate reliable activation of the sensorimotor network and eventually can be used for assessing plastic changes associated with FES rehabilitation treatment. *Hum Brain Mapp* 30:963–975, 2009. © 2008 Wiley-Liss, Inc.

Key words: functional electrical stimulation; functional MRI; induced wrist extension-flexion movements; motor and somatosensory systems; reproducibility; neurorehabilitation

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INTRODUCTION

Functional electrical stimulation (FES) is a widely applied technique in medical treatment, physical therapy and sports training. Specific applications include treatment of muscle atrophy, build-up of muscle mass, endurance training, pain treatment, as well as functional movement therapy of paralyzed patients after brain or spinal cord injury (SCI) [Mangold and Keller, 2003, 2004]. The principle of FES lies in generating action potentials by short

bursts of electrical pulses. The action potentials propagate along axons towards the target muscles resulting in a contraction [Popovic et al., 2001a). Since electrical stimulation activates nerves rather than muscles and the propagation of the electric impulse occurs along the axons, the motor nerves should not be deafferented [Peckham and Knutson, 2005]. Possible peripheral mechanisms of FES include a training effect resulting in improved fitness and strength of the remaining motor units, improvement of flexibility and range of motion of affected limbs resulting in voluntary efforts becoming more effective, and reduced spasticity in the affected muscles [Rushton, 2003]. FES is preferably applied when the lower motor neurons are excitable and the neuromuscular junctions, as well as the muscles, are intact. This is usually the case in patients with complete and incomplete SCI, stroke, head injuries, cerebral palsy, and multiple sclerosis [Peckham and Knutson, 2005]. Several reports have demonstrated that motor training causes cortical reorganization [Karni et al., 1995; Muellbacher et al., 2001; Nudo et al., 1996; Pascual-Leone et al., 1995] and somatosensory inputs lead to changes in the cortical excitability [Kaelin-Lang et al., 2002; Ridding et al., 2000, 2001]. FES uses both somatosensory inputs and passive movements as means to improve motor performances [Bütefisch et al., 2004; Uy et al., 2003]. Passive movements are frequently used in medical therapy when the affected limb, due to weakness or disability, cannot be moved voluntarily. Neuroimaging studies demonstrated that passive movements result in cortical reorganization, meaning mere external treatment caused changes in functional brain activations to resemble the ones elicited by active movements [Carel et al., 2000; Loubinoux et al., 2001; Lotze et al., 2003; Weiller et al., 1996]. However, Lotze et al. [2003] and a recent study from Kaelin-Lang et al. [2005] found that active training leads to better motor performance and more prominent increases in fMRI activation than passive training. Their findings consolidate the pivotal role of voluntary drive in motor learning and neurorehabilitation.

Functional electrical stimulation merges these training approaches, in that it allows repetitive movements, generates a somatosensory input and can be actively and passively applied. However, the functional brain correlates of FES-elicited movements have yet to be determined.

The main scope of this study was to test the feasibility and reliability of FES in a MR-environment. Should the FES approach be successful, it would provide the means for assessing the central correlates of specific rehabilitation treatment and its effects on cortical organization. To our knowledge, only one study so far applied neuromuscular stimulation on healthy subjects in the fMRI environment [Han et al., 2003]. This study reported findings only from three cortical regions of interest: namely primary motor, primary somatosensory, and supplementary motor areas (SMA). Here we demonstrate the feasibility of performing fMRI during a simple FES-elicited motor task in healthy subjects and report activation patterns from the entire brain. We used a block experimental design, as well as an

event-related design, to demonstrate the possible application of FES using two standard fMRI paradigms. We expected to observe identical activated areas elicited with both experimental approaches because the stimulation is thought to produce robust brain activations that do not vary as function of the experimental design. Furthermore, we addressed intra-subject reproducibility by performing repeated measurements in the same subject. Within the context of rehabilitation, it is important to know whether a treatment effect can be differentiated from intra-subject variability or methodological variations.

METHODS

Subjects

Fifteen healthy male ($n = 7$) and female ($n = 8$) right-handed subjects (mean age 31.27 years, SD 7.85) participated in the study after given informed consent. Handedness was assessed with the Edinburgh Handedness Inventory [Oldfield, 1971], which showed a moderate to strong right-handedness for all subjects (mean 86.6, SD 15.1, range 60–100). The experiment was conducted with the approval of the local Ethics Committee.

Stimulation Device and Parameters

FES was carried out with the portable system “Compex Motion” [Keller et al., 2002]. The device is a microcontroller-based system with four current-regulated stimulation channels and is controlled with a chip card programmed by custom made software. For the fMRI experiments, only two channels were used. We first ran the same fMRI-protocol (see data acquisition) as with the healthy subjects using a water bottle phantom. Recorded images were objectively evaluated and no obvious artifacts or image distortions were observed. We applied asymmetric, biphasic, charge balanced rectangular pulse shapes¹. The depolarizing pulse had four times higher amplitude but was four times shorter than the charge compensating pulse. The depolarizing pulses had a width of 200 μs ² and frequency of 20 Hz³. The wrist extensor muscles (WEM) and wrist flexor muscles (WFM) were each stimulated by a separate channel with a pair of 50 mm $\times$ 50 mm, “Synapse,” self-adhesive electrodes (Ambu A/S, Baltorpbakken 13, 2750 Ballerup, Denmark). For the WEM, the depolarizing electrode

¹Biphasic pulse forms are believed to be better suited for surface stimulation. The first pulse generates the action potential (AP) and the secondary pulse removes the injected charge from the body [Peckham and Knutson, 2005; Popovic et al., 2001b].

²By means of short pulses more efferent compared to afferent nerves will be stimulated. Important is the selective stimulation of the relevant muscle groups [Keller and Dewald, 2004].

³To keep muscle fatigue at minimum and still producing smooth tetanic muscle contractions a pulse repetition frequency range in the range of 20–30 Hz is recommended [Keller and Dewald, 2004].

Figure 1.

Experimental paradigm. **(a)** Electrode placement and maximal extent of electrically stimulated extension and flexion movement. **(b)** Event-related design. 22 single extension and flexion movements of each 1 s duration were electrically elicited in an alternating pattern with an interstimulus interval lasting 17.05–

21.95 s. Total duration: 900 s. **(c)** Block design. 6 rest and 6 stimulation blocks each lasting 21 s. The stimulation condition consisted of a repetitive extension flexion movement, stimulating alternatively WEM and WFM for 1 s. Total duration: 252 s.

was placed on the forearm close to the elbow over the m. extensor carpi radialis longus and brevis, m. extensor digitorum communis, m. extensor carpi ulnaris, while the charge removing electrode was placed proximal to the wrist. For the WFM, the AP generating electrode was placed on the forearm distal to the elbow over the motor points of m. brachio-radialis, m. flexor pollicis longus with the charge removing electrode being placed distally under the wrist. The stimulation amplitude of the depolarizing pulse for both WEM and WFM was individually determined by palpation—a standard procedure in the clinical setting. Initially, current amplitude was increased stepwise by 1mA until muscle twitches could be sensed by the examiner, a clear sign of motor activation of the wrist muscles. Then, the stimulation amplitudes used during the experiment were adjusted to 150% of the individual motor threshold amplitude and the stimulation frequency was set to 20 Hz to achieve strong muscle contraction resulting in robust passive movements of the wrist in its range of motion between 50–70° for extension and flexion respectively (Fig 1a). However, some subjects felt discomfort and required lower amplitudes that were subsequently reduced. The resulting stimulation current amplitudes were in the range from 9–23 mA.

Stimulation Induced Wrist Extension-Flexion Paradigms

Using a stimulation induced wrist extension-flexion task gives us the possibility to compare the cerebral activation patterns of FES-elicited movements with previous experience (Table I) using similar motor [Carel et al., 2000; Curt et al., 2002; Loubinoux et al., 2001; Lotze et al., 2003; Naito et al., 2002] and sensory [Arienzo et al., 2006; Del Gratta et al., 2000; Sutherland and Tang, 2006] tasks. We predicted similar activation patterns within the primary and secondary motor and somatosensory areas as well as subcortical regions such as thalamus and cerebellum. Moreover, stimulation of the wrist is widely applied in rehabilitation treatments and is less likely to elicit head movements because these movements are considered an ignorable local event, especially when executed at a slow pace. Subjects were placed in the scanner with their right arm positioned along their body and supported by a pad to allow unobstructed flexion-extension movements of the wrist. The head was fixed with foam cushions in the MR head coil and straps around to torso were used to diminish any additional movements. Subjects were asked not to perform any voluntary movements of their finger and

TABLE I. fMRI Studies investigating a) active and / or passive movement of the wrist and b) the effect of electrical stimulation at the wrist

Task	Main activation loci to activated/stimulated wrist			Reference
	Contralateral	Ipsilateral	Bilateral	
a) Active and passive wrist movements	SIMI, SMA, cingulate	Cerebellum	IPL	Carrel et al., 2000
Active and passive wrist movements	SIMI, SMA, cingulate		SIMI, PMC, frontal cortex, SPL, IPL, cerebellum	Loubinoux et al., 2001
Active wrist movements	MI, SI, insula, thalamus, putamen		SMA, SII, SPL, dPMC, vPMC, caudal cingulate motor	Curt et al., 2002
Motor imagery of wrist movement and kinesthetic stimulation	SIMI, cingulate motor area, SMA, dPMC, IPS	Cerebellum		Naito et al., 2002
Active and passive wrist movements	MI, SI, SII, thalamus	Cerebellum		Lotze et al., 2003
b) Electric stimulation of median nerve at the wrist	SPL, SI, SMA		SII, PFC, STS	Del Gratta et al., 2000
Electric stimulation of median nerve at the wrist			SI	Sutherland and Tang, 2006
Electric stimulation of median nerve at the wrist	SI		SII, insula, ACC, SMA	Arienzo et al., 2006

Abbreviations: ACC, anterior cingulate cortex; dPMC, dorsal premotor cortex; IPL, inferior parietal lobule; MI, primary motor area; PFC, prefrontal cortex; SI, primary somatosensory area; SII, secondary somatosensory area; SMA, supplementary motor area; SPL, superior parietal lobule; STS, superior temporal sulcus; vPMC, ventral premotor cortex.

wrist or contractions of the arm muscles. During the scanning procedure, subjects were told to keep their eyes closed. An event-related experiment was followed by a block experiment in the same imaging session. In the event-related design, an “event” consisted of a single 1-s stimulation of either WEM or WFM. In total 22 extension and 22 flexion movements were evoked. The interstimulus interval had a range of 17.05–21.95 s. The event-related design lasted 900 s (Fig. 1b). The block design consisted of six stimulation and six rest blocks, starting with the latter. One block lasted 21 s. Within the stimulation block, the WEM and WFM were each stimulated in an alternating pattern for 1 s (1 Hz) resulting in 11 extension and 10 flexion movements. The block design lasted 252 s (Fig. 1c).

Data Acquisition

MRI was performed at 3.0-T MR system (Philips Medical Systems, Eindhoven, The Netherlands) equipped with an 8 channel SENSE[®] head coil. For the functional acquisitions a T2* weighted, single-shot, field echo, EPI sequence of the whole brain (TR = 3,012 ms, TE = 40 ms, flip angle = 82°, FOV = 220 mm × 220 mm, acquisition matrix = 128 × 128, in-plane resolution = 1.7 × 1.7 mm, slice thickness = 3 mm) with a SENSE factor of 2 was applied to collect signals from 39 contiguous slices. The event-related design consisted of 300 functional scans; the block design of 84 scans. Preceding each functional measurement, five

dummy scans were performed in order to achieve magnetic field homogeneity. For testing intra-subject reproducibility, six subjects underwent the sequence (block design, event-related design) three consecutive times within the same scanning session. Anatomical images of the whole brain were additionally obtained by using a 3D, T1-weighted, field echo sequence (TR = 20 ms, TE = 2.3 ms, flip angle = 20°, in-plane resolution = 0.9 mm × 0.9 mm, slice thickness = 0.75 mm, 210 slices).

Data Analysis

Image preprocessing and data analysis was performed using BrainVoyager QX 1.7.9[®] software package (Brain Innovation B.V., Maastricht, The Netherlands). Data preprocessing included 3D motion correction by means of tri-linear interpolation, spatial smoothing applying a Gaussian filter of 4 mm FWHM, and temporal smoothing including linear trend removal and application of high pass filter with 3 cycles in time course (3 cycles/number of scans × TR). For the event-related design a correction for slice scan-time was performed by sinc interpolation. All images were co-registered to the participant's T1-weighted high-resolution anatomical scan, spatially normalized into standard stereotaxic space [Talairach and Tournoux, 1988]. In the single subject analysis the stimulation condition was modeled using a general linear model (GLM) convolved with the standard two gamma haemodynamic response function resulting in *t*-contrast maps corrected for multiple

comparisons with $q(\text{FDR}) < 0.05$ showing the contrast FES vs. rest. FDR has a higher power than Bonferroni correction as the threshold varies automatically across subjects with consequent gain in sensitivity. The parameter q has the advantageous feature of being comparable across studies. The correction accounts for cluster size, i.e. the bigger the cluster the more unlikely are unrandomly activations, hence accounting for less correction [Genovese et al., 2002]. Analysis was performed on each subject to identify the network involved in the stimulation condition by comparing the activation with the rest condition. Group analysis was performed using random effects procedure to generalize the data to the population level. Single t -contrast maps were used as input. The data were corrected for serial correlations and multiple comparisons using the most conservative FDR threshold that revealed robust individual activations.

For determining intrasubject variability, a post-hoc region of interest (ROI) approach as described by Bosch [2000] was used. From all areas identified during the group analysis, we defined five functional ROI, namely SMA, primary motor and somatosensory cortex (MI/SI), secondary somatosensory cortex (SII), anterior-cingulate cortex (ACC) and cerebellum. These regions were selected according to the literature since these regions have been reported as principle components of passive training [Carel et al., 2000; Loubinoux et al., 2001; Lotze et al., 2003; Weiller et al., 1996] and in wrist extension-flexion tasks [Carel et al., 2000; Loubinoux et al., 2001; Curt et al., 2002; Naito et al., 2002; Lotze et al., 2003]. For each subject and run single t -contrast maps (FES vs. rest) of the whole brain were calculated to obtain the relevant coordinates of the peak of activation in the five ROIs. The location of these coordinates within the specified ROIs was verified based on the following anatomical landmarks: SMA was defined from vertex to the cingulate sulcus and from the precentral sulcus posteriorly to the line crossing perpendicular the AC-PC line at the level of the anterior commissure (see Chainay et al., 2004 for details). MI/SI was defined as the anterior and posterior bank of the central sulcus [Kollias et al., 2001] and the hand area as the hook-shaped segment of the central sulcus [Yousry et al. 1997]. SII comprised the post-central parietal operculum in the upper bank of the lateral sulcus (see Eickhoff et al., 2006 for details). The ACC was defined as the cortex lying within the *cingulate* sulcus [Fink et al., 1997; Arienzo et al., 2006]. For the cerebellar ROI we have chosen Larsell's lobule V and vermal V representing the somatotopic organization of fingers and wrist, respectively [Grodd et al., 2001]. For each subject and for each ROI we identified three local maxima (i.e. one for each run), resulting in 90 data points. Subsequently, a cube with a side length of three voxels was defined with its center at the local maxima resulting in the final ROI.

In case it occurred that a local maximum was localized more than a side length of the cubes we chose the adjacent local maximum which was the closest to the other two centers resulting in three cubes with their centers within the same ROI. Single GLMs were again applied to the newly defined ROIs generating β -values for each run in

order to evaluate the reliability across different individuals and experimental sessions. The resulting β -values were used as input for repeated measures ANOVA performed for each ROI separately, with time as a within-subject factor to test whether the haemodynamic responses collected from the three subsequent intra-session runs differ significantly. Furthermore, the approach described by was applied to assess the agreement between the measurements. For each ROI we plotted pair wise the mean of two measurements against the difference of the two measurements, resulting in three plots per ROI (measurement 1 (T1) vs. measurement 2 (T2), T1 vs. T3, T2 vs. T3). As proposed by Bland and Altman [1986] a good agreement is achieved when differences are less than two standard deviations. The reason for choosing an analysis of cubes instead of areas of activated voxels was two-fold: significant activated areas may differ in shape and amount of voxels between different runs in the same subject; voxels located at the border of these areas are close to threshold, which may lead to reduced mean z -values. The data were corrected for serial correlations and the threshold was set at $P < 0.05$ uncorrected in order to achieve full cubes. No further corrections were applied. For the event-related data, an additional comparison of the corresponding time courses (z -transformed) within the ROI was performed.

RESULTS

The Complex Motion stimulator did not distort the image quality of the functional and anatomical scans as no artifacts were present in any of the images. Furthermore, the subjects did not sense any differences in the intensity of the stimulation before and while scanning. No sensations of burning or other subjective discomfort were reported during the scanning sessions.

Group Analysis—Block Design

The contrast FES vs. rest condition (Table II, Fig. 2) FDR, $q < 0.03$ elicited activation patterns in MI/SI, intraparietal sulcus and superior parietal lobule contralateral to the stimulated right wrist. Bilateral activations were found in SMA, ACC, SII and ventral premotor cortex (vPMC). Ipsilateral activation was observed in the dorsal premotor (dPMC) cortex and insula. Subcortical regions were also significantly activated including the ipsilateral thalamus and contralateral putamen. Cerebellar activation (denotations after Grodd et al., 2001) was found mainly in ipsilateral Larsell's lobule HV spreading to the anterior vermis (vermal V). Minor contralateral activation was found in Larsell's lobule V.

Group Analysis—Event-Related Design

The activation pattern found in the event-related design during FES was similar to that of the block design (Table III; Fig. 3) FDR, $q < 0.001$. However, activation areas con-

TABLE II. Activated brain regions in block design identified by random effect group analysis for all subjects ($N = 15$) [$t(14) > 4.79$, corrected for multiple comparisons $FDR < 0.03$]

Cluster	Functional region	Contralateral					Ipsilateral				
		x	y	z	Max t	no. voxels	x	y	z	Max t	no. voxels
SFG	SMA	-6	-13	64	5.398936	46	3	-10	61	6.107354	88
PrCG, PoCG, IPS	SI	-42	-28	55	8.243153	4038					
	MI	-30	-25	64	6.796949	0					
	IPS	-27	-31	43	5.812412	0					
SPL		-27	-43	58	5.568961	97					
Cingulate	ACC	0	-7	52	5.39774	27	3	2	46	5.308772	17
dPMC							45	-4	46	5.705	59
SMG	SII						57	-28	43	6.629631	186
IPL							33	-46	37	6.016366	20
STG, RO, SMG	SII	-48	-31	22	6.721656	1066	57	-34	25	8.381711	1823
RO	SII						48	-1	7	5.600565	45
vPMC		-51	-4	10	6.041226	219	54	2	16	6.5513	591
Insula	Posterior						39	-1	4	6.360892	151
	Anterior						36	14	7	7.247239	149
IFG							45	35	10	6.317161	148
Putamen		-27	-4	7	8.584658	258					
Thalamus							12	-10	10	5.067441	3
Cerebellum	ant. Cerebellum						12	-49	-17	7.760526	1101
	Vermis	-3	-58	-2	7.132509	289	-21	-61	-20	5.485753	47

Coordinates depict voxel with the highest t -value. Abbreviations: ACC, anterior cingulate cortex; dPMC, dorsal premotor cortex; IFG, inferior frontal gyrus; IPS, intraparietal sulcus; MI, primary motor area; PrCG, precentral gyrus; PoCG, postcentral gyrus; RO, rolandic operculum; SFG, superior frontal gyrus; SI, primary somatosensory area; SII, secondary somatosensory area; SMA, supplementary motor area; SMG, supramarginal gyrus; SPL, superior parietal lobule; STG, superior temporal lobe; vPMC, ventral premotor cortex.

TABLE III. Activated brain regions in event-related design identified by random effect group analysis for all subjects ($N = 15$) [$t(14) > 6.83$, corrected for multiple comparisons $FDR < 0.001$]

Cluster	Functional region	Contralateral					Ipsilateral				
		x	y	z	Max t	no. Voxels	x	y	z	Max t	no. Voxels
SFG	SMA	-6	-16	67	7.368715	4	9	-10	67	8.271598	53
PCS	SI	-24	-37	64	7.982056	38					
PrCG	MI	-24	-25	67	9.724324	85					
SPL	SI	-24	-46	55	11.44937	242					
PoCG, LS	SI	-51	-25	52	12.610755	1280					
IPL	SI	-33	-34	46	9.067326	696					
Cingulate	Anterior cingulate						3	17	34	10.221973	735
	Mid cingulate	-3	-4	46	10.554811	320	6	8	40	10.143863	695
		-6	-13	49	8.425615	34					
	Postcingulate	-12	-43	49	7.508058	6					
PoCG, SMG, LS	SII	-51	-25	19	11.711649	1922	54	-34	28	15.149926	2723
PrCG, Insula	vPMC	-42	-4	13	12.71619	871					
Insula		-39	-13	-2	9.505557	341	30	5	13	9.816894	396
							33	-19	7	7.553749	24
PrCG, IFG	vPMC						51	-4	10	11.59573	708
IFG		-48	5	1	9.569894	41					
Thalamus		-15	-22	7	9.832382	464	6	-16	10	8.626976	42
Putamen		-27	-10	7	7.649752	3					
Vermis		0	-58	-5	7.527245	8					
Cerebellum							12	-49	-17	7.529644	55

Coordinates depict voxel with the highest t -value. Abbreviations: ACC, anterior cingulate cortex; IPL, inferior parietal lobule; LS, lateral sulcus; MI, primary motor area; PoCG, postcentral gyrus; PrCG, precentral gyrus; SFG, superior frontal gyrus; SI, primary somatosensory area; SII, secondary somatosensory area; SMA, supplementary motor area; SMG, supramarginal gyrus; SPL, superior parietal lobule; vPMC, ventral premotor cortex.

Figure 2.

Block design. Statistically significant activation maps FES vs. Rest ($t(14) > 4.79$, FDR $q < 0.03$ corrected). The cluster threshold was set at 10 voxels. Top row: coronar view, anterior-posterior direction; bottom row: transversal view, superior-inferior direction. Convention for lateralization is shown: R, right hemisphere; L, left hemisphere.

tained voxels with higher t -values when compared to those from the block design. During electrical stimulation contralateral activation was present in SI and MI. Bilateral activations were found in several cortical areas including SMA, SII, vPMC, ACC, and insula. Activated subcortical regions comprised bilateral thalamus and contralateral putamen. Cerebellar activations were observed in vermal VB and VII, as well as ipsilateral Larsell's lobule V.

Intrasubject Variability

Intrasubject variability has been tested in five functional ROIs selected by their consistent activation in both block and event-related experiments in all single subjects as well

as in the group analysis. Previous studies have shown that these areas are implicated in passive training [Weiller et al., 1996; Carel et al., 2000; Loubinoux et al., 2001; Lotze et al., 2003] and in wrist extension-flexion tasks [Carel et al., 2000; Loubinoux et al., 2001; Curt et al., 2002; Naito et al., 2002; Lotze et al., 2003]. They included SMA, MI/SI, SII, ACC, and cerebellum. Our analysis showed a good reproducibility in repeated measurements. ANOVAs for both block and event-related design did not demonstrate a significant effect of time. The assessment of agreement for the repeated measurements within the block- and event-related designs showed minor differences, which, according to Bland and Altman [1986] were within the limits of agreement (mean difference ± 2 SD). However, two out-

Figure 3.

Event-related design. Statistically significant activation maps FES vs. Rest ($t(14) > 6.83$, FDR < 0.001 corrected). Top row: coronar view, anterior-posterior direction; bottom row: transversal view, superior-inferior direction. Convention for lateralization is shown: R, right hemisphere; L, left hemisphere.

TABLE IV. Reproducibility of three consecutive measurements for block design and event-related design in six subjects

ROI	Subject	Block design			Event-related design		
		x	y	z	x	y	z
SMA	BULI	-4.5 ± 6.36	-15 ± 2.12	68.5 ± 2.12	-4 ± 1.73	-16 ± 0.00	64 ± 3.00
	BURO	-7 ± 1.73	-9 ± 1.73	59 ± 6.93	-1 ± 1.73	-10 ± 0.00	62 ± 1.73
	EICH	-6 ± 0.00	-16 ± 0.00	69.5 ± 0.71	-9 ± 3.00	-16 ± 0.00	58 ± 6.00
	PREL	-5 ± 1.73	-16 ± 0.00	61 ± 0.00	-3.3 ± 0.58	-16 ± 0.00	63.7 ± 0.58
	ROST	-3 ± 3.00	-22 ± 3.00	54 ± 4.58	-3 ± 0.00	-22 ± 0.00	51 ± 1.73
	MEZE	0 ± 0.00	-10 ± 0.00	57 ± 1.73	-2 ± 1.73	-11 ± 1.73	60 ± 1.73
MISI	BULI	-39 ± 0.00	-22 ± 0.00	55 ± 0.00	-34 ± 1.73	-28 ± 0.00	61 ± 0.00
	BURO	-32 ± 1.73	-34 ± 0.00	55 ± 0.00	-30 ± 0.58	-34 ± 0.00	55.3 ± 0.58
	EICH	-36 ± 3.00	-24 ± 1.73	49 ± 6.00	-35 ± 1.73	-31 ± 3.00	60 ± 1.73
	PREL	-34 ± 1.73	-37 ± 5.20	62 ± 3.46	-30 ± 0.58	-31 ± 0.58	63.7 ± 0.58
	ROST	-32 ± 6.36	-43 ± 0.00	52 ± 0.00	-37 ± 1.73	-41 ± 1.73	57 ± 1.73
	MEZE	-35 ± 1.73	-28 ± 0.00	44 ± 1.73	-30 ± 0.00	-27 ± 1.73	43 ± 0.00
SII	BULI	-48 ± 4.24	-40 ± 21.21	14.5 ± 10.61	-46 ± 1.15	-25 ± 0.00	19 ± 0.00
	BURO	-53 ± 6.93	-20 ± 12.12	23 ± 1.73	-42 ± 0.00	-19 ± 0.00	22 ± 0.00
	EICH	-47 ± 1.73	-24 ± 3.46	13 ± 0.00	-48 ± 6.00	-32 ± 3.46	22 ± 1.73
	PREL	-54 ± 3.00	-20 ± 1.73	19 ± 0.00	-53 ± 1.73	-19 ± 0.00	19 ± 0.00
	ROST	-51 ± 0.00	-45 ± 1.73	25 ± 0.00	-59 ± 1.73	-30 ± 1.73	21 ± 1.73
	MEZE	-45 ± 3.00	-20 ± 1.73	23 ± 1.73	-48 ± 3.00	-20 ± 1.73	24 ± 1.73
ACC	BULI	-9 ± 0.00	-8.5 ± 6.36	46 ± 0.00	-7 ± 3.46	-10 ± 0.00	46 ± 0.00
	BURO	-11 ± 1.73	-18 ± 6.93	43 ± 5.20	-0.3 ± 0.58	4 ± 1.73	43 ± 0.00
	EICH	-5 ± 1.73	-29 ± 1.73	42 ± 1.73	-3 ± 5.20	-4 ± 3.00	43 ± 3.00
	PREL	-7 ± 4.58	-16 ± 3.00	48 ± 1.73	-4 ± 1.73	-14 ± 1.15	50.7 ± 1.53
	ROST	-7 ± 1.73	-8 ± 1.73	41 ± 1.73	-6 ± 0.00	-17 ± 1.73	43 ± 0.00
	MEZE	-9 ± 0.00	-31 ± 0.00	43 ± 0.00	-3 ± 0.00	-13 ± 0.58	45 ± 1.73
CEREBELLUM	BULI	18 ± 0.00	-46 ± 0.00	-20 ± 0.00	30 ± 0.00	-46 ± 0.00	-20 ± 0.00
	BURO	3.46 ± 0.00	0 ± 0.00	1.73 ± 0.00	4.58 ± 0.00	1.73 ± 0.00	0 ± 0.00
	EICH	12 ± 0.00	-50 ± 1.73	-20 ± 3.00	24 ± 10.82	-39 ± 6.24	-27 ± 4.58
	PREL	16 ± 1.73	-49 ± 3.00	-15 ± 1.73	21 ± 0.00	-49 ± 0.58	-16 ± 1.73
	ROST	6 ± 3.00	-49 ± 7.94	-9 ± 4.58	3 ± 3.00	-60 ± 1.73	-13 ± 1.73
	MEZE	18 ± 3.00	-48 ± 1.73	-17 ± 0.00	3 ± 0.00	-62 ± 1.73	-8 ± 0.00

Mean and standard deviations of individual talairach coordinates per ROI. Abbreviations: ACC, anterior cingulate cortex; MI/SI, primary motor / somatosensory area; SII, secondary somatosensory area; SMA, supplementary motor area.

liers were found: in the context of block design, one participant's difference for T1 vs. T2 slightly exceeded 2SD in SII. In context of event-related approach, one volunteer revealed a difference for T1 vs. T2 that slightly exceeded 2SD in MI/SI. Plots are available as supplementary data. The defined cubes around the peak activations in both block and event-related experiments overlapped, suggesting a reliable quantification of the repeated measurements (Table IV). The analysis of the time courses within the event-related design revealed a good match for each functional run (Fig. 4).

DISCUSSION

The motivation of this study was to show the safe application of FES in the MR-scanner, the comparison of two standard fMRI-paradigms using FES leading to similar cortical activation maps, and the demonstration of reproducibility of repeated measurements. Our results demonstrate that FES can be safely performed in the MR scanner,

aiming to investigate the sensorimotor network activated during FES-elicited movements. No image artifacts were evoked and the stimulation was not influenced by the large magnetic field. FES elicited comparable activation patterns in both block and event-related design. Repeated measurements within the same subjects demonstrated overlapping regions of activation and similar time courses in three consecutive runs. Furthermore, ANOVA showed no significant time effect supporting a good intra-subject reproducibility of the results. A good agreement of measurement is achieved when differences lie between the limits of 2SD [Bland and Altman, 1986], as it is demonstrated by our results. Only in two out of 30 instances, minor differences were found slightly above this limit. However, remaining pair wise comparisons in the respective ROIs showed a good agreement leading to our suggestion of reproducibility. These data indicate that the technique is suitable and may be used in longitudinal patient studies for assessing plastic changes associated with FES rehabilitation treatment.

Figure 4.

Individual time courses of six subjects in five ROI in three consecutive runs within event-related design. Color represents order of runs: 1, red; 2, green; 3, blue. Bold curves represent ROIs which have been relocated adjacent to other 2 ROIs (see text for details).

Cerebral Activation Patterns of FES-Elicited Wrist Movements

The stimulation-induced wrist extension-flexion paradigm used in this study activated motor and somatosensory areas, which are concordant to those found in previous studies using either voluntary movements or sensory stimulations of the wrist [Carel et al., 2000; Loubinoux et al., 2001; Curt et al., 2002; Naito et al., 2002; Lotze et al., 2003]. There is only one previous report [Han et al. 2003] on cortical activation patterns using neuromuscular electrical stimulation to elicit wrist extension movements in healthy volunteers. Their analysis was restricted to the MI/SI, PMC and SMA. However, several other cortical and subcortical areas such as, SII, ACC, insula, thalamus, putamen, and cerebellum have been shown to activate during passive training [Weiller et al., 1996; Carel et al., 2000; Lotze et al., 2003; Cic-

carelli et al., 2005] and have been implicated in functional recovery after rehabilitative therapy in patients with stroke [Johansen-Berg et al., 2002]. Therefore, our study reports the effects of FES on the entire primary and secondary motor and somatosensory networks.

Five distinct brain areas, namely MI/SI, SMA, SII, ACC, and cerebellum, known to contribute to active and passive motor tasks, showed significant and reproducible activations in our study. Strong activation has been elicited in MI/SI extending to the same degree in both somatosensory and motor areas adjacent to the central sulcus. These areas are closely connected, send efferent inputs to and receive afferent inputs from the distal extremities. Their co-activation was expected considering the nature of our stimulation and the motor output it produced. Activation of the primary motor cortex has been previously observed with passive movements even without electrical stimula-

tion [Weiller et al., 1996; Han et al., 2003; Lotze et al., 2003; Ciccarelli et al., 2005].

In line with previous studies using wrist extension-flexion tasks [Carel et al., 2000; Loubinoux et al., 2001; Curt et al., 2002; Naito et al., 2002; Han et al., 2003] and in keeping with our predictions, we found activations in the SMA contralateral to the stimulated wrist. SMA plays an essential role in learning and initiation of a movement, as well as its execution [Picard and Strick, 1996]. However, it is also reasonable that the electrical stimulus also contributed to SMA activation as this region is sensitive to somatosensory input [Picard and Strick, 1996; Del Gratta et al., 2000; Barba et al., 2005; Arienzo et al., 2006].

Bilateral activation within the SII was consistent in all subjects and was related both to the passive motor movement elicited by the FES and the sensory component of the electrical stimulation. Studies investigating the effect of passive training on cortical plasticity [Carel et al., 2000; Loubinoux et al., 2001; Lotze et al., 2003; Ciccarelli et al., 2005] consistently report bilateral activations in SII. Moreover, several studies using electrical stimulation of the median nerve [Del Gratta et al. 2000; Arienzo et al., 2005; Sutherland and Tang, 2006] or stimulation of the fingers [Deuchert et al., 2002] found bilateral activation in SII. Ferretti et al. [2003], demonstrated a functional segregation of the SII in an anterior and a posterior area. The former was activated during nonpainful and painful galvanic nerve stimulation, while the latter showed activation increase, which was related to the increase of pain. Our findings show a broadly extended activation pattern within SII encompassing both anterior and posterior parts, and despite the nonpainful nature of our stimulus, a certain degree of unpleasant feeling may accounted for this observation. Individual attentive processes might also account for the observed activation patterns. Sterr et al. [2007] showed a modulation of SI and SII by attention. Subjects who perceived the stimulus as unpleasant presumably attended more to the stimulus.

Activation of the ACC is more likely attributed to the processing of the electrical stimulus itself rather than the passive movement of the wrist. The previously mentioned reports on passive training do not consistently report activation in cingulate areas. Carel et al. [2000] and Loubinoux et al. [2001] described activation within the cingulum, whereas others did not [Weiller et al., 1996; Lotze et al., 2003; Ciccarelli et al., 2005]. However, studies using somatosensory stimulation [Ploghaus et al., 1999; Peyron et al., 1999; Wager et al., 2004; Mohr et al., 2005; Arienzo et al., 2006; Christmann et al., 2007] consistently demonstrate activations in the cingulate cortex.

Activation in cerebellum was mainly ipsilateral. Two main foci were found, one in vermal V and the other in ipsilateral Larsell's lobule V. This finding is in line with the sensorimotor mapping of Grodd et al. [2001]. Fingers seem to be localized more lateral, whereas the wrist is somatotopically localized closer to the midline of the cerebellum in vermal V. Extension and flexion of the wrist co-acti-

vated also the fingers probably due to electrical stimulation of adjacent finger extension and flexion muscles. This pattern of cerebellar activation is in line with other studies using passive movements [Carel et al., 2000; Loubinoux et al., 2001; Lotze et al., 2003; Ciccarelli et al., 2005]. The cerebellum plays an important role in the coordination and fine tuning of motor sequences [Trepel, 1999]. A study using electrical stimulation of the lower extremities [Smith et al., 2003], reported that afferent spinocerebellar information from muscle, joint and tactile receptors is important for the preparation and correction of ongoing movement. Takanashi et al. [2003], using also electrical stimulation demonstrated a similar somatotopical organization within the cerebellum. We conclude that the observed cerebellar activation pattern in our study has been elicited by the passive movement, as well as by the electrical stimulation itself.

Activation of Pain Network?

As previously mentioned, the stimulation was well tolerated, though not comfortable for all subjects. Two subjects, who were initially willing, eventually did not participate in the study due to uncomfortable sensations related to the electrical stimulation. Despite the nonpainful character of the stimulus, activations within SMA and ACC may also be related to these subjective sensations of discomfort. The subjects in our study were lying in the scanner with their eyes closed anticipating the next burst of electrical impulses, which was the only stimulus perceived along the ongoing scanner noise. Arienzo et al. [2006] reported that SMA and ACC may play a role in individual processing of the electric stimulation in that the same stimulus is differently perceived by each subject. Studies investigating pain found activation within the SMA [Arienzo et al., 2006], ACC, insula, prefrontal cortex, thalamus, hippocampal formation and the cerebellum [Ploghaus et al., 1999; Peyron et al., 1999; Wager et al., 2004; Mohr et al., 2005; Arienzo et al., 2006]. Moreover, studies investigating the anticipation of pain [Ploghaus et al., 1999; Wager et al., 2004] also reported activation in the same cortical areas.

Experimental Design

We used both a block design and an event-related design to record cortical activation patterns. Our goal was not to directly compare these experimental approaches but to evaluate whether both experimental approaches result in activation of the same neuronal networks. In general, a block design shows robust results, has an increased statistical power and its BOLD signal change is relatively large related to baseline (see Amaro and Barker, 2006 for review), but it is also susceptible to habituation and anticipation [Liu et al., 2001]. The event-related approach is advantageous in detecting transient changes in the BOLD signal, measuring unpredictable events and depicting the temporal dynamics of response [Rosen et al., 1998; Liu et al., 2001; Amaro and Barker, 2006]. The illustrations of

event-related time courses (see Fig. 4) demonstrate that the haemodynamic response function of different brain regions was different for the same stimulus. This possibility of getting closer insight into the haemodynamic response of activated areas may potentially prove essential for studying recovery of motor functions following spinal cord injury or stroke. In our study, the two designs produced robust activations of the sensorimotor network, with the event-related design showing activation maps with higher *t*-values as compared to the blocked design applying the same threshold. This difference may be attributed to habituation and anticipation effects associated with the block design, in that subjects got used to the enduring stimulation, lasting for 21 s, which was repeated in a fixed order. Although learning processes were not expected to play an important role we cannot rule out that a learning process may have occurred. Even in the context of the passive stimulation used in our experiment, an episodic memory representation of the simple task (frequency, monotonous stimulation etc.) may have been formed in association with the experimental context (MRI, block design) [Loubinoux et al., 2001] which may also account for the decreased activity observed for the block design as compared to the event-related design.

A potential limitation of this study is that one cannot distinguish between the effects of stimulation and the effect of potentially voluntary wrist movement. With respect to the latter, we suggest that in the event-related design voluntary wrist movements can be excluded because the stimulation occurred in a random fashion and lasted only one second.

Despite obvious advantages of using an event related design, in the context of clinical studies, we propose the use of a block design for the following reasons. First, the results obtained from the block design are equivalent in strength to those collected during the event-related design. Second, the duration of the block design is considerably shorter, which makes it more comfortable for patients and increases the feasibility of clinical studies. Third, event-related designs have a lower statistical power compared to block designs as the ratio of task period to rest period is smaller [MacIntosh et al., 2004]. Lastly, the block fMRI design is more similar to the real therapeutic use of FES, which is also applied in blocks of stimulation.

Reproducibility

Reproducibility was tested in six subjects undergoing the experiment three times within the same session. Intrasubject variability of local peak maxima and time courses within the predefined ROIs was ignorable as subjects showed robust activations within the previously discussed somatosensory network in both block and event-related design. Size and location of activation maps varied moderately across individuals. Similar findings have been reported in fMRI studies investigating the reproducibility of motor tasks [Tegeler

et al., 1999, Loubinoux et al., 2001; Havel et al., 2006] and somatosensory stimulations [Kong et al., 2007] pointing out functional anatomic variations or different cognitive strategies. Yoo et al. [2005], using a sequential finger tapping task, demonstrated that intra-session recordings yielded slightly better reproducibility measures as compared to ones obtained in other seven sessions, which were approximately eight weeks apart. In our study, long-term reproducibility was not tested but nevertheless, similar to what has been observed in previous studies, intrasession short-term reproducibility was high despite of minor variations in regional activations. Thus, we conclude that FES fMRI should be a reliable means for assessing plastic changes within the cortical areas related to rehabilitative therapy.

Monitoring Rehabilitation

Several studies emphasize the beneficial effects of FES in a combined motor therapy [Chae and Yu, 1999; Barbeau et al., 2002; Rushton, 2003]. The initial FES-therapy starts with a strengthening program followed by the functional training [Popovic et al., 2001a]. We demonstrated that fMRI experiments during FES are feasible and can be potentially applied to track rehabilitation induced recovery over time. Training related behavioral gains can be correlated with fMRI patterns in cortical activation to provide insight on plastic changes related to the specific rehabilitation treatment over time. So far there have been only few studies relating changes of the sensorimotor network over the course of a specific rehabilitation therapy [Liepert et al., 2000; Binkofski et al., 2001; Johansen-Berg et al., 2002; Dobkin et al., 2004; Winchester et al., 2005; Hamzei et al., 2006]. The Complex Motion stimulator used in our study, emphasizes the practice of a simple functional movement, such as wrist extension-flexion, relevant to daily activities that can also be practiced within the fMRI environment to follow cortical changes related to functional gains. This approach, in combination with behavioral outcome measures, should be able to monitor with adequate sensitivity the progress of the patient [Dobkin, 2003].

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