Interaction of Electrical Stimulation and Voluntary Hand Movement in SII and the Cerebellum During Simulated Therapeutic Functional Electrical Stimulation in Healthy Adults

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Abstract: The therapeutic application of functional electrical stimulation (FES) has shown promising clinical results in the rehabilitation of post-stroke hemiplegia. It appears that the effect is optimal when the patterned electrical stimulation is used in close synchrony with voluntary movement, although the neural mechanisms that underlie the clinical successes reported with therapeutic FES are unknown. One possibility is that therapeutic FES takes advantage of the sensory consequences of an internal model. Here, we investigate fMRI cortical activity when FES is combined with voluntary effort (FESVOL) and we compare this activity to that produced when FES and voluntary activity (VOL) are performed alone. FESVOL revealed greater cerebellar activity compared with FES alone and reduced activity bilaterally in secondary somatosensory areas (SII) compared with VOL alone. Reduced activity was also observed for FESVOL compared with FES alone in the angular gyrus, middle frontal gyrus and inferior frontal gyrus. These findings indicate that during the VOL condition the cerebellum predicts the sensory consequences of the movement and this reduces the subsequent activation in SII. The decreased SII activity may reflect a better match between the internal model and the actual sensory feedback. The greater cerebellar activity coupled with reduced angular gyrus activity in FESVOL compared with FES suggests that the cortex may interpret sensory information during the FES condition as an error-like signal due to the lack of a voluntary component in the movement. *Hum Brain Mapp* 33:40–49, 2012. © 2011 Wiley Periodicals, Inc.

Key words: functional electrical stimulation; voluntary movement; fMRI; SII; cerebellum

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INTRODUCTION

Stroke survivors require intensive rehabilitation therapy to regain lost motor function and there is an increasing demand for evidence-based therapies that will accelerate and augment this process. Several different methodological approaches have been reported in the literature including constraint induced movement therapy, bilateral training, robot assisted training, and peripheral electrical stimulation [e.g. Blanton et al., 2008; Kwakkel et al., 2008; Sheffler and Chae, 2007; Stewart et al., 2006].

The neural mechanisms that underlie the clinical benefits reported in these and other therapies are of increasing interest. Ward and Cohen, [2004] have suggested that it is important to maximize the neuronal input to the affected area. Neuromuscular electrical stimulation enhances sensory input via externally driven movement. It can involve repetitive electrical stimulation (ES) of passive muscle to drive simple movements [e.g. Chae et al., 1998; Powell et al., 1999], or patterned stimulation to elicit functional movements [for a comprehensive recent review see Sheffler and Chae, 2007]. Functional electrical stimulation (FES) was used initially as a neuroprosthetic [Liberson et al., 1961; Moe and Post 1962] but has recently been used as a therapeutic intervention [e.g. Popovic et al., 2002, 2004]. The therapeutic application of FES has shown promising clinical results in the rehabilitation of stroke and, to a lesser extent, in spinal cord injury. Recent studies suggest that the effect of FES is optimal when the patterned electrical stimulation is delivered in close synchrony with the attempted voluntary movement.

It is possible that the clinical results reported with therapeutic FES are associated with the enhanced cortical plasticity resulting from the cumulative effects of FES-induced cortical excitability together with the excitability due to voluntary activation. Both ES and FES have been shown to produce changes in cortical excitability [Barsi et al., 2008; Blickenstorfer et al., 2009; Khaslavskaja et al., 2002; Knash et al., 2003; Ridding and Rothwell, 1999; Rossini and Pauri, 2000]. Furthermore, the repetition of even a simple movement can produce changes in cortical excitability that lead to a transient reorganization in motor connectivity [Classen et al., 1998]. Moreover, active involvement in task performance leads to a substantial increase in cortical excitability compared to nonskilled or passive training [Perez et al., 2004] and when combined with FES [Barsi et al., 2008].

A good understanding of the mechanisms by which therapeutic FES interacts with the central nervous system may allow us to improve the therapy. Electrical stimulation has been proposed to work via a sensorimotor coupling mechanism whereby increased proprioceptive signals from evoked movements activate the somatosensory cortex thereby increasing motor corticoneuronal excitability [Cauraugh et al., 2000; Luft et al., 2002; Ridding and Taylor, 2001; Rosenkranz and Rothwell, 2006; Sawaki et al., 2006; Woldag and Hummelsheim, 2002]. The increased motor cortical excitability may then facilitate

greater voluntary activation of the relevant neuronal network, thereby leading to improved function [Wu et al., 2005]. It is possible that the additional proprioceptive and/or somatosensory information provided by the electrical stimulation is used in a forward internal model.

The concept of the forward internal model is a widely accepted tenant in motor control. The internal model hypothesis posits that there exist neural mechanisms that mimic the input/output characteristics of motor commands and compare this idealized output to actual performance signaled in the form of sensory feedback [Ito, 1970, 2005; Wolpert et al., 1995; Wolpert and Ghahramani, 2000]. Internal models predict the sensory consequences of self-generated movements using efference copies of motor commands [von Holst, 1954] and they calculate feedforward motor commands from desired trajectory information. It is believed that parts of the construction of the internal model and its comparison with actual performance is carried out in the cerebellum [Blakemore et al., 1998b, 1999, 2001; Ito, 1970, 2005]. An accurate movement prediction then attenuates the sensation in the somatosensory cortex [Blakemore et al., 1998b]. These mechanisms are proposed to underlie motor adaptation/learning by using discrepancies between ideal and actual trajectories as sensory error signals to update internal model parameters in order to perform better the next time around.

The internal model concept may be important in rehabilitation because the model can be updated as the state of the limb changes. Therefore rehabilitation may need to emphasize techniques that promote the formation of appropriate internal models rather than simple repetition of movements [Krakauer, 2006]. To determine if internal models are appropriately incorporated during FES-assisted voluntary movement, one must test if internal model networks are appropriately engaged during the task.

Functional magnetic resonance imaging (fMRI) is a non-invasive technique to study brain function that can be used to document the relationship between cortical reorganization and the recovery of motor function [Ward et al., 2003]. Blickenstorfer et al. [2009] demonstrated that fMRI experiments during FES are feasible and that fMRI could be used to monitor cortical organization. They observed significant and reproducible changes in activation with FES in distinct brain areas including primary motor cortex (MI), primary somatosensory cortex (SI), secondary somatosensory cortex (SII), supplementary motor area (SMA), anterior cingulate cortex (ACC), and cerebellum.

We designed an fMRI experiment to study brain activity in healthy adults evoked with four hand grasp tasks involving voluntary motor activation (VOL), patterned electrical stimulation of finger flexor/extensor muscles to effect movement without voluntary activation (FES), and voluntary activation performed together with FES (FESVOL). Based on the studies of Blakemore et al [1998b, 1999, 2001], which specifically test mechanisms of the internal model networks, we hypothesized that FESVOL, as opposed to FES, would activate the motor part of the cerebellum [Grodh

et al., 2001], in particular to make predictions of the sensory consequences of motor commands. In turn, this should reduce the SII activity in FESVOL compared with FES due to a better prediction of the sensory input.

METHODS

Participants

Seventeen healthy adult volunteers (8 female; 9 male) were recruited for the study. The participants were screened for any history of neuromuscular disorder (mean age, 29 ± 3 years; range, 25–40 years). Informed written consent was provided prior to participation in the study. The investigation complied with the declaration of Helsinki and was approved by the Regional Ethics Committee for Aarhus County.

Instrumentation

The participants lay supine on the scanner bed with their arms resting comfortably by their side for the duration of the experiment. The head was secured and movement was minimized with foam padding. The arms were supported as necessary and the right elbow was fixed only allowing movement of the hand. A cylindrical rod was grasped with the right hand, and held in a manner that allowed full finger flexion and extension. An optic fiber goniometer (Measurand S720 ShapeSensor) was fixed to the lateral aspect of the right index finger to monitor the extent of finger flexion/extension.

Patterned neuromuscular electrical stimulation was used to effect finger flexion movements in some trials. The stimuli were delivered at 50 Hz with 200 μ s pulses and controlled by a commercial FES stimulator (Actigrip, Neurodan A/S, Denmark). Finger flexion and extension were delivered on two separate channels through round surface stimulation electrodes (Pals - Platinum Neurostimulation Electrodes, diameter = 1.25") fixed to the skin with adhesive gel. The electrodes were positioned with cathodes over the motor points of the finger flexors (flexor digitorum profundus and flexor digitorum superficialis) and extensors (extensor digitorum communis) and a common anode located on the forearm near the wrist.

The stimulation pattern was triggered with a push-button switch held in the left hand. Each button press initiated a stimulation pattern that produced 1.5 s of finger extensions to open the fingers, followed by 2 s of finger flexion to produce hand grasp of a handle, then 1.5 s finger extension to release the handle. The timing and characteristics of the stimulation was designed to closely mimic the finger flexion/extension stimulation used in clinical FES therapy for hand grasp [Popović et al., 2002].

Prior to the data collection, the electrode position and stimulation intensity were adjusted to produce the best possible grasping movement of the fingers. The electrode positions were carefully selected to ensure that finger extension/flexion movement was as natural as possible. The stimulation pattern was designed to mimic activity of

fingers typical of slow grasping and releasing. The pulse duration, frequency, and amplitude (current) were set to minimize discomfort during stimulation yet produce a finger flexion/extension movement that would allow the participant to grasp and hold a 50-cl bottle of water without voluntary assistance [Barsi et al., 2008]. While the magnitude of stimulation varied from one participant to another, the range of stimulation current intensity ranged from 7 to 12 mA for flexion and 10 to 15 mA for extension. The flexion/extension movements were monitored with goniometry.

Procedure

MR scanning was conducted while the participants performed different tasks involving repetitive flexion/extension movement of the fingers of the right hand (VOL, FES, FESVOL) and a control task (REST). In the VOL task, the participant voluntarily grasped and released the cylindrical rod. In the FES task, the grasp/release movement was elicited by patterned electrical stimulation of the finger flexor/extensor muscles with no voluntary contribution to the movement. In the FESVOL task the grasp/release movement was performed as described for the FES condition but with the addition of voluntary activation. In the control task, REST, the participants performed no movement with the right hand. The participant performed one extra condition in which the participant was asked to imagine the fingers grasping and releasing the cylinder (IMAG). The results from the analysis of IMAG are not included in this study as they are not central to the hypotheses. In all conditions, the participants pressed a trigger button with the left hand to initiate the trial, although stimulation was only delivered during the FES and FESVOL conditions. A visual cue was provided to indicate when the participant should trigger the stimulation sequence.

The five tasks were implemented in a block design paradigm with each block corresponding to one task. Each block (VOL, FES, FESVOL, IMAG and REST) lasted 30 s, separated by 6 s intervals of no activity. The order of VOL, FES, FESVOL, IMAG, and REST was randomized and each task was repeated five times.

Throughout the experiment the participants viewed a computer display via a mirror mounted on the head coil. During the 6-s interval that preceded each block of trials the display showed a red circle to indicate that no movement was to be performed, and a line of text showing the next condition that the participant was required to perform (VOL, FES, FESVOL, IMAG, or REST). At the beginning of the block, the circle was changed to green, thus cuing the participant to press the trigger button with the left hand. The green light was turned on four times during each block to cue the button press. The participants were instructed to press the button once as soon as they saw the green indicator. The participants were trained immediately prior to the experimental session for ~20 min until they were comfortable with the procedure.

MRI

Functional images of the BOLD response were acquired with a GE Sigma HDx 3T scanner (General Electric, Milwaukee, WI). A gradient-echo EPI sequence (TR = 3 s, 90° flip angle) was used to acquire 35 slices (4 mm thickness, no gap, interleaved slice acquisition). In total, 303 volumes were acquired in each session, with the first three volumes discarded to account for T1 saturation effects. High-resolution structural images were acquired in the same session (TE = 2.9 ms, flip angle = 20, 256 × 256 acquired matrix).

Data Analysis

Image analysis was performed using Matlab 7.0 and SPM2. The 300 volume images were automatically coregistered and realigned to the first volume image of the fMRI run to correct for head movement during the scans. The data were then normalised to a standard EPI template in MNI space. Spatial smoothing was done with a Gaussian filter with a FWHM of 10 mm.

In the first level analysis, Statistical Parametric Maps were calculated for each participant modelling each condition as a block. Three contrasts were made with the REST condition (VOL vs. REST, FES vs. REST, and FESVOL vs. REST) and four between-condition contrasts (FESVOL vs. FES, FESVOL vs. VOL, FES vs. VOL, FES vs. FESVOL) were computed.

In order to correct for structured noise an AR(1) process was fitted to the data and a high pass filter with cut off at 128 s was employed. Because of the slow design, the high pass filter has removed some parts of the paradigm; however, this filter only influences the number of false negatives while correcting for the false positives that would otherwise have been produced from scanner drift.

Summary statistics were taken to a second-level random effect group analysis (ANOVA based on estimated contrast images). The resulting statistical parametric *t* maps were FDR corrected for multiple comparisons at $P < 0.05$. Peak activations within activated clusters were identified and superimposed on a single participant T1-weighted structural MRI (SPM2 template image).

The two types of commonly used inference methods are those that control the family wise error rate (FWE; Nichols and Hayasaka, 2003] versus those that control the false discovery rate (FDR; Genovese and Wasserman, 2002]. Bonferroni and Random Field Theory thresholds are two methods that control FWE, i.e. the chance of one or more false positives. FDR is more sensitive than traditional methods because it uses a more lenient metric for false positives. Both FWE and FDR can be applied voxel-wise, as a threshold on a statistic image, or cluster-wise, as a threshold on the size of clusters after applying an arbitrary cluster-forming threshold. Only the results that survived the FDR correction at $P < 0.05$ are reported in this study.

RESULTS

Kinematics

The range of finger movement was quantified for each trial as the peak-to-peak amplitude between finger flexion and extension. A one-way repeated measures ANOVA revealed no significant difference ($P = 0.747$) in movement range between FES, VOL, or FESVOL.

Neural Activation

Table I summarises the VOL, FES, and FESVOL contrasts with respect to REST. Table II summarizes the FESVOL vs. FES, FESVOL vs. VOL, FES vs. VOL, and FES vs. FESVOL contrasts. Below the most important results are illustrated. The details of the cytoarchitectonic allocation and probabilities for all the areas at each position are included in Tables I and II.

VOL vs. REST resulted in activity in a network of cortical areas well known to be involved in motor tasks including contralateral primary motor cortex (M1) and primary somatosensory cortex (S1) and secondary somatosensory cortex (SII), see Table I. These activations were accompanied by ipsilateral cerebellum, contralateral middle frontal gyrus and ipsilateral superior and inferior parietal gyrus.

FES vs. REST resulted in activation in an extended network in the contralateral M1 and S1 and bilaterally in SII. Additional activation was observed in the ipsilateral lobe of the cerebellum, bilaterally in middle frontal gyrus, ipsilaterally in the superior parietal gyrus, ipsilateral thalamus, and in ipsilateral subcortical structures including the putamen (Fig. 1A and Table I).

FESVOL vs. REST

Compared with REST, the network activated in the FESVOL condition largely overlapped with that activated by the FES condition, and included the contralateral sensorimotor cortices, ipsilateral cerebellum and inferior parietal cortex (Fig. 1B and Table I).

FESVOL vs. FES revealed greater FESVOL activity in the contralateral and ipsilateral lobes of the cerebellum (Fig. 1C). The opposite contrast, FES vs. FESVOL, revealed a difference in angular gyrus (IPC (PGa)), SMA and inferior (IFG), middle (MFG) and superior frontal gyrus (SFG) which is due to decreased activation in angular gyrus, MFG, SFG and SMA during FESVOL and only increased activation in MFG during FES (Fig. 2A,D and Table II).

FES vs. VOL

FES stimulation on its own resulted in significant increase in the BOLD signal bilaterally in SII compared with voluntary movement (Fig. 2B and Table II).

FESVOL vs. VOL

Stimulation combined with voluntary movement compared with voluntary movement resulted in significant

TABLE I. Results of random effect group analysis, FDR corrected, for VOL versus REST, FES versus REST, and FESVOL versus REST

Contrast	Anatomic Area	Contralateral				Ipsilateral			
		<i>x</i>	<i>y</i>	<i>z</i>	<i>t</i>	<i>x</i>	<i>y</i>	<i>z</i>	<i>t</i>
VOL versus REST	M1	−30	−26	54	13.02				
	S1	−38	−26	64	14.32				
	SII	−58	−28	38	12.18				
	Cerebellum Vermis					6	−60	−16	9.33
	MFG	−36	42	34	3.66				
	SPG					14	−68	54	4.47
FES versus REST	IPG					52	−32	50	14.34
	M1	−28	−24	54	13.21				
	S1	−38	−28	60	12.44				
	SII	−58	−24	18	12.92	50	−32	48	10.88
	Cerebellum Crus 1					46	−54	−32	3.79
	Vermis					6	−62	−16	6.77
	FMG	−44	34	32	3.52	40	48	0	4.29
	SPG					14	−68	56	4.42
	Thalamus					12	−14	6	4.89
FESVOL versus REST	Putamen					22	10	−2	5.65
	M1	−28	−26	54	14.63				
	S1	−36	−28	62	14.47				
	SII	−60	−28	18	16.1	62	−22	22	13.27
	Cerebellum VI					8	−64	−14	11.25
	Vermis					2	−76	−14	9.29
	Crus2					8	−72	−14	6.45
	IPG					54	−32	52	11.01

Anatomic labels, MNI coordinates of peak activation, and *t* are included.

increase of the BOLD signal bilaterally in SII (Fig. 2C and Table II).

DISCUSSION

The aim of this study was to gain a better understanding of the cortical activity elicited when neuromuscular electrical stimulation is combined with voluntary effort. We hypothesized that the FESVOL task would show greater cerebellar

activity than would the FES task alone, because the additional information afforded by the voluntary component of the movement would be used in the generation of an internal model within the cerebellum. This, in turn, would reduce the SII activity due to a better prediction of the sensory input. Bilateral cerebellar activity was indeed greater when the stimulation was combined with voluntary activity (Fig. 1C) and key differences in activation were observed bilaterally in secondary somatosensory areas (Fig. 2C) when FESVOL was contrasted with VOL alone, thus confirming

TABLE II. Results of random effect group analysis, FDR corrected, for FESVOL versus FES, FES versus FESVOL, FESVOL versus VOL, and FES versus VOL

Contrast	Anatomic Area	Contralateral				Ipsilateral			
		<i>x</i>	<i>y</i>	<i>z</i>	<i>t</i>	<i>x</i>	<i>y</i>	<i>z</i>	<i>t</i>
FESVOL Versus FES	Cerebellum VI	−6	−68	−22	7.85	16	−68	−14	5.97
	Crus 1	−16	−74	−26	6.09				
	VIII					8	−70	−30	4.66
FES Versus FESVOL	Angular gyrus IPC (Pga)					58	−50	25	6.21
	SMA					14	16	63	5.25
	IFG					42	16	27	5.81
	MFG					34	50	8	
	SFG					22	10	59	11.1
FES versus VOL	SII	−60	−30	8	7.68	54	4	6	6.13
FESVOL versus VOL	SII	−40	−20	14	5.17	58	−22	14	6.95

Anatomic labels, MNI coordinates of peak activation, and *t* are included.

Figure 1.

Neural activation for **(A)** FES vs. REST, **(B)** FESVOL vs. REST, and **(C)** FESVOL vs. FES. Activations during FES vs. REST mostly overlapped with activations during FESVOL vs. REST. The direct contrast FESVOL vs. FES revealed more activity in the contralateral and ipsilateral lobes of the cerebellum. Results are based on

a group random effect ($N = 17$, FDR corrected at $P < 0.05$). **D:** A contrast estimate from the cerebellum with the three movement conditions. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

the hypothesis. In addition, the FESVOL condition produced less activation of angular gyrus, SMA and IFG, MFG and SFG than did neuromuscular stimulation alone (Fig. 2A,D). One interpretation of this result is that the combination of voluntary activity with FES-driven motor activity may help to make the movement more predictable.

FES and the FESVOL Activates Much the Same Network as VOL

Not surprisingly, VOL resulted in activity in a network of cortical areas that is well known to be associated with motor tasks (see Table I). The FES and the FESVOL conditions both activated much the same network as the VOL condition. The most notable difference is a bilateral SII activation in the FES vs. REST and FESVOL vs. REST contrasts, as opposed to contralateral SII activity in the VOL vs. REST contrast. In addition, the bilateral cerebellar activation in FESVOL as opposed to ipsilateral cerebellum in FES and VOL is noticed when each of the 3 tasks was contrasted to REST. The activation by electrical stimulation of these areas is consistent with previous studies of electrically evoked motor activity observed with MEG [Lin and Forss, 2002], PET [Ledberg et al., 1995], and fMRI [Backes et al., 2000; Davis et al., 1995; Del et al., 2000; Ibanez et al., 1995; Kampe et al., 2000; Smith et al., 2003; Spiegel et al., 1999].

The activation of the cerebellum in FES and FESVOL condition is in agreement with two previous studies [Blicken-

storfer et al., 2009; Smith et al., 2003]. Both studies reported cerebellar activity that accounted for 50% of the observed responses when neuromuscular electrical stimulation was applied to the leg at the motor threshold level. In a similar paradigm to the present study, Blickenstorfer et al. [2009] observed mainly ipsilateral cerebellar activation during electrical stimulation of the wrist extensor and flexor muscles.

During the FES condition, our participants were instructed not to voluntarily contribute to the movement. The activation of the contralateral M1 in FES (see Table I) could be due to activation of muscle spindle and cutaneous afferents [Golaszewski et al., 2004]. Primary motor cortex activation has been observed previously in FES [Blickenstorfer et al., 2009] and during passive arm movement [Weiller et al., 1996].

Cerebellum in FESVOL—Predicting the Sensory Consequences of Action

As indicated (Fig. 1C and Table II) the only areas, where FESVOL showed significantly more activity than FES was bilaterally in the cerebellum. It is well known that the cerebellum is involved in predicting the sensory consequences of actions [Blakemore et al., 1998a; Carlsson et al., 2000]. When participants perform voluntary movements, they are better at predicting the sensory consequences or their movements. We therefore hypothesized that the FESVOL condition would lead to increased cerebellar

Figure 2.

Neural activations and contrast estimates for FES vs. FESVOL (A), FES vs. VOL (B), and FESVOL vs. VOL (C). The significant clusters for these contrasts were in the angular gyrus, inferior, middle and superior frontal gyrus, and SMA (A), SII bilaterally (B), and SII bilaterally (C). Results are based on group random effect ($N = 17$, FDR corrected at $P < 0.05$). Contrast estimates

are for the right angular gyrus, right IFG, right MFG, right SFG and right SMA (A), left SII and right SII (B), bilaterally SII (C) from the three conditions FES, FESVOL and VOL. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

activation compared with the FES condition, due to the voluntary component of the movement. Our finding supports this hypothesis (Fig. 1C). The hypothesis is further supported by the lack of significant difference in the cerebellum between FESVOL and VOL, see below.

No significant activation was observed in the primary sensorimotor cortices or the secondary somatosensory areas in the FES vs. FESVOL contrast. The number of activated voxels in contralateral sensorimotor cortices was similar in the FES and FESVOL conditions when compared with REST (15217 and 16843 respectively, Fig 1A,B). This suggests a saturation of the signal from the motor network when participants executed the tasks both in FES and FESVOL. However, in some individual participants we did find differences between these conditions. Taskin et al. [2006] reported contralateral S1 and M1 activity in chronic stroke patients when the unaffected index finger was stimulated whereas stimulation of the affected side was associated with reduced contralateral primary sensorimotor cortex activation.

SII Reduction in FESVOL

Significant increases in activity were found in secondary somatosensory areas bilaterally both when comparing FES

with VOL (Fig. 2B) and FESVOL with VOL (Fig. 2C). Secondary somatosensory areas activity has also been reported in other electrical stimulation paradigms. For example, Backes et al. [2000] stimulated the median nerve while participants performed a selective attention task and observed enhanced secondary somatosensory area activity which they ascribed to selective attention.

The increased bilateral activity is likely due to afferent input reaching both contralateral and ipsilateral secondary somatosensory areas either via SI or through direct somatosensory peripheral input [Taskin et al., 2006].

Secondary somatosensory areas are regarded as a site for higher-order processing of sensory information and sensorimotor integration [Colby and Goldberg, 1999]. Bilateral activity in secondary somatosensory areas was reported by brushing the fingers and the palm of the hand with a rough sponge [Polonara et al., 1999], by vibration stimulation applied to the left thumb [Maldjian et al., 1999], during median nerve stimulation [Backes et al., 2000], and wrist flexion/extension stimulation [Blickenstorfer et al., 2009].

These findings might suggest that the activation of secondary somatosensory areas, which was also seen when comparing FES and VOL, may be a result of the unusual

sensory stimulation. However, we observed no difference in other areas associated with the pain matrix [Apkarian et al., 2005] e.g., in cingulate gyrus or the insula. This is in accordance with statements given by participants that the electrical stimuli were not perceived as painful.

The analysis did not reveal significant activations in the primary sensorimotor cortices or cerebellum, and the number of activated voxels in cerebellum ipsilaterally was comparable in FESVOL and VOL conditions when seen against rest (6,069 and 6,045 voxels, respectively). This is different from the FES results (1,776 voxels) and it supports the claim that using FES without voluntary movement may lead to a deficit in the cerebellar activation when compared with normal voluntary movement.

As previously noted, the combination of electrical stimulation and voluntary activation in our FESVOL condition may have facilitated the prediction of the sensory input, which would then facilitate the perception of a self-generated movement. The cerebellum is a key area in computing this prediction. This interpretation is supported by the fact that we found no significant difference in cerebellar activity between FESVOL and VOL. Less SII activity was observed in FESVOL compared with FES, although this finding was not statistically significant. This area is an integration site for multiple sensory feedback circuits and it is a key region in distinguishing between self-generated and nonself-generated movement [Blakemore et al., 1998a, 1999]. The decreased SII activity may reflect a better match between the internal model and the actual sensory feedback.

FESVOL: Making the Electrical Stimulation Part of One's Own Movement

Significant differences between FES and FESVOL were found in angular gyrus, SMA, IFG, MFG, and SFG. These were manifested through a decrease in FESVOL in all areas and only a very small increase during FES in MFG (Fig. 2A,D). Farrer et al. [2008] observed increased activation in angular gyrus, MFG, and IFG during a task where participants experienced a perturbed sense of agency, i.e. they had less control over their own movements. In the present experiment decreased angular gyrus activation is observed when participants perform a combination of the electrically induced movements and voluntary movements (FESVOL). Although the present finding is not directly comparable, the angular gyrus decrease during FESVOL could be interpreted as a lack of error signal similar to that observed by Farrer et al. [2008].

The increased cerebellar (Fig. 1C) and decreased angular gyrus (Fig. 2A) during FESVOL compared with FES suggests that voluntarily activating the muscles in parallel to the electrical stimulation may be important in perceiving the electrically evoked movement as less surprising than FES alone.

An alternative explanation for the FESVOL finding is that the voluntary effort reduces the SII activation and

increases the cerebellar activation, and on top of this activation the electrical stimulation activates the SII but not the cerebellum. This condition would then look more like the VOL condition, which is likely better integrated than the FES alone condition. In both interpretations, the activation pattern elicited by FESVOL is consistent with the notion that FESVOL may play a role in making the electrical stimulation part of one's own movement. In part, this might explain the belief among FES practitioners that therapeutic FES appears to produce better clinical results than does FES training alone.

Methodological Considerations

The high pass filter used in the present analysis was introduced in order to remove any scanner drift that potentially could influence the signals. The paradigm in itself is rather slow, meaning that on average the repetition of the same tasks is slower than once every 128 s. However, the randomisation of the event order removes any systematic error induced by this choice of filter. Because the high pass filter removes some of the signal, we can be certain that none of the present results risks being false positives, instead the HP filter may have given rise to false negatives.

The protocol was developed to mimic the manner in which therapeutic FES is applied clinically. However, the extension of the results to the stroke population should be done cautiously. While a proper control study should be carried out with post-stroke participants, the present study provides the necessary proof of principle to do so.

Mechanism of the FES-Augmented Voluntary Activation (FESVOL) and Clinical Implication of the Results

Functional imaging studies of the motor system in people who have recovered from stroke-induced hemiparesis have described task-related brain activation that is over and above controls in contralesional sensorimotor and premotor cortex, ipsilesional cerebellum, bilateral supplementary motor area and parietal cortex [Weiller et al., 1996]. Increased activation has been observed contralaterally in M1, S1 and SMA; bilaterally in IPC and SII, and ipsilaterally in cerebellum during passive wrist movements [Ward et al., 2003]. They also observed increased ipsilesional S1 and M1 activation in one patient who had good motor recovery but did not observe this activation in another patient who had poor recovery.

Peripheral electrical stimulation has been proposed to work through a sensorimotor coupling mechanism [Cauraugh et al., 2000; Woldag and Hummelsheim, 2002]. Increased proprioceptive signals from evoked movements are thought to strongly activate the somatosensory cortex [Cauraugh et al., 2000; Rosenkranz and Rothwell, 2006], thereby increasing motor corticoneuronal excitability [Luft

et al., 2002; Ridding and Taylor, 2001; Sawaki et al., 2006]. The increased motor cortical excitability may facilitate greater voluntary activation of the relevant neuronal network [Wu et al., 2005] and lead to improved function. By combining patterned electrical stimulation with attempted voluntary movement, the movement might be more interpreted as one's own and, like ordinary voluntary movement, coactivate the motor control regions, and the sensory-feedback areas. This coactivation may be crucial in motor recovery at the brain level.

CONCLUSIONS

Our study demonstrates that neuromuscular stimulation combined with voluntary activation produces more activation of the cerebellum and less activation of secondary somatosensory cortex than does neuromuscular stimulation alone. This suggests that the act of voluntarily activating the muscles in parallel with stimulation-evoked movement may make the movement more predictable than stimulation alone and, ultimately, make the movement more one's own.

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