

Neural Coupling of Cooperative Hand Movements: A Reflex and fMRI Study

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The neural control of “cooperative” hand movements reflecting “opening a bottle” was explored in human subjects by electromyographic (EMG) and functional magnetic resonance imaging (fMRI) recordings. EMG responses to unilateral nonnoxious ulnar nerve stimulation were analyzed in the forearm muscles of both sides during dynamic movements against a torque applied by the right hand to a device which was compensated for by the left hand. For control, stimuli were applied while task was performed in a static/isometric mode and during bilateral synchronous pro-/supination movements. During the dynamic cooperative task, EMG responses to stimulations appeared in the right extensor and left flexor muscles, regardless of which side was stimulated. Under the control conditions, responses appeared only on the stimulated side. fMRI recordings showed a bilateral extra-activation and functional coupling of the secondary somatosensory cortex (S2) during the dynamic cooperative, but not during the control, tasks. This activation might reflect processing of shared cutaneous input during the cooperative task. Correspondingly, it is assumed that stimulation-induced unilateral volleys are processed in S2, leading to a release of EMG responses to both forearms. This indicates a task-specific neural coupling during cooperative hand movements, which has consequences for the rehabilitation of hand function in poststroke patients.

Keywords: bilateral reflex responses, hand function, motor control, secondary somatosensory cortex, unilateral nerve stimulation

Introduction

In contrast to the lower limbs, a great variety of uni- and bimanual functional hand/arm movements exist that requires a specific neural control. In monkeys, it was suggested that the supplementary motor area (SMA) of one hemisphere influences the motor outflow of both hemispheres (Jenny 1979; Rouiller et al. 1994). Furthermore, the primary (Donchin et al. 1998; Kermadi et al. 1998) and nonprimary motor cortex (Tanji et al. 1987) as well as the prefrontal cortex (Theorin and Johansson 2010) are assumed to play an essential role in the execution of bimanual tasks. Previous research has indicated that distributed neural networks coordinate interlimb coordination including cortical and subcortical areas (Kazennikov et al. 1999; Stephan et al. 1999; Kermadi et al. 2000; Debaere et al. 2001; Swinnen 2002), and their involvement might be task-specific (Ohki and Johansson 1999; Bracewell et al. 2003; Wiesendanger and Serrien 2004; White et al. 2008; Alberts and Wolf 2009; Heitger et al. 2012).

Most human studies on bimanual tasks involve the performance of bilateral separate, symmetrical, or reciprocal movements (Kelso et al. 1979; Marteniuk et al. 1984; Fowler et al. 1991; Donchin et al. 1998; Swinnen 2002; McCombe Waller and Whittall 2008; Liuzzi et al. 2011), or object manipulation

tasks (Johansson et al. 2006; Theorin and Johansson 2007), while cooperative hand movements are rarely studied (for review, see Obhi 2004). So far it has been demonstrated by functional magnetic resonance imaging (fMRI; Puttemans et al. 2005; Johansson et al. 2006; Theorin and Johansson 2007; Grefkes et al. 2008; Goble et al. 2010) and magnetoencephalography (Disbrow et al. 2001), the brain activation pattern during bimanual hand movements is task- and condition-dependent. This includes the activation of the SMA, the primary motor cortex (M1), the premotor cortex (PMC), and the secondary somatosensory cortex (S2). However, the role of these cortical areas has not yet been investigated during cooperative hand movements.

The task investigated here, that is, a “bottle opening” movement against a defined resistance, requires bimanual “cooperative” movements, in which one hand supports the action of the other one in order to complete the task. Although many daily tasks involve cooperative hand movements, little is known about the underlying neural mechanisms.

The distribution of electromyographic (EMG) responses in arm muscles evoked by nerve stimulation allows analysis of the connectivity of neural circuits involved in a specific task (Michel et al. 2008; Dietz et al. 2011). In cases of uni- or bilateral separate arm movements, this approach is known to evoke EMG responses in the forearm muscles ipsilateral to the stimulation site (Zehr and Kido 2001). It is expected that, during cooperative hand movements, a neural coupling is reflected in reflex EMG responses to unilateral nerve stimulation in the forearm muscles of both sides.

Additionally, we used fMRI in order to identify brain areas involved in the cooperative hand movement task as complementary information. This includes the assumption that the supraspinal pathways and centers, mediating the bilateral reflex EMG responses, can be detected by the imaging study. The aim was to identify the cortical areas involved in the cooperative hand movements and whether they differ from those activated in the control conditions. We hypothesize that the neural coupling during cooperative hand movements is achieved by an exchange of information from each hand to both hemispheres at a brainstem level, followed by a processing of the afferent input in specific cortical sensori-motor areas (e.g., SMA, PMC, and S2), which leads to an appropriate control of cooperative hand movements. Since S2 is suggested to be involved in the integration of information from the 2 sides of the body (Lin and Forss 2002) and is modulated by task effort (Heuninckx et al. 2005; Goble et al. 2010), we hypothesize that neural processing of cooperative hand movements can be achieved by an involvement of S2. Subsequently, we performed psycho-physiological interactions (PPIs) and functional connectivity (FC) analyses to estimate the functional

coupling between brain regions of interest (ROIs) with relation to task performance.

Methods

General Procedures and Experimental Conditions

This study was approved by the Ethics Committee of the Canton of Zurich and conformed to the standards set by the Declaration of Helsinki. All subjects were informed about the experiment and gave written consent for their participation. The “electrophysiological” recordings were performed in 12 right-handed (Oldfield 1971) healthy volunteers (mean age 27.3 years, range 25–32 years; 4 males). Twenty right-handed healthy volunteers (mean age: 33 ± 9.8 years; 13 males) participated in the “fMRI study.” Four of the volunteers participated in both studies. Only right-handed subjects were chosen in order to avoid an additional variable that could influence the results.

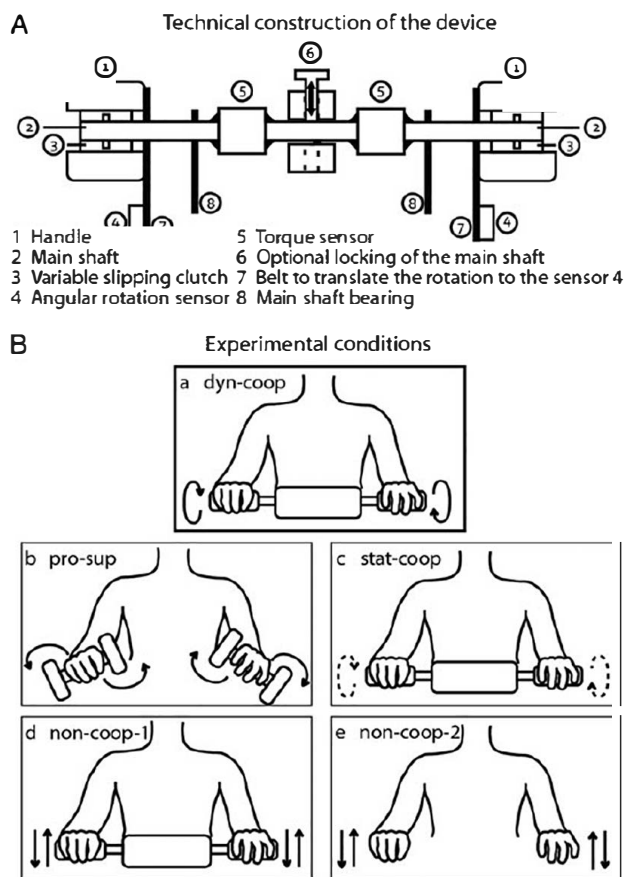


Figure 1. Experimental set-up and experimental conditions. (A) Technical construction of the device. There are 2 torque sensors (typ. burster 8645) marked as (5). These 2 sensors separately measure the torque signals of the 2 sides. The main shaft (2) is unlocked resulting in one shaft connecting the 2 sides of the device for torque transmission. The 2 position sensors (4) were located on each handle separately. The device shown allows the performance of dynamic bilateral cooperative and static bimanual hand movements against a resistance. During the dynamic and static tasks, the torque exerted by the right hand was transmitted to the left hand for compensation and counteraction. The torques exerted on each side were indicated on a screen in front of the subject. (B) Experimental conditions. Schematic drawings of all experimental conditions included in the study. The main condition was the performance of dynamic cooperative hand movements (a, dyn-coop). The controls were: bilateral pro- and supination movements (b, pro-sup); static (isometric) cooperative hand movements (c, stat-coop); synchronous up and down wrist movements (with approximately the same movement amplitude and velocity as in a) holding the device (d, non-coop-1), and reciprocal left-right up and down wrist movements without device (e, non-coop-2). The conditions a and b were applied in both the electrophysiological and fMRI studies. The condition c was only applied in the electrophysiological study and conditions d and e only in the fMRI study.

Electrophysiological Study

A device that allows the performance of cooperative movement tasks of the upper limbs was constructed together with the Swiss Federal Institute of Technology Zurich (ETHZ) for the electrophysiological experiments (patent registration number E 11167554). The device comprises 2 handles representing a bottle that is placed horizontally in front of the subject (Fig. 1A). The diameters of the 2 handles corresponded approximately to the 2 ends of a normal bottle (right 5 and left 7 cm). Torque and angular rotation sensors allowed the recording of torsional moments and the position of the handles on both sides. For the cooperative movement task, the 2 ends of the “bottle” were mechanically connected, that is, when a torque was applied on one side it became transmitted to the other side. Therefore, the resistance was constant throughout a movement cycle on both sides. This cooperative mode was either used dynamically (the handles could be turned in opposite directions against a predefined resistance) or statically (the handles were blocked for reciprocal rotation).

The maximum torque (MaxT) of each subject was determined in the static mode of the device. The highest value of 3 attempts was taken. For the 2 experimental conditions, the resistance of the device was set to 20% MaxT. In the dynamic task (dyn-coop), subjects performed rhythmic “opening” movements, that is, extension of the right wrist and flexion of the left wrist (frequency of 45/min, indicated by a metronome), with the right hand counteracted by the left hand, that is, both hands were free to rotate during the dynamic task. A visual feedback about the torques applied to the device by both hands was provided through a potentiometer. In one control task (stat-coop), subjects exerted a bimanual reciprocal isometric/static torque of 20% MaxT on the handles (indicated again on a screen placed in front of the subject), with the right forearm extensors counteracted by the left flexor muscles thus mimicking the opening task. An additional control task consisted in a frequently investigated upper limb task (Swinnen 2002), that is, bilateral synchronous pro-/supination movements (pro-sup; frequency of 40–50/min) with freely held dumb-bells (1 or 2 kg, depending on the EMG background activity which had to match the EMG activity during the dynamic task as good as possible). This task was chosen for control as we expected a similar dynamic proprioceptive input becomes generated as during the dyn-coop task. Each of the 3 motor tasks was performed approximately 80 times. Figure 1B shows an overview over the setups for the different experimental conditions.

Recording of Biomechanical and Electromyographic Signals

The angular position and torque signals were measured separately for both sides. EMG recordings were made using surface electrodes placed over the forearm flexor (Musculus flexor carpi ulnaris) and extensor (M. extensor carpi radialis) muscles and over the M. deltoideus pars clavicularis muscles of both arms. All signals were sampled at 1000 Hz and recorded using Soleasy v. 4.1 (ALEA Solutions GmbH Software and Instrumentation, Switzerland). EMG signals were amplified (10 000-fold) and band-pass filtered (30–300 Hz). Afterwards, the signals were transferred together with biomechanical signals to a personal computer via an analog-to-digital converter. Further processing of the data was done using Soleasy v. 4.1. EMG signals were offset corrected, rectified, and band-stop filtered (45–55 Hz) before root mean square (RMS) values, averages, and grand averages were calculated.

Ulnar Nerve Stimulation

The distal part of the ulnar nerve was randomly stimulated 15 times per side at the onset of movement cycles at the right or left forearm for the release of reflex responses in the arm muscles. The stimulation electrodes (2.63 cm² in size; Neuroline 700, Ambu, Ballerup, Denmark) were placed over the ulnar nerve at both wrists with an interelectrode space of 2 cm.

Electrical pulses were administered by an Electro Stimulator (AS 100, Alea Solutions, Zurich, Switzerland). Each electrical stimulus consisted of a train of 4 biphasic pulses with 2 ms duration per pulse and a frequency of 200 Hz resulting in total stimulus duration of 17 ms. The intensity was set on 1.5 times motor threshold (MT). MT was defined as the lowest intensity leading to a visible twitch of the M. abductor digiti minimi. It was determined by stepwise increasing the intensity. This

nonnoxious stimulation intensity (1.5 MT) is known to evoke cutaneous reflexes (Yang and Stein 1990). A similar stimulus paradigm has previously been used to investigate neural limb coupling during locomotion in healthy subjects (Michel et al. 2008; Dietz et al. 2009) and poststroke patients (Kloter et al. 2011).

In a pilot study, we compared the effects of median, radial, and ulnar nerve stimulation. The bilateral responses to ulnar nerve stimulation were more reproducible, and the stimuli were less painful than median nerve stimulation. Superficial radial nerve stimulation was more difficult to perform (perception threshold is a quite subjective measure). Therefore, we used ulnar nerve stimulation in our study. The stimulation electrodes were attached with a surgical tape after determining the optimal stimulation site. The MT of each person was checked to confirm that it was constant during and after the experiment.

The stimuli were randomly released every third to sixth cyclic movement triggered by a change in torque of 0.035 Nm, that is, about 100 ms after the start of the opening (dyn-coop) movement of the right hand and every 5–9 s during the control tasks. A dummy signal was released at the same time point without stimulation and was used to record the nonstimulated EMG, that is, background activity.

Reflex Data Analysis

Reflex responses were analyzed by calculating the RMS of EMG signals including all samples within a time window of 50–200 ms after the start of stimulation. The window was chosen according to the appearance of the main components of the reflex responses. The responses were compared with the RMS of background EMG activity within the same time window following “dummy” stimulations using a multivariate General Linear Model (GLM) with post hoc paired *t*-test with Bonferroni correction. The factors for the GLM were condition, stimulation side, and recording site.

The responses were mostly suppressive. The amplitude of the reflex response (maximal negativity/suppression; maximal positivity/facilitation) was compared with that of background activity in the nonstimulated recordings. The onset of reflex responses was determined manually. The differences in latency were also compared by a GLM with post hoc paired *t*-test with Bonferroni correction. Pearson correlations were applied in order to evaluate the similarities between the shape of the EMG response patterns recorded from the right forearm extensors and left forearm flexor muscles during the dyn-coop opening task, following unilateral nerve stimulation on the ipsilateral and contralateral sides, respectively.

fMRI Study

For the fMRI study, a hand-held MR-compatible device was used corresponding to the bottle device used in the EMG experiment, constructed by the ETHZ. In total, 20 volunteers performed the dyn-coop condition with the left hand resisting the opening movements guided by the right hand (ca. 20% MaxT) with a frequency of 45/min, so that the right extensors and left flexors were activated.

For control, the same participants performed a bilateral synchronous pro-sup movement task of both arms, with a frequency of 45/min while holding fMRI-compatible dumb-bells of 500 g. Additionally, 13 (out of 20) randomly selected volunteers performed 2 additional “non-coop” tasks. During the “non-coop-1” task, they held the device and executed symmetrical wrist extension and flexion movements (cf. Fig. 1B, non-coop-1). The rationale for this choice of task was to have a control task in which subjects performed synchronized (in-phase) but noncooperative wrist movements. This control was included to see whether activation of a brain region is exclusively influenced by the factor “cooperative movement” or by the factor wrist movement during extension and flexion movements in the dyn-coop task. During the “non-coop-2” task, subjects performed the same reciprocal hand wrist movements during the dyn-coop condition but without holding the device (cf. Fig. 1B, non-coop-2). Thus, the factor “bimanual hand movement” was kept constant, but the factor “hand cooperation” was minimized.

For all tasks, pacing was achieved by visual cues, which were shown via a mirror system, indicating the start of the requested

movement (movement onset was further controlled by the experimenter). The synchronization between the fMRI clock and the temporal onset of the visual cues was controlled by Presentation (www.neurobs.com/presentation). Each task was performed separately (6 min duration) and was arranged in a block design: During each block, 7 opening-closing or pronation-supination movements were followed by rest periods of 8–10 s. For each experimental condition, participants performed 10 blocks (=70 trials). Task presentation was randomized across subjects to avoid order effects. To prevent head movements during the fMRI scan, a neck-pad was used to fixate the head. In addition, subjects were only included if overall head motion was <1.5 mm in translation and 1.5° in rotation. We therefore believe that any task-related activity was not influenced by head motion.

fMRI Acquisition

For all tasks, fMRI was performed at the University Hospital of Zurich on a Philips Ingenia 3-T whole-body MRI system (Philips Medical Systems, Best, The Netherlands) and an 8-channel head coil. Functional data were obtained in 180 scans per run using 30 transverse slices covering the whole brain in oblique orientation. Slices were acquired in an interleaved order, using a sensitivity-encoded (SENSE, factor 1.8), single-shot, echo planar imaging (EPI) technique (echo time = 35 ms, repetition time = 2000 ms, field of view = 220 × 220 mm, voxel size: 2.75 × 2.75 × 4 mm, resliced: 1.72 × 1.72 × 4 mm, flip angle: 78°). SENSE imaging was applied to shorten readout trains in a single shot in EPI, to reduce susceptibility artifacts, and to improve spatial resolution (Boujraf et al. 2009). Four dummy scans were acquired at the beginning of each run and discarded in order to establish a steady state in T_1 relaxation for all functional scans.

Preprocessing

Data were analyzed using MATLAB 7.9 (Mathworks, Inc., Natick, MA, USA) and SPM8 (Wellcome Department of Cognitive Neurology, London, UK). For each subject, functional images were realigned, normalized to the EPI template provided by the Montreal Neurological Institute (MNI brain), resliced to 2 × 2 × 2 mm voxel size, and smoothed using 8-mm full-width at half-maximum Gaussian kernel. An autoregressive model of the first order was used to account for serial correlations. High-pass filtering with standard 128 s cutoff eliminated slow signal drifts. The Anatomical Automatic Labeling Toolbox for SPM8 was used to identify activated regions (Tzourio-Mazoyer et al. 2002).

Regions of Interest Analysis

Before testing for fMRI signal changes related to cooperative hand movements (i.e., dyn-coop vs. pro-sup), we first estimated the average activation strength (i.e., parameter estimates) across the dyn-coop and pro-sup tasks (F-contrast, $P < 0.05$, family-wise error [FWE] corrected for multiple comparisons) in ROIs known to be involved in bimanual hand movements (Puttemans et al. 2005; Grefkes et al. 2008). The spatial coordinates of the individuals ROIs were determined following the definition of Grefkes et al. (2008): the M1 region has to be located in the precentral gyrus and central sulcus near the hand knob (MNI coordinates in this study: left M1: -34 -26 56 and right M1: 36 -26 56), the PMC in the lateral precentral sulcus (MNI coordinates: left PMC: -50 -2 44 and right PMC: 52 -2 46), the SMA in the dorsal medial wall within the interhemispheric fissure (MNI coordinates: 0 -19 48), and the S2 region in the upper bank of the Sylvian fissure (MNI coordinates: left S2: -56 -16 14 and right S2: 54 -14 18). Subsequent analyses were performed for ROIs, placed in S1 and in the insular cortex. For each subject, the time series of all ROIs were extracted in a sphere region (radius = 4 mm).

fMRI Data Analysis

A standard hemodynamic response function was used for convolution of the model regressors. First-level analyses were conducted using a voxel-wise GLM, which reflects a flexible generalization of an ordinary/simple linear regression (Friston et al. 1995). Each task was entered as regressors into 4 separate GLMs: dyn-coop and pro-sup

($n = 20$), and non-coop-1 and non-coop-2 ($n = 13$). Session-specific motion parameters were modeled as covariates of no interest. Second-level random effect analyses were conducted using a full-factorial design. The following 2 contrasts were estimated: “dyn-coop versus pro-sup” ($n = 20$) and “dyn-coop versus average (pro-sup and non-coop-1/2)” ($n = 13$). All fMRI results were shown on a cluster-corrected (Forman et al. 1995; Slotnick et al. 2003) voxel threshold of $P < 0.001$ (spatial extent: $k \geq 42$ voxels). The cluster size threshold for the selected P -values was estimated using Monte Carlo simulations (http://afni.nimh.nih.gov/pub/dist/doc/program_help/AlphaSim.html). The cluster threshold method was applied to control for the overall type I error. Only gray matter-related fMRI signal changes will be reported.

Psycho-Physiological Interactions and Functional Connectivity

PPI is a brain imaging method of estimating the functional coupling between a brain region and the rest of the brain with relation to the performance of a particular cognitive task (Friston et al. 1997). In this study, the psychological vector was separately modeled for 2 types of bimanual hand movements: (1) dyn-coop and (2) pro-sup. For example, the PPI-specific GLM for the dyn-coop task contains 3 regressors: The interaction term (blood oxygen level-dependent [BOLD] response \times psychological vector), main effect of BOLD activity from a given ROI, and main effect of psychological vector (e.g., dyn-coop). To extend the concept of factorial designs to PPIs, the basic idea is to substitute (neural) activity from one cerebral region for one of the factors:

$$Y = ROI \times \beta_1 + (B2 - B1) \times \beta_2 + [ROI \times (B2 - B1)] \times \beta_3 + G \times \beta_4 + \epsilon,$$

with ROI: functional ROI (substitutes original factor A), β : beta weights $B1/B2$: factor B (with 2 levels), and ϵ : error term. $[ROI \times (B2 - B1)] \times \beta_3$ reflect the interaction term, and $ROI \times \beta_1$ and $(B2 - B1) \times \beta_2$ reflect the main effects. The following seeds were used for the PPI analysis: right and left, S2, right and left M1, and right and left PMG, and SMA. The analysis was computed for the contrast “dyn-coop task > pro-sup task” and for the reversed contrast.

We used the SPM toolbox conn (v13i, <http://www.nitrc.org/projects/conn/>) to perform the FC analysis. White matter, cerebrospinal fluid, and the 6 motion parameters were used as covariates of no interest. Only the white matter and cerebrospinal fluid signals were removed to avoid any bias introduced by removing the global signal (i.e., gray matter) (Behzadi et al. 2007; Murphy et al. 2009). This approach should “normalize” the distribution of voxel-to-voxel connectivity values as effectively as including the global signal as a covariate of no interest, but without the potential problems of the latter method. Although we did not record respiration and cardiac responses, it has been demonstrated that nonneural physiological noise (e.g., cardiac and respiratory signal) can successfully be removed by the CompCor algorithm (Behzadi et al. 2007) as implemented in the conn toolbox. Bivariate correlations were calculated as a measure of strength of FC, to examine cross-correlations of BOLD signal time series between ROIs. For each individual, the fMRI time series were extracted for each ROI using MarsBaR (Brett et al. 2002 <http://marsbar.sourceforge.net/>) after the fMRI time series had been spatially smoothed, temporally filtered (0.01–0.1 Hz), normalized (to the MNI template), and motion corrected. The signal of a given ROI was then averaged for 4-mm diameter spheres. The same ROIs as for the PPI analysis were used. Task-specific (dyn-coop and pro-sup) statistical results were represented at $P \leq 0.05$ (FWE-corrected for multiple comparisons).

Results

Electrophysiological Recordings

An opening movement cycle took a mean of 485 ms. The movement onset of the left and right hands during the dyn-coop task was analyzed using the changes in hand position (angular rotation sensors) at both handles. According to this analysis, both hands started almost simultaneously with the dynamic opening torque exerted by the right-hand and the

left-hand compensatory torque (difference between right and left hands: 18 ± 18 ms).

During the different tasks, reflex responses measured in proximal and distal arm muscles following unilateral ulnar nerve stimulation showed approximately the same behavior, that is, a unilateral (ipsilateral) EMG response during the control tasks and a bilateral response during the dyn-coop task. For further analysis, only the forearm flexors and extensor muscles were included.

Figure 2 shows an example of the EMG signal recordings from the right extensor muscles and the biomechanical signals of torque and position of both sides from one volunteer during the performance of the dyn-coop (Fig. 2A) and stat-coop (Fig. 2B) tasks. During the dynamic task, segmented EMG responses appeared in the right extensor muscles following right and left ulnar nerve stimulation, whereas in the nonstimulated movements they did not. In the static task, a response was only discerned in the ipsilateral muscle.

In the dyn-coop task, the reflex EMG responses evoked by the stimulation consisted mainly of suppressive responses on both sides. These were further evaluated for their similarities in terms of latency, duration, and amplitude (Fig. 3a,b). In contrast, during the stat-coop task, reflex responses appeared only ipsilateral to the same stimulation (Fig. 3c).

Figure 3 shows the overall averages of the reflex EMG responses in the right extensor and left flexor muscles to ipsilateral (Fig. 3A) and contralateral (Fig. 3B) ulnar nerve stimulation during dyn-coop movements (Fig. 3a,b). The mean background EMG activity is shown as gray area. The RMS values of all reflex responses (time window 50–200 ms) in the dyn-coop task were significantly different from background EMG activity (stimulation ipsilateral $P < 0.01$, contralateral $P < 0.05$). The same difference was found after ipsilateral stimulation in the stat-coop task (Fig. 3c; $P < 0.05$) and in the pro-supin task (Fig. 3d; $P < 0.005$) but not following contralateral stimulation, where no response could be detected.

In Figure 3, the stimulation artifact lasted for the first 17 ms on both sides. The responses in the right extensor muscles to right (ipsilateral) ulnar nerve stimulation (Fig. 3Aa) appeared with an early response (ER) that had a latency of 25 ± 3.1 ms, followed by a first suppressive response (N1) peaking at a latency of 43 ± 6.0 ms after onset of right-side stimulation and a first facilitative wave (P1) with a peak at 59 ± 7.2 ms. The peak of the second suppressive wave (N2) was reached at 86 ± 10.1 ms and the following plateau-like activity (P2) was observed at 120 ± 20.3 ms. Following left (contralateral) ulnar nerve stimulation (Fig. 3Ba), the EMG response onset in the right extensor was observed at 61 ± 8.8 ms, the peak of the suppressive wave (N2) occurred at a latency of 87 ± 7.7 ms, and the plateau-like activity (P2) was reached again at 104 ± 8.7 ms. The grand averages of late right extensor responses to ipsi- and contralateral nerve stimulation were similar in their latencies, durations, and amplitudes.

Figure 3 also shows the corresponding EMG responses in the left flexor muscles following left and right ulnar nerve stimulation (Fig. 3b). Following left (ipsilateral) ulnar nerve stimulation (Fig. 3Ab), an ER (onset 24 ± 3.7 ms) was followed by a suppressive peak (N1) with a latency of 48 ± 5.8 ms, a facilitative peak (P1) at 69 ± 10.8 ms, and a second suppressive peak (N2) at 96 ± 18.4 ms. The plateau-like activity (P2) was reached again at 121 ± 22.9 ms. Stimulation of the right (contralateral) ulnar nerve (Fig. 3Bb) was followed by a suppressive

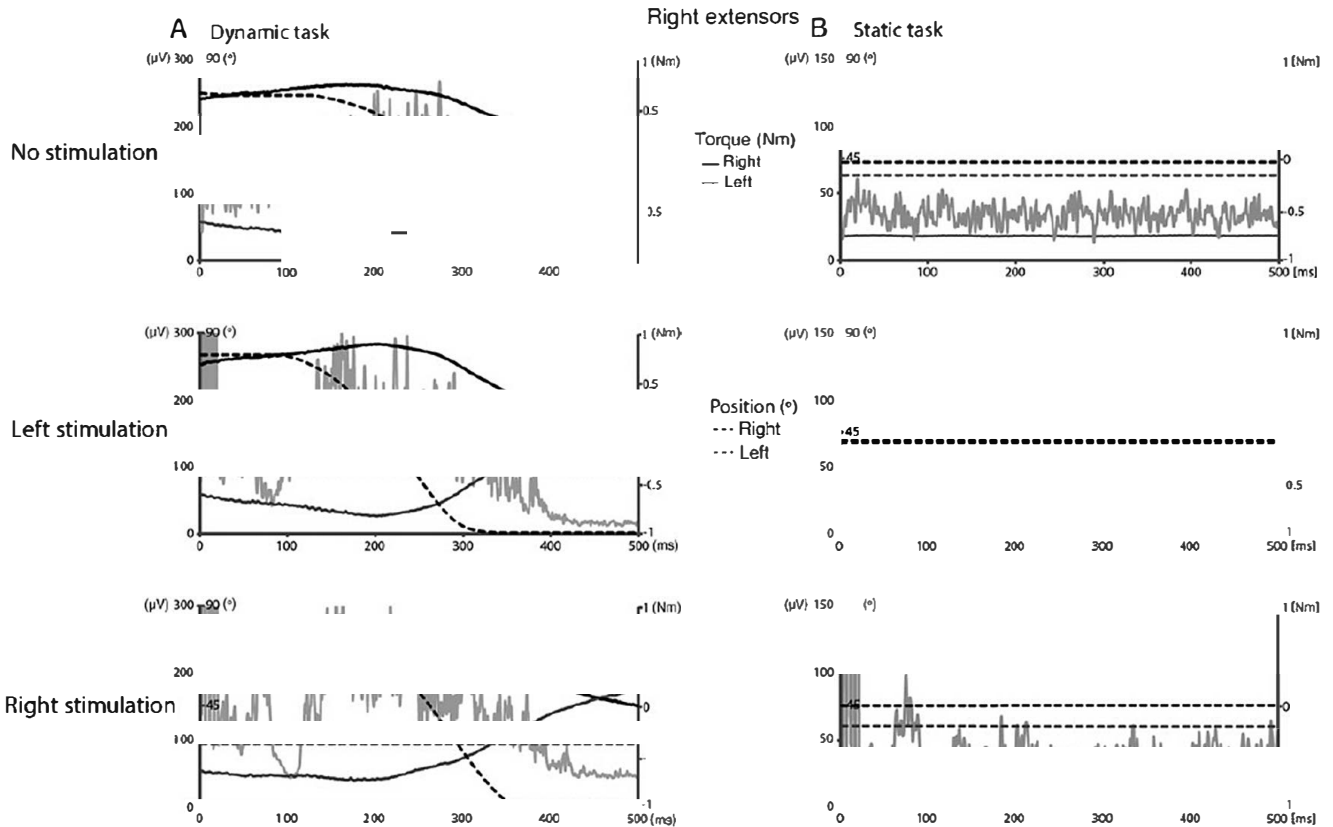


Figure 2. EMG and biomechanical signals. Individual example of the dyn-coop and the stat-coop tasks. Biomechanical signals and right forearm extensor muscle EMG (average of 15 trials) from one subject. (A) Dynamic and (B) static (bimanual) tasks. The stimulated (left and right ulnar nerve) and nonstimulated conditions are displayed. In addition, the torque (solid lines) and position (dotted lines) signals of the right (black) and left (gray) side are shown. Negative sign stands for flexion while positive sign stands for extension torque. Note the 2 ordinate scales on the left side of every graph [EMG activity (μV) on the outside and position ($^{\circ}$) on the inside] and one on the right side [torque (Nm)]. Note also the different amplitude calibrations for the EMG signals in A and B.

EMG response in the left flexor muscle starting at 66 ± 8.5 ms with a peak suppression (N2) at 88 ± 7.7 ms, followed by a peak facilitation (P2) at 109 ± 5.1 ms.

The background activity and EMG response amplitudes were about 3 times larger in the extensor than in the flexor muscles. In addition, the response amplitudes in the extensor muscles (suppressive peaks) were smaller following contralateral compared with ipsilateral stimulations (not significant, $P=0.057$).

Figure 3c,d shows the EMG responses in the right forearm extensors following ipsilateral (Fig. 3A) and contralateral (Fig. 3B) ulnar nerve stimulation during the control tasks: Static (Fig. 3c) and pro-sup (Fig. 3d) tasks. In contrast to the responses in the right-arm muscles during the dyn-coop task (Fig. 3Ba,b), no distinct EMG responses could be detected in the right extensor muscle when the left (contralateral) ulnar nerve was stimulated (Fig. 3Bc,d). In the static task (Fig. 3c), the EMG responses in the right extensor muscle following ipsilateral nerve stimulation appeared with a suppressive peak (N1) at a latency of 47 ± 5.6 ms, followed by a facilitative peak (P1) at a latency of 66 ± 6.5 ms, a second suppressive peak (N2) at 96 ± 15.3 ms, and a late facilitative peak (P2) at 141 ± 21.7 ms. Similar responses appeared in the left flexor muscle following left ulnar nerve stimulation (not shown).

Also in the pro-sup task (Fig. 3d), EMG responses were only present in the muscles of the stimulated arm. The EMG responses in the right extensor muscle following ipsilateral nerve stimulation appeared with a suppressive peak (N1) at a latency of 52 ± 4.8

ms, followed by a facilitative peak (P1) at a latency of 73 ± 6.3 ms, a second suppressive peak (N2) at 106 ± 12.7 ms, and a late facilitative peak (P2) at 148 ± 29.8 ms.

The response pattern (early and late reflex complexes; ER to P2) to ipsilateral stimulation was similar in latency, duration, and amplitude during the dyn-coop and the control tasks (Fig. 3A). Only during the dyn-coop task, a late reflex complex (N2 and P2) appeared also at the contralateral, nonstimulated side (Fig. 3B), which again was similar in latency, duration, and amplitude to the late ipsilateral reflex complex.

The level of background activity in the extensor muscles was about 3 times larger (RMS values: 154–45 μV) in the dynamic compared with the static condition. When the amplitude of the EMG responses was compared with that of background EMG (same time interval in nonstimulated movements), it amounted to 65% in the dynamic and 60% in the static task. The difference in the background activity is thought to be due to the fact that a dynamic movement against a torque of 20% MaxT produces a stronger muscle activation compared with the static/isometric muscle contraction with a 20% MaxT.

fMRI Recordings

Figure 4A shows robust mean fMRI signal changes across the dyn-coop and pro-sup tasks in the SMA, PMC, and M1 as well as in the cerebellum and higher visual areas (including V5). However, the parameter estimates (Fig. 4B) did not differ

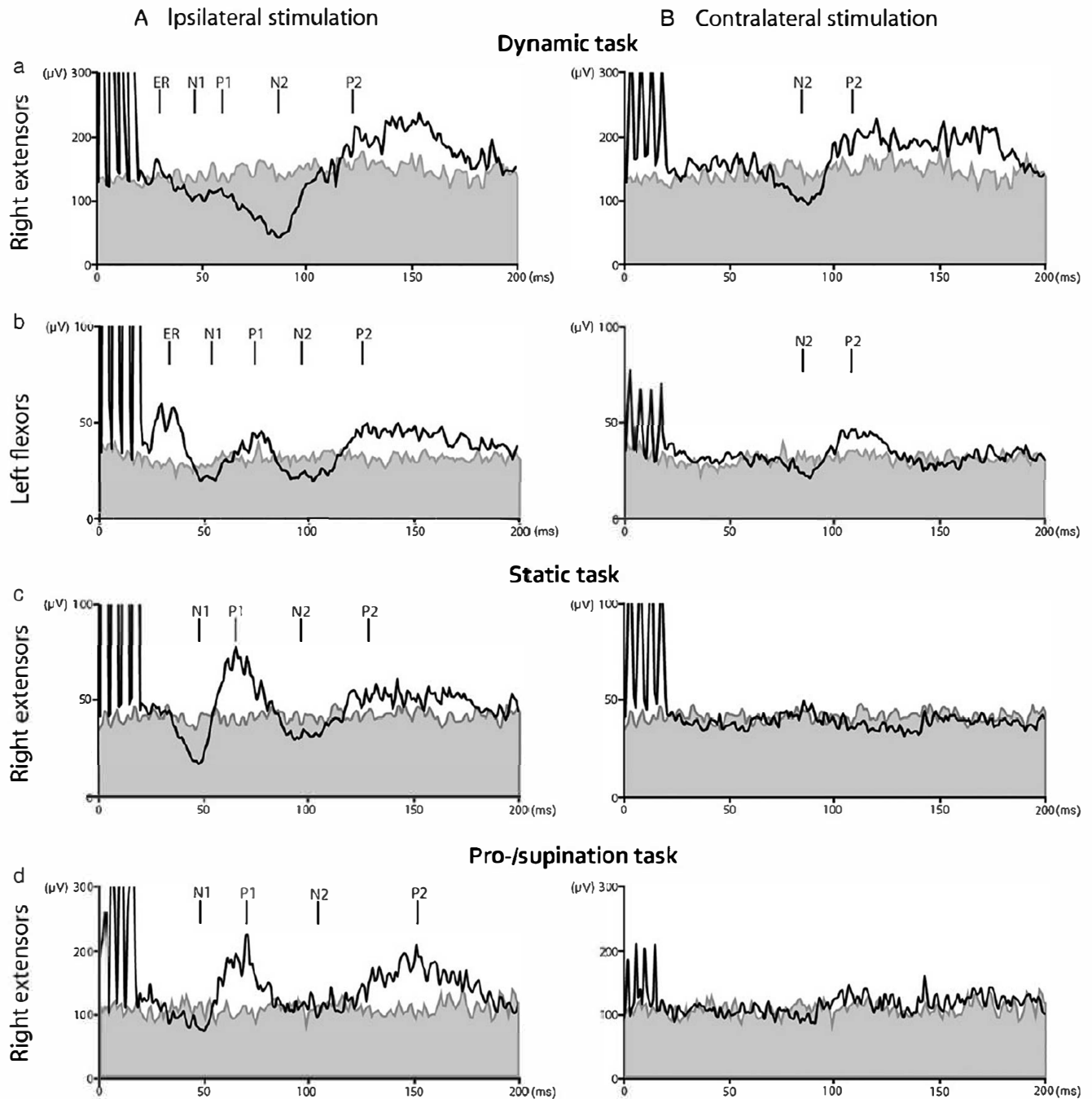


Figure 3. Cooperative hand movements: Electrophysiological recordings. Grand averages ($n = 12$ subjects) of the EMG responses in the right forearm extensor (a) and the left forearm flexor (b) during the “dynamic” cooperative “opening” task to ipsilateral (A) and contralateral (B) ulnar nerve stimulations. Grand averages ($n = 12$ subjects) of the EMG responses in the right extensors during the “static/isometric” opening task (c) and during the pro-supin task (d) to ipsilateral (A) and contralateral (B) ulnar nerve stimulation. Stimulations were randomly released either on the right or left side at the beginning (~15%) of the movement cycle. The stimulation artifact lasts over the first 17 ms. The gray area shows the level of background activity. ERs, first negativity (N1), and first positivity (P1) appeared only after ipsilateral stimulations (a). Peak negativity (N2) and positivity (P2) occurred in all 4 conditions displayed. Note the different amplitude calibrations.

between dyn-coop and pro-sup in these regions. The contrast dyn-coop versus pro-sup elicited exclusively bilateral activation patterns in the S2 (Brodmann area, BA, 43) at a voxel threshold of $P < 0.001$ (cluster-corrected, $k \geq 42$ voxels) as shown in Figure 5A and Table 1A. Parameter estimates were significantly higher for the dyn-coop than for the pro-sup condition (Fig. 5A, right S2: $P < 0.001$ and left S2: $P < 0.001$). As shown in Figure 5B and Table 1B, the contrast between

“dyn-coop versus average pro-sup and non-coop” still revealed bilateral S2 activation at a voxel threshold of $P < 0.001$ (cluster-corrected, $k \geq 42$ voxels), and a weaker activation of the left insular cortex (BA 13), cerebellum (lobes 3–5), right posterior thalamus, and bilateral S1 (BA 2/3). S1 activity was especially strong if the dyn-coop task was compared with the non-coop-2 task ($P < 0.0001$, data not shown), that is, a task in which subjects did not hold any device but performed out-phase hand

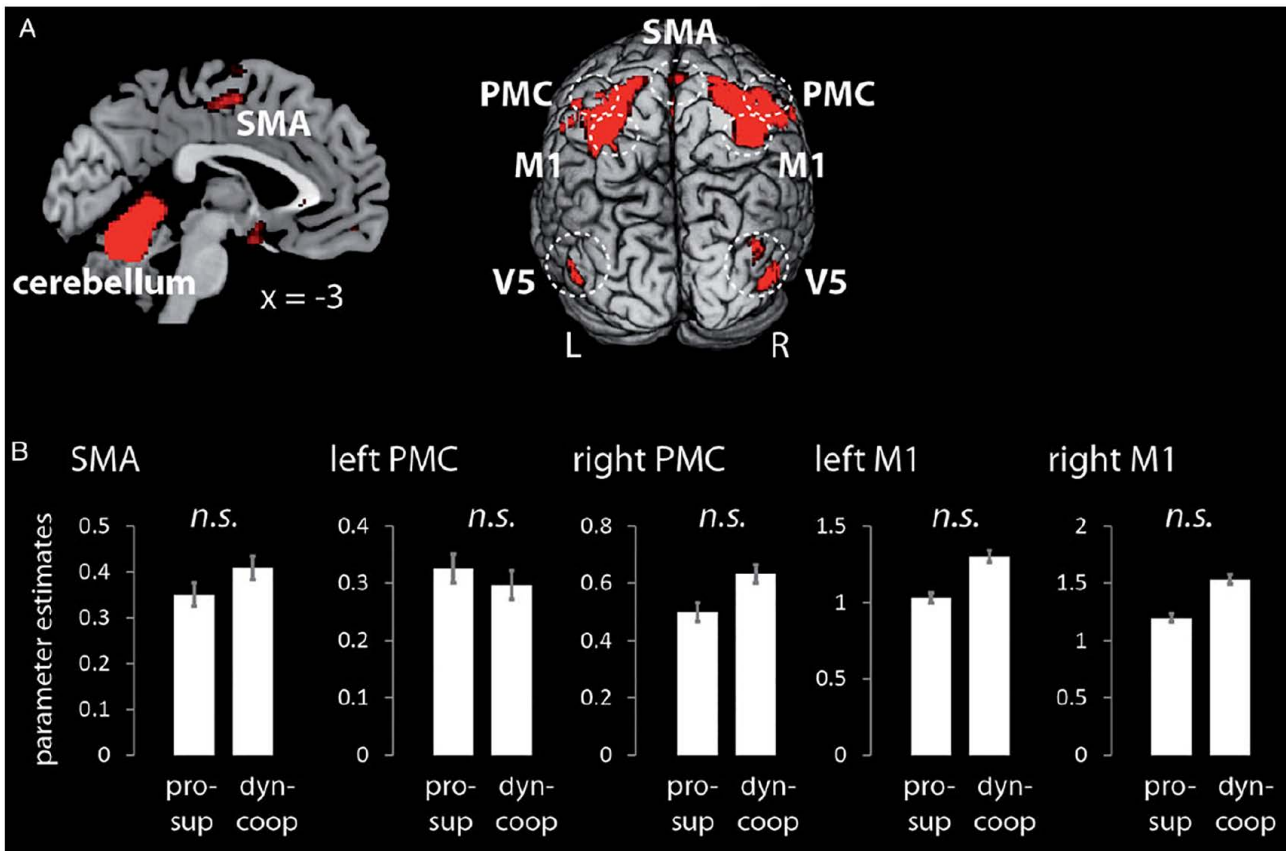


Figure 4. Cooperative and pro/sup hand movements: fMRI recordings. The 2- and 3-dimensional illustrations in (A) show the mean activity across the contrast “dyn-coop and pro-sup” task ($P < 0.001$, FWE-corrected, F-contrast). Robust activations were seen in the SMA, M1, and PMC regions as well as in the cerebellum and higher visual areas. The parameter estimates (with standard deviations) shown in (B) were not different between the dyn-coop and pro-sup tasks.

movements. At a more liberal threshold ($P < 0.005$, cluster-corrected) also in the contrast dyn-coop versus pro-sup, additional activations to S2 were observed bilaterally in S1 (Supplementary Fig. 1). Only the left insular cortex (MNI: $-38 -14 12$, Table 1B, $P = 0.01$) but not its homologous counterpart (MNI: $38 -14 12$) or literature-based insular cortex ROIs (Heuninckx et al. 2005; MNI: $-36 24 -8$ and $-36 -2 6$) showed stronger activity for dyn-coop relative to all control conditions.

The age of the subjects was not correlated to the right S2 ($r = -0.21$, $P = 0.37$) or left S2 ($r = 0.35$, $P = 0.13$) activity for the dyn-coop task (assessed by Pearson’s correlations).

The PPI analysis for the between-task comparison showed significant results only for the contrast dyn-coop task versus pro-sup task ($P < 0.001$, cluster-corrected with $k \geq 42$), but not vice versa (see Supplementary Table 1). A main finding was that a preselected seed was never “connected” to its homologous counterpart. In general, results were rather unspecific and did not show a unique pattern within intra or interregional seeds. In contrast, the FC analysis revealed that the 2 S2 ROIs were functionally connected during the dyn-coop task only ($t = 3.75$). In addition, the left M1 and right M1 ROIs show a functional connection ($t = 6.21$). At this statistical threshold, no functional coupling between any of the ROIs was observed for the pro-sup task.

Discussion

The aim of this study was to explore the neural control of cooperative hand movements by electrophysiological and fMRI

recordings. The main result was that only during the performance of a cooperative opening movement. EMG responses appeared in the forearm muscles of both arms, independent of which side was stimulated. Correspondingly, fMRI showed a bilateral functional coupling of the S2 regions during the dyn-coop task, but not in the control tasks. Although, in most bimanual tasks, an integrated control structure might be used. The present study suggests relevant task-specific differences in the neural control.

Task-Specific Neural Hand Coordination

In the present study, we observed a task-specific neural coupling during dynamic cooperative hand movements. Previous electrophysiological research in this field has focused mainly on the execution of unilateral or separate bimanual movements, (Donchin et al. 1998; Swinnen 2002; White et al. 2008). A task-dependent amplitude modulation of unilateral EMG responses in upper limb muscles to magnetic brain stimulation (Datta et al. 1989) and to cutaneous nerve stimulation (Zehr and Kido 2001) with larger amplitudes during a dynamic compared with a static muscle contraction (Zehr and Kido 2001) were described. Only ipsilateral EMG responses were also recorded in both control conditions investigated here.

This reflex behavior differs profoundly from that found during cooperative hand movements and represents the novel result of this study. Exclusively during the dynamic cooperative hand movements, a distinct contralateral EMG response pattern (N2–P2 complex) appeared in forearm muscles with

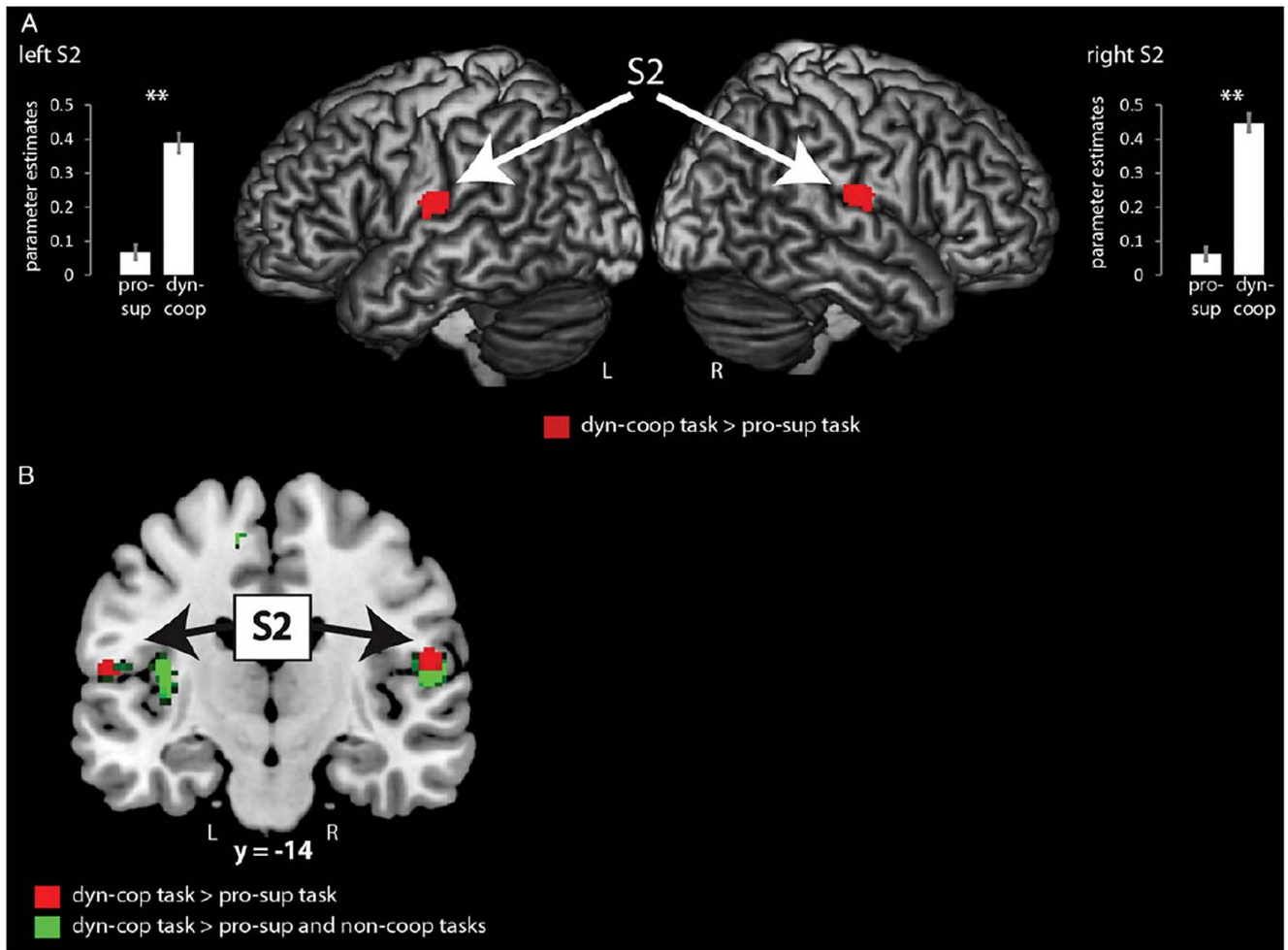


Figure 5. Cooperative versus noncooperative hand movements: fMRI recordings. The 3-dimensional illustration in (A) shows bilateral S2 activation for the contrast dyn-coop versus pro-sup ($P < 0.05$, cluster-corrected with $k \geq 42$). Additionally, in both hemispheres, parameter estimates for S2 were significantly higher for the dyn-coop than for the non-coop tasks (** $P < 0.001$). (B) shows the bilateral S2 activations for the contrast dyn-coop versus pro-sup (labeled in red) and for the contrast dyn-coop versus non-coop (labeled in green) on an axial slice. L: left hemisphere, R: right hemisphere.

Table 1

Areas of the brain showing significantly greater BOLD signal changes for the (A) contrast "dyn-coop task > pro-sup task" ($P < 0.001$, cluster-corrected with $k \geq 42$) and (B) the contrast "dyn-coop task > average pro-sup task and noncoop tasks" ($P < 0.001$, cluster-corrected with $k \geq 42$)

Region	Brodmann area	MNI coordinates			t-value
		x	y	z	
(A) Contrast "dyn-coop task > pro-sup task"					
Left postcentral gyrus (S2)	43	-58	-16	14	4.25
Right postcentral gyrus (S2)	43	54	-16	14	4.19
(B) Contrast "dyn-coop task > average pro-sup task and noncoop tasks"					
Left postcentral gyrus (S2)	43	-58	-16	14	3.78
Right postcentral gyrus (S2)	43	54	-16	14	5.03
Left insula	13	-38	-14	12	3.87
Right posterior thalamus		16	-22	-2	3.53
Cerebellum		0	-50	-4	4.77
Left postcentral gyrus (S1)	3	-46	-20	52	4.59
Right postcentral gyrus (S1)	2/3	50	-20	46	4.33

approximately the same latency (80 ms) as the late complex (N2–P2) of the ipsilateral, stimulated side. Therefore, different neural circuitries are suggested to be involved during cooperative and noncooperative hand movements.

In the muscles ipsilateral to the nerve stimulation, the response pattern was more complex, combining early (ER and

N1–P1 complex), similar to reflex responses elicited during control tasks, and long-latency (N2–P2 complex) reflex components present also on the contralateral, nonstimulated side only during the dyn-coop task. The distribution of reflex responses to a unilateral afferent volley reflects a task-specific, functionally meaningful, neural coupling of upper limbs, that is, the processing of an artificial input by (coupled) neural circuits. This coupling obviously depends on the performance of cooperative hand movements ("opening a bottle"), as the coupling did not occur when the task was mimicked in the static (stat-coop) condition or during the pro-sup task. The mostly suppressive action of the responses might reflect a transient blockage of processing the natural afferent input.

It might be argued that the high level of background EMG in the forearm extensor (compared with flexor) muscles (cf. Fig. 3a) contributes to the bilateral N2–P2 responses. However, this is rather unlikely as (1) the extensor background EMG level was similar during the pro-sup control task (Fig. 3d), but a response appeared only ipsilateral to the stimulation site and (2) the same bilateral N2–P2 pattern was obtained in the left flexors (Fig. 3b) during the dyn-coop task, although the background EMG level was low compared with the extensor activity (cf. Fig. 3c).

Task-Specific Involvement of CNS Areas

We suggest that such a task-specific neural coupling represents an operational rule, which occurs within the spinal cord, brainstem, and supraspinal circuitries. There is spinal decussation and bilateral termination of cervical corticospinal projections in the cervical cord of monkeys (Rosenzweig et al. 2009), which could account for the bilateral long-latency response pattern seen in the dyn-coop condition. Stimulation of reticulospinal cells can also lead to bilateral response patterns (Drew et al. 1996; Brocard et al. 2010). Such a mechanism was assumed to mediate bilateral arm muscle responses to unilateral leg nerve stimulation during locomotion of stroke subjects (Kloter et al. 2011). Although locomotor function differs basically from cooperative hand movements, the underlying task-dependent neural coupling of limbs might be achieved in a similar way. Nevertheless, it is not possible to conclude from the present experiments whether either one or both mechanisms are involved.

One has to be aware that the electrophysiological and fMRI recordings represent connected studies, which provide complementary information since both experimental parts examined cooperative hand movements. They can, however, not directly be linked with each other. Thus, the fMRI study does not allow direct conclusions to be drawn in relation to the electrophysiological findings. Based on our fMRI findings, we suggest that the pathways and brain areas involved in the generation of the bilateral reflex responses become reflected in the bilateral activation of S2 during cooperative hand movements (i.e., dyn-coop vs. pro-sup). Using a different set-up, this assumption is supported by observations in humans (Disbrow et al. 2001) and nonhuman primates (Whitsel et al. 1969) as S2 receives afferent inputs from receptor fields of both hands.

Earlier it was hypothesized that a single integrating center is involved in the control of bimanual movements (Wiesendanger and Miles 1982; Peters 1985; Jagacinski et al. 1988), and that the connectivity between the homologous primary motor cortices is mediated by the corpus callosum (Liuzzi et al. 2011). The latter mechanism would be in line with the observation that patients who undergo callosotomy are unable to perform these tasks (Preilowski 1972).

However, our fMRI results do not provide evidence for a single integrating center but for the existence of a brain region, that is, S2 bilaterally, which is specifically involved in the coordination of cooperative hand movements but not in the control tasks. If the contrast dyn-coop versus pro-sup task was analyzed, one could argue that we have not identified regions that are responsive to cooperative hand movements as the observed activation differences could simply be due to different proprioceptive input to S2. However, our results do not support this assumption, as bilateral S2 activation was still present after subtraction of the non-coop tasks, which involve both in-phase (non-coop-1 task) and out-phase (non-coop-2 task) bimanual hand movements. Thus, S2 activation appears to be task-dependent and might be modulated by an “additional/stronger coordinative effort” (Heuninckx et al. 2005; Wenderoth et al. 2005; Goble et al. 2010) during the dyn-coop task. Therefore, the “task-specific” bilateral activation of the S2 areas does not exclude an S2 activation in other bimanual movement tasks not investigated here.

In addition, an S1 activation was found especially in the contrast “dyn-coop versus non-coop-2”, although it was weaker than S2 activation. This S1 activation has to be due to cooperative hand movements and not to out-phase wrist movements.

Hence, we would conclude that successful integration of active cooperative hand movements (integration sensory information of both body parts) is primarily achieved by S2 with an additional involvement of S1.

It has been hypothesized that S2 plays a role in the human mirror system (Avikainen et al. 2002), because an active suppression of S2 occurred during action observation. Yet, this finding is unlikely to explain our results as visual observation of the hand was minimized during scanning. Furthermore, S2 seems to play an important role in proprioception (Lin et al. 2000). Although proprioception from the wrist movements was similar for both the dyn-coop and the pro-sup tasks, the shared bimanual afferent input during the dyn-coop task might be meaningful for the S2 activation. It is known that S2 activity increases during attentive cutaneous tasks (e.g., Nelson et al. 2004; Jung et al. 2012). It would thus seem reasonable that the dyn-coop condition included greater attention to the bimanual cutaneous information that signaled the activity of the opposite limb during rotation of the device.

S2 is also suggested to be involved in the exchange and integration of information from the 2 sides of the body (Lin and Forss 2002). After unilateral limb stimulation, S2 cortices of both hemispheres are activated and thus, S2 is thought to have a role in combining somatosensory information from the 2 sides of the body to allow its interhemispheric unification (Hari et al. 1998), which is in line with our fMRI results. In addition, the spatial extent of fMRI activation in the S2 (and ventral parietal areas) in humans is larger for bilateral hand stimulation than for unilateral (Disbrow et al. 2001). This further supports our suggestion that S2 is engaged and required in the interhemispheric processing of afferent input during cooperative hand movements. The functional connectivity analysis revealed that the left and right S2 areas (in addition to M1) were functionally connected only for the dyn-coop condition. Thus, a stronger connectivity between the right and the left S2 exists for the dyn-coop task relative to the pro-sup task. This finding supports the idea of an interaction and coupling between the 2 cortical areas involved in the execution of the cooperative task.

There was no specific dyn-coop-related activation of the SMA, (right) insular cortex (Heuninckx et al. 2005), or any other cortical regions (e.g., M1 and PMC) (Grefkes et al. 2008) nor an age-related increase in S2 activity within our subject sample (Heuninckx et al. 2005; Goble et al. 2010), suggested to be characteristic for other bimanual hand movements. The absence of an age-by-task correlation is not surprising, as activations (including S2) for coordinated bimanual hand movements do only show an age-dependency for the elderly (subjects > 60 years; Heuninckx et al. 2005; Goble et al. 2010), but not for young, adults. However, the nonsubtracted fMRI data show robust activation of the SMA, PMC, and M1 in all experimental hand movement tasks performed in this study, that is, these cortical areas are obviously nonspecifically involved in all bimanual movement tasks. The main difference in the neural organization of cooperative hand movements is the involvement of S2.

Consequences for Hand Rehabilitation

Task-specific training effects are well established on the basis of both animal experiments (Edgerton et al. 1997; de Leon et al. 1998a, 1998b) and studies in humans (for reviews, see Dietz 2002, 2008). An established approach for hand rehabilitation after a stroke is “constraint-induced movement therapy”

(Liepert et al. 1998; for reviews, see Taub et al. 1999; Liepert 2010; Nijland et al. 2011). Using this approach, the paretic limb is trained exclusively and compensation or involvement of the unaffected limb is avoided. According to observations made here, the neural structure and interhemispheric information transfer mediating cooperative movements should additionally be trained in order to achieve an improved performance in everyday tasks that require cooperative hand movements.

Conclusion

On the basis of both reflex and fMRI analyses, we conclude that combining and integrating somatosensory information from dynamic cooperative hand movements is task specifically mediated by S2. Consequently, the afferent volley produced by unilateral nerve stimulation is thought to be processed by an interaction of the S2 areas through the corpus callosum. The similarity in latency of the N2–P2 complex of the reflex EMG responses indicates a joint release from supraspinal centers to the arm muscles of both sides. This together with the simultaneous start of bilateral hand movements to “open the bottle” suggests a common release of executor signals to forearm extensors and flexors. The present data provide evidence that bilateral S2 areas are involved in such cooperative bimanual actions. It remains for further studies to determine the exact pathways involved in the generation of the bilateral reflexes described.

Supplementary Material

Supplementary can be found at: <http://www.cercor.oxfordjournals.org/>

Notes

The device used for this study was constructed in the Sensory-Motor Systems Lab of the ETH Zürich (Prof R. Riener). We thank Dr Michelle Starkey for her helpful comments and editing of the manuscript and Amanda Genewein and Sarina Bürer for assisting in the experiments. *Conflict of Interest:* None declared.

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