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ORIGINAL ARTICLE

Action-Dependent Processing of Touch in the Human Parietal Operculum and Posterior Insula

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Abstract

Somatosensory input generated by one's actions (i.e., self-initiated body movements) is generally attenuated. Conversely, externally caused somatosensory input is enhanced, for example, during active touch and the haptic exploration of objects. Here, we used functional magnetic resonance imaging (fMRI) to ask how the brain accomplishes this delicate weighting of self-generated versus externally caused somatosensory components. Finger movements were either self-generated by our participants or induced by functional electrical stimulation (FES) of the same muscles. During half of the trials, electrotactile impulses were administered when the (actively or passively) moving finger reached a predefined flexion threshold. fMRI revealed an interaction effect in the contralateral posterior insular cortex (pIC), which responded more strongly to touch during self-generated than during FES-induced movements. A network analysis via dynamic causal modeling revealed that connectivity from the secondary somatosensory cortex via the pIC to the supplementary motor area was generally attenuated during self-generated relative to FES-induced movements—yet specifically enhanced by touch received during self-generated, but not FES-induced movements. Together, these results suggest a crucial role of the parietal operculum and the posterior insula in differentiating self-generated from externally caused somatosensory information received from one's moving limb.

Key words: active touch, dynamic causal modeling, insula, parietal operculum, somatosensation

Introduction

When picking a cherry from a tree, we are quite sensitive to the feel of the cherry as we touch, grasp, and pull it—yet we are almost insensitive to sensations evoked by our arm and fingers performing the action (i.e., feedback from the joints, muscles, and skin). This means that within one sensory modality, our brain can distinguish sensory inputs that have been caused by external objects (e.g., the cherry) from those that have been directly caused by our action (i.e., proprioceptive and cutaneous inputs from our skin stretching, muscles contracting, and joints moving). This is a behaviorally crucial distinction that is likely enabled by emphasizing the externally caused components of somatosensory information relative to its bodily (self) caused components (Gibson 1962; Klatzky et al. 1985; Nelson 1996; Parkinson et al. 2011; Juravle et al. 2017). In the brain, this

remarkable capacity may be implemented by selectively adjusting the gain of cell populations in the somatosensory cortex that process these different kinds of ascending information (Adams et al. 2013; Brown et al. 2013; cf. Miall and Wolpert 1996; Wolpert 1997).

Psychophysiological and brain imaging studies have provided abundant evidence for an attenuation of somatosensation during and prior to active movement, usually accompanied by a signal decrease in the primary somatosensory cortex (S1; Cohen and Starr 1987; Haggard and Whitford 2004; Bays et al. 2005; Voss et al. 2006; Parkinson et al. 2011; Palmer et al. 2016). At higher levels of the somatosensory hierarchy, the picture is less clear. Human functional magnetic resonance imaging (fMRI) studies have found reduced secondary somatosensory cortex (S2) activity when participants touched one of their (non-moving) hands themselves versus when the touch was generated by an experimenter or a machine (Blakemore et al. 1998, 1999; Shergill et al. 2013). This suggests an attenuation of S2 activity depending on the predictability of somatosensory inputs, which is greatest when these inputs are self-generated. Conversely, other studies have demonstrated an increased responsiveness of the parietal operculum/S2 to sensory inputs during finger movements compared with stimulation at rest (Huttunen et al. 1996; cf. Forss and Jousmäki 1998; Lin et al. 2000). Several studies did not find any significant difference in the attenuation of somatosensory electro- or magnetoencephalography (EEG/MEG) signals caused by tactile stimulation during self-generated versus externally generated movements (Rushton et al. 1981; Tinazzi et al. 1997; Nakata et al. 2003; cf. Williams and Chapman 2002). Nakata et al. (2003) found that active versus passive movements enhanced some of the longer latency signal components in the S2.

In sum, these results suggest that, while somatosensory attenuation or "gating" may happen at low levels of somatosensory processing, at higher levels of the somatosensory hierarchy—for example, in the parietal operculum—both an attenuation and an enhancement of ascending sensory information may be in play. These areas therefore are likely candidates for an implementation of the action-dependent weighting of self-generated versus externally caused somatosensory components. However, most of the above study designs were not aimed at disambiguating externally caused somatosensory components from those self-caused by bodily movement and lack essential comparisons. Most importantly, to answer this question, one has to compare active and passive movements that generate equally predictable somatosensory consequences (Stenner et al. 2014; Kaiser and Schütz-Bosbach, 2018).

Here, we examined tactile processing during movement using a balanced factorial study design; active and passive finger movements were generated by the same muscles, and the received touch was triggered by a certain state (position) of the finger in both movement types (Fig. 1). Crucially, the tactile stimulus was thus an equally expected and predictable sensory consequence of body movement during self-generated and functional electrical stimulation (FES)-induced movements. We hypothesized that the processing of touch to the moving finger would nevertheless depend upon action, i.e., that touch would be differently processed in the somatosensory cortex during self-generated than during FES-induced movements. To test this hypothesis, we measured brain activity with fMRI and modeled the underlying distributed neuronal responses in terms of directed connectivity and synaptic gain control with dynamic causal modeling (DCM).

Materials and Methods

Participants

A total of 16 healthy, right-handed volunteers (7 female, mean age = 29 years, range = 20–39) participated in the experiment after having given written informed consent. The sample size was determined following a recent related fMRI experiment, in which we detected significant ($P < 0.05$, family-wise error [FWE] corrected for multiple comparisons) main and interaction effects on the voxel level using an analogous 2×2 factorial design in an active versus passive movement paradigm (Limanowski, Sarasso et al. 2018). The experiment was approved by the ethics committee of the Charité University Hospital Berlin and conducted in accordance with this approval.

Experimental Set-up and Procedure

During the experiment, participants lay comfortably inside the MR scanner with their right hand on the right side of their body, supported by foam pads (Fig. 1A). The participants' task was to flex and extend their right middle finger, or to let the FES flex and extend the same finger—this was the first factor of our design. The second factor comprised tactile stimulation of the (actively or passively) moving middle finger in half of the conditions, where the application of the tactile stimulus was triggered when the finger reached half of its maximum flexion; this was measured in real-time via an MR-compatible data glove worn on the participant's right hand. The sensation was analogous to tapping onto an object, without hindering movement execution (details below).

Our design was a 2×2 factorial design with the factors "action" ("self-generated movement, FES-induced movement") and "touch" ("touch applied during movement, no touch applied during movement"); see Figure 1C. The resulting conditions were the following: self-generated movement with touch (ST); self-generated movement without touch (S); FES-induced movement with touch (FT); and FES-induced movement without touch (F). Each condition was presented in 16 s blocks (i.e., 8 flexion-extension movements; Fig. 1D) and 4 times per run in randomized order, resulting in 16 condition presentations (separated by 16 s rest periods) and about 9 min run length. Each participant completed 4 of these experimental runs, and an additional tactile localizer run (see below), which was designed to identify the somatotopical representation of the finger versus arm stimulation locations.

Task Design

We instructed and trained participants to flex their finger as much as possible, yet without touching the palm of their hand. Then, we calibrated the FES to elicit this movement as closely as possible (details below). The finger movements were paced at 0.5 Hz by an auditory cue presented every 2 s via headphones. Prior to the start of each condition block (self-generated or FES-induced movement), participants were presented a high or a low double tone, which informed them about the upcoming condition, i.e., instructed them whether they should actively move their finger during the next condition or whether they should let the FES elicit the movement. To signal the end of each condition and to prevent participants from counting the beats, the last tone within each condition was a double tone again. All tones were also presented in the FES-induced movement conditions to match the sensory input of the self-generated movement conditions. Participants were told that the tactile impulses were task-irrelevant.

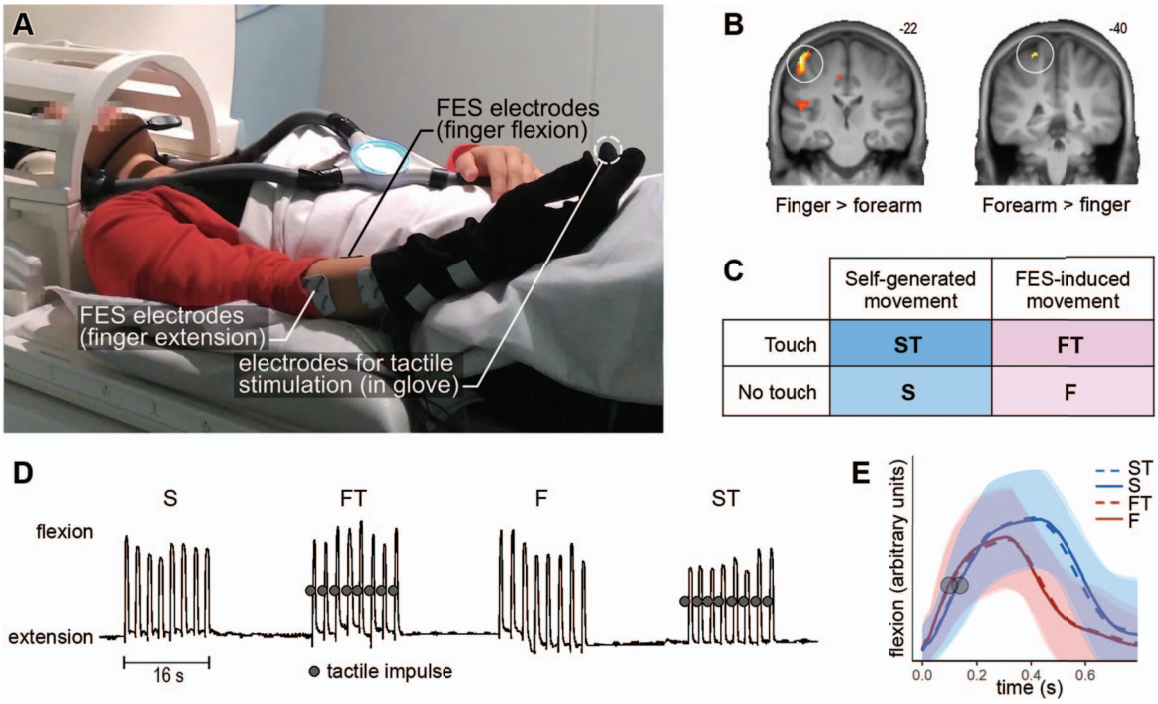

Figure 1. Experimental set-up and design. (*A*) Movement of the participant's right middle finger was paced at 0.5 Hz by auditory cues. The movements were either self-generated or induced by FES applied via pairs of adhesive electrodes at the respective flexor and extensor muscles of the right forearm. During half of the conditions, brief, clearly notable but non-painful electrotactile impulses were delivered to the moving finger halfway throughout the movement, via another pair of electrodes; an MR-compatible data glove was used to measure the finger movements and to determine an individually predefined flexion threshold at which the administration of tactile stimuli to the moving finger was triggered. (*B*) Results from the passive electrotactile localizer run showing somatotopically distinct representations of the finger versus forearm stimulation sites in the left S1 (displayed at $P < 0.001$, uncorrected; see Results for details). (*C*) Table showing the cells of our 2×2 factorial design, i.e., ST/S = self-generated movements with/without touch; FT/F = FES-induced movements with/without touch. (*D*) Excerpt of the recorded glove data from a representative participant, i.e., the finger movements in 4 subsequent conditions (16 s blocks à 8 movements, randomly presented, separated by 16 s rest periods). The gray dots schematically indicate the administration of electrotactile impulses halfway throughout finger flexion (not extension) in conditions ST and FT. (*E*) Plot showing the grand averaged movements with standard deviations per condition (with gray dots schematically indicating the application of the tactile stimulus).

All participants were thoroughly pretested outside of the scanner room to ensure that the FES was calibrated so as to induce a sufficiently large middle finger movement without moving other body parts (the wrist or other fingers) and without the middle finger flexing so far as to touch the palm. We also ensured that the electrotactile impulses were clearly perceived at the tip of the moving finger even during FES-induced movements. After this initial calibration, participants were recalibrated (for both FES and electrotactile stimulation) after lying down in the scanner. Before the actual experiment, participants completed a practice session inside the MR scanner to familiarize themselves with all the instructions and conditions.

FES

Participants' forearm muscles were stimulated via a medically compliant FES device (Rehastim 1, HASOMED). The current-controlled stimulator (controlled via universal serial bus (USB) using serial messages with a latency <1 ms) was powered by an internal battery and galvanically isolated from the computer's USB port and from any external power source; the stimulator was placed outside the scanner room, and the cables for the electrodes were passed through a waveguide. Electrical impulses were generated by the computer-controlled stimulation unit and applied via 4 medically compliant adhesive electrodes as shown in Figure 1A. The flexor and extensor muscles were stimulated using 2 independent and off-phased stimulation channels. Each channel comprised of 2 30×30 mm pre-gelled electrodes; for participants with a smaller arm radius (and thus smaller musculature), we reduced the electrodes to 20×20 mm. Flexing the middle finger was achieved, in isolation with respect to wrist flexion and other finger flexion, by actuating the "flexor digitorum profundus" with 2 electrodes placed at the median nerve. Conversely, extending the middle finger was achieved by actuating the "extensor digitorum" with electrode pads placed directly at the central section of the "extensor digitorum communis". These muscles were stimulated using a biphasic waveform at 100 Hz. The flexor stimulation comprised 35 pulses (around 0.35 s), and the extensor stimulation comprised 50 pulses (around 0.5 s). The amplitude (0–30 mA) and pulse width (100–400 μs) of the waveform were calibrated per participant. These stimulation parameters depended on the participant's muscle mass and fat tissue present in the forearm locations where the electrodes were placed. To illustrate the stimulation parameters, we take one exemplary participant: flexor stimulation at 9 mA with a 150 μs pulse width and extensor stimulation at 11 mA with a 200 μs pulse width. During behavioral piloting, we ensured that this FES set-up could induce non-painful finger flexion-extensions that seemed natural to participants. To ensure the comparability between self-generated and FES-induced finger movements, participants were instructed to mimic the FES-induced movements as closely as possible when performing the movements themselves.

Electrotactile Stimulation of the Moving Finger

Tactile stimulation of the moving finger was realized via electrotactile impulses delivered via a pair of medically compliant adhesive electrodes attached to the right middle finger's first phalanx (cf. Ruben et al. 2001). The impulses were 200 µs long monophasic square wave pulses generated by a bipolar constant current stimulator (Digitimer DS7). The stimulator was placed outside the scanner room, and the cables for the electrodes were passed through a waveguide. The intensity of electrical stimulation was individually adjusted (range of stimulation current amplitudes, 4.8–20.0 mA) to ensure that it resulted in a clear but non-painful tactile percept localized to the middle finger's tip. Single electrotactile impulses were triggered by the moving middle finger reaching a fixed, individually calibrated flexion threshold, as registered by the data glove (see below). Occasionally, despite careful individual calibration, individual tactile impulses were missed or presented twice due to inconsistent or insufficient movements. On average, only 1.0% of tactile pulses were missed, and 3.7% of tactile pulses were doubled (one outlier run of one participant was excluded from analysis because almost all tactile impulses were doubled). These missed or superfluous tactile impulses were modeled as separate regressors (of no interest) in the fMRI analysis (see below).

Movement Recording via Data Glove

Participants wore an MR-compatible data glove (5DT Data Glove MRI) on their right hand, which was used to monitor and record their finger movements and to trigger the administration of the tactile impulses. The data glove measured each finger's flexion individually via sewn-in optical fiber cable sensors (1 sensor per finger, 8 bit resolution per sensor, 60 Hz sampling rate) and has been successfully used in previous fMRI studies on motor control and adaptation (Limanowski et al. 2017). Prior to scanning, the glove was carefully calibrated to fit each participant's individual finger movement range (if necessary this was repeated between runs). The glove's data were also used to trigger the administration of the electrotactile impulses to the moving middle finger: for each participant, we determined a point halfway through the finger flexion. When this point was crossed during their flexion (not during extension), this triggered the electrotactile impulses as described above. Movement amplitude within conditions, logged by the data glove, was included as a covariate in the fMRI analysis (see below). We tested for differences in movement amplitude and duration across conditions by means of nonparametric (due to non-normal distribution of the data) Friedman's test.

Tactile Localizer

After the experiment, participants completed a tactile localizer run (9 min) to identify the somatotopical representation of locations affected by electrical stimulation of the finger (tactile impulses) versus forearm (FES). Weak (sub-motor threshold) FES and electrical finger stimulation were presented in random order in 16 s blocks separated by 16 s rest periods. Before the localizer run, the intensity of FES was calibrated to be notable but below the motor threshold, i.e., it did not produce finger movement. For a stronger tactile effect, the frequency of electrotactile stimulation at the finger was increased (during the 16 s stimulation blocks, trains of 4 tactile stimuli were presented during 500 ms, separated by 500 ms rest intervals).

Analysis of Movement Data

To segment and analyze the glove data, flexion peaks of each movement were identified (using RStudio; http://www.rstudio.com/). In a window of 1500 ms length centered at the flexion peak, movement onset was then defined as the first point where velocity exceeded both a velocity threshold (5% of peak velocity in the respective time window) and an extension threshold (20% of maximum flexion). Movement offset correspondingly was defined as the point where velocity fell below the threshold (after the flexion peak had been reached). To test for differences in movement amplitude and duration between the conditions, we computed a repeated measures analysis of variance (ANOVA) with the conditions of the experiment as factor and subjects as random effects, separately for movement durations and amplitudes. Post hoc comparisons of individual conditions were performed via Tukey Contrasts with Holm–Bonferroni correction for multiple comparisons. To visualize the different time courses of the movement trajectories in our 4 conditions, the finger movement data were partitioned into non-overlapping time-windows of 2000 ms duration, starting 200 ms before the respective auditory cue was presented. Then, these data were averaged by condition and normalized to a common onset position. See Figure 1*E* for the resulting trajectories and Supplementary Table S1 for the results of the statistical comparisons.

FMRI Data Preprocessing and SPM Analysis

The fMRI data were recorded using a 3 T scanner (Tim Trio, Siemens) with a 12-channel head coil. *T2*∗-weighted images were acquired using a gradient echo-planar imaging sequence ($3 \times 3 \times 3$ mm^3 voxels, 20% gap, matrix size = 64×64, 37 slices, interleaved ascending slice acquisition, TR = 2000 ms, TE = 30 ms, flip angle = 70°). For each participant, we recorded 5 runs à 270 functional images and a *T1*-weighted structural image (3D MPRAGE, voxel size = $1 \times 1 \times 1$ mm^3, FOV = 256×256 mm^2, 176 slices, TR = 1900 ms, TE = 2.52 ms, flip angle = 9°). FMRI data were preprocessed and analyzed using SPM12.5 (www.fil.ion.ucl.ac.uk/spm/). Artifacts at the slice level were corrected using the ArtRepair toolbox (Mazaika et al. 2009; on average 0.26% of slices corrected). Images were corrected for slice acquisition time differences, realigned and resliced, normalized to MNI space with DARTEL (resliced to 2 mm voxels), spatially smoothed with an 8 mm full width at half maximum (FWHM) Gaussian kernel, detrended (Macey et al. 2004), and images featuring excessive (0.5 mm scan-to-scan) movement were interpolated (ArtRepair; on average less than 0.01% of volumes corrected). We fitted a general linear model (GLM, 128 s high-pass filter) to each participant. Each movement was modeled as an onset regressor with 0 s duration, which effectively resulted in a block-like regressor when modeling all 8 successive movements of each condition. With this approach we were able to exclude occasional (rare, see above) flexions that were not sufficiently large to trigger tactile impulses and model them as a separate regressor of no interest; occasional (rare) double tactile impulses were likewise modeled as a regressor of no interest. We controlled for potential effects due to the variability of movements within each condition by including movement amplitude as a parametric modulator for each respective condition (except for one participant, whose glove data were not saved). Note that these covariates do not affect estimates of amplitude differences between conditions. The 5 principal components accounting for the most variance in the cerebrospinal fluid or white matter signal time course

(Behzadi et al. 2007) were added to the GLMs alongside the realignment parameters as regressors of no interest. We did not find any evidence for potential artifacts—induced by the electrical stimulation—when inspecting individual contrast and residual images. Correspondingly, the number of slices and volumes corrected by the ArtRepair toolbox was compatible with other studies, in which we had not used electrical stimulation, for example, Limanowski et al. (2017).

On the first level, we calculated contrasts of each condition versus baseline. The resulting contrast images were entered into a group-level flexible factorial design with the factors "action" ("self-generated movement, FES-induced movement") and "touch" ("touch applied during movement, no touch applied during movement") and an additional factor modeling the subject constants. The first-level finger versus arm stimulation contrast images of the tactile localizer run were entered into a one-sample *t*-test on the group level. Statistical significance was assessed using a voxel-wise statistical threshold of $P < 0.05$, FWE corrected for multiple comparisons; we only report significant activations larger than one voxel. Our main hypothesis was to find interaction effects between action and touch in touch-sensitive areas. Therefore, we looked for such effects within an a priori restricted search space defined by all significant voxels obtained from contrasting touch against no touch at $P < 0.001$, uncorrected, i.e., FWE correction was applied within these voxels only ("small volume correction"). The resulting statistical parametric maps (SPMs) are projected onto the mean normalized structural image at $P < 0.05$, FWE corrected threshold. The group-level and single subject-level SPMs (unthresholded T-maps) relating to all reported results can be inspected online at https://neurovault.org/collections/4208/. Contrast estimates were extracted from as an average of all significant ($P < 0.05$, FWE corrected) voxels of each activation difference using the rfxplot toolbox for SPM (Gläscher 2009). The SPM Anatomy toolbox (Eickhoff et al. 2005, 2006; Kurth et al. 2010) was used for anatomical reference where possible.

DCM of BOLD Responses

To investigate the effective connectivity changes underlying the observed interaction effect of self-generated movements and tactile inputs in the posterior insular cortex (pIC), the measured blood oxygen level dependent (BOLD) signal time series were subjected to DCM12.5 as implemented in SPM12. DCM (Friston et al. 2003) is a Bayesian framework that allows one to construct generative models of neuronal responses of a set of coupled brain regions, and based on this model, generates a prediction of measured brain activity, for example, predicted BOLD signal time series. DCM thus allows one to model how observed changes in brain activity were caused by changes in effective connectivity among a set of brain regions under a specific network architecture, i.e., by modulations of extrinsic (between-regions) and/or intrinsic (within region, self-inhibitory) connections by factors like experimental manipulations.

Our DCM analysis focused on the observed interaction effect of action and touch in the left pIC, as determined by our SPM analysis. Our aim was to quantify context (i.e., action) dependent changes in effective connectivity underlying the observed interaction effect—the different processing of somatosensory (tactile) inputs depending on whether or not the movement was self-generated—in the pIC. Our specific hypotheses were based on Bayes optimal weighting of various sources of sensory evidence. In predictive coding formulations of active inference, this translates into optimizing the condition or context-sensitive precision of ascending prediction errors at various levels in the sensorimotor hierarchy (Friston and Kiebel 2009; Feldman and Friston 2010; Shipp 2016). Physiologically, this leads to the hypothesis that condition specific effects would be manifest as changes in coupling strength as determined by DCM. This follows from the fact that changes in the precision are thought to be mediated in terms of the excitability or postsynaptic sensitivity of certain (pyramidal) cell populations to intrinsic (within region) or extrinsic (between regions) afferents. Here, we assume that such gain modulations manifest themselves as relative amplitude variations of the BOLD signal in the respective brain region and, in terms of effective connectivity, into modulations of specific afferent (between or within region) connections to this region.

Based on the results of our SPM analysis, we focused on the pIC's connections with the S2 (which showed a significant main effect of touch and a significant activation by each movement condition; see Supplementary Fig. S1) and the supplementary motor area (SMA) (which showed a significant main effect of action, i.e., self-generated > FES-induced movements). We therefore connected the left pIC to the S2 (assuming pIC was located higher in the somatosensory hierarchy; cf. Friedman et al. 1986; Kurth et al. 2010; Keysers et al. 2010) and to the SMA (cf. Parkinson et al. 2011). Furthermore, the S2 was connected to two regions of the left S1, which were identified to represent somatosensory information from the two stimulation sites—the finger ($S1_{fng}$) and the forearm ($S1_{arm}$)—in a separate passive tactile localizer run and which showed effects of tactile stimulation and FES, respectively (Fig. 1B, cf. Supplementary Figs S2 and S5). All connections were reciprocal, in addition to self-connections on each node (Fig. 3B). For each of these regions, time series were summarized as the first eigenvariate of all voxels within 6 mm spherical volumes of interest (VOIs) centered on each participant's local maximum. The individual peaks were identified by the following contrasts: self-generated > FES induced movements for the SMA, touch > no touch for the $S1_{fng}$ and S2, FES-induced > self-generated movements for the $S1_{arm}$, and the interaction contrast for the pIC; the location of the peaks was restricted to within 12 mm Euclidean distance of the group peaks obtained from the respective contrasts (using peaks obtained from the somatosensory localizer run for the S1 locations). VOIs within each participant were not overlapping. See Supplementary Table S3 for individual VOI coordinates. The time series were adjusted for confounding effects (i.e., session means, missed or double movements, movement regressors, and physiological noise regressors).

We defined sensory inputs as entering the system at both (somatotopically distinct) S1 locations and allowed for modulation of all connections by the contextual effects of action (self-generated > FES-induced movements, i.e., (ST + S)-(FT + F)) and the effect of touch received during each movement type (i.e., ST-S and FT-F). The resulting parameter estimates can therefore be interpreted as changes in connectivity induced by action and the effects of touch during active and passive movements. We inverted the resulting full model for each participant using a hierarchical parametric empirical Bayesian procedure for DCM (Friston et al. 2016). We then used Bayesian model reduction (BMR; Friston and Penny 2011) to identify the optimal combination of parameters (modulations by action and touch, encoded by the DCM.B matrix) that best explained the observed BOLD signal time series: a space of reduced models was tested against the full model, that is, various combinations of coupling

parameters switched on or off were evaluated using a step-wise "greedy search" algorithm to identify those modulations that contributed to model evidence and to prune away those that did not (i.e., shrink them to their prior expectation of 0). Only parameters with a posterior probability greater than 0.75 were retained, which in DCM is commonly interpreted as positive evidence for the contribution of a parameter to model evidence (i.e., a model including that particular parameter notably outperforms the same model without it). Finally, for an unbiased, evidence weighted estimate of the optimal parameters, we applied Bayesian model averaging over retained (reduced) models within Occam's window (Penny et al. 2010).

Results

Movement Characteristics

All participants were able to perform the task and to maintain a close similarity of self-generated and FES-induced movements. An ANOVA revealed significant differences in movement amplitude ($F(3,42) = 4.57$, $P < 0.01$) and duration ($F(3,42) = 9.84$, $P < 0.01$) between self-generated and FES-induced movements. Post hoc comparisons with Holm–Bonferroni correction for multiple comparisons revealed that on average, FES-induced movements were of about 14% smaller amplitude (S vs. F, $P < 0.01$; ST vs. FT, not significant) and 140 ms shorter than self-generated movements (S vs. F, $P < 0.001$; ST vs. FT, $P < 0.001$). The main difference appeared during the extension phase (i.e., the finger extension was somewhat quicker during FES-induced movements), but both movement conditions were closely matched during the flexion phase (Fig. 1E). Note that the tactile stimulus was delivered automatically at a predefined threshold during flexion in both movement types. Importantly, there were no significant differences in movement amplitude or duration between conditions with versus without touch (i.e., the comparisons S vs. ST and F vs. FT were not significant). See Supplementary Table S1 for details.

Somatotopical Representation of Finger versus Forearm Stimulation Sites

We tested for a somatotopically distinct representation of electrotactile stimulation applied to the passive (non-moving; in order to be unbiased by movements) right middle finger versus to the right forearm (FES stimulation location) in a separate functional localizer run. Contrasting electrotactile stimulation at the finger against stimulation at the forearm revealed significant ($P < 0.05$, FWE corrected for multiple comparisons) activations in the S1 ($x = -50$, $y = -22$, $z = 62$, $T = 9.09$; see Fig. 1B and Supplementary Fig. S2 for details); further activations were found in the S2 (assigned to OP4 and OP1, cf. Eickhoff et al. 2006; $x = -48$, $y = -26$, $z = 12$, $T = 5.15$, $P < 0.001$, uncorrected). The converse contrast revealed a more posterior and superior location in the S1 ($x = -24$, $y = -40$, $z = 68$, $T = 4.28$, $P < 0.001$, uncorrected). These results demonstrate that cutaneous inputs delivered to the finger (i.e., electrotactile impulses) and arm locations (i.e., associated with the FES) were represented at somatotopically distinct locations in the S1 and that tactile stimulation of the non-moving right middle finger activated mainly OP4 and OP1 of the contralateral S2.

Main Effects of Action and Touch

The analysis of data from the main experiment revealed a significant main effect of action in the SMA (self-generated > FES-induced movements, contrast (ST + S)—(FT + F), $P < 0.05$, corrected, Fig. 2, cf. Supplementary Fig. S3); further activation differences were located in the primary motor, premotor, and prefrontal cortex but did not survive correction for multiple comparisons (see Supplementary Table S2 and Fig. S4). The converse contrast (FT + F)—(ST + S) revealed significantly greater activations by FES-induced movements in the left S1, the bilateral S2 (spanning to posterior parts of the insula), and in left temporoparietal regions. Thus, activity in somatosensory areas was generally attenuated during self-generated movements. The location of the peak activation difference in the left S1 matched the anatomical location responding more strongly to sub-motor threshold FES at the forearm against the finger locations, as identified in an independent passive tactile localizer run conducted in each participant (Fig. 1B). This activation was clearly somatotopically distinct from the activation produced in more lateral regions of S1 by tactile stimulation of the finger and likely reflected somatosensation generated by the FES at the forearm (Supplementary Fig. S5). Contrasting movements with touch against those without touch (ST + FT)—(S + F) revealed significantly stronger responses in the left S2 (areas OP1 and OP4; Fig. 2, cf. Supplementary Table S2); further activation differences in the left S1 were found at uncorrected thresholds (Supplementary Fig. S6). The S2 areas that we observed to be activated here corresponded to those activated by passive tactile stimulation of the finger > forearm location in the tactile localizer run (Supplementary Fig. S7). The reverse contrast (S + F)—(ST + FT) revealed no significant activation differences.

Interaction between Action and Touch in the Posterior Insula

Next, we tested our main hypothesis—that the effects of action and touch would interact in higher-level brain areas dedicated to somatosensory processing. Indeed, the contrast (ST-S)—(FT-F) revealed a significant interaction effect within areas activated by touch, with the peak located in the left pIC (peak: $x = -38$, $y = -18$, $z = 12$, $T = 4.92$, $P < 0.05$, corrected; Fig. 2), i.e., a significantly greater increase in the BOLD response to touch during self-generated than during FES-induced movements. The interaction peak was located notably more medially than the location activated by stimulation of the passive (non-moving) middle finger in the tactile localizer run. The reverse interaction contrast (FT-F)—(ST-S) revealed no significant effects in touch-sensitive areas (cf. Supplementary Table S2 and Fig. S8).

Action-Dependent Changes in Effective Connectivity

Next, we used DCM to quantify action-dependent changes in effective connectivity within the sensorimotor hierarchy identified by our SPM analysis to explain the observed interaction effect between action and touch in the left pIC. Based on our SPM analysis, we connected the pIC to the SMA (main effect of action, i.e., self-generated > FES-induced movements) and the left S2 (main effect of touch); the two regions of the left S1 representing somatosensory inputs from the finger ($S1_{fng}$) and forearm ($S1_{arm}$), respectively, received sensory inputs and were connected to the S2 (cf. Fig. 1B). We hypothesized that the interaction effect in the pIC—the different response to tactile inputs depending on whether or not the movement was

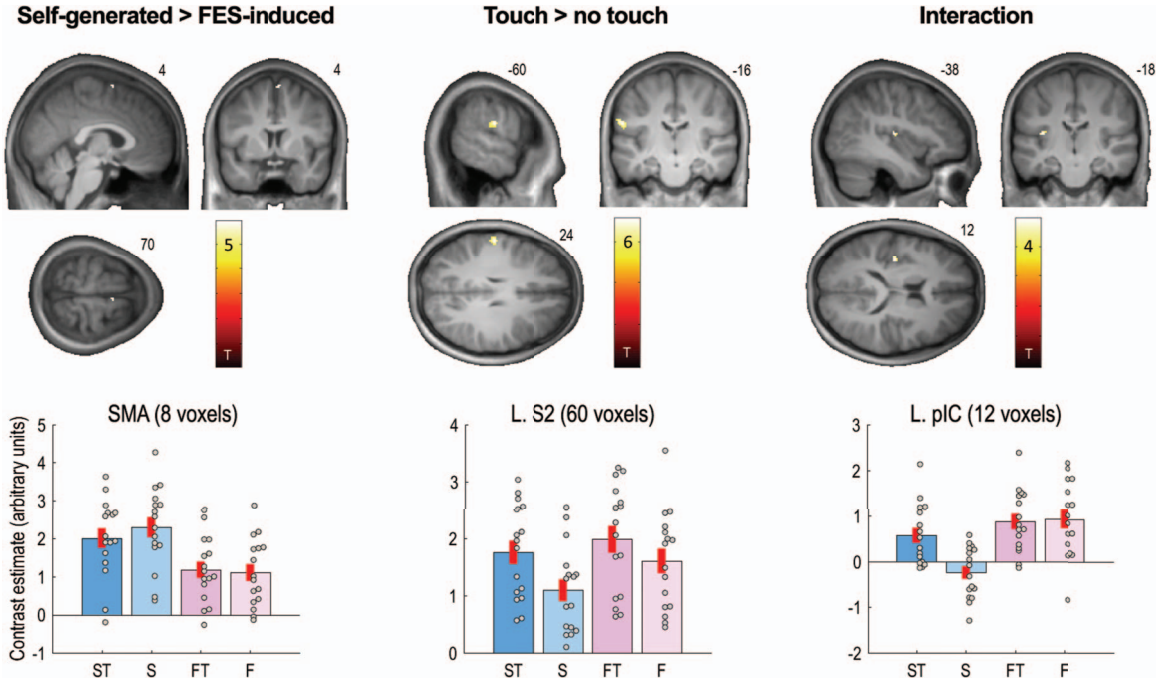

Figure 2. Significant ($P < 0.05$, FWE corrected for multiple comparisons) activation differences obtained from the SPM analysis. Self-generated movements were associated with a significantly stronger activation of the SMA than the analogous movements induced by FES, i.e., contrast of (ST + S)—(FT + F). Tactile stimulation during movement significantly increased activity in the S2, i.e., contrast of (ST + FT)—(S + T). Crucially, there was a significant interaction effect between action (self-generated vs. FES-induced movements) and touch in the left pIC, i.e., the contrast of (ST-S)—(FT-F) showed a significantly greater response difference between right finger movements with and without touch to the moving finger, when the movements were self-generated than when they were FES-induced. See Supplementary Table S2 for details and Fig. S4 for further activations. The corresponding SPMs are available at https://neurovault.org/collections/4208/. The bar plots show the group-level contrast estimates for each condition (with standard errors of the mean) averaged across the significant voxels indicated for each activation difference; the individual participants' contrast estimates are shown as gray dots.

self-generated—would be a result of action-dependent precision weighting of prediction errors, manifest as changes in the sensitivity of the pIC to its afferents. In other words, we hoped to see evidence for increases in the strength of directed connectivity to the pIC when touch was applied during self-generated movements.

The results of this analysis revealed a generally positive baseline (i.e., context-independent) influence of connections "ascending" the somatomotor hierarchy in our full model, i.e., from the S1 to the S2 and from there via the pIC to the SMA—while the reciprocal connections were inhibitory—and, consistent with the SPM results, a positive driving effect of sensory inputs on the $S1_{fng}$ (as expected, stronger by movements with touch) and of FES on the $S1_{arm}$ (see Supplementary Table S4). Crucially, BMR (Fig. 3A) revealed evidence for several action-dependent connectivity differences: self-generated > FES-induced movements were associated with a relatively inhibited "forward" connectivity from the $S1_{arm}$ via the S2 and the pIC to the SMA; in other words, these connections were stronger during FES. The sensitivity of the $S1_{arm}$ was likewise increased during FES-induced movements (i.e., $S1_{arm}$ self-inhibition was lower). Self-generated movements were, moreover, associated with an increased influence of the $S1_{fng}$ on the S2, of the SMA on the pIC, and of the S2 on the $S1_{arm}$, alongside a generally decreased self-inhibition of the SMA. Importantly, touch received during self-generated movements increased the influence of ascending connections from the S2 via the pIC to the SMA; moreover, the $S1_{fng}$ showed reduced self-inhibition—suggesting an increased sensitivity to touch received during self-generated movements. Conversely, there was no evidence for similar modulatory effects during FES-induced movements, suggesting that touch did not affect these connections during passive (i.e., FES-induced) movement. See Figure 3 (cf. Supplementary Table S4 and Fig. S9) for details.

Discussion

We compared brain activity evoked by processing touch received at a moving body part during self-generated actions versus passive movements induced by electrical stimulation of the same muscles. Our main finding was that during self-generated movements, touches administered to the moving finger substantially increased the response of a region in the upper bank of the (multisensory) pIC, whereas no such increase was observed during FES-induced movements. Furthermore, we found significantly stronger activation of the SMA during self-generated than during FES-induced movements, which is in line with its previously described role in the initiation of actions (Deecke and Kornhuber 1978; Fried et al. 1991; Haggard and Whitford 2004; Haggard 2008; Nachev et al. 2008; Nguyen et al. 2014; Limanowski, Sarasso et al. 2018). Conversely, FES-induced movements were associated with increased activity in the contralateral S1, S2, and insula, which is in line with previous studies and likely reflects the fact that the FES caused additional somatosensory input, which was not predicted by the motor system (cf. Blickenstorfer et al. 2009; Francis et al. 2009; Iftime-Nielsen et al. 2012; Christensen and Grey 2013; Gandolla et al. 2014). FES-induced movements

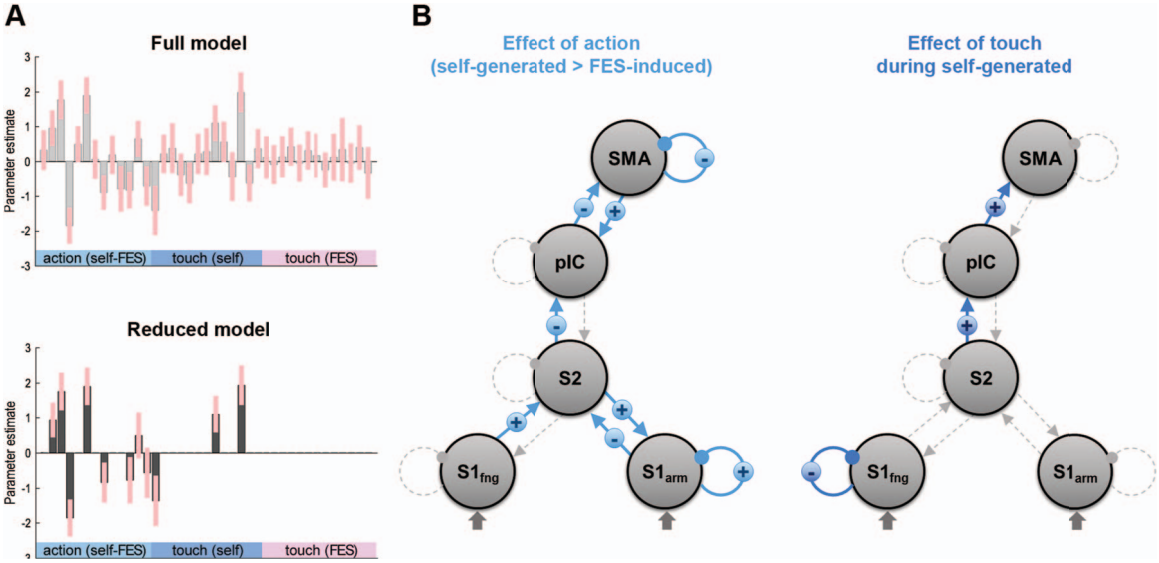

Figure 3. Results of the DCM analysis showing action-dependent modulations of connectivity within the somatomotor hierarchy identified in our SPM analysis. (*A*) Results of the BMR testing for all possible combinations of modulatory effects on connectivity. The plots show the parameter estimates with 90% posterior confidence intervals of the full model (top) and the optimal reduced model (bottom; Bayesian model averages of retained parameters), indicating how strongly each coupling parameter was modulated by action (self-generated—FES-induced movements) and touch received during self-generated movements (ST-S) or FES-induced movements (FT-F), respectively. The sign of the modulation indicates the relative difference in modulation strength. The retained modulation effects are schematically depicted in (*B*); colored lines indicate modulations by touch (positive/negative = relatively increased/decreased influence, e.g., "+" indicates a stronger coupling modulation during self-generated than during FES-induced movement); dashed lines indicate latent (unmodulated) connections; thick arrows indicate driving inputs by movement. See Supplementary Table S4 and Fig. S9 for details.

were also associated with significantly increased activity in temporo-parietal areas, which have previously been linked to a loss of a sense of agency (Farrer et al. 2008; Limanowski et al. 2017). This suggests that participants were indeed in a passive state when moved by means of FES. Tactile stimulation during movement significantly activated the contralateral parietal operculum (S2) and the posterior insular cortex, consistent with previous findings demonstrating the importance of the S2 and insula in somatosensory processing and sensorimotor integration (e.g., Forss and Jousmäki 1998; Ruben et al. 2001; Hinkley et al. 2007; Preusser et al. 2014).

Our DCM analysis showed, firstly, action-dependent modulations of connectivity that suggested a relatively stronger influence of "forward (ascending)" connections from the S2 via the pIC to the SMA under FES-induced movements—in other words, a relatively reduced influence of these connections during self-generated movements—which supports the hypothesis that self-generated somatosensory input is generally attenuated during movements. The $S1_{arm}$ showed increased sensitivity to its inputs (i.e., reduced self-inhibition) during FES-induced movements, which is in line with the SPM results and suggests that this region processed somatosensory inputs from the FES at the forearm. Conversely, the SMA showed reduced self-inhibition during self-generated movements, which following predictive coding formulations, could imply an increase in the precision afforded movement priors to generate action (cf. Feldman and Friston, 2010; Adams et al. 2013). There was also an enhanced influence of the "descending" connections from the SMA to the pIC, and from the S2 on the $S1_{arm}$ during self-generated movements, which translates into a relatively increased inhibitory effect during FES. Tentatively, these changes may be interpreted as a suppression of FES-induced responses in lower sensory areas; however, they could also be linked to processes underlying somatosensory attention and awareness (similar to changes recurrent connectivity between the S1 and the S2, cf. Auksztulewicz et al. 2012).

Secondly and importantly, our DCM analysis revealed evidence for an increased excitatory influence of the S2 on the pIC, and of the pIC on the SMA, when touch was received during self-generated movements. In contrast, there was no positive evidence that touch had any modulatory effect on our model's connectivity during FES-induced movements. This implies that during self-generated movements (i.e., actions), the somatomotor hierarchy differentiated between self- and externally generated somatosensory signals—and communicated especially the latter "forward" from sensory to high-level motor areas. Note that although the connection from the $S1_{fng}$ to the S2 was not modulated by touch (possibly due to the weak main of touch in the S1), it was generally enhanced during self-generated movements, which could effectively have contributed to the same differentiating process.

Consistent with predictive coding accounts of hierarchical recurrent connectivity (cf. Friston and Kiebel 2009; Bastos et al. 2012; Adams et al. 2013), the baseline connectivity within our model's hierarchy was characterized by positive connections "ascending" from the $S1_{fng}$ via the S2 and the pIC to the SMA, while the reciprocal connections were inhibitory. Thus, we propose that during self-generated movements, ascending somatosensory (proprioceptive) prediction errors generated by the moving body could have been more effectively resolved by "motor" (i.e., proprioceptive) predictions from, for example, the SMA (cf. Miall and Wolpert 1996; Adams et al. 2013; Brown et al. 2013; Juravle et al. 2017), which would explain why the overall activation level of the pIC and the S2 and their ascending afferent connections were attenuated during self-generated movements. Importantly, this distinction between self-generated and externally caused somatosensory prediction errors could only be made during self-generated

movements, since during FES-induced movements all inputs were externally generated and therefore "unpredicted" by the motor system.

In sum, our results imply a role of the posterior insula in somatomotor integration that goes beyond the previously demonstrated somatosensory attenuation or "gating" in the S1 and even in the S2 (cf. Tsumoto et al. 1975; Chapin and Woodward, 1982; Cohen and Starr 1987; Haggard and Whitford 2004; Bays et al. 2005; Voss et al. 2006; Parkinson et al. 2011; Palmer et al. 2016). Some previous studies have suggested that crucial somatomotor integration processes take place in medial opercular regions (Huttunen et al. 1996; Forss and Jousmäki 1998; Lin et al. 2000; Hinkley et al. 2007; cf. Juravle et al. 2017), potentially corresponding to the human homologue of the monkey "ventral somatosensory area" (Cusick et al. 1989; Eickhoff et al. 2006). The insular cortex in general seems to be a high-level associative, multisensory area located upstream of the S2 in the somatosensory system (Eickhoff et al. 2006; Tsakiris et al. 2006; Keysers et al. 2010; Kurth et al. 2010; Limanowski et al. 2014). A tactile "what stream" for conscious somatosensory perception and object recognition has been proposed, flowing from the S1 via the S2 to the insula (Dijkerman and de Haan 2007; cf. Murray and Mishkin 1984; Romo and Salinas 2001). This idea is supported by empirical evidence for an involvement of the pIC in object recognition, haptic processing, and exploratory or goal-directed hand movements (Friedman et al. 1986; Qi et al. 2002; Horie et al. 2005; Ishida et al. 2013; Preusser et al. 2014; Juravle et al. 2016).

Our results advance on these findings by showing that the pIC is involved in differentially weighting externally caused (relative to self-, i.e., action-generated) somatosensory information and propagating it to high-level motor regions—likely as potentially action-relevant cues for object interaction—which may constitute a later or "higher" stage of somatosensory processing than gating effects implemented at lower levels of the hierarchy. Note that we observed the above activation and connectivity changes, despite the fact that—by design—the timing and onset of self-generated and FES-induced movements, as well as the time at which the touch was received during both movement types, was rendered equally predictable, i.e., participants could form the same expectations about these stimuli. This speaks to previous results, suggesting an influence of basic "motor predictions" that are exclusively generated by the motor system during action on the weighting of information or prediction error in the somatosensory cortex (Miall and Wolpert 1996; Adams et al. 2013; Brown et al. 2013; cf. Juravle et al. 2017). The importance of the SMA implied by our results further resonates with proposals that descending precision control originates from high-level premotor regions upstream of M1 (Cunnington et al. 2002; Haggard and Whitford 2004; Voss et al. 2006; Christensen et al. 2007; Grefkes et al. 2008; Parkinson et al. 2011; Nguyen et al. 2014).

It should be noted that in the present study the self-generated and FES-induced movements differed in terms of amplitude and duration. However, these differences were practically very small (particularly small in the flexion phase in which the tactile stimuli were delivered) and are unlikely to have caused the observed interaction effects. More importantly, within each condition there was no difference between movements with and without touch; therefore, the observed interaction effect cannot have been produced by differences in movement characteristics. Nevertheless, it may be useful to measure responses with EEG or MEG during a similar paradigm to examine the effects of potential timing differences between movement onset and touch application (that we could not address with our block design and the limited temporal resolution of fMRI). It should further be noted that our DCM analysis does not exclude a potential—not modeled—involvement of other regions such as, for example, the ventral premotor cortex in motor prediction or cued movement (cf. Romo and Schultz 1987; Cunnington et al. 2002; Christensen et al. 2007). Another point to be followed up by future work is the fact that the peak activation in the SMA was located in the right hemisphere (although the activation was bilateral at a more liberal threshold; Supplementary Fig. S3), which could be due to a less somatotopical, more complex organization of the SMA (cf. Nachev et al. 2008). Finally, given that predictive coding implies a tight link between action, somatosensory attenuation, and self-other distinction (cf. Adams et al. 2013; Brown et al. 2013), an interesting question for future work is how our findings may relate to the phenomenology of agency (cf. Haggard 2008; Synofzik et al. 2008; Christensen and Grünbaum 2018).

To conclude, we observed that during self-generated, but not FES-induced movements, touch to the moving finger increased activation in the contralateral pIC. This effect was likely mediated by an augmented feedforward communication of externally generated somatosensory information from the S2 via the pIC to the SMA during self-generated movements, despite a generally attenuated coupling during self-generated relative to FES-induced movements. These coupling changes could underlie the brain's capacity to relatively attenuate self (action) generated somatosensory reafference, yet simultaneously augment externally generated somatosensory information received at the moving limb, which is needed for somatosensory discrimination during active touch and haptic exploration.

Supplementary Material

Supplementary material is available at *Cerebral Cortex* online.

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Notes

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Author Contributions

J.L., P.L., and F.B. designed the study; J.L., J.K., and P.L. acquired the data; J.K. analyzed the behavioral data; J.L. analyzed the fMRI data; J.L. wrote the manuscript; P.L., J.K., P.B., K.F., and F.B. commented on the manuscript.

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