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ORIGINAL ARTICLE

Voluntary inhibition of pain avoidance behavior: an fMRI study

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Abstract Behavioral inhibition has classically been considered to rely upon a neural network centered at the right inferior frontal cortex [rIFC; Aron et al. (8:170–177, 2004; 18:177–185, 2014)]. However, the vast majority of inhibition studies have entailed exogenous stop signals instructing participants to withhold responding. More recent work has begun to examine the neural underpinnings of endogenous inhibition, revealing a distinct cortical basis in the dorsal fronto-median cortex [dFMC; Brass and Haggard (27:9141–9145, 2007); Kühn et al. (30:2834–3843, 2009)]. Yet, contrary to everyday experiences of voluntary behavioral suppression, the paradigms employed to investigate action inhibition have thus far been somewhat artificial, and involve little persuasive motivation to act. Accordingly, the present fMRI study seeks to compare and contrast intentional with instructed inhibition in a novel pain paradigm that recruits 'hot' incentive response systems. Participants received increasing thermal stimulation to their inner wrists, and were required to occasionally withhold their natural impulse to withdraw from the compelling pain sensation at peak temperature, in both instructed and free-choice conditions. Consistent with previous research, we observed inhibition-related activity in the dFMC and the rIFC. However, these regions displayed equivalent activation levels for both inhibition types. These data extend previous research by demonstrating that under ecologically valid conditions with a strong motivation to act, both stopping networks operate in concert to enable suppression of unwanted behavior.

Keywords Behavioral inhibition · Volition · Effort · Self-control · Pain

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Introduction

Self-control permits individuals to fulfill their goals, keep their promises, and conform to societal norms (Baumeister et al. 2007). Successful self-regulation often depends on the ability to suppress the urge to act impulsively (Muraven and Baumeister 2000). This can be witnessed in everyday examples ranging from the relatively innocuous (e.g., abstaining from eating a second donut) to the potentially dire (e.g., refraining from striking another person in a fit of rage). While failure at the former example might prove disappointing for the individual, poor impulse control as displayed in behaviors stemming from violence, addiction, or unconstrained emotion can be particularly damaging on a broad social scale. The ability to successfully delay gratification and inhibit one's urges is predictive of long-term outcomes such as job success, health, self-esteem, and helping behavior/aggression (Mischel et al. 2011; Tangney et al. 2004). Crucially, this control must originate within the person for it to be effective repeatedly and over time; merely adhering to external rules and laws is insufficient when high levels of regulatory effort must be exerted.

At the neural level, behavioral inhibition has classically been considered to rely upon a network centered at the

right inferior frontal cortex (rIFC; see Aron et al. 2004, 2014 for reviews). In the vast majority of these studies, participants were instructed to withhold a response upon the appearance of an external stop signal (e.g., Aron and Poldrack 2006; Chikazoe et al. 2007, 2009; Garavan et al. 1999, 2002). Yet, in naturalistic settings, inhibition of unwanted behavior is typically based on internal decisions rather than on external instructions. For instance, a person who is trying to give up smoking will not rely on an external stop signal, but rather on their internal willpower in order to resist the temptation to light a cigarette (Muraven 2010). More recent studies have begun to address this issue by adding a choice condition in which participants freely choose between performing or withholding a response (see Filevich et al. 2012 for a review). These studies have revealed a distinct cortical basis for endogenous[1] inhibition in the dorsal fronto-median cortex (dFMC; Brass and Haggard 2007, Brass and Haggard 2008; Kühn et al. 2009). In their 'What-When-Whether' model of intentional action, Brass and Haggard (2008) proposed that the dFMC may constitute a 'veto area' serving a final decision as to whether or not to execute an already prepared action plan, making this brain region essential for the exertion of self-control. Converging evidence suggests that these "veto" signals might be implemented by the pre-SMA, which has been shown to be functionally connected with the dFMC during intentional inhibition (Kühn et al. 2009, 2014) and also plays a pivotal role in externally guided response inhibition, presumably via direct and indirect projections to the motor cortex (Cai et al. 2012; Nachev et al. 2008; Swann et al. 2012).

However, although these studies were able to extend the scope of prior studies involving purely externally guided response inhibition, the paradigms have thus far employed relatively artificial experimental settings, lending participants little prior motivation to act or inhibit. Decisions were thus based on rather arbitrary choices and arguably might not have required genuine self-control. It therefore remains an open question whether the distinction between externally triggered and intentional inhibition is also valid in situations where a very strong response tendency has to be inhibited. One can argue that in such situations strong intentional control is required regardless of whether one decides to inhibit or is externally cued. In the present study, we sought to address this question and examine the neural basis of intentional inhibition in a more ecologically valid setting that recruits 'hot' incentive response systems (Metcalfe and Mischel 1999). Pain was selected as the behaviorally relevant stimulus for our purposes, as the organism is strongly motivated to avoid the pain sensation (Campbell and Misanin 1969; Elliot 2006). Moreover, despite its strong prepotency, the pain avoidance response can at times be voluntarily suppressed when higher-order goals call for such behavior (cf. Morsella 2005). Accordingly, management of the pain avoidance response can be seen as a classical instance of self-control over one's basic drives. In the present study, participants received thermal stimulation to alternating inner wrists, and were required to occasionally withhold their natural impulse to withdraw from the compelling pain sensation at peak temperature, in both instructed and free-choice conditions. This allowed us to investigate the neural basis of endogenous and exogenous inhibition of behavior under the presence of a strong urge to act. Based on the aforementioned findings, we expected the dFMC to be involved in endogenous inhibition, and the rIFC in exogenous inhibition. In addition, we wanted to explore whether or not the previously reported independence of the neural networks involved in these two forms of inhibition still holds under motivationally salient conditions.

Materials and methods

Participants

Twenty-one native Dutch speakers (7 males) participated in the study (mean age = 22.2 years, SD = 3.6); each reported as healthy and had no history of neurological, pain, or circulatory disorders. The data from the second run of participant 6 were excluded prior to analysis due to excessive head movements (>5 mm). All participants gave written informed consent, and the study was approved by the Medical Ethical Review Board of the Ghent University hospital, in accordance with the declaration of Helsinki. Participants were right-handed, as assessed by the Edinburgh Inventory (Oldfield 1971), and were compensated thirty-five euros for their participation.

Experimental procedure

Pain tolerance threshold determination

Pain was induced via a thermode connected to a Medoc PATHWAY device (MEDOC, Haifa, Israel), an apparatus designed for the induction of thermal pain using cold or hot stimulation. The temperature at which participants felt a sufficient amount of pain was determined during a pre-test session taking place 1 week prior to scanning. Participants were exposed to 26 trials in which the thermal sensation gradually increased over 5 s from 32 °C to a randomized destination temperature between 45 and 50 °C (in

[1] We use the term 'endogenous' synonymously with 'voluntary' and 'intentional' to denote an internal locus of the decision to perform or withhold an action.

increments of .25 °), a slope comparable to the experimental trials. After each trial, the thermode returned instantly to baseline temperature, and participants were asked to rate their perceived pain on a scale from zero to eight, with zero being no pain and eight being the worst possible pain. The destination temperature employed in the main experiment was computed for each participant as the highest temperature at which they rated their pain as a six.[2] This method was revealed during piloting to yield more accurate tolerance threshold measurements than merely requiring participants to indicate the maximum heat they could withstand when exposed to a steadily increasing temperature. Importantly, participants were free to press a button at any point during the threshold determination in order to terminate the trial.

Task and stimuli

Participants received thermal pain stimulation during each trial, applied via a thermode to alternating inner wrists. The images of three geometric shapes (triangle, square, circle) were used as cues to indicate the trial type. Depending on the cue, participants were requested to select one of the following response options: press the button as quickly as possible in order to terminate the trial ('directed action', 25 % of trials), inhibit this response and endure the pain for an additional 2 s ('directed inhibition', 25 % of trials), or make a voluntary decision to either button press immediately or persist ('choice action' and 'choice inhibition', respectively, combined equaling 50 % of trials). In the latter case, participants were requested to choose both options approximately equally often over the course of the experiment, but not to use any particular strategies (e.g., simple response alternations), or to decide in advance of the presentation of the cue. Adherence to these instructions was subsequently assessed by calculating each participant's Random Number Generation 2 (RNG2; an index optimized for two-choice response sequences) score using the program RgCalc (Towse and Neil 1998). RNG2 scores range from 0 to 1, with 1 indicating complete sequence predictability. A pilot study had revealed that participants are typically around 200 ms slower to respond on choice action trials than on directed action trials, presumably reflecting the additional time needed for the decision process. Accordingly, to make stimulation as similar as possible across action conditions, 200 ms of thermal stimulation was added to directed action trials, following the button press.

Each trial began with the presentation of a fixation cross for 5 s, during which time the temperature of the thermode began to gradually increase from a baseline of 32 °C to the participant's individually determined tolerance threshold. Subsequently, one of the three task cues appeared in place of the fixation cross, and persisted for the remainder of the pain stimulation. The temperature remained at tolerance threshold for the next 2 s, or until the participant pressed the button to terminate both the pain stimulation and the trial. Participants responded with the index or middle finger of the arm not being stimulated (thereby providing a response time for action trials). This was followed by a 6-s rest period. Afterwards, prompts were presented for 2 s each, asking participants for verbal ratings (collected via a microphone inside the scanner bore) of their perceived pain and their subjective 'urge to terminate the trial by pressing the button' (both on a scale of 0–8). Participants were then cued to alternate the arm placed atop the thermode, and were given 10 s in which to accomplish this task with the assistance of an experimenter who stood near the scanner bore. The experimenter also placed a small sandbag over the to-be stimulated wrist in order to lend weight and prevent the participant from inadvertently withdrawing from the pain source rather than button pressing. Each trial ended with an additional 6-s rest period. A schematic overview of a possible trial in the choice condition is presented in Fig. 1. The assignment of geometric shapes to trial types was counterbalanced across subjects. Each participant had to perform 80 trials in total, being divided into two runs of 40 trials presented in randomized sequence. In each run, participants were given 20 trials in which they were cued to make a decision, 10 trials in which they were cued to push and 10 trials in which they were cued to inhibit their withdrawal response. Importantly, participants were free to press a button to immediately terminate the thermal sensation at any point during the experiment.

Behavioral data preparation

Errors in the form of responding on a directed inhibition trial led to the exclusion of 0.77 % of trials (13 out of 1,680 total trials; number of excluded trials per participant: $M = 0.62$, $SD = 0.92$) from both behavioral and fMRI analysis. No errors were committed via failing to press the response button on a directed press trial. Pain and urge ratings were analyzed using a repeated-measures ANOVA with INSTRUCTION (directed vs. choice) and RESPONSE (action vs. inhibition) as within-subjects factors. Reaction times on action trials were analyzed as a function of INSTRUCTION via two-tailed paired-samples *t* tests.

fMRI data acquisition and preprocessing

Data were acquired with a 3T Siemens Magnetom Trio MRI system (Siemens Medical Systems, Erlangen,

[2] This temperature is henceforth referred to as the individual participant's tolerance threshold.

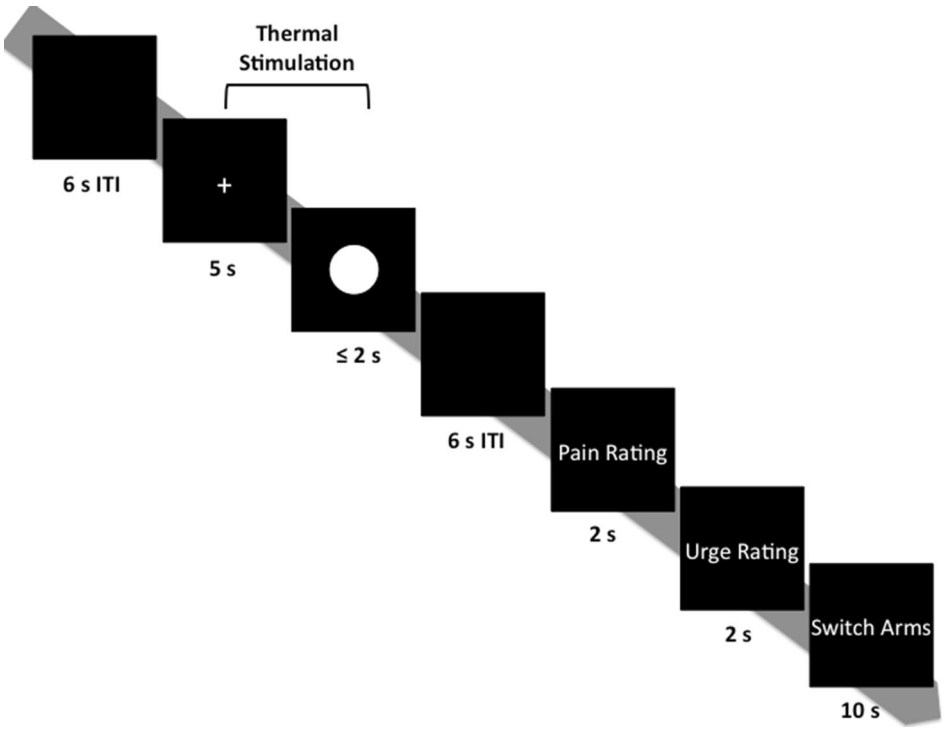

Fig. 1 Schematic of a sample trial in the choice condition

Germany) using a 32-channel radiofrequency head coil. Subjects were positioned headfirst and supine in the magnet bore. First, 176 high-resolution anatomical images were acquired using a T1-weighted 3D MPRAGE sequence (TR = 2,250 ms, TE = 4.18 ms, TI = 900 ms, image matrix = 256 × 256, FOV = 256 mm, flip angle = 9°, and voxel size = 1 × 1 × 1 mm). Whole-brain functional images were then collected using a T2-weighted echo-planar imaging (EPI) sequence, sensitive to blood oxygen level-dependent contrast (TR = 2,000 ms, TE = 35 ms, image matrix = 64 × 64, FOV = 224 mm, flip angle = 80°, slice thickness = 3.0 mm, distance factor = 17 %, voxel size 3.5 × 3.5 × 3.0 mm, and 30 axial slices). A varying number of images were acquired per run due to individual differences in choice behavior and reaction times.

All data were preprocessed and analyzed using Matlab and the SPM8 software (Wellcome Department of Cognitive Neurology, London, UK). To account for possible T1 relaxation effects, the first four scans of each EPI series were excluded from the analysis. First, a mean image for all scan volumes was created, to which individual volumes were spatially realigned using rigid body transformation. Thereafter, they were slice time corrected using the first slice as a reference. The structural image of each subject was coregistered with their mean functional image after which all functional images were normalized to the Montreal Neurological Institute (Montreal, Quebec, Canada) T1 template. The images were resampled into 3.5 × 3.5 × 3.5 mm voxels and spatially smoothed with a Gaussian kernel of 8 mm (full width at half maximum). A high-pass filter of 128 Hz was applied during fMRI data analysis.

Statistical analyses

The first-level statistical analyses were performed using a general linear model (GLM, Friston et al. 1995). Of primary interest were the brain regions involved in the implementation of intentional inhibition, or the decision to intentionally inhibit. We therefore used the onset of the task cue as the main event of interest in the GLM. It is important to note that all trials were identical in terms of stimulation up to and including cue onset, and for an average of 750 ms afterwards (i.e., average time it took to respond in action trials). Based on the factorial design, four regressors were defined reflecting the experimental conditions ('directed action', 'directed inhibition', 'choice action', and 'choice inhibition'). Temporal derivatives of these regressors were added to the model, and six additional regressors defining head movements were also included to account for any residual movement-related effects. All regressors were convolved with a canonical hemodynamic response function (HRF). Contrast images were computed separately for each participant to compare parameter estimates of the relevant conditions.

These contrast images were advanced to the second level, using a random-effects within-subject flexible-

factorial design as implemented in SPM8 with factors INSTRUCTION (directed vs. choice) and RESPONSE (action vs. inhibition). First, we examined the main effects to reveal brain areas that are (1) more active on inhibition trials than on action trials, and (2) more active on choice trials than on directed trials. In a second step, we directly contrasted intentional inhibition with externally guided inhibition to reveal the brain areas that are specifically engaged in the internal decision to inhibit the pain avoidance response. To control for false-positive rates, combined voxel activation intensity and cluster extent thresholds corrected for multiple comparisons were determined using 3dClustSim (http://afni.nimh.nih.gov/pub/dist/doc/program_help/3dClustSim.html). This widely used correction method is applied to statistical contrast images at the group level and estimates the probability of observing false-positive (random fields of noise) clusters of a given size, as a function of a given voxelwise p value. The 3dClustSim program considers the size of the image (number of voxels), the voxelwise statistical values, and the spatial correlations over voxels (spatial smoothness) and runs a user-specified number of Monte Carlo simulations to generate an appropriate null-distribution. Here, 10,000 Monte Carlo simulations were run, taking into account the whole-brain search volume and the estimated smoothness of each axis (x, y, and z) of the respective group SPMs. Probability estimates of a random field of noise were generated, producing a cluster of voxels of a given extent for a set of voxels passing a voxelwise p value threshold of 0.001. Given this voxelwise threshold, the simulations determined that cluster sizes of 20.0–23.5 voxels, depending on the specific contrast analysis, corresponded to a combined threshold of $p < .05$ (corrected). Whole-brain analyses were supplemented with region-of-interest (ROI) analyses. ROIs were generated using MARSBAR toolbox for use with SPM 8 (Brett et al. 2002).

Results

Behavioral results

Proportion of choices

For choice trials, participants were able to follow the instruction to choose both options equally often, and inhibited their response on average in 49.9 % of the trials (range = 37.5–65 %; SD = 7.3 %).

Randomness of choice response sequences

Participants displayed a mean RNG2 index of 0.724 (SD = .008). Individual scores were compared to 21 randomly generated sets of two-choice response sequences (RNG2 $M = 0.723$, SD = .007) in an independent samples t test. Participants' choice trial responses did not differ significantly from the randomly generated samples [$t(40) = .376$, $p = .709$], suggesting that they did not use simple alternation strategies as a means of conforming to the experimental instructions.

Reaction times

As expected, response times were significantly slower on choice trials than on directed trials, $t(20) = 6.68$, $p < .001$ (directed = 597 ms, choice = 903 ms), suggesting that participants did not make their decisions in advance of the cue. The 306 ms difference in RTs between choice and directed trials thus slightly exceeded the 200 ms adjustment of stimulation length for directed trials, which was baBehavioral resultssed on the results of behavioral pilot studies.

Subjective pain ratings

The analysis of pain ratings revealed main effects of INSTRUCTION [$F(1,20) = 7.205$, $p = .014$, $\eta p = .265$] and RESPONSE [$F(1,20) = 43.479$, $p < .001$, $\eta p = .685$] as well as a significant interaction [$F(1,20) = 5.591$, $p = .028$, $\eta p = .218$]. Participants rated inhibit trials as more painful than action trials (presumably due to the greater stimulation duration), with directed inhibit trials receiving the highest pain ratings (directed action: $M = 4.24$, SE = 0.25; choice action: $M = 4.28$, SE = 0.25; directed inhibition: $M = 5.50$, SE = 0.21; choice inhibition: $M = 5.03$, SE = 0.24). A post hoc t test revealed that pain ratings did not differ between directed action and choice action trials, $t(20) = .217$, $p = .831$. The latter finding suggests that, in spite of the slight mismatch between RT and stimulation length in directed trials (i.e., the fact that thermal stimulation persisted for an additional 200 ms after a response was given; see "Materials and methods" section for rationale), subjective pain perception was equivalent for choice and directed trials.

Subjective urge ratings

The analysis of urge ratings revealed a significant interaction of INSTRUCTION and RESPONSE [$F(1,20) = 7.194$, $p = .014$, $\eta p = .265$], driven by the choice condition and reflecting that participants experienced similar urges on directed trials, but when given a choice, their urges were concordant with their decisions (i.e., a higher urge to press on action trials). No main effects were significant (directed action: $M = 4.00$, SE = 0.34; choice action: $M = 4.23$, SE = 0.34; directed inhibition: $M = 3.78$, SE = 0.33; choice inhibition: $M = 3.24$, SE = 0.24).

Objective thermal stimulation

Due to the constraints of the Medoc software, some slight variation in thermode temperature is inherent throughout the course of the experiment (see Fig. 2), yet participants did not appear to use either temperature at cue onset or peak temperature (typically occurring 100 ms after cue onset) as factors in their decision to press or inhibit. Mean thermode temperatures were computed per participant at both cue onset and thermal peak for each of the choice conditions. Two-tailed paired-samples t tests revealed that mean temperature at onset and peak did not differ significantly between choice inhibit and press trials, $t(20) = .037$, $p = .971$ and $t(20) = .142$, $p = .889$, respectively. Grand mean onset temperature was 49.23 °C (SD = 0.45), while grand mean peak temperature was 50.00 °C (SD = 0.47). Participants' tolerance thresholds did not correlate with reaction times, mean reported pain, or proportion of inhibition on choice trials (all ps > .169).

fMRI results

Whole-brain analyses

We first analyzed the main effect of RESPONSE to reveal the brain areas that exhibit stronger activation on inhibition trials than on action trials (see Fig. 3). As expected, activity was found within the right inferior frontal gyrus (rIFG) extending into the adjacent insular cortex. The location was similar to that observed in previous studies investigating externally guided inhibition (e.g., Aron and Poldrack 2006; MNI $x, y, z = 44\ 12\ 8$). Another cluster was located in the anterior medial PFC (amPFC), encompassing the dFMC coordinates reported in previous studies on intentional inhibition (Brass and Haggard 2007; Kühn et al. 2009). Two additional clusters were located in the ventral part of the anterior supplementary motor area (pre-SMA) and the right inferior parietal lobule (IPL), both areas that have previously been implicated in intentional and externally guided action inhibition (e.g., Filevich et al. 2012; Kühn et al. 2009). Secondly, we analyzed the main effect of INSTRUCTION in order to identify brain regions that show increased activity on choice trials compared with directed trials (Fig. 3). Activity was found in the medial frontal wall, extending from the pre-SMA and with the majority of activation located within the rostral cingulate zone (RCZ), bilaterally in the dorsolateral prefrontal cortex (dlPFC), and in the right IPL. This is in accordance with previous descriptions of a frontoparietal 'choice network' engaged in internal action decisions (e.g., Haggard 2008; Mueller et al. 2007). Finally, we contrasted 'choice inhibition' trials with 'directed inhibition' trials to examine which brain areas are specifically involved in intentional (vs. externally guided) inhibition. This analysis revealed a single cluster of activity in the right dorsal pre-SMA. The reverse contrast (directed versus choice inhibition) yielded no significant activity. For a complete overview of significant activations, see Table 1.

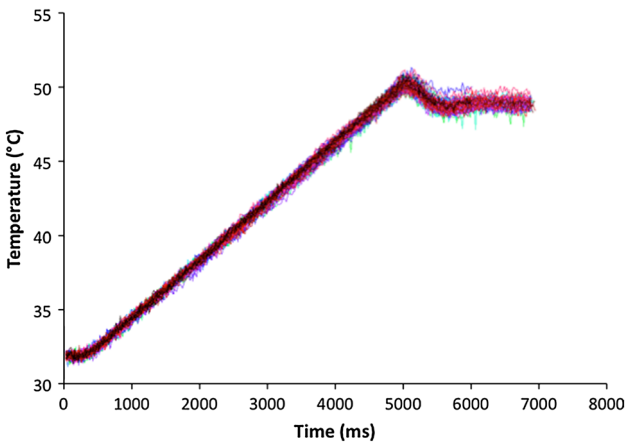

Fig. 2 Composite of all 80 trials for an exemplar participant, representing actual stimulation temperatures. Note each trial is displayed in a distinct color and the overlap of the slope indicates equivalent stimulation across experimental trials

Region-of-interest (ROI) analyses

Based on the results of the whole-brain analysis, we conducted an additional series of ROI analyses. In the first set, we were interested in further examining the role of the dFMC. Given the absence of a difference in dFMC activity between the two inhibition conditions in the whole-brain analysis, we sought to test whether there was a sub-threshold difference between inhibition conditions that could not be detected in the whole-brain contrast. To this end, we generated a spherical ROI (radius = 10 mm, MNI peak −7 42 21) centered on the peak dFMC coordinate reported by Kühn et al. (2009) in order to provide an independent non-circular analysis (see Kriegeskorte et al. 2009). This analysis yielded a significant main effect of INSTRUCTION, $F(1,20) = 9.663$, $p = .006$, reflecting increased activity on choice trials compared with directed trials. The effect of RESPONSE was significant as well, $F(1,20) = 4.604$, $p = .044$, indicating greater activation on inhibition trials than on action trials.[3] Moreover, there was a significant interaction between the factors, $F(1,20) = 4.554$, $p = .045$ (see Fig. 4). Post hoc comparisons revealed, however, that the interaction was driven by

[3] A similar pattern of results was observed with a spherical ROI centered on the peak amPFC coordinate derived from the present study. However, these results are not displayed here due to the non-independence of ROI selection and analysis.

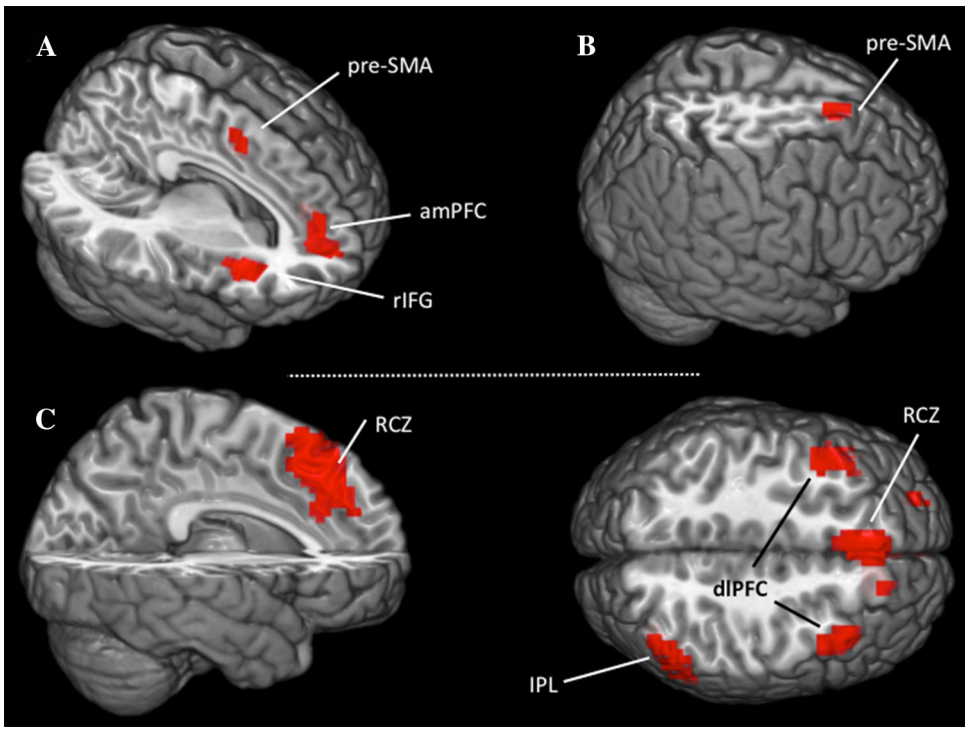

Fig. 3 Activation maps of the whole-brain contrasts, comparing **a** inhibition versus action; **b** choice inhibition versus instructed inhibition; and **c** choice versus instructed trials. Note activation maps were thresholded at $p < .001$ (uncorrected), with a minimum cluster size of 22 contiguous voxels (see "Materials and methods section for details)

increased activity on choice action trials compared with directed action trials, $t(20) = 3.689$, $p = .001$, whereas activity did not differ between the two inhibition conditions, $t(20) = 1.000$, $p = .329$. Altogether, the above ROI analysis confirms that in the context of pain avoidance behavior, the dFMC showed reliable activation related to behavioral inhibition, but did not furthermore depend upon the level of instruction.

The second set of ROI analyses elaborated on activity in the right insula, an area that has been implicated in pain processing (e.g., Ingvar 1999). In particular, we sought to examine to what extent inhibition-related activity in this region was in fact driven by the demand to inhibit a response rather than merely a consequence of the lengthier thermal stimulation on these trials, compared with press trials. With this in mind, we performed two analyses. In a first step, we defined an ROI corresponding to the right insula based on anatomical criteria drawn from the Anatomy toolbox for SPM (Eickhoff et al. 2005). Thereafter, we computed each participant's mean pain ratings separately for each experimental condition and correlated these ratings with the respective percent signal change within the ROI. Correlations were Bonferroni-corrected for multiple comparisons. If activity in the insula was driven by differences in the amount of pain, then it should co-vary with the subjective ratings regardless of the experimental condition. Yet no such correlations were found between mean pain ratings and percent signal change within any of the four conditions, ps $> .240$, suggesting that activity in the insula was driven by the demand to inhibit a pain avoidance response and not by mere differences in pain levels.

To further elaborate on this conclusion, we performed an additional whole-brain analysis contrasting high-pain trials with low-pain trials across all experimental conditions, based on a median split of the individual pain ratings. This analysis should reveal brain areas that are generally sensitive to the level of subjective pain, irrespective of the experimental condition. Indeed, the anterior cingulate cortex (ACC, MNI peak at −1 10 41) and precentral gyrus (MNI peak at −60 −4 10) were the only regions to exhibit stronger activity on high- versus low-pain trials; the ACC has frequently been implicated in processing of pain (Rainville et al. 1997; Wager et al. 2004). In contrast, no difference was observed in the right insula, confirming our conclusion that activity of this region was driven by the demand to withhold a response and not by different levels of pain (see Fig. 5).

We conducted a third set of ROI analyses to address the post hoc question of how inhibition in our paradigm should be characterized; does inhibition target the response finger that can terminate the thermal stimulation via button press or instead the stimulated hand (thereby maintaining the posture of the stimulated wrist and avoiding withdrawal)? To answer this question, we first defined bilateral ROIs of the motor hand area based on the main effect of action reported in Table 1. Spherical ROIs with a radius of 10 mm were defined over the peak left and right motor cortex coordinates (left: −46 −21 62; right: 48 −21 62).

Table 1 Overview of activation clusters revealed by the whole-brain analyses. Montreal Neurological Institute (MNI) coordinates reflect the peak voxel of a given cluster

Region	Voxels	MNI coordinates			*Tmax*
		x	*y*	*z*	
Main effect inhibition: inhibit > press					
Right inferior frontal gyrus	127	41	24	6	5.26
Anterior insula		38	10	10	4.33
Anterior median prefrontal cortex	77	10	46	10	4.50
Inferior parietal lobule	26	52	−32	30	4.08
Pre-supplementary motor area	28	10	4	48	4.00
Main effect choice: choice > directed					
Pre-supplementary motor area	500	16	18	66	5.82
Rostral cingulate zone		−4	38	34	5.10
Rostral cingulate zone		6	32	30	5.09
Left dlPFC	77	−43	10	48	5.53
Left inferior frontal gyrus	67	−50	24	−1	4.69
Superior frontal gyrus	23	−22	60	24	3.69
Right dlPFC	57	44	21	48	5.05
Inferior parietal lobule	122	55	−56	38	4.94
Choice inhibit > directed inhibit					
Pre-supplementary motor area	31	16	18	66	4.66
Effect of pain level, median split: high pain > low pain					
Anterior cingulate cortex	41	−1	10	41	3.85
Precentral gyrus	28	−60	−4	10	4.54
Main effect action: press > inhibit					
Right motor cortex	352	48	−21	62	11.22
Left motor cortex	302	−46	−21	62	7.55

Beta values were collapsed across hemispheres (i.e., the right hand response was coded as the stimulated hand and the left hand response as the effector hand in the right hemisphere, while the left hand response was coded as the stimulated hand and the right hand response as the effector hand in the left hemisphere) and subjected to a repeated-measures ANOVA with factors RESPONSE (action vs. inhibition) and HAND (effector vs. stimulated). This analysis revealed a significant main effect of RESPONSE, $F(1, 20) = 107.987$, $p < .001$, reflecting greater activity on action trials, a non-significant main effect of HAND, $F(1, 20) = .335$, $p = .569$, and a significant interaction, $F(1, 20) = 131.724$, $p < .001$ (see Fig. 6). We conducted post hoc *t* tests between the effector hand and the stimulated hand on both trial types to specify the interaction. As expected, on action trials activity was greater in the effector hand than in the stimulated hand, $t(20) = 8.071$, $p < .001$. Importantly, however, on inhibition trials activity in the effector hand was reduced when compared with the stimulated hand, $t(20) = 5.718$, $p < .001$. Overall, activity did not differ between action trials and inhibition trials in the stimulated hand, $t(20) = .219$, $p = .829$. These results suggest that inhibition in our paradigm was directed only towards the instrumental response that could terminate the pain indirectly via a button press, rather than towards the "hard-wired" withdrawal response of the stimulated hand. It should be further noted that the weight of the sandbag placed over the stimulated wrist would make the latter response option quite difficult.

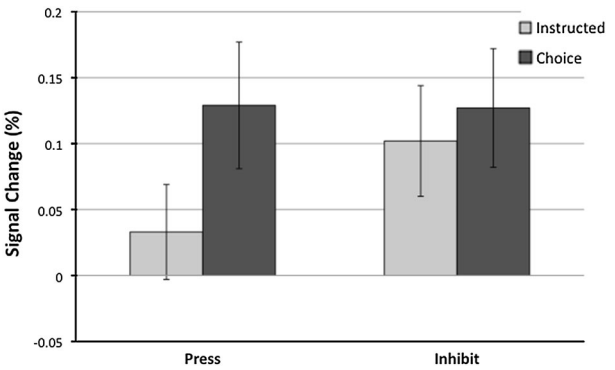

Fig. 4 Results of the fronto-median ROI analysis. A spherical ROI (radius = 10 mm) was centered at the peak dFMC coordinate (−7 42 21) derived from the study of Kühn et al. (2009). Values represent the mean percent signal change (beta values) and standard errors

Discussion

The present study sought to investigate the neural basis of intentional inhibition in the context of pain avoidance

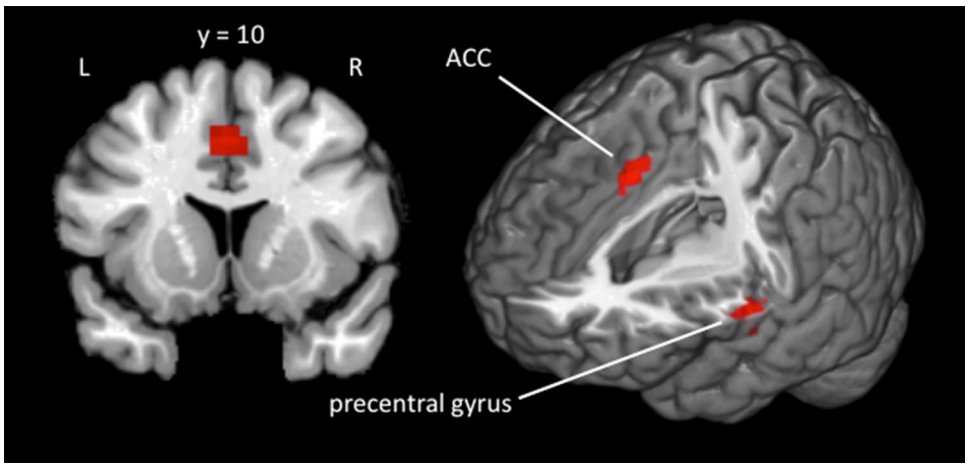

Fig. 5 Main effect of high versus low pain, across conditions. Note activation maps were thresholded at $p < .001$ (uncorrected), with a minimum cluster size of 22 contiguous voxels (see "Materials and methods section for details)

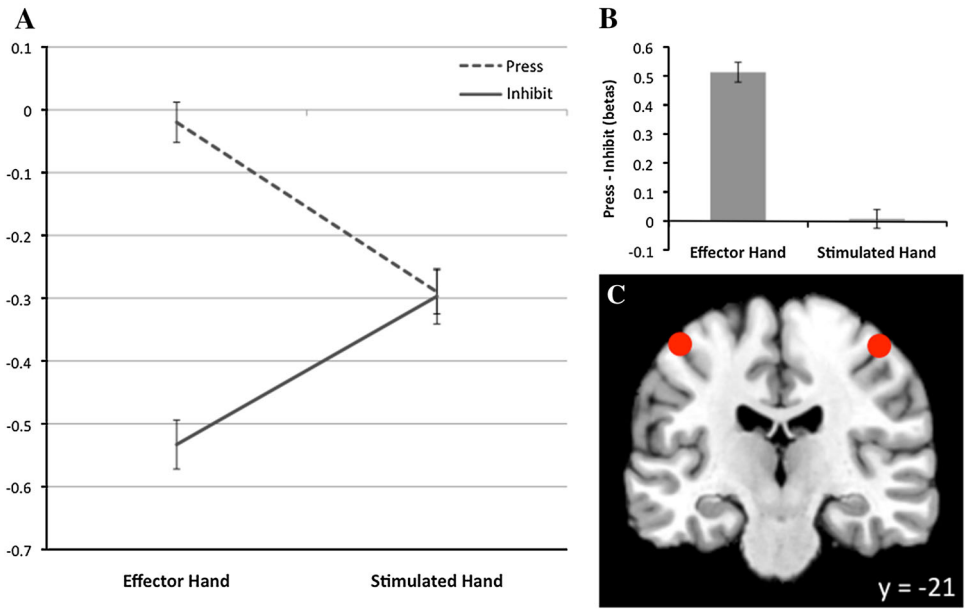

Fig. 6 **a** Motor cortex activation pattern for effector and stimulated hands. Values represent the mean percent signal change (beta values) and standard errors. **b** Activation difference scores (press–inhibit) for each hand. **c** Locations of the peak coordinates used to draw motor cortex ROIs

behavior. Using thermal stimulation permitted us to create an experimental setting that requires genuine self-control in order to withhold responding, representing a major step towards a more ecologically valid investigation of the intentional inhibition of action. In this context, we observed brain activity mirroring previous findings concerning both intentional and externally guided inhibition. There was little overt difference between inhibition types, indicating that the two forms of inhibition are more strongly linked under motivationally salient conditions. Furthermore, inhibition seemed to be specifically directed towards the effector implementing the instrumental response. Below we discuss the implications of our findings for theories on the neural basis of action inhibition and self-control.

The role of the dFMC in self-control

Our finding that the dFMC was activated more strongly for response omissions than for response executions replicates a growing body of research that has indicated the prominent role of this area in the withholding of actions (Filevich et al. 2012). As our paradigm employed quite a different procedure than previous intentional inhibition studies,[4] this finding strengthens the conclusion that the dFMC is in fact critical for the voluntary cancellation of an action,

[4] Previous studies employed either a modified version of the 'Libet task' (Brass and Haggard 2007) in which self-paced button presses are occasionally omitted, or a 'ramp task' (Kühn et al 2009), also requiring participants to occasionally withhold from responding.

independent of a particular experimental context. Yet in contrast with previous studies, we found that the dFMC showed equivalent activity for both intentional and externally guided inhibition. Given that the urge to withdraw from a pain source is intrinsically very high, it seems plausible that the level of instruction had a reduced impact upon the recruitment of self-regulatory processes in our paradigm. Rather, suppression of the pain avoidance urge might generally require a high degree of self-control, necessitating strong intentional engagement even under externally guided instruction.

Interestingly, the dFMC activation in our study was located slightly more rostrally than in previous inhibition studies, and was encompassed by parts of the anterior medial PFC that have been implicated in self-referential thought processes (e.g., Johnson et al. 2006; Mitchell et al. 2005). This could imply that the role of the dFMC in intentional inhibition is more general than previously assumed. We have recently proposed that its contribution should be characterized as general disengagement from otherwise prepotent intentions, plans, and urges (Lynn et al. 2014) rather than as pure motor suppression. Cancelling an action that has already been prepared is one such instance, requiring disengagement from the motor intention (e.g., Brass and Haggard 2007; Kühn et al. 2009). However, similar activity has also been found when participants need to distance themselves from negative emotions (Kühn et al. 2011) or cigarette cravings (Brody et al. 2007), and to quit loss-chasing (Campbell-Meiklejohn et al. 2008). In addition, the dFMC has also been implicated in mentalizing, which is assumed to rely upon disengagement from the otherwise dominant self-perspective (e.g., Brass et al. 2005; Brass et al. 2009). We therefore believe that disengagement provides a useful integrative concept for explaining the dFMC's involvement in these diverse functions. However, as this view is thus far based primarily on reverse inference, further research will be necessary to test this idea and to reveal the precise contribution of the dFMC to self-control.

Pre-SMA

The only region that exhibited stronger activity for intentional inhibition than for externally guided inhibition was the pre-SMA. This region has been shown to be connected with the dFMC anatomically (Johansen-Berg et al. 2004) and functionally (Kühn et al. 2009), typically with the assumption that the dFMC feeds top-down stopping signals to the pre-SMA, which in turn implements inhibition via connections with motor areas (Cai et al. 2012; Kühn et al. 2009). The differential activation levels in the pre-SMA for the two inhibition types are therefore likely related to differences in the way that suppression of the pain avoidance response is implemented in the respective trials. The immediacy of action decisions could be of particular importance in this respect. In externally guided trials, the cue directly informs participants about the outcome, thereby triggering an instantaneous cancellation of the response (Verbruggen and Logan 2008). In choice trials, on the other hand, participants may implement a continual delay of the response rather than a singular decision not to act, as the veto can theoretically be implemented at any time throughout the trial. Accordingly, increased activation of the pre-SMA with intentional inhibition could be related to decision uncertainty on choice trials, and the continuous rather than instantaneous suppression of the pain avoidance response. Examining the pre-SMA's connectivity with other regions implicated in inhibition may help to clarify its contributions to different types of behavioral inhibition (similar to Herz et al. 2014).

Insular cortex

An interesting aspect of our results involves the activation of the right anterior insula, which we found in conjunction with the rIFG related to both types of behavioral inhibition. Given the numerous processes to which this region has been linked, a conclusive interpretation of its role in our paradigm seems difficult to obtain. Previous studies have shown that the insula might be involved in inhibitory control (e.g., Forstmann et al. 2008; Hodgson et al. 2007), yet is also a well-known component of the pain matrix (Garcia-Larrea and Peyron 2013; Ingvar 1999; Peyron et al. 2000), and as such, activation of this region might be considered a mere consequence of the longer stimulation duration in inhibition trials compared with press trials. However, several points related to the design and analysis of our study suggest that this is not entirely the case. First, our model was based on brain activity time-locked to the instructional cue, thus a time point at which all conditions were equivalent in terms of pain stimulation, and remained so for an additional 750 ms, on average. Second, contrasting trials with high vs. low levels of subjective pain yielded only activity within the ACC, another well-established component of the pain matrix (e.g., Garcia-Larrea and Peyron 2013), but no differential activity in the insula. Third, the ROI analysis of the right insula (applying a median split based on the subjective pain ratings) revealed no significant correlations between mean pain ratings per condition and percent signal change within each region of the insula. Accordingly, we are confident that the inhibition-related activation of the insula in our study is not exclusively related to the differential levels of pain that accompanied those trials. Importantly, previous intentional inhibition studies that did not involve somatic stimulation have also reported activity in the insula (Brass and

Haggard, 2007; Campbell-Meiklejohn et al. 2008; Kühn et al. 2009). Although only speculative at this point, this could imply that the role of the insula in the context of self-control reflects affective evaluation of the behavioral outcome (see Brass and Haggard 2010).

A hierarchical model of motivated self-control

On a larger scale, the findings of the present study indicate that previous views on the structure of behavioral inhibition must be reconsidered in light of motivational factors. In particular, the co-activation of both previously described inhibition networks could imply that self-control involves two stopping systems that rely on external components and internal components, respectively, and that the degree of their interplay depends on the individual's motivational state. In 'cold' or urge-free situations, the two systems operate in isolation and are largely distinguishable. In this context, intentional inhibition reflects primarily the endogenous decision to cancel an ongoing behavior, and it is less clear to what extent such inhibition reflects genuine motor suppression or rather higher-order disengagement (see Lynn et al. 2014, for a theoretical account of the latter view). Externally guided inhibition, on the other hand, assesses the rapid implementation of behavioral suppression, absent decisional aspects, as the response outcome is fully determined by the environment. However, given the presence of a strong behavioral urge, such as the desire to avoid physical pain, the two systems must necessarily interact to enable successful suppression of the urge, regardless of the level of instruction. In this context, both the decisional and the implementation aspects of behavioral inhibition must continuously be reinforced in order to adhere to the circumstantial demands. Future research will be necessary to test this idea more directly. For instance, comparing intentional and externally guided inhibition in both 'hot' and 'cold' response systems within the same subjects could provide direct evidence for the aforementioned view.

Conclusion

The present study investigated the neural basis of the intentional inhibition of pain avoidance behavior. Replicating previous work, we found the dFMC, rIFG extending into the insula, and pre-SMA to exhibit activity related to suppression of the pain withdrawal urge, when compared with executing an abating response. However, this pattern was observed regardless of the locus of the inhibit decision, suggesting that the degree of intentional engagement depends on one's motivational state. Our paradigm therefore provides a novel and ecologically valid context for the investigation of intentional inhibition, but future studies will be needed to determine whether everyday instances of exogenous and endogenous inhibition are dissociable.

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References

Aron AR, Poldrack RA (2006) Cortical and subcortical contributions to Stop signal response inhibition: role of the subthalamic nucleus. J Neurosci Off J Soc Neurosci 26:2424–2433

Aron AR, Robbins TW, Poldrack RA (2004) Inhibition and the right inferior frontal cortex. Trends Cogn Sci 8(4):170–177

Aron AR, Robbins TW, Poldrack RA (2014) Inhibition and the right inferior frontal cortex: one decade on. Trends Cogn Sci 18(4): 177–185

Baumeister RF, Vohs KD, Tice DM (2007) The strength model of self-control. Curr Dir Psychol Sci 16(6):351–355

Brass M, Haggard P (2007) To do or not to do: the neural signature of self-control. J Neurosci Off J Soc Neurosci 27(34):9141–9145

Brass M, Haggard P (2008) The what, when, whether model of intentional action. Neurosci Rev J Bringing Neurobiol Neurol Psychiatry 14:319–325

Brass M, Haggard P (2010) The hidden side of intentional action: the role of the anterior insular cortex. Brain Struct Funct 214:603–610

Brass M, Derrfuss J, von Cramon DY (2005) The inhibition of imitative and overlearned repsonses: a functional double dissociation. Neuropsychologia 43:89–98

Brass M, Ruby P, Spengler S (2009) Inhibition of imitative behavior and social cognition. Philos Trans R Soc Biol Sci 364:2359–2367

Brett M, Anton JLL, Valabregue R, Poline JBB (2002). Region of interest analysis using an SPM toolbox. Abstract presented at the 8th International Conference on Functional Mapping of the Human Brain, Sendai, Japan, June 2–6, 2002. In: NeuroImage (Vol. 16, p. abstract 497)

Brody AL, Mandelkern MA, Olmstead RE, Jou J, Tiongson E, Allen V, Cohen MS (2007) Neural substrates of resisting craving during cigarette cue exposure. Biol Psychiatry 62:642–651

Cai W, George JS, Verbruggen F, Chambers CD, Aron AR (2012) The role of the right presupplementary motor area in stopping action: two studies with event-related transcranial magnetic stimulation. J Neurophysiol 108(2):380–389

Campbell BA, Misanin JR (1969) Basic drives. Annu Rev Psychol 20:57–84

Campbell-Meiklejohn DK, Woolrich MW, Passingham RE, Rogers RD (2008) Knowing when to stop: the brain mechanisms of chasing losses. Biol Psychiatry 63:293–300

Chikazoe J, Konishi S, Asari T, Jimura K, Miyashita Y (2007) Activation of right inferior frontal gyrus during response inhibition across response modalities. J Cogn Neurosci 19:69–80

Chikazoe J, Jimura K, Hirose S, Yamashita K, Miyashita Y, Konishi S (2009) Preparation to inhibit a response complements response inhibition during performance of a stop-signal task. J Neurosci Off J Soc Neurosci 29:15870–15877

Eickhoff SB, Stephan KE, Mohlberg H, Grefkes C, Fink GR, Amunts K, Zilles K (2005) A new SPM toolbox for combining probabilistic cytoarchitectonic maps and functional imaging data. NeuroImage 25:1325–1335

Elliot AJ (2006) The hierarchical model of approach-avoidance motivation. Motiv Emot 30(2):111–116
Filevich E, Kühn S, Haggard P (2012) Intentional inhibition in human action: the power of "no". Neurosci Biobehav Rev 36(4):1107–1118
Forstmann BU, Jahfari S, Scholte HS, Wolfensteller U, van den Wildenberg WPM, Ridderinkhof KR (2008) Function and structure of the right inferior frontal cortex predict individual differences in response inhibition: a model-based approach. J Neurosci Off J Soc Neurosci 28:9790–9796
Friston KJ, Frith CD, Frackowiak RS, Turner R (1995) Characterizing dynamic brain responses with fMRI: a multivariate approach. Neuroimage 2(2):166–172
Garavan H, Ross TJ, Stein EA (1999) Right hemispheric dominance of inhibitory control: an event-related functional MRI study. Proc Natl Acad Sci USA 96:8301–8306
Garavan H, Ross TJ, Murphy K, Roche AP, Stein EA (2002) Dissociable executive functions in the dynamic control of behavior: inhibition, error detection and correction. NeuroImage 17:1820–1829
Garcia-Larrea L, Peyron R (2013) Pain matrices and neuropathic pain matrices: a review. Pain 154(Suppl 1):S29–S43 (Melzack 1990)
Haggard P (2008) Human volition: towards a neuroscience of will. Nat Rev Neurosci 9(12):934–946
Herz DM, Christensen MS, Bruggemann N, Hulme OJ, Ridderinkhof KR, Madsen KH, Siebner HR (2014) Motivational tuning of fronto-subthalamic connectivity facilitates control of action impulses. J Neurosci 34(9):3210–3217
Hodgson T, Chamberlain M, Parris B, James M, Gutowski N, Husain M, Kennard C (2007) The role of the ventrolateral frontal cortex in inhibitory oculomotor control. Brain J Neurol 130:1525–1537
Ingvar M (1999) Pain and functional imaging. Philos Trans R Soc Lond 354(1387):1347–1358
Johansen-Berg H, Behrens TEJ, Robson MD, Drobnjak I, Rushworth MFS, Brady JM, Matthews PM (2004) Changes in connectivity profiles define functionally distinct regions in human medial frontal cortex. Proc Natl Acad Sci USA 101(36):13335–13340
Johnson MK, Raye CL, Mitchell KJ, Touryan SR, Greene EJ, Nolen-Hoeksema S (2006) Dissociating medial frontal and posterior cingulate activity during self-reflection. Soc Cogn Affect Neurosci 1:56–64
Kriegeskorte N, Simmons WK, Bellgowan PSF, Baker CI (2009) Circular analysis in systems neuroscience: the dangers of double dipping. Nat Neurosci 12(5):535–540
Kühn S, Haggard P, Brass M (2009) Intentional inhibition: how the "veto-area" exerts control. Hum Brain Mapp 30(9):2834–2843
Kühn S, Gallinat J, Brass M (2011) "Keep calm and carry on": structural correlates of expressive suppression of emotions. PLoS One 6:e16569
Kühn S, Haggard P, Brass M (2014) Differences between endogenous and exogenous emotion inhibition in the human brain. Brain Struct Funct 219(3):1129–1138
Lynn MT, Muhle-Karbe PS, Brass M (2014) Controlling the self: the role of the dorsal frontomedian cortex in intentional inhibition. Neuropsychologia 65:247–254
Metcalfe J, Mischel W (1999) A hot/cool-system analysis of delay of gratification: dynamics of willpower. Psychol Rev 106(1):3–19
Mischel W, Ayduk O, Berman MG, Casey BJ, Gotlib IH, Jonides J, Shoda Y (2011) "Willpower" over the life span: decomposing self-regulation. Soc Cogn Affect Neurosci 6(2):252–256
Mitchell JP, Banaji MR, Macrae CN (2005) The link between social cognition and self-referential thought in the medial prefrontal cortex. J Cogn Neurosci 17:1306–1315
Morsella E (2005) The function of phenomenal states: supramodular interaction theory. Psychological Review 112(4):1000–1021
Mueller V, Brass M, Waszak F, Prinz W (2007) The role of the preSMA and the rostral cingulate zone in internally selected actions. NeuroImage 37(4):1354–1361
Muraven M (2010) Practicing self-control lowers the risk of smoking lapse. Psychol Addict Behav 24(3):446–452
Muraven M, Baumeister RF (2000) Self-regulation and depletion of limited resources: does self-control resemble a muscle? Psychol Bull 126(2):247–259
Nachev P, Kennard C, Husain M (2008) Functional role of the supplementary and pre-supplementary motor areas. Nat Rev Neurosci 9:856–869
Oldfield RC (1971) The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9:97–113
Peyron R, Laurent B, García-Larrea L (2000) Functional imaging of brain responses to pain. A review and meta-analysis. Neurophysiol Clin Clin Neurophysiol 30(5):263–288
Rainville P, Duncan GH, Price DD, Carrier B, Bushnell MC (1997) Pain affect encoded in human anterior cingulate but not somatosensory cortex. Science (N Y) 277:968–971
Swann NC, Cai W, Conner CR, Pieters TA, Claffey MP, George JS, Aron AR, Tandon N (2012) Roles for the pre-supplementary motor area and the right inferior frontal gyrus in stopping action: electrophysiological responses and functional and structural connectivity. Neuroimage 59(3):2860–2870
Tangney JP, Baumeister RF, Boone AL (2004) High self-control predicts good adjustment, less pathology, better grades, and interpersonal success. J Personal 72(2):271–324
Towse JN, Neil D (1998) Analyzing human random generation behavior: A review of methods used and a computer program for describing performance. Behav Res Methods Instrum Comput 30(4):583–591
Verbruggen F, Logan GD (2008) Response inhibition in the stop-signal paradigm. Trends Cogn Sci 12:418–424
Wager TD, Rilling JK, Smith EE, Sokolik A, Casey KL, Davidson RJ, Cohen JD (2004) Placebo-induced changes in FMRI in the anticipation and experience of pain. Science (N Y) 303:1162–1167