

ORIGINAL ARTICLE

Spontaneous Brain Activity Predicts Task-Evoked Activity During Animate Versus Inanimate Touch

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Abstract

The spontaneous activity of the brain is characterized by an elaborate temporal structure with scale-free properties as indexed by the power law exponent (PLE). We test the hypothesis that spontaneous brain activity modulates task-evoked activity during interactions with animate versus inanimate stimuli. For this purpose, we developed a paradigm requiring participants to actively touch either animate (real hand) or inanimate (mannequin hand) stimuli. Behaviorally, participants perceived the animate target as closer in space, temporally more synchronous with their own self, and more personally relevant, compared with the inanimate. Neuronally, we observed a modulation of task-evoked activity by animate versus inanimate interactions in posterior insula, in medial prefrontal cortex, comprising anterior cingulate cortex, and in medial superior frontal gyrus. Among these regions, an increased functional connectivity was shown between posterior insula and perigenual anterior cingulate cortex (PACC) during animate compared with inanimate interactions and during resting state. Importantly, PLE during spontaneous brain activity in PACC correlated positively with PACC task-evoked activity during animate versus inanimate stimuli. In conclusion, we demonstrate that brain spontaneous activity in PACC can be related to

the distinction between animate and inanimate stimuli and thus might be specifically tuned to align our brain with its animate environment.

Key words: animate stimuli, perigenual anterior cingulate cortex, scale-free brain dynamics, spontaneous brain activity, task evoked activity

Introduction

The spontaneous activity of the brain shows an intricate temporal structure that is characterized by scale-free properties, that is, long-range temporal correlations (LRTCs) (Linkenkaer-Hansen et al. 2001; He et al. 2010; Ciuciu et al. 2012, 2014; He 2014). LRTCs as measured for instance by the power law exponent (PLE) are related to a higher time-lagged autocorrelation indicating that the past pattern of a system has a stronger influence on its future dynamics, implying stronger low-frequency Blood Oxygen Level Dependent (BOLD) signal fluctuations and higher glucose metabolism in the brain (He et al. 2010; He 2011; Fransson et al., 2013). Recent functional magnetic resonance imaging (fMRI) studies demonstrated that the degree of LRTCs predisposes the neural processing of motor (Palva et al. 2013) and sensory stimuli (Huang et al. 2015; He 2011) as well as private self-consciousness (Huang et al. 2016). Together, these studies suggest that spontaneous activity's scale-free properties may shape task-evoked activity and associated behavioral features including consciousness (Northoff and Huang 2017; Zhang et al. 2017). The exact neural mechanisms of such rest-stimulus interaction including the relevant neuronal features (He 2013; Huang et al. 2015; Northoff et al. 2010) as well as the exact kind of external stimuli that are preferentially mediated by the spontaneous activity's scale-free properties remain unclear.

Several studies show the sensitivity of the self to naturalistic environments as featured by animate stimuli (Adolphs 1999; New et al. 2007; Sui et al. 2012). For instance, interactions with animate stimuli (as distinguished from inanimate ones) are of crucial importance for a healthy development of the self and its neural underpinnings (Schore 2000; Rakison and Poulin-Dubois 2001; Trevarthen and Aitken 2001; Pfeifer and Peake 2012; Mucci 2017). Moreover, early life social experiences related to the animate environment impact the spatiotemporal structure of the brain's spontaneous activity even during later adulthood (Bluhm et al. 2009; Nakao et al. 2013; Duncan et al. 2015). Departing from this background, one would expect that the animacy of a stimulus might provide the ground for social cognition of other persons by approaching them as animate selves rather than as mere objects (Gallese 2014). Such intersubjective phenomenon may be operationalized in terms of perceived time and space similarity between self and other: the more the spatial and temporal features of a stimulus (Northoff and Huang 2017) are similar to the self (Hasson and Frith 2016), the more that stimulus will be perceived as another animate self. One would consequently assume that animate stimuli should be perceived as more similar to an individual's self in both time (more synchronous with the individual self) and space (closer to the individual self). This was the main background and hypothesis for our behavioral experiment (Fig. 1, left part).

The distinctive role of animate stimuli in task-evoked neural activity (Caramazza and Shelton 1998; New et al. 2007; Pratt et al. 2010; Gobbin et al. 2011; Bonin et al. 2014; Van Arsdall et al. 2014) is well known. Moreover, the spontaneous activity

of the brain, specifically its temporal structure, has been shown to be closely related to an individual's self (Qin and Northoff 2011; Bai et al. 2016; Davey et al. 2016; Huang et al. 2016; Wolff et al. 2018). Taken together with the assumed perceived similarity between self and animate stimuli, one would expect that the spontaneous activity's spatiotemporal structure, for example, its scale-free properties as indexed by PLE, should predict task-evoked activity in response to animate stimuli, compared with inanimate stimuli. That is the main background and hypothesis for the fMRI investigation (Fig. 1, right part).

For this purpose, we developed a paradigm (Ebisch et al. 2014; Scalabrini et al. 2017) that required participants to actively touch animate or inanimate targets. Touch is one of the most primary and direct forms of interaction with external stimuli, as it involves an active component, that is, the participant's actual touching of targets, which strengthens the personal involvement (Legrand 2006; Prescott et al. 2011).

To this aim we conducted a behavioral and an fMRI study. In the behavioral study, we tested whether participants perceive animate and inanimate targets differently. Given the importance of the animate environment for us and our social behavior (Frith and Frith 1999; Fonagy and Target 2002; Fonagy et al. 2007; Schilbach et al. 2012, 2013), and based on the recently suggested temporospatial theory of consciousness (TTC) (Northoff 2014a, 2014b; Northoff and Huang 2017), we hypothesized that the perception of a target in time, in space and the degree of self-relatedness, that is, personal relevance, will be considered phenomenally different for the animate stimuli compared with the inanimate stimuli.

In the fMRI study, we tested for task-evoked activity and functional connectivity (FC) during animate versus inanimate

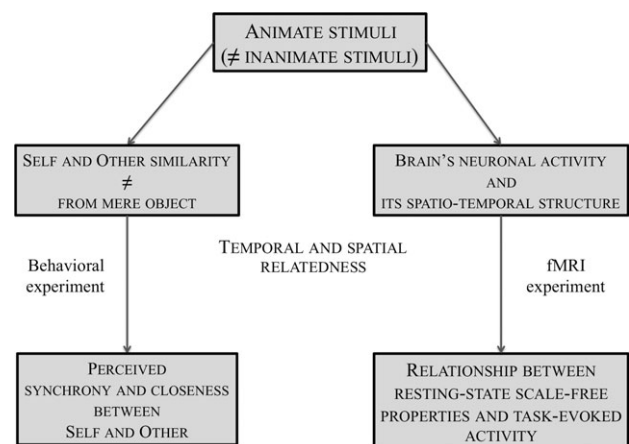


Figure 1. Visualization of the main hypothesis for the behavioral and fMRI experiment considering the relation with the animate stimuli. Left part: animate stimuli (as distinguished from the inanimate stimuli) are perceived as more synchronous in time with and closer in space to the individual self. Right part: resting state scale-free properties are related to task evoked activity in response to animate versus inanimate stimuli.

interactions and we investigated how these interactions were related to the brain's spontaneous activity.

Previous studies reported differential task-evoked activity in somatosensory cortex and other regions, like the insula, during the visual perception of either animate or inanimate touch (Keysers et al. 2004; Ebisch et al. 2008, 2011). Other studies further demonstrated the involvement of insula, anterior cingulate cortex and somatosensory cortex, in mediating touch and its personal relevance (Critchley 2005; Tsakiris et al. 2007; Craig 2002, 2009, 2010; Ebisch et al. 2011).

We hypothesized that regions which are differentially activated (task-evoked activity) and interconnected (generalized psychophysiological interaction [gPPI]) by animate versus inanimate interactions would be those regions related to the processing of somatosensory, affective, and self-related information. We further expected that the regions that functionally interact during the animate versus inanimate condition are also functionally connected during the resting state (resting state FC [rsFC]). Finally, we tested the hypothesis that the task-induced differentiation in these regions could be predicted by the temporal structure of brain's spontaneous activity in the same regions as measured by PLE.

Methods

Participants

A total number of 106 participants was recruited for the study. Overall, 74 participants (age 20–38; mean = 24.34; standard deviation = 2.70; 36 participants were females) were recruited for the behavioral study.

In total, 32 right-handed male participants (age 21–33; mean = 25.4; standard deviation = 2.82), not participating in the behavioral study, were recruited for fMRI scanning (these were the same as those included in our previous study, Scalabrini et al. 2017). While the previous investigation was focused on the anticipation of the interaction with the stimuli, using the same dataset, here we focus on the active touch component to strengthen the subjective personal involvement in the online interaction with animate and inanimate stimuli. All participants had normal or corrected-to-normal vision capabilities. None of the participants reported a history of neurological or psychiatric disease, or substance abuse. Written informed consent was obtained from all participants after full explanation of the study procedure, in line with the Declaration of Helsinki. The Ethics Committee for Biomedical Research of the provinces of Chieti and Pescara approved the experimental protocol.

Behavioral Study

To investigate the psychological features of participants' perception of animate versus inanimate stimuli, we developed a behavioral experiment. Similar to the fMRI task, participants were asked to follow directions on a 13 inch-screen of a laptop (60 cm the distance between the monitor and the participant) and to touch (i.e., stroke) the hand of another individual (animate target) or the mannequin's hand (inanimate target; size = 24 cm from the base to the top of the finger) with an wooden object (16 cm × 10 cm × 4.5 cm) covert on the bottom (but not on top were the participant was holding the object) with velvet (inducing a pleasant sensation when brushing on someone's skin) or sandpaper (inducing an unpleasant sensation when brushing on someone's skin). The distance between the participant's hand and the animate or inanimate hand was 15 cm. Different materials were used to make the context of the

experiment more naturalistic. The object mediating the touch was used to avoid direct physical contact between the participant and the target, that is, controlling for confounds due to differences in sensation between the conditions (the hand of the participant actively touching the hand of a volunteer or a mannequin hand). Participants could only see the hand of the other individual and the mannequin's hand.

The behavioral task was composed of 2 trials per condition, since more repetitions did not yield any significant changes for the purpose of the experiment. After the task, participants were asked to answer the questions (translated from Italian): 1) "How much did you personally identify with or relate to the other?" and "How much did you personally identify with or relate to the mannequin?" to assess personal relevance, that is, self-relatedness; 2) "How much you had the feeling you were in synchrony with the other?" and "How much you had the feeling you were in synchrony with the mannequin?" to assess the perception of the target in time—synchrony reflects a temporal aspect of perception, that is, a subjective sense of simultaneity of experience in time during the interaction with the target; 3) "How close did you feel the other?" and "How close did you feel the mannequin?" to assess the perception of the target in space—closeness reflects a spatial aspect of perception, that is, a subjective sense of the distance in space between the self and the target during the interaction. Finally, controlling for a possible confounding variable we also assessed 4) familiarity: "How much did you feel familiar with the other?" and "How much did you feel familiar with the mannequin?".

To indicate the degree of personal relevance, that is, self-relatedness, perception of time, perception of space and familiarity for the 2 different targets (animate vs. inanimate), participant's responses were obtained by drawing a horizontal line on a Visual Analogue Scale (vertical line of 10 cm) ranging, for example, from low self-relatedness to high self-relatedness. Ratings were quantified by measuring the distance in mm between the lower point of the line and the sign of the participant on the scale.

Paired sample t-tests were performed to compare the scores attributed to the active touch of the animate target with those attributed to the inanimate target for all the 4 constructs. In addition, to establish if there were associations between the scores related to the constructs for either the active touch of the animate target or of the inanimate target, we calculated Spearman correlation coefficients (participant-based) with a 95% confidence interval (CI) based on 1000 bootstrap samples. Bonferroni correction for multiple comparisons was performed on the obtained correlation coefficients and only *P*-values (before correction) < 0.05/number of calculated correlations were considered significant.

Moreover, we calculated partial correlations between self-relatedness, perception of time and perception of space for the touch of the animate target, while controlling for the effect of familiarity being considered a possible confounding variable. In a second step, we calculated partial correlations between familiarity, perception of space and perception of time for the touch of the animate target, while controlling for the effect of self-relatedness. We performed the same analyses for the inanimate touch condition.

fMRI Data Acquisition

A total of 32 subjects completed resting state fMRI acquisition. In total, 21 out of the 32 participants (age 21–30; mean = 24.9; standard deviation = 2.45) also completed task fMRI acquisition. For each participant, BOLD contrast functional imaging was performed with a Philips Achieva scanner (Andover, MA)

at 3 T at the Institute of Advanced Biomedical Technologies, Chieti, Italy.

An initial T1-weighted anatomical (3D TFE pulse sequence) was acquired with the following parameters: field of view = 240 mm; voxel size = (1 mm × 1 mm × 1 mm); TR 8.1; TE 3.7. Two resting-state fMRI runs (number of fMRI frames/run: 180) and 8 task fMRI runs (number of fMRI frames/run: 235) were acquired in a single fMRI session (T2* weighted EPI sequence with TR = 2000 ms; TE = 35 ms; 31 slices; slice thickness = 3.5 mm; in-plane voxel size = 2.875 × 2.875; field of view = 230 mm; flip angle = 90°).

Experimental Procedure and Materials

Resting-State fMRI

During the 2 resting-state fMRI runs (6 min each), participants were instructed to watch a white fixation cross presented on a black screen, think of nothing in particular and keep their eyes open (they were monitored through a video camera placed in the MRI room).

Task-fMRI

During the task fMRI runs (8 runs of 7.8 min each), a wooden table was placed on the participant's legs. During the experiment, the participant's right hand was resting on an object placed in the center of the table. The object consisted of a brush covert on the bottom with velvet (inducing a pleasant sensation when brushing on someone's skin) or sandpaper (inducing an unpleasant sensation when brushing on someone's skin). In this way, the participant performing the touch did not directly perceive any sensory consequences induced by the different target or by the different materials by its own, while being aware of the consequences for the target.

An inanimate target (mannequin hand) and an animate target (the hand of another volunteer who was standing next to the scanner) were both placed next to the participant's hand (Fig. 2). To keep the participants naïve about whose hand was placed on the table, they were not introduced to the other person prior to the experiment and it was not possible for them to see the hand or the individual they touched during the experiment. To avoid systematic effects of the location where the animate and inanimate target were placed, their position was pseudorandomized throughout the experiment (i.e., on the right and left side of the participant's hand). Before each individual fMRI run, the participant was informed about on which side of his own hand the animate and inanimate target was

placed. The behavioral performance accuracy of participant was monitored during the experiment through a video camera placed in the MRI room.

The participant completed a series of active touch and no-touch trials. Active touch was performed through an object to avoid the direct physical sensation of touching the different targets, that is, the hand of a volunteer (receiver) or a mannequin hand. Trial order was randomized. Each trial, either active touch or no-touch, started with a visual cue consisting of a black and white line drawing. The drawing indicated the target of the touch (what had to be touched by the participant), that is, the animate (the hand of another volunteer who was standing next to the scanner) or the inanimate target (a mannequin hand). The visual cues were presented for a duration of 1000 ms and were always followed by a red fixation cross. After 3000 ms, the red fixation cross could become either green (touch trials; duration = 6000 ms) or black (no touch trials; variable duration = 14 000/16 000/18 000 ms).

In this study we focused essentially on active touch (active touch trials) without considering the no-touch trials that were investigated in a previous research (Scalabrini et al. 2017). Thus, 2 main conditions could be distinguished: the active touch of an animate target (32 trials) and the active touch of an inanimate target (32 trials). Since it was not predictable for the participant whether he had to perform the touch, he was forced to be prepared to touch either the animate or the inanimate target after every visual cue.

This task emphasizes various aspects: 1) participants were actively involved in the task instead of being passive-spectators to make the experiment more ecological and emphasize the intrinsic relation with the animate environment (Fotopoulou and Tsakiris 2017; Northoff and Huang 2017), allowing us to investigate the context of an online interaction with the animate target; 2) a slow event-related fMRI design was used (ITIs = 14 000/16 000/18 000 ms) instead of fast event-related fMRI design; and 3) the task was preceded by resting state acquisitions to study the relation between rest and task conditions.

fMRI Data Analysis

The fMRI data analyses were performed in 4 steps. Firstly, we defined the brain regions in which neural activity was modulated by the task, in particular by the contrast between the animate and inanimate target ($\Delta\beta_{act}$). It is known that spontaneous activity might be carried over to task-evoked activity by being included in the latter as background—that has been demonstrated by the persistence of the ongoing activity's FC operating in the background during task-evoked activity (Smith et al. 2009). Therefore, and given that brain regions are unlikely to function in isolation, we analyzed context-dependent FC (gPPI) (McLaren et al. 2012) during task by studying the functional relationships of the task-based regions of interest (ROIs) with other regions of the brain. Transitioning from task to rest, we then tested for the overlap between task context-dependent (gPPI) and rsFC, taking the regions from the gPPI as ROIs. Finally, we tested whether the resulting ROIs from our analyses play a central role in mediating the rest-task relation by performing resting state PLE analysis and correlating PLE (β_{PLE}) with task-evoked activity ($\Delta\beta_{act}$).

Preprocessing and Task fMRI Analysis

Preprocessing procedures of the fMRI data were implemented in Analysis of Functional NeuroImages software (AFNI; Cox 1996;

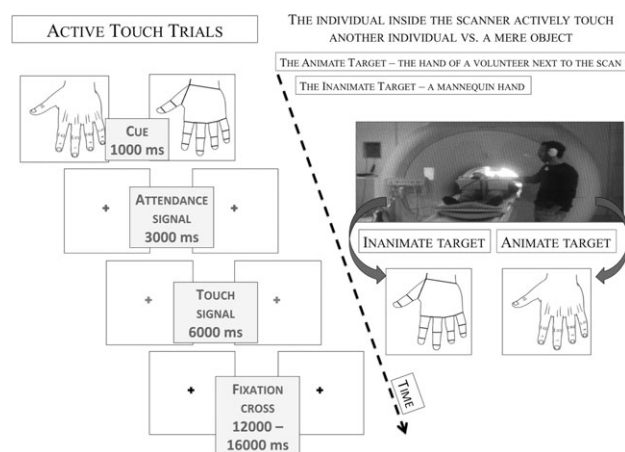


Figure 2. Visualization of the experimental stimuli and procedure.

<http://afni.nimh.nih.gov/afni>) including: 1) slice timing correction; 2) rigid body correction/realignment within and across runs. Six head motion parameters, 3 translational and 3 rotation parameters, were estimated and frame-wise realignment was performed using AFNI's *3dvolreg* command. After the estimated motion parameters were visually inspected, participants with head motion larger than ± 2 mm translation or $\pm 2.5^\circ$ rotation were eliminated (Johnstone et al. 2006); 3) co-registration with high-resolution anatomical images; 4) spatial normalization into Talairach stereotactic space; 5) resampling to $3 \times 3 \times 3$ mm³ voxels; and 6) regression of linear and nonlinear drift (equivalent to a high-pass filtering of 0.0067 Hz), head motion and its first-order temporal derivative, and mean time series from the white matter (WM) and cerebrospinal fluid (CSF) to control for non-neural noise (Fox et al. 2005). The WM and CSF masks were eroded by one voxel (Chai et al. 2012) to minimize partial voluming with gray matter; 7) spatial smoothing with an 8 mm full-width at half-maximum isotropic Gaussian kernel.

Trial onsets were defined for a deconvolution analysis (*3dDeconvolve* in AFNI) using a general linear model approach (GLM) to estimate activity parameters (β_{act}). Separate predictors were established for the 8 different types of trials (Touch animate/inanimate target, pleasant/unpleasant valence, No-touch animate/inanimate target, pleasant/unpleasant valence) and modeled using a 10 s BLOCK function in AFNI. The different events were time-locked departing from the cue. In addition, the 6 head motion parameters and their derivatives calculated in the preprocessing steps were included in the GLM analysis.

In order to assess voxel clusters modulated by the task, we performed a whole brain repeated measures 2x2 ANOVA with the factors "target" (levels: animate and inanimate) and "valence" (levels: pleasant and unpleasant). The principal contrast of interest concerned the active touch of the animate target versus the active touch of the inanimate target (animate target – inanimate target: $\Delta\beta_{act}$).

To estimate the probability of false positive clusters, results were corrected via Monte Carlo simulation as implemented in the AFNI program *3dClustSim* using a threshold of $P < 0.001$ and cluster size > 50 voxels, to obtain a corrected significance level of $\alpha < 0.01$. The power of cluster size corrections using the updated version of *3dClustSim* has been recently demonstrated in a recent paper (Cox et al., 2017).

The coordinates of the voxel clusters showing statistically significant effects were compared with the Talairach atlas available in AFNI software to label them in terms of anatomically defined regions and Brodmann areas (BA).

Task Functional Connectivity—gPPI

The generalized procedure of psychophysiological interactions (McLaren et al. 2012) was used to calculate the condition-specific FC of ROIs modulated by the task. The gPPI procedure consisted in the following steps: 1) physiological seeds were obtained extracting the mean activity from non-zero voxels included in each ROI; 2) psychological variables for each regressor were created as vectors with the same temporal length as the seeds, and with a binary value of 1 or 0 for each TR, depending if the condition represented by the regressor was or was not active at that TR; 3) for each seed, extracted activity was deconvolved with a standard gamma function, and 4) multiplied with the psychological vector of each regressor; 5) each resulting vector, for each condition (pleasant/unpleasant touch animate/inanimate target), was re-convolved with the gamma function, and used as a PPI regressor.

Therefore, the model comprised a total of 17 regressors of interest as well as nuisance regressors for motion, WM, and CSF. At the single subject level, a general linear model was performed for each ROI. At the group level, a whole brain repeated measures 2x2 ANOVA with factors target (levels: animate and inanimate) and valence (levels: pleasant and unpleasant) was run in AFNI to study the context-dependent FC (β_{fc}) of each ROI. Particularly, we focused on the animate versus inanimate contrast. Results were corrected via Monte Carlo simulation (using *3dClustSim*), setting a threshold of $P < 0.001$ and a cluster size > 50 voxels, to obtain a corrected significance level of $\alpha < 0.01$.

In addition, to explore whether there were statistically significant modulations of the BOLD response for the performance of an animate target and an inanimate target touch (active touch trials) we performed a ROI-based analysis in the ROIs identified by the FC analysis. Individual BOLD responses induced by touch performance were extracted from the clusters showing a significant difference in context-dependent FC among conditions of interest. Task-induced activity (β_{act}) values for each of these independent ROIs were then calculated from the average estimates of the voxels included in each ROI.

A repeated measures 2x2 ANOVA with factors target (levels: animate and inanimate) and valence (levels: pleasant and unpleasant) was performed on these β_{act} values to establish if there was a significant difference in neuronal activity during the active touch of the animate target and the active touch of the inanimate target.

Resting-State fMRI Analysis: FC

To assess if the ROIs that were modulated in terms of FC during the animate target touch were intrinsically connected, we performed a seed-based FC analysis for the resting-state periods. For this analysis, seed ROIs were chosen as the clusters in which the FC was modulated across conditions of interest (animate vs. inanimate).

The same preprocessing steps described above were performed on resting state data with the addition of temporal band-pass filtering ($0.01 < f < 0.1$ Hz) to reduce low-frequency drift and high-frequency respiratory/cardiac noise (Van Dijk et al. 2010; He 2011). Given the methodological issues recently raised (Murphy and Fox 2017), global signal regression (GSR) was not included in the preprocessing of the resting state fMRI data and was only used in a second step as a control analysis.

A voxel-wise FC map for each seed was computed as a map of temporal correlation coefficients between BOLD time course in each brain voxel and BOLD time course averaged across voxels in the seed regions (right PACC and posterior insula [PI]). The correlation coefficients were then transformed into z-values by means of the Fisher *r*-to-*z* transformation, to improve normality for group-level analysis. This procedure produced spatial maps in which the values of voxels represented the strength of the correlation with the ROIs. The z-values were entered into a one-sample t-test in a voxel-wise manner to determine which brain regions showed significant positive or negative connectivity with the seed ROIs.

Once we obtained the FC map for each seed ROI, a voxel-wise intersection analysis between these maps was performed to test for overlapping connectivity patterns between the seed ROIs (PACC and PI). This allowed to establish whether the ROIs interacting during the task (i.e., ROIs resulting from the gPPI analysis showing differential interactions during the animate and the inanimate target touch) were also functionally connected during the resting state.

All results were corrected using *3dClustSim* in AFNI, setting a threshold of $P < 0.001$ and a cluster size > 50 voxels, to obtain a corrected significance level of $\alpha < 0.01$.

Relationship Between Resting-State Activity (PLE) and Task Induced Activity

We analyzed if differential neuronal activity for the animate and the inanimate target touch could be predicted by the spontaneous neuronal activity in the same ROIs during an independent resting state.

For this purpose, the PLE, a measure of the temporal structure of low-frequency fluctuations (Bullmore et al. 2001), was calculated for the resting state fMRI runs (Huang et al. 2015). PLE is considered suitable for the measure of scale-free dynamics of fMRI data (He 2011; Huang et al. 2015, 2016). Comparing different methods for computing fMRI time series complexity, Rubin et al. (2013) demonstrated power spectrum based methods such as PLE being among the most robust measures.

Scale-free dynamics are mathematically characterized by a power spectrum following the formula $P \propto 1/f^\beta$, where, P is the power, f is the frequency, and β is called the “power-law exponent” (Bullmore et al. 2001). After preprocessing, the time course per voxel was normalized to zero mean and unit variance (z-value, Stephens et al. 2013). Using methods previously optimized for fMRI (Rubin et al. 2013), the normalized power spectrum of the fMRI signal was computed for each voxel using the AFNI program *3dPeriodogram*. Similarly to the Welch’s method, the power spectra of the 2 resting state runs were averaged to reduce noise caused by imperfect and finite data, in exchange for reducing the frequency resolution. The power spectrum of the BOLD signal was further smoothed with a Hamming window (HW) of 7 neighboring frequency bins (HW = 7, Huang et al. 2016). In the next step, the averaged power spectra across voxels within the task modulated ROIs were extracted for each participant. The power spectrum was fitted with a power-law function $P \propto 1/f^\beta$ using a least-square estimation (in a log frequency by log power plot) in the frequency range of 0.01–0.1 Hz (He 2011).

Finally, the power-law exponent, β_{PLE} , of each participant’s task modulated ROIs was defined as the slope of the linear regression of log-power on log-frequency.

To establish if there was an association between PLE measures during the resting state and task induced activity in the ROIs, we performed Spearman correlation analyses (participant-based) with a 95% CI based on 1000 bootstrap samples between resting state activity (β_{PLE} values) and task-activity (β_{act} values) for the difference between the animate and the inanimate touch. Bonferroni correction for multiple comparisons was performed on the obtained correlation coefficients, such that only P values below $P < 0.05/\text{number of calculated correlations}$ were considered significant.

PLE Control Analysis

We performed different control analyses for resting state PLE and correlations with task evoked activity:

i) To test the goodness of fit for scale invariance in the fMRI signal from particular region of interests we adapted a goodness of fit test developed for testing power-law distributions (Clauset et al. 2009) and used by other authors in fMRI studies (He 2011; Tagliazucchi et al. 2013). For each ROI, time series were extracted for each subject and subjected to PLE analysis

for the resting state runs. The 1000 time series of fractional Gaussian noise (fGn) with the same length and standard deviation as the original ROI time series were generated. Fractional Gaussian noise is a parsimonious model of stationary scale-free dynamics (Beran 1994). Each synthetic fGn time series was subjected to the same PLE analysis as the original resting state data. The P value is defined as the fraction of synthetic time series with standard deviations of residuals from best fit that is larger than the original standard deviations of residuals from best fit of the fMRI time series. The larger the P -value, the more plausible the fGn model is for representing the original fMRI time series, and the better the fit of the original data to a scale-free distribution. The hypothesis that the fMRI signal is scale-free is plausible if the resulting P value is greater than 0.1, otherwise it is ruled out (Clauset et al. 2009; He 2011; Tagliazucchi et al. 2013).

ii) We applied different HWs (HW = 3, 5, 9, 15) on the PLE calculation to test if the correlation between resting state activity (PLE) and task induced activity could be affected by different smoothing parameters.

iii) The correlation between PLE and the Δ -target for the task induced activity was also controlled for all leave-one-out cohorts (N analyses with $N-1$ participants where each participant is excluded at a time).

iv) To confirm the robustness of our frequency domain analysis (PLE) we also independently calculated the Hurst exponent in the time domain with detrended fluctuation analysis (H-DFA) (Linkenkaer-Hansen et al. 2001; He 2011) as a control index and calculated their correlation. Specifically, DFA measures the scaling of the root-mean-square fluctuation of the integrated and linearly detrended signals, $F(T)$, as a function of time window size, T . The fluctuation $F(T)$ is of the form $F(T) = T^H$, where H is the scaling exponent.

v) We performed Spearman correlation analyses (participant-based) with a 95% CI based on 1000 bootstrap samples between resting state activity (H-DFA) and task-activity (β_{act} values) for the difference between the animate and the inanimate touch.

vi) In addition to the inclusion of motion correction procedures in resting state fMRI data preprocessing, we controlled if our results were possibly explained by the effect of participants’ movements. Firstly, we tested the goodness of fit for scale invariance for the motion parameters to demonstrate their scale-free properties. If the motion parameters during the resting state have been considered scale-free, we calculated the PLE of the 6 motion parameters. Finally, we tested if the motion PLEs during the resting state correlated with 1) PLE of BOLD times series during the rest state and 2) BOLD responses (β_{act} values) during task-evoked activity (animate vs. inanimate touch trials).

vii) To evaluate the specific relevance of the temporal structure (as measured by PLE) rather than the mere variance of resting state neural activity, we also calculated other local dynamics of the resting state (see Huang et al. 2016), like amplitude of low frequency fluctuations (ALFF), regional homogeneity (ReHo) and standard deviation of BOLD signal (SD; See Supplementary Methods). ROI-based correlation analysis between resting state PLE and these other measures was performed to control for measure specificity.

viii) Moreover, we controlled for the specificity of the correlation between resting state PLE and task induced activity in PACC, performing the same correlation analysis in PACC with the other resting state measures (ALFF, ReHo, SD).

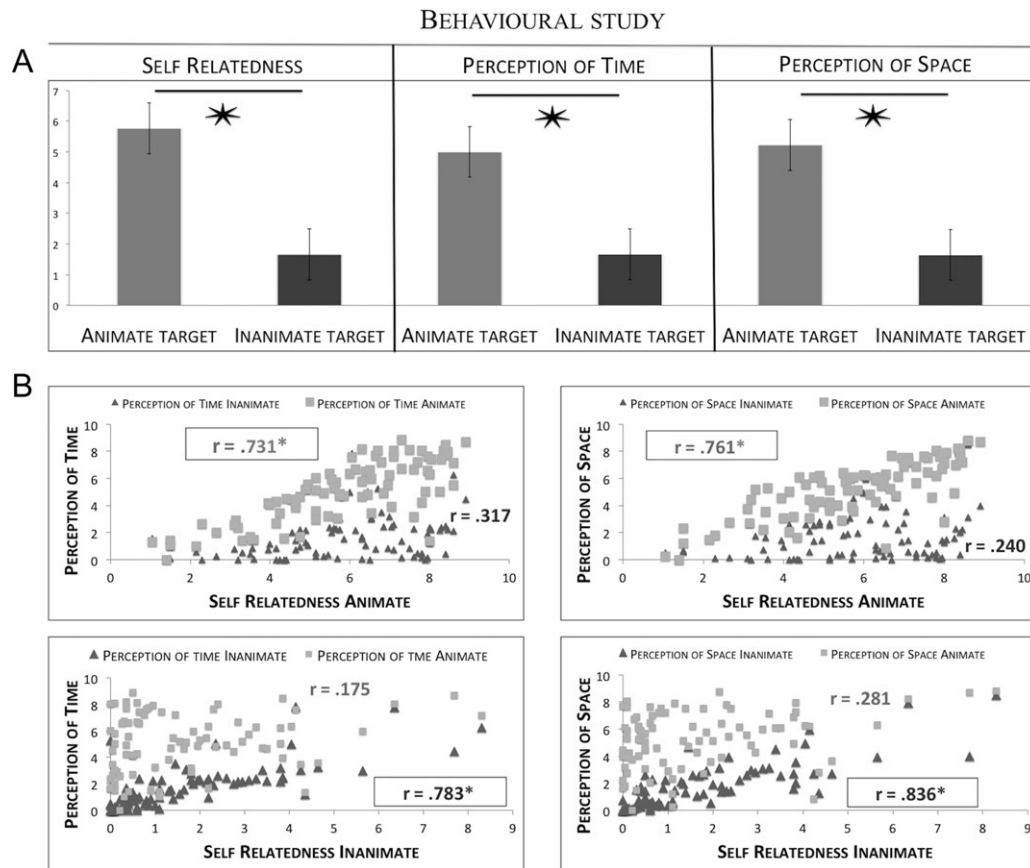


Figure 3. (A) Paired sample t-test for the constructs of self-relatedness, perception of time and perception of space for the animate and inanimate target. Graphs showing average values and standard errors for the experimental conditions. * $P < 0.001$. (B) Scatter plots showing predictive power (Spearman correlation) of self-relatedness with perception of time and with perception of space for animate and inanimate conditions, respectively.

Results

Behavioral Data

The behavioral data in 74 participants showed the following results. Using paired t -tests, we observed a significant difference in personal relevance, that is, self-relatedness, of the animate target (mean = 5.66; SD = 1.91) and of the inanimate target (mean = 1.65; SD = 1.77): the animate target showed significantly higher values than the inanimate target ($t = 18.524$; $P = 0.00001$). This was complemented by differences regarding the perception of target in time (PT, $t = 14.121$; $P = 0.00001$) and the perception of target in space (PS, $t = 15.126$; $P = 0.00001$). Both time and space perception were significantly higher for the animate target (PT animate: mean = 4.92; SD = 2.20; PS animate: mean = 5.02; SD = 2.12), compared with the inanimate target (PT inanimate: mean = 1.63; SD = 1.58; PS inanimate: mean = 1.62; SD = 1.64) (Fig. 3A). Moreover, we observed a significant difference ($t = 9.257$; $P = 0.00001$) in familiarity for the animate target (mean = 4.42; SD = 2.12) and familiarity for the inanimate target (mean = 2.18; SD = 1.91).

Finally, we investigated the relationship between self-relatedness, time perception and space perception regarding animate versus inanimate targets. We observed that self-relatedness of animate targets only significantly correlated with perception of time and space of animate targets (Fig. 3B). The same was true for the relationship between self-

relatedness of inanimate targets and time/space perception of inanimate targets. In contrast, we neither observed any significant relationship between animate self-relatedness and inanimate time/space perception nor the reverse (i.e., inanimate self-relatedness and animate time/space perception, Table 1).

Taken together, the results show that the animate target is perceived as more personally relevant, compared with the inanimate target. This is supported by the association of a greater perception of self-relatedness with a more synchronous perception in time as well as with an increased perception of closeness in space for the animate target, whereas the inanimate target is perceived as less self-related, as less synchronous in time and distant in space.

Additionally, we controlled for the possible confounding effect of familiarity. Partial correlation analysis was performed for self-relatedness, perception of time and perception of space, while controlling for the effect of familiarity. We found that for the animate target, controlling for the effect of familiarity as a confounding variable, self-relatedness remained significantly associated with perception of time ($r = 0.653$, $P < 0.00001$, Bonferroni corrected, 95% CI: [0.469 0.808]; standard error [SE] = 0.090) and with perception of space ($r = 0.700$, $P < 0.00001$, Bonferroni corrected, 95% CI: [0.515 0.843]; SE = 0.082). Perception of time also remained significantly associated with perception of space ($r = 0.694$, $P < 0.00001$, Bonferroni corrected, 95% CI: [0.570 0.806]; SE = 0.060).

Table 1 Spearman correlation coefficients with a 95% confidence interval (CI) based on 1000 bootstrap samples for the bivariate associations between self-relatedness, perception of time and perception of space and their 2 main conditions (Animate vs. Inanimate), respectively (N = 74)

	Self-relatedness		Perception of time		Perception of space	
	Animate	Inanimate	Animate	Inanimate	Animate	Inanimate
SR Animate	X	$r = 0.343$ Low = 0.160 Upp = 0.539 SE = 0.099	$r = 0.731^*$ Low = 0.566 Upp = 0.848 SE = 0.099	$r = 0.317$ Low = 0.151 Upp = 0.545 SE = 0.099	$r = 0.761^*$ Low = 0.608 Upp = 0.867 SE = 0.069	$r = 0.240$ Low = 0.029 Upp = 0.433 SE = 0.108
SR Inanimate		X	$r = 0.175$ Low = -0.063 Upp = 0.408 SE = 0.119	$r = 0.783^*$ Low = 0.607 Upp = 0.884 SE = 0.071	$r = 0.281$ Low = 0.045 Upp = 0.487 SE = 0.114	$r = 0.836^*$ Low = 0.744 Upp = 0.896 SE = 0.039
PT Animate			X	$r = 0.347$ Low = 0.134 Upp = 0.531 SE = 0.102	$r = 0.761^*$ Low = 0.620 Upp = 0.854 SE = 0.058	$r = 0.191$ Low = -0.023 Upp = 0.392 SE = 0.109
PT Inanimate				X	$r = 0.327$ Low = 0.143 Upp = 0.576 SE = 0.110	$r = 0.818^*$ Low = 0.651 Upp = 0.920 SE = 0.071
PS Animate					X	$r = 0.301$ Low = 0.065 Upp = 0.509 SE = 0.110
PS Inanimate						X

* $P < 0.0013$ after Bonferroni correction for multiple comparisons.

Note: SR = self-relatedness; PT = perception of time; PS = perception of space; Low = lower; Upp = upper; SE = standard error. Bold values represent the significant ones.

Regarding the inanimate condition, controlling for the effect of familiarity as a confounding variable, self-relatedness remained significantly associated with perception of time ($r = 0.429$, $P < 0.0001$, Bonferroni corrected, 95% CI: [0.253 0.639]; SE = 0.095) and with perception of space ($r = 0.546$, $P < 0.0001$, Bonferroni corrected, 95% CI: [0.329 0.624]; SE = 0.101). Perception of time also was significantly associated with perception of space ($r = 0.669$, $P < 0.0001$, Bonferroni corrected, 95% CI: [0.477 0.840]; SE = 0.100).

When analyzing the association between familiarity, perception of time and perception of space, while controlling for the effect of self-relatedness, no significant results were detected regarding both the animate and the inanimate conditions.

For the animate condition, controlling for self-relatedness, familiarity did show significant correlations neither with perception of time ($r = 0.138$, $P = 0.244$) nor with perception of space ($r = 0.143$, $P = 0.229$), while perception of time significantly correlated with perception of space ($r = 0.449$, $P < 0.0001$, Bonferroni corrected, 95% CI: [0.131 0.669]; SE = 0.133).

For the inanimate condition, controlling for self-relatedness, familiarity did not show any significant correlation with perception of time ($r = 0.194$, $P = 0.100$) and with perception of space ($r = 0.221$, $P = 0.060$), while perception of time showed a significant association with perception of space ($r = 0.593$, $P < 0.0001$, Bonferroni corrected, 95% CI: [0.335 0.793]; SE = 0.125).

This additional control analysis showed that the degree of personal relevance of the animate target is unlikely to be explained by a confounding effect of familiarity. In other words, these results exclude the effect of familiarity as a potential confounding variable at a behavioral level.

Task-Evoked Activity of fMRI BOLD Signal: Animate Versus Inanimate Target

We performed a repeated measures ANOVA to identify voxel clusters modulated by the task. The analysis yielded a significant effect for the target, that is, animate versus inanimate ($F = 14.81$; $\alpha \ll 0.01$) in 3 clusters (Fig. 4): an extensive medial prefrontal cortex cluster (mPFC) that also included voxels in perigenual anterior cingulate cortex (PACC); a cluster located in right posterior insula (PI); and a cluster in medial superior frontal gyrus (mSFG). We did not find any significant effect for valence and for the interaction target \times valence with the same statistical threshold.

As it can be seen in the bar graphs in Figure 4, the cluster located in the mPFC showed differential activity for the active touch of the animate target (slightly increased activity compared with baseline) in comparison with the active touch of the inanimate target (decreased activity compared with baseline). By contrast, bar graphs in Figure 4 show decreased activity in right PI during the active touch of the animate target, whereas no appreciable activity change was observed during the active touch of the inanimate target. Lastly, bar graphs in Figure 4 show a significantly increased activity for the touch of the animate target versus the touch of the inanimate target in mSFG.

Context-Dependent FC: gPPI

To evaluate the context-dependent connectivity, gPPI was performed using as seed regions the ROIs resulting from the task

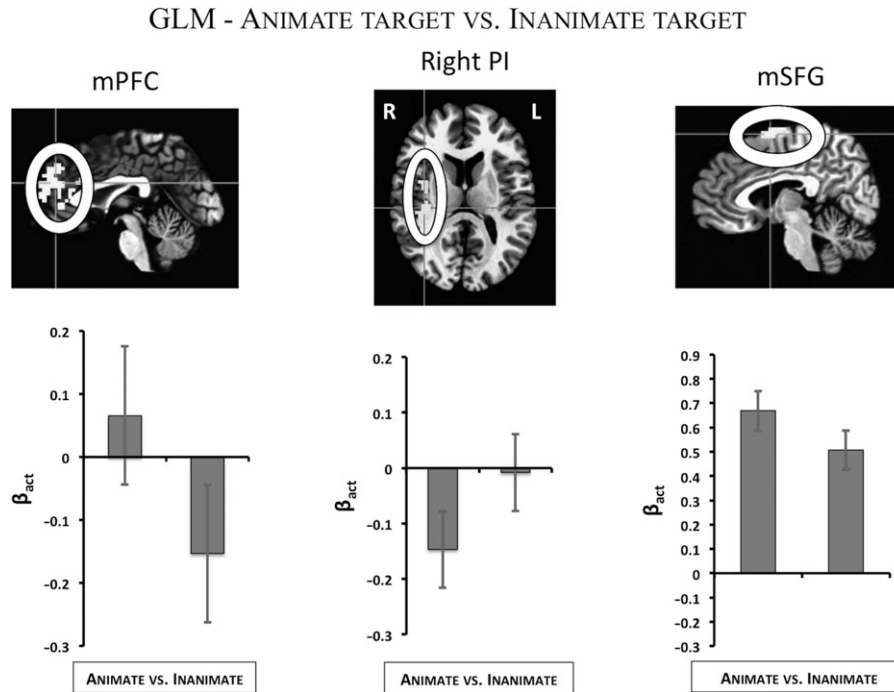


Figure 4. Task induced activity: Group statistical maps of whole brain voxelwise ANOVA for the main contrast, that is, animate versus inanimate target ($F = 17.68$; $P = 0.00001$; $\alpha < 0.001$) in medial prefrontal cortex (mPFC: an extensive cluster comprising also voxels in perigenual anterior cingulate cortex), in posterior insula (PI) and in medial superior frontal gyrus (mSFG). Bars show the average of β_{act} values and standard errors. R = Right; L = Left.

evoked fMRI ANOVA. This allowed to identify voxel clusters whose FC with the seed ROIs was significantly modulated by the different contexts (animate and inanimate) during the task.

At the group level, the ANOVA on context-dependent connectivity with right PI as seed region elicited a significant effect for the main contrast (animate vs. inanimate, $F = 12.61$, $\alpha < 0.01$) in right PACC (Fig. 5A).

No significant effects were found for the factor valence, and for the interaction between target and valence. The ANOVA on context-dependent connectivity with the other ROIs used as seed region, respectively, did not elicit any significant results with the same statistical threshold.

As indicated in Figure 5A, results showed negative connectivity values between PI and PACC during the animate condition, but not during the inanimate condition. Given that task-evoked activity was separately modeled in the gPPI procedure (as described in McLaren et al. 2012), this FC likely reflects a distinct effect, which is not related to task evoked activity. This is further supported by the lack of correlation between context-dependent connectivity in the animate versus inanimate condition and task-evoked activity ($\Delta\beta_{act}$) for the contrast animate versus inanimate (in PACC $r = -0.209$ $P = 0.363$; in PI $r = -0.281$ $P = 0.218$).

Finally, we took the PACC cluster resulting from the whole-brain gPPI as a ROI and extracted task-evoked activity (β_{act} values resulting from the GLM analysis). A repeated measures ANOVA yielded a significant difference ($F = 18.07$, $P < 0.001$) in task-induced activity between the touch of an animate target and the touch of an inanimate target (Fig. 5B), while we did not find any significant result for valence and for the interaction target \times valence.

In sum, these gPPI results show the existence of a context-dependent FC between PI and PACC indicating a significant

negative correlation between the 2 regions during the animate condition.

Resting State fMRI: FC of PACC and PI

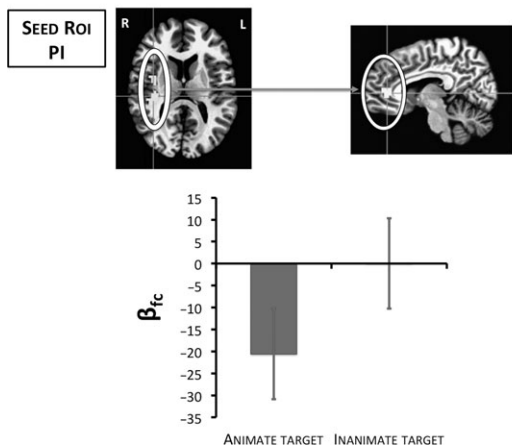
We conducted resting state FC analyses based on long-range correlations of low frequency BOLD fluctuations in all brain voxels (Fox and Raichle 2007). Resting state FC analysis with seed ROI right PI yielded a map consisting of right and left PI extending to postcentral gyrus and somatosensory regions, PACC, right and left inferior temporal gyrus, and left and right inferior frontal gyrus ($t = 8.72$; $\alpha < 0.01$).

Resting state FC analysis with seed ROI right PACC yielded significant FC in several regions including a more extended region in the PACC, right and left PI, PCC, thalamus, caudate nucleus, inferior frontal gyrus, right and left middle temporal gyrus, and parahippocampal gyrus ($t = 8.72$; $\alpha < 0.01$).

To test whether PACC and right PI, which were functionally connected during the animate context as shown by the context-dependent connectivity analysis, were also intrinsically connected during the resting state we created an intersection map from the resting state FC maps from the 2 seeds. The intersection of the 2 FC maps (statistical thresholds: $t = 91.76$; $\alpha < 0.01$) showed overlapping FC with PACC and PI in 4 brain regions: PACC, right PI, left PI and right paracentral lobule (Table 2). To further confirm these results, we repeated the same analysis including GSR. The resulting intersection map ($t = 36.31$; $\alpha < 0.01$) showed positive connectivity values in PACC and PI, and negative connectivity values in right and left superior parietal lobule, right and left postcentral gyrus, and in presupplementary motor area.

Taken together, rsFC results show (with and without GSR) that the connection between right PACC and right PI is not only animate context-dependent, but that these regions also functionally interact during the resting state (Fig. 6).

A FUNCTIONAL CONNECTIVITY - ANIMATE TARGET VS. INANIMATE TARGET



B TASK EVOKED ACTIVITY – ROI BASED ANALYSIS

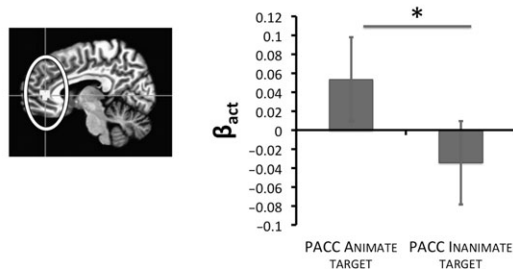


Figure 5. Functional connectivity: generalized psychophysiological interaction (gPPI). (A) Group statistical maps of whole brain voxelwise generalized psychophysiological interactions (gPPI) for the main contrast, that is, animate versus inanimate target. Bars show the average of gPPI- β_{fc} values and standard errors. For the animate target condition the bar shows negative connectivity values between PI and PACC. The bar for the inanimate target condition represents no significant connectivity values between PI and PACC. (B) ROI-based analysis on PACC: repeated measures 2×2 ANOVA on β_{act} values resulting from the general linear model. Bars show the average of the β_{act} values for the animate and the inanimate condition and standard errors. R = Right; L = Left.

Resting State fMRI: Correlation Between Resting State PLE and Task Induced Activity

Based on previous results showing that the resting state's scale-free properties predict self-consciousness in fMRI and EEG (Huang et al. 2016; Wolff et al. 2018) and anticipation of touch (Scalabrini et al. 2017), we tested whether the resting state scale-free properties, as indexed by PLE, of the neurofunctionally relevant regions for the animate context are related to task induced activity during actively touching animate and inanimate targets. Based on the results from the FC analyses during rest and task, the PACC cluster from the gPPI analysis was also included in the analysis of correlation between resting state PLE and task induced activity. To investigate the proper contribution of mPFC, all the voxels in the anterior cingulate cortex based on the AFNI-supplied Talairach-Tournoux atlas (TT Deamon) were separated from the mPFC cluster (Fig. 7; $x = 1$ $y = 43$ $z = 26$; 146 voxels).

The obtained resting state PLE values across participants ($n = 32$) in right PACC (mean = 0.71; SD = 0.26), right PI (mean = 0.47; SD = 0.25), mPFC (mean = 0.75; SD = 0.21), mSFG (mean = 0.69; SD = 0.25) are in accordance with previous studies (He 2011; Huang et al. 2016, 2017). Like in recent study (Huang et al. 2016), our data show a remarkable degree of intersubject variation in the degree of resting state PLE (see also He 2013, Huang et al. 2017).

Correlations were calculated between resting state PLE in these regions (β_{PLE}) and differential task-evoked BOLD response amplitude in the same regions during the touch of the animate target and the inanimate target (β_{act} Δ -target) (Table 3 and Fig. 7). A positive and significant correlation between resting state PLE and Δ -target was observed in right PACC ($r = 0.747$, $P = 0.0001$; Bonferroni corrected; 95% CI: [0.418 0.906]; SE = 0.124). In contrast, we did not obtain a significant correlation in right PI ($r = -0.010$, $P = 0.964$, 95% CI Lower: [-0.408 0.425]; SE = 0.213); in mPFC and in ($r = -0.135$, $P = 0.559$, 95% CI: [-0.315 0.535]; SE = 0.126); in mSFG ($r = -0.366$, $P = 0.101$ 95% CI: [-0.095 0.727]; SE = 0.091). Moreover, an almost significant correlation was also observed between resting state PLE and activity induced by the animate target in PACC ($r = 0.429$, $P = 0.053$; 95% CI: [0.007 0.703]; SE = 0.180; see Table 3 for more details).

A series of control analyses were conducted with respect to PLE:

- i. By simulating 1000 time series with a stochastic Gaussian process of known long-range temporal dependence, we

Table 2 Brain regions showing a modulation of BOLD response by different experimental conditions and statistical information. C-Mass and peak coordinates refer to Talairach space.

Brain region	Broadmann's area	C-Mass coordinates x,y,z	Peak coordinates x,y,z	Cluster size	F/t	α
Task interaction contrast (Corresponding to Fig. 4): Touch of the animate target vs. Touch of the Inanimate target						
mPFC	BA 9/32	1; 42; 23	2; 41; 2	187 voxels	14.81	<<0.01
Right PI	BA 13	35; -20; 13	33; -22; 13	122 voxels	14.81	<<0.01
mSFG	BA 6	5; 0; 62	5; 8; 59	70 voxels	14.81	<<0.01
gPPI interaction contrast (corresponding to Fig. 5): Touch of the Animate target vs. Touch of the Inanimate target (seed ROI = right PI $x: 35; y: -20; z: 13$)						
PACC	BA 10/32	9; 39; 10	5; 42; 7	52 voxels	3.515	<0.01
RESTING STATE intersection contrast (corresponding to Fig. 6): rsFC right ACC \cap rsFC right PI						
PACC	BA10/BA32	2; 45; 9	2; 47; -1	224 voxels	91.76	<<0.01
Right PI	BA 13	38; -23; 16	32; -23; 11	118 voxels	91.76	<<0.01
Left PI	BA 13	-36; -26; 17	-31; -28; 11	54 voxels	91.76	<<0.01
Right paracentral lobule	BA 31	1; -32; 42	8; -25; 44	58 voxels	91.76	<<0.01

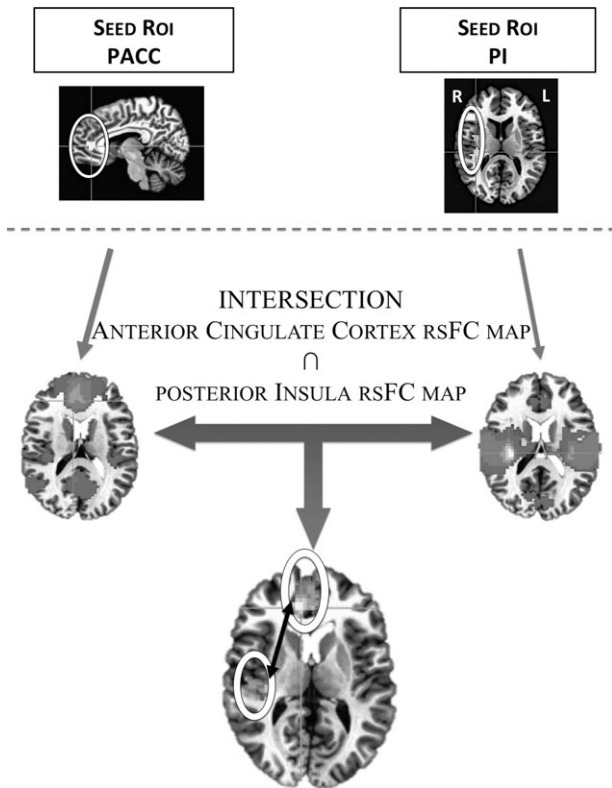


Figure 6. Visualization of resting state functional connectivity maps for right PACC ($t = 8.72$; $\alpha < 0.01$) for right PI ($t = 8.72$; $\alpha < 0.01$) and intersection map (right PACC \cap right PI; $t = 91.76$; $\alpha < 0.01$). R = right; L = left.

first showed that the fMRI signal is scale-free by analyzing the goodness of fit indices (i.e., right PI $P = 0.64$; right PACC $P = 0.51$; mPFC $P = 0.45$; mSFG $P = 0.48$). Thus, PLE is a suitable measure to quantify the scaling exponent of the fMRI signal.

- ii. To test the robustness of our results, we applied different smoothing parameters to determine the PLE values, more specifically by varying HW size (HW = 3, 5, 9, and 15). These analyses showed that the correlation of resting state PLE with task induced activity in PACC was not affected by different HWs (Table 3);
- iii. The correlation between β_{PLE} and the $\Delta\beta_{act}$ for the task induced activity was controlled for all leave-one-out cohorts (N analyses with $N-1$ participants where each participant is excluded at a time) showing that this procedure did not affect significance of the correlation coefficients for right PACC (min: $r = 0.717$ $P = 0.0003$; max: $r = 0.800$, $P = 0.00002$);
- iv. To validate the PLE that is based on the frequency-domain, we applied a time-domain method (DFA) to test for their correlation. As expected, we observed a strong correlation between the 2 measurements in all the ROIs (for right PACC, $r = 0.818$, $P = 0.00001$, 95% CI: [0.603 0.928]; SE = 0.086; for right PI, $r = 0.729$, $P = 0.00001$, 95% CI: [0.438 0.879]; SE = 0.111); for mPFC, $r = 0.703$, $P = 0.0003$, 95% CI: [0.279 0.836]; SE = 0.055; for mSFG, $r = 0.620$, $P = 0.001$, 95% CI: [0.279 0.741]; SE = 0.055).
- v. In accordance with the resting state PLE—resting state DFA correlation, we also conducted task correlation analyses with resting state DFA, which yielded similar results

compared with resting state PLE and task evoked activity for $\Delta\beta_{act}$ and the touch of the animate target: correlation between resting state H-DFA and $\Delta\beta_{act}$ (animate target – inanimate target) in PACC during task induced activity ($r = 0.544$, $P = 0.011$, 95% CI: [0.182 0.778]; SE = 0.156). A correlation between resting state H-DFA and task induced activity during the touch of the animate target was also observed in PACC ($r = 0.517$, $P = 0.016$; 95% CI: [0.061 0.802]; SE = 0.191), whereas no significant correlation between resting state H-DFA and task induced activity during the touch of the inanimate target was obtained in PACC ($r = 0.209$; $P = 0.363$). Concerning right PI, we did not observe significant correlation between resting state H-DFA and $\Delta\beta_{act}$ ($r = -0.262$; $P = 0.252$), between resting state H-DFA and task induced activity during the touch of the animate target ($r = -0.136$; $P = 0.556$) or between resting state H-DFA and task induced activity during the touch of the inanimate target ($r = 0.005$; $P = 0.982$). Concerning mPFC, we did not observe significant correlation between resting state H-DFA and $\Delta\beta_{act}$ ($r = 0.008$; $P = 0.972$), between resting state H-DFA and task induced activity during the touch of the animate target ($r = 0.225$; $P = 0.326$) or between resting state H-DFA and task induced activity during the touch of the inanimate target ($r = 0.198$; $P = 0.389$). Concerning mSFG, we did not observe significant correlation between resting state H-DFA and $\Delta\beta_{act}$ ($r = 0.023$; $P = 0.921$), between resting state H-DFA and task induced activity during the touch of the animate target ($r = -0.418$, $P = 0.059$) or between resting state H-DFA and task induced activity during the touch of the inanimate target ($r = -0.401$, $P = 0.071$).

- vi. We tested if our results were possibly explained by motion during resting state fMRI scanning.

a) We calculated the PLE values for the 6 motion parameters (motion- ΔA -P, mean = 0.92, SD = 0.18; motion- ΔR -L, mean = 0.88, SD = 0.18; motion- ΔI -S, mean = 0.87, SD = 0.16; motion-Yaw, mean = 0.67, SD = 0.18; motion-Pitch, mean = 0.90, SD = 0.14; motion-Roll, mean = 0.37 SD = 0.21).

b) By simulating 1000 time series with a stochastic Gaussian process of known long-range temporal dependence, we first showed that motion parameters are scale-free analyzing the goodness of fit indices (motion- ΔA -P $P = 0.50$; motion- ΔR -L, $P = 0.58$; motion- ΔI -S, $P = 0.58$; motion-Yaw, $P = 0.35$; motion-Pitch, $P = 0.50$; motion-Roll, $P = 0.30$).

c) We did not find any significant correlation between the resting state PLE of BOLD time series in PACC or PI (used as a control) and the PLE of the motion parameters (PACC with motion- ΔA -P, $r = 0.26$ $P = 0.14$; PACC with motion- ΔR -L, $r = -0.054$, $P = 0.77$; PACC with motion- ΔI -S, $r = 0.099$, $P = 0.59$; PACC with motion-Yaw, $r = 0.15$, $P = 0.41$; PACC with motion-Pitch, $r = -0.45$, $P = 0.43$; PACC with motion-Roll, $r = 0.032$, $P = 0.86$; PI with motion- ΔA -P, $r = -0.10$, $P = 0.57$; PI with motion- ΔR -L, $r = -0.26$, $P = 0.89$; PI with motion- ΔI -S, $r = 0.08$, $P = 0.66$; PI with motion-Yaw, $r = 0.40$, $P = 0.02$; PI with motion-Pitch, $r = -0.18$, $P = 0.32$; PI with motion-Roll, $r = 0.21$, $P = 0.24$).

d) We did not find any significant correlation between the task-evoked activity in PACC or PI and PLE of the motion parameters (e.g., Δ -target in PACC with motion- ΔA -P, $r = 0.20$ $P = 0.11$; motion- ΔR -L, $r = 0.09$, $P = 0.67$; motion- ΔI -S, $r = 0.17$, $P = 0.46$; motion-Yaw, $r = 0.02$, $P = 0.94$; motion-Roll, $r = 0.23$, $P = 0.32$).

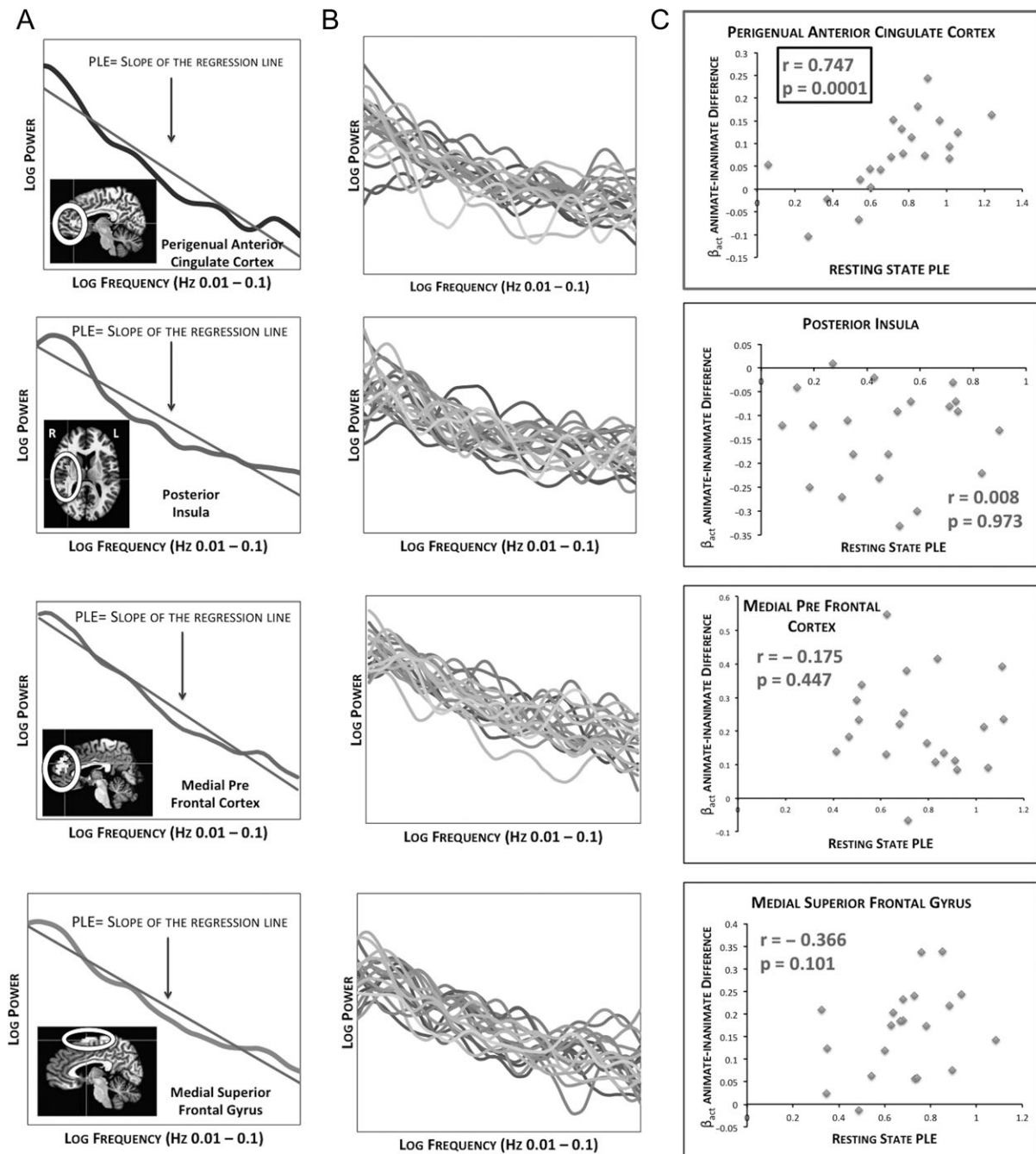


Figure 7. Resting State Power Law Exponent (PLE) and correlation with task-evoked activity. (A) The power-law exponent (PLE) was defined as the slope of the linear regression of log-power on log-frequency corresponding to the straight-line regime. (B) The power spectra of all subjects in right PACC, right PI, mPFC and mSFG. Different lines represent individual subjects. (C) Scatter plots displaying the relationship between the resting state power law exponent (PLE) in PACC, PI, mPFC, mSFG, and the Δ -target (β_{act} animate target – inanimate target difference) for the task evoked activity in the very same regions. A significant correlation was observed between resting state PLE in PACC and Δ -target in PACC during task ($r = 0.747$, $P = 0.0001$, remaining significant after Bonferroni correction).

e) Partial correlations between the resting state PLE in PACC (β_{PLE}) and task-evoked activity in PACC ($\Delta\beta_{act}$) during the task evoked activity, controlling for the effect of the PLE of motion parameters during the resting state, confirmed a significant correlation ($r = 0.68$; $P = 0.001$).

f) These results demonstrate that our findings are not influenced by the effect of the movements during the resting state.

- vii. To test for the resting state PLE specificity, we performed a control analysis with other resting state measures (ALFF, ReHo, and SD) that characterize some properties of local dynamics of neural activity. No significant correlation between resting state PLE and the other resting state measures was observed (see Supplementary Materials and Table S1).
- viii. In addition to the previous analysis, we tested for the specificity of the correlation between resting state PLE and

Table 3 Statistics of the correlations between the resting state PLE and task induced activity (β_{act}) in Perigenual Anterior Cingulate Cortex (PACC), right Posterior Insula (PI), in medial Prefrontal Cortex (mPFC) and in medial Superior Frontal Gyrus (mSFG) for the animate – inanimate difference (Δ -target), for the active touch of the animate target and for inanimate target respectively.

Resting State PLE	Perigenual anterior cingulate cortex				Posterior insula				Medial prefrontal cortex				Superior medial frontal gyrus			
	Δ -target		Inanimate		Δ -target		Inanimate		Δ -target		Inanimate		Δ -target		Inanimate	
	Animate	Inanimate	Animate	Inanimate	Animate	Inanimate	Animate	Inanimate	Animate	Inanimate	Animate	Inanimate	Animate	Inanimate	Animate	Inanimate
HW = 7	$r = 0.747^*$	0.429	0.042	0.010	0.045	0.117	0.168	0.304	0.274	0.366	0.069	-0.029	0.069	0.366	0.103	0.902
	$P = 0.0001$	0.053	0.852	0.964	0.845	0.614	0.495	0.180	0.229	0.103	0.767	0.902	0.103	0.103	0.767	0.902
HW = 3	$r = 0.762^*$	0.438	0.042	0.126	0.253	0.247	0.132	0.315	0.115	0.310	0.060	-0.029	0.310	0.310	0.060	-0.029
	$P = 0.00005$	0.047	0.858	0.586	0.268	0.281	0.568	0.162	0.619	0.171	0.797	0.902	0.171	0.171	0.797	0.902
HW = 5	$r = 0.744^*$	0.436	0.051	0.126	0.245	0.227	0.121	0.307	0.090	0.358	0.058	-0.032	0.358	0.358	0.058	-0.032
	$P = 0.0001$	0.048	0.027	0.586	0.248	0.322	0.601	0.175	0.698	0.111	0.801	0.889	0.111	0.111	0.801	0.889
HW = 9	$r = 0.747^*$	0.429	0.042	0.188	0.260	0.191	0.164	0.296	0.150	0.400	0.049	-0.053	0.400	0.400	0.049	-0.053
	$P = 0.0001$	0.053	0.858	0.414	0.256	0.407	0.451	0.192	0.516	0.072	0.832	0.819	0.072	0.072	0.832	0.819
HW = 15	$r = 0.731^*$	0.418	0.039	0.205	0.258	0.179	0.162	0.292	0.285	0.422	0.017	-0.088	0.292	0.292	0.017	-0.088
	$P = 0.0001$	0.059	0.867	0.372	0.258	0.437	0.482	0.199	0.210	0.057	0.942	0.703	0.199	0.057	0.942	0.703

* $P < 0.0042$ after bonferroni correction for multiple comparisons. Note: Rs = resting state; PLE = power law exponent.

task induced activity correlation in PACC. No significant correlation between the other resting state measures (ALFF, ReHo, and SD) and task induced activity in PACC was observed (see Supplementary Materials and Table S2).

In sum, our data show that the degree of the scale-free activity during a resting state in specifically PACC predicts neuronal differentiation between animate and inanimate targets during task-evoked activity. This suggests that the interindividual variability in the scale-free properties of PACC resting state activity is related to the interindividual variability in differentiating between animate and inanimate target during task evoked activity in the same region.

Discussion

We aimed to test whether the scale-free properties of brain's spontaneous activity, as indexed by PLE, can predict interactions with animate (as distinguished from inanimate) stimuli. Our behavioral results demonstrated that participants subjectively perceived animate stimuli as closer in space, as temporally more synchronous with the self, and as more personally relevant. Thus, the animate stimuli were phenomenally considered as more similar and aligned with the self. The fMRI results showed that task-evoked activity in right PI, in a cluster encompassing mPFC and PACC, and in mSFG significantly differentiated between animate and inanimate stimuli. Moreover, we found that right PI and PACC are functionally connected in the animate context as well as during the resting state. Finally, interindividual differences in task-evoked activity during animate versus inanimate stimuli were predicted by interindividual differences in the scale-free properties of the brain spontaneous activity as indicated by PLE, specifically in PACC. Together, our results provide behavioral and neuronal evidence for a differential processing of animate versus inanimate stimuli. Intriguingly, we demonstrate that the spontaneous activity's scale-free properties in PACC could be preferentially tuned to process animate stimuli, which, as we suggest, allows to align the brain to the immediate naturalistic—animate environment.

Behavioral Findings

The behavioral results indicated a significant psychological difference between animate and inanimate targets on all the dimensions investigated. Active interaction with animate reality, that is, other individuals, is perceived as closer in space, as temporally more synchronous with the own self, and as more personally relevant (i.e., self-related), compared with the inanimate target. Synchronicity, closeness and self-relatedness represent a subjective perception of self-similarity for the animate target—the other may consequently be perceived as another self, for example, an animate self, rather than as mere object (that has no self at all). Our behavioral data are well in accordance with other reports suggesting that conspecifics may be approached as having similar inner experiences like ourselves (Mandler 1992; Meltzoff and Brooks 2001; Gallese 2003, 2014; Hurley 2008; Northoff and Panksepp 2008; Northoff 2016a).

To control for possible confounding factors, we also evaluated the effect of familiarity of the stimuli. In accordance with previous conceptual and empirical investigations (Qin and Northoff 2011; Qin et al. 2012), various control analyses for familiarity support that, although self-relatedness and familiarity are correlated concepts, the difference between animate and inanimate cannot be explained by familiarity. Therefore, perceived similarity of spatial and temporal features (Hasson

and Frith 2016) may be considered representative for a social relation between two selves as distinct from a relation between self and object (Thompson and Varela 2001; Northoff 2017; Northoff and Huang 2017). This supports our hypothesis that the animate target is not only approached as being similar to the self, but that such intersubjective phenomenon can also be operationalized in terms of perceived time and space similarity (Fingelkurts et al. 2013; Northoff and Huang 2017).

Task-Evoked Activity

The behavioral data are complemented by the fMRI results. Analysis of task-evoked activity showed that 3 clusters (right PI, mPFC comprising PACC, and mSFG) (Fig. 4) are involved in differentiating between animate and inanimate targets. We also found a different degree of context-dependent FC among PI and PACC between animate and inanimate conditions (Fig. 5). Similar regions have been reported in previous experiments concerning touch paradigms (Tsakiris et al. 2007; Craig 2002, 2009, 2010; Ebisch et al. 2011). Our study extends these findings by showing that the neuronal activity of these regions during an active touch paradigm allows to distinguish between animate and inanimate stimuli.

The mSFG (BA 6) is associated with various aspects of motor execution, such as motor initiation, planning and sequencing (Catalan et al. 1998; Schubotz and von Cramon et al. 2001, 2002). Our findings extend previous knowledge about the relationship between brain activity and the environment, showing that the recruitment of this sensorimotor region is increased when interacting with animate targets, possibly enhancing coordination of motor execution. Interestingly, this region may be part of a larger network putatively involved in simulating the other's sensorimotor experiences during social interaction and integrating this information with one's motor coordination (Hurley 2008; Gallese 2014).

The PI is central in interoexteroceptive processing, in regulating physiological reactivity and homeostatic states of the own body (Craig 2002, 2003, 2004, 2009; 2011; Critchley 2005; Menon and Uddin 2010; Northoff et al. 2011; Seth 2013), while mPFC and PACC have been frequently associated with the sense of self and socioemotional processing (Kelley et al. 2002; Northoff and Bempohl 2004; D'Argembeau et al. 2005; Gillihan and Farah 2005; Northoff et al. 2006; Supekar et al. 2010; van der Meer et al. 2010; D'Argembeau 2013; Murray et al. 2015; Sui and Humphreys 2015). We further expanded the functional characterization of these regions by showing their importance in distinguishing animate from inanimate stimuli.

Particularly, analysis of task-evoked activity showed unchanged neuronal activity in mPFC, while the same was true for the more specific PACC region obtained by gPPI (Figs 4 and 5B) during the animate target touch. By contrast, the inanimate target touch induced decreased activity in these regions. Such an absence of any substantial change during the animate condition in mPFC and PACC may reflect its "default" functionality (Raichle 2015; Qin and Northoff 2011), whereas the decreased activity in mPFC and PACC during the inanimate condition suggests a suppression of that default. An opposite activity pattern was observed in PI that exhibits decreased activity during animate targets and no activity change during inanimate targets.

Considering the task-evoked activity findings, we assume that PACC and mPFC, maintain their default activity during animate stimuli. This goes along with a suppression of one's own body-related activity in PI, at least when we actively interact with someone else's body as when actively touching an

animate target. These activity patterns in PACC and PI could emerge from their interaction, given that context-dependent FC (gPPI) showed that right PI and PACC are negatively correlated only during the active touch of the animate target, but not of the inanimate target. However, as gPPI does not provide information about the directionality of inter-regional interactions, the interpretation of the context-dependent connectivity between PI and PACC activity requires further studies.

The fact that the PACC maintained its default functionality during animate condition suggests that the other individual is perceived as related to the own self. Such "virtual self-expansion" of the self (Sui and Humphreys 2015; Northoff 2016a) is also supported by our behavioral findings showing that the animate target was perceived as closer to the self.

Resting State Activity—Brain's Spontaneous Activity Predicts Animate Task-Evoked Activity

Our main aim was to investigate how the spontaneous brain activity, as indexed by PLE, can be related to the task-evoked neuronal activity during interactions with animate versus inanimate stimuli. Firstly, transitioning from task to rest, we showed that PI and PACC were also intrinsically connected during the resting state. This implies that these regions play a central role in the rest-task relation. Secondly, we investigated the scale-free properties of resting state activity in the resulting ROIs from our analyses and tested whether they predicted the task-evoked activity. Such a predisposition of spontaneous brain activity for animate stimuli is further supported by the resting state PLE results. Consistent with previous studies, our data showed that the spontaneous brain activity during an independent resting state period is characterized by scale-free properties, like many systems found in nature (Chialvo 2010; He et al. 2010) and as observed in fMRI signals (He et al. 2010; He 2011; Huang et al. 2015, 2016). Extending previous studies, the fMRI analyses showed that the differentiation between the animate and inanimate targets in PACC during task-evoked fMRI could be predicted by the resting state activity as indexed by PLE in the same region.

Interestingly, this was true only for PACC, but not for the PI, mPFC, or mSFG. This result suggests that PACC's scale-free resting state properties are specifically related to a differentiation of animate from inanimate stimuli in task-evoked activity. Analogous findings of specific relations between scale-free properties and mental features have been observed regarding the self (Huang et al. 2016) and consciousness (Zhang et al. 2017). This is well in line with our finding of animate task evoked activity being specifically predicted by resting state PLE (rather than ALFF, ReHo, and SD). More generally, this points to the relevance of the stochastic temporal structure of the resting state in shaping the processing of the animate stimuli, including their spatial and temporal features. The finding that PACC was connected with PI both during the interaction with animate stimuli and during an independent resting state period suggests a neural predisposition (Northoff 2013, 2014a, 2014b) of spontaneous activity during a resting state for functional interactions between PI and PACC during task-evoked activity in relation to animate versus inanimate stimuli. Such relationship could reflect the role of PACC in self-other similarity (Kelley et al. 2002; Benoit et al. 2010; Northoff 2017) and at the same time of PI in self-other distinction (Ebisch et al. 2011) as 2 complementary processes for the interaction with the animate environment.

Limitations

Some limitations of the study have to be mentioned. The fMRI study did not directly address the psychological components of the associated behavioral experiment regarding the animate and inanimate targets. However, we were primarily interested in designing an ecological–naturalistic experiment where the individual in the MRI scanner is not only passively receiving stimuli, but is actively interacting with the external animate–inanimate environment. Future studies may attempt to disentangle the different psychological domains involved during the interaction with external reality and may want to investigate other modalities of interaction different from touch. Nevertheless, future research may also want to combine behavioral and fMRI data for the analysis of brain activity.

Conclusions

We here demonstrate for the first time that the brain spontaneous activity predisposes the processing of animate stimuli (as distinguished from inanimate ones). Our fMRI results highlight particularly the role of PI and PACC in mediating animate features as distinguished from inanimate features of external targets. Most important, interindividual differences in task-evoked activity in PACC distinguishing animate from inanimate stimuli, were predicted by interindividual differences in the scale-free properties of spontaneous brain activity in the same region. Taken together, the findings show that the brain's spontaneous activity in PACC is central in the preferential processing of animate stimuli. We therefore assume that the spontaneous activity's scale-free properties allow our brain to attune to our immediate animate environment.

The results also carry major implications for both psychopathology and artificial intelligence (AI). For instance, patients suffering from major depressive disorder or trauma related disorders often perceive themselves and their environment as live-less and thus as inanimate rather than animate (Northoff 2016b, 2016c). Following our results, this tendency may be related to abnormal scale-free properties in their spontaneous activity which may have lost its tuning to animate (rather than inanimate) stimuli. Finally, concerning AI, following our findings, AI needs to be designed in such way that intrinsic activity is aligned with the respective environmental context as, for instance, by preferentially processing animate stimuli.

Supplementary Material

Supplementary material is available at *Cerebral Cortex* online.

Funding

Canadian Institute of Health Research, Michael Smith Foundation, EJLB-Canadian Institute of Health Research, Canada Research Chair to G. Northoff; by the National Natural Science Foundation of China (No. 31271195); by the grant from the Ministry of Science and Technology of China, National Key R&D Program of China (2016YFC1306700) and from the European Union's Horizon 2020 Framework Programme for Research and Innovation under the Specific Grant Agreement No. 785907 (Human Brain Project SGA2).

Notes

Conflict of interest: The authors declare no competing financial interests.

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