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Resting state glutamate predicts elevated pre-stimulus alpha during self-relatedness: A combined EEG-MRS study on "rest-self overlap"

Yu Bai[1], Takashi Nakao[2], Jiameng Xu[3,4,5,6], Pengmin Qin[3,7,4], Pedro Chaves[3], Alexander Heinzel[8], Niall Duncan[3,9], Timothy Lane[7,4,10,5], Nai-Shing Yen[5,6], Shang-Yueh Tsai[5,11], and Georg Northoff[3,7,4,5,9]

[1]Department of Psychology, Nagoya University, Nagoya, Japan
[2]Department of Psychology, Graduate School of Education, Hiroshima University, Higashi-Hiroshima, Japan
[3]Institute of Mental Health Research, University of Ottawa, Ottawa, Canada
[4]Brain and Consciousness Research Center, Departments of Psychiatry and Radiology, Taipei Medical University-Shuang Ho Hospital, New Taipei City, Taiwan
[5]Research Center for Mind, Brain and Learning, National Chengchi University, Taipei, Taiwan
[6]Department of Psychology, National Chengchi University, Taipei, Taiwan
[7]Graduate Institute of Humanities in Medicine, Taipei Medical University, Taipei, Taiwan
[8]Department of Nuclear Medicine, RWTH Aachen, Aachen, Germany
[9]Centre for Cognition and Brain Disorders (CBBD), Normal University Hangzhou, Hangzhou, China
[10]Institute of European and American Studies, Academia Sinica, Taipei, Taiwan
[11]Graduate Institute of Applied Physics, National Chengchi University, Taipei, Taiwan

Recent studies have demonstrated neural overlap between resting state activity and self-referential processing. This "rest-self" overlap occurs especially in anterior cortical midline structures like the perigenual anterior cingulate cortex (PACC). However, the exact neurotemporal and biochemical mechanisms remain to be identified. Therefore, we conducted a combined electroencephalography (EEG)-magnetic resonance spectroscopy (MRS) study. EEG focused on pre-stimulus (e.g., prior to stimulus presentation or perception) power changes to assess the degree to which those changes can predict subjects' perception (and judgment) of subsequent stimuli as high or low self-related. MRS measured resting state concentration of glutamate, focusing on PACC. High pre-stimulus (e.g., prior to stimulus presentation or perception) alpha power significantly correlated with both perception of stimuli judged to be highly self-related and with resting state glutamate concentrations in the PACC. In sum, our results show (i) pre-stimulus (e.g., prior to stimulus presentation or

Correspondence should be addressed to: Georg Northoff, Mind, Brain Imaging and Neuroethics, Royal Ottawa Healthcare Group, University of Ottawa Institute of Mental Health Research, 1145 Carling Avenue, Room 6467, Ottawa ON K1Z 7K4, Canada. E-mail: georg.northoff@theroyal.ca; www.georgnorthoff.com; Timothy Lane, Brain and Consciousness Research Center, Taipei Medical University-Shuang Ho Hospital, New Taipei City, Taiwan. E-mail: timlane13@gmail.com

Yu Bai and Takashi Nakao equally contributed to this article.

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perception) alpha power and resting state glutamate concentration to mediate rest-self overlap that (ii) dispose or incline subjects to assign high degrees of self-relatedness to perceptual stimuli.

Keywords: Self-referential processing; Perigenual anterior cingulate cortex; MRS; EEG; Glutamine.

The concept of "self" has been investigated by philosophers for millennia; recently, however, it has also become a major topic in neuroscience. Imaging studies that investigate the self-relatedness of stimuli reveal strong neural recruitment of subcortical and cortical midline structures (CMS) during presentation of stimuli specifically related to self (Northoff et al., 2006; Qin & Northoff, 2011). These regions include the ventromedial prefrontal cortex, the perigenual anterior cingulate cortex (PACC), as well as subcortical regions like the ventral striatum and the ventral tegmental area. This set of midline regions also forms the core of the default-mode network (DMN), which has been associated with particularly high resting state activity (Buckner, Andrews-Hanna, & Schacter, 2008; Raichle et al., 2001).

Importantly, several studies (D'Argembeau et al., 2005; Qin et al., 2012; Schneider et al., 2008; Whitfield-Gabrieli et al., 2011) discovered overlap between resting state activity and self-related activity in anterior CMS like the PACC. In these regions, high self-related stimuli seem to correlate with less deviation from resting state activity, relative to low self-related activity. But the mechanisms of this neural overlap between resting state and self-related activity, what we have dubbed the *rest-self overlap*, remain unclear.

The brain's resting state activity or intrinsic activity has come increasingly into focus recently (Northoff, 2014a, 2014b). The term "resting state activity" is paradoxical though since it denotes exactly the opposite, namely that the brain is never at rest. While a continuous level at rest can be found throughout the whole brain in any region, resting state activity in DMN and especially the midline regions seems to show some peculiarities in that it is particularly high and variable (see Northoff, 2014a, 2014b; Raichle et al., 2001). How though do these specific features of the midline regions' resting state activity impact subsequent stimulus-related activity during the processing of especially self-related stimuli? We currently do not know. The observed rest-self overlap suggest special relationship between, for instance, pre-stimulus activity levels (that somehow in a yet unclear way must be related to the task-free the resting state) and stimulus-induced activity during high self-related stimuli.

Several studies have combined functional magnetic resonance imaging (fMRI) and electroencephalography (EEG) in demonstrating that pre-stimulus activity can indeed predict neural and behavioral effects of subsequent stimuli and tasks (for overviews, see Northoff, Qin, & Nakao, 2010; Sadaghiani, Hesselmann, Friston, & Kleinschmidt, 2010). For example, the level of pre-stimulus (e.g., prior to stimulus presentation or perception) activity in the fusiform face area, as measured with fMRI, predicts both the degree of neural activity during subsequent stimulus presentation and whether a given stimulus is perceived as a face or a vase (for an excellent overview, see Sadaghiani et al., 2010; for similar results, albeit with different tasks, see Hsieh, Colas, & Kanwisher, 2012; Park & Rugg, 2010; Shibata et al., 2008). Several analogous investigations have been carried out using EEG: here power or phase patterns of the resting state, or pre-stimulus (e.g., prior to stimulus presentation or perception) activity, predict neural and behavioral stimulus-related activity during decision-making and perceptual tasks (Ai & Ro, 2014; Linkenkaer-Hansen, Nikulin, Palva, Ilmoniemi, & Palva, 2004; Nakao, Bai, Nashiwa, & Northoff, 2013; van Dijk, Schoffelen, Oostenveld, & Jensen, 2008; Weisz et al., 2014).

But whether pre-stimulus (e.g., prior to stimulus presentation or perception) or resting state activity enables prediction of how subjects will respond to *self-related stimuli* has not yet been investigated. Because of the observed rest-self overlap, and reasoning by analogy, we conjectured that pre-stimulus (e.g., prior to stimulus presentation or perception) activity can be employed to predict neural activity when subjects perceive or render judgments about self-related stimuli. In other words, the working hypothesis is—pre-stimulus (e.g., prior to stimulus presentation or perception) or resting state activity may enable us to predict whether the subject perceives or judges any given stimulus as self-related, on a scale that ranges from high to low. Investigating high self-related stimuli, several EEG studies showed changes around 150–400 ms and especially lower (8–9 Hz) alpha band power changes post-stimulus (Justen, Herbert, Werner, & Raab, 2014; Mu, Fan, Mao, & Han, 2008; and, for a recent review on EEG studies of self, Knyazev, 2013). These findings, however, leave untested the question as to whether pre-stimulus or resting state activity affects self-related stimulus-induced activity on either neural (viz., stimuli-induced electrophysiological activity) or behavioral levels (viz., judging stimuli for their degree of self-relatedness, high or low).

In addition to investigating pre-stimulus (e.g., prior to stimulus presentation or perception) electrophysiological activity, because this activity is mediated by the excitation-inhibition balance (EIB) and that balance has been successfully modeled as due to glutamate–GABA interaction, especially in the lower frequency bands upon which we focus, we sought to identify this activity's biochemical substrate. Although inhibitory GABA has recently been shown to mediate EEG task-evoked measures like gamma band oscillations (Lally et al., 2014; Muthukumaraswamy, Edden, Jones, Swettenham, & Singh, 2009), studies on excitatory glutamate modulation of EEG measures have been reported less widely (for exceptions, see Lally et al., 2014; for animal studies, see Morales-Villagrán, Medina-Ceja, & López-Pérez, 2008). Glutamate is an excitatory transmitter that fMRI and magnetic resonance spectroscopy (MRS) analyses have shown to mediate resting state activity, including both intra-regional activity levels and trans-regional functional levels (Duncan, Enzi, Wiebking, & Northoff, 2011; Duncan et al., 2013; Enzi et al., 2012; also see Falkenberg, Westerhausen, Specht, & Hugdahl, 2012; Scheidegger et al., 2012). Such glutamatergic modulation of the resting state suggests that glutamate might mediate the influence of pre-stimulus state activity on stimulus-related activity. But the hypothesis remains untested, both in general and in the case of self-related stimuli.

Accordingly, the general aim of our combined EEG-MRS study was to investigate both electrophysiological and biochemical correlates of the relationship between (i) resting state activity and (ii) stimulus-related activity while subjects perceive and render judgments concerning self-related stimuli. In short, we investigated the electrophysiological and biochemical mechanisms of the rest-self overlap. More specifically, our first aim concerned whether pre-stimulus (e.g., prior to stimulus presentation or perception) activity levels can be marshaled so as to predict how stimuli are perceived and classified as either high or low self-related. We hypothesized that pre-stimulus (e.g., prior to stimulus presentation or perception) activity in the lower alpha range (8–9 Hz) would precede those stimuli that subjects perceived or judged to be high self-related. To test this hypothesis, we conducted an EEG study wherein subjects were shown a standardized set of pictorial stimuli that they were required to assess as high or low self-related.

Our second aim comprised investigating glutamatergic modulation of pre-stimulus (e.g., prior to stimulus presentation or perception) activity changes. Toward that end, using MRS, we studied the same subjects who had participated in the EEG study with both EEG and MRS being measured in a random sequence. By so doing we were able to measure glutamate concentrations in several regions: PACC, dorsolateral prefrontal cortex (DLPFC), occipital cortex (OCC), and thalamus (THA). Based upon the rest-self overlap considerations adumbrated above, we hypothesized that glutamate in the PACC—but not in the other regions—would mediate elevated pre-stimulus alpha power at frontal regions for stimuli that subjects assessed as high self-related. Our group has abundant experience in combining MRS with other imaging modalities (Duncan et al., 2011, 2013; Enzi et al., 2012; Hayes et al., 2013; Northoff, 2007; Wiebking et al., 2014); this experience enabled us to link pre-stimulus (e.g., prior to stimulus presentation or perception) activity levels (as measured in EEG) to biochemical modulation by resting state glutamate concentration (as measured in MRS).

EXPERIMENTAL PROCEDURES

Subjects

Twenty-seven students were recruited from a local university to participate in this experiment and each was given a modest remuneration. Of the 27, data sets for 11 were excluded, both because of EEG or MRS artifact and because of the hypothesis-driven need to identify an equal distribution of high and low self-related responses. Thus, results reported here are for a total of 16 participants. All participants were right-handed, had normal or corrected-to-normal vision, and no history of neurological disorders; they were also 20 years of age, or older, as 20 is the age of the majority in Taiwan. Informed consent was obtained after the experiment was explained and after each participant was carefully screened. IRB approval for this project was granted by the Taipei Medical University-Joint Institutional Review Board (approval no.: 201209022).

Overall design

EEG was employed while participants viewed various emotional and nonemotional pictures. First, these pictures were just perceived, while participants exercised no judgment. Second, participants were required to evaluate or render judgment: to judge whether the objects or events in the pictures are personally relevant (viz., high or low self-related). While their EEG was being recorded, participants were able to choose between high and low by pressing a button available to them.

MRS measurement of Glx, the combined concentration ratio of glutamate/glutamine to creatine, was employed in order to separate glutamate and glutamine so as to identify differential correlation findings for both substances (e.g., Duncan, Wiebking, & Northoff, 2014). Target regions were the PACC, DLPFC, OCC, and the THA. After concluding both EEG and MRS, participants were asked to perform subjective ratings of the pictures' distinct dimensions (emotional valence, arousal, meaningfulness, personal relevance, as well as time and space perception).

Visual stimuli

Participants were presented with 114 emotional and neutral pictures from the International Affective Picture System (IAPS). The selection of the pictures was based upon previous ratings (Libkuman, Otani, Kern, Viger, & Novak, 2007) for the dimensions personal relevance (viz., high and low self), valence and arousal, as well as ratings from Schneider et al. (2008), Northoff et al. (2009), and Grimm et al. (2006, 2009). Based upon these ratings, stimuli were balanced with regard to valence, arousal, and self-relatedness. This allowed us to vary single dimensions such as self-relatedness (personal relevance) while leaving the other dimensions (valence and arousal) maximally unaltered. The dimensions of self-relatedness, emotional valence, and arousal were all balanced in their high and low degrees; this means that there were no significant differences in the stimuli themselves concerning all three dimensions. Having balanced the dimensions in this way made it possible to attribute our subjects' assessments of stimuli during EEG to the subjects themselves (viz., their individual or subjective preferences) rather than to the stimuli or objective features of the stimuli.

All pictures were presented twice, in a randomized sequence. By pressing a button, they could render a judgment of high or low self-relatedness/personal relevance. After 10–14 s of fixation presentation (pre-stimulus), pictures were presented to participants for a 3 s period of "pure" perception, a period during which participants were not asked to do anything. This period was followed by a fixation cross with a varied duration of 3–5 s (see Figure 1). The fixation cross, in turn, was followed by a judgment period, wherein only the question requesting a judgment—but not the picture—was shown. Judgments concerned self-relatedness, as explained above. The judgment period lasted for 3 s and was followed by a period of 1–2 s to allow for a blink. The main focus for EEG analysis was on the period prior to the perception of the stimulus that we coin "pre-stimulus." In contrast, the judgment period only served for behavioral purpose to obtain the subject's ratings of the preceding picture. Hence, in the following the term "pre-stimulus" refers to the period that immediately precedes the presentation of the stimulus, the perception period, rather than the judgment period.

EEG data acquisition and analysis

EEG data were recorded using a Neuroscan amplifier (Compumedics Neuroscan, Charlotte, NC, USA) and Ag/AgCl electrodes through a 64-channel cap (according to the International Ten-Twenty System) referenced to the nose tip. Data were sampled at 1000 Hz with DC recording. The impedance of each electrode was kept below 5 kΩ and 60 Hz was notched. The electrooculogram was recorded by two pairs of electrodes, one pair above and below the right eye and the other on the outer canthus of each eye. A ground electrode was attached to the middle of the forehead.

EEG data analysis was performed using EEGLAB toolbox (Delorme & Makeig, 2004) running under Matlab 7.9.0 (The Mathworks Inc., Natick, MA, USA). Data were filtered using a low-pass filter 120 Hz, and a high-pass filter of 1 Hz for the EEG data. Stimulus-locked data epochs starting from 3000 ms before and 3000 ms after the stimulus onset were extracted.

Artifact rejection

Epochs with irregular noise were identified and rejected using a computer algorithm based on abnormal statistical distribution, as well as by inferences from visual inspection (Delorme, Sejnowski, & Makeig, 2007). Typical physiological artifacts (e.g., eye blinks, eye movement, and muscle potentials) were retained for the independent component analysis (ICA). The

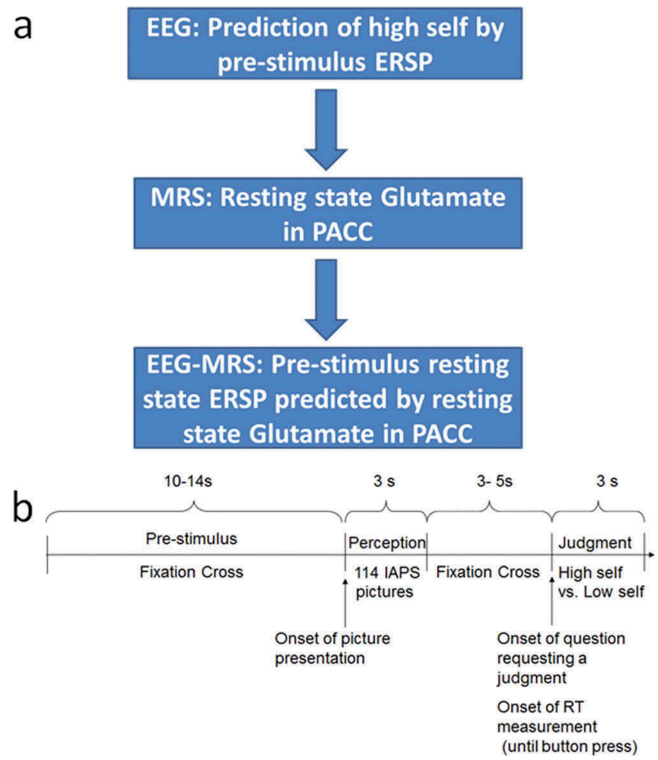

Figure 1. Experimental design and paradigm. The figure illustrates the three stages of our experimental design (a) and paradigm (b). (a) Our experimental design comprised three stages: the first stage consisted in measuring EEG during perception of stimuli and their subsequent assessment as high or low self-related. The second stage complemented the first by measuring resting state glutamate in MRS. For the third stage, resting state glutamate was correlated with pre-stimulus EEG. We need to detail the term "pre-stimulus ERSP". The term "pre-stimulus" refers to the period that immediately precedes the presentation, for example, pure perception of the stimulus (rather than the period preceding the judgment). The term ERSP refers usually to stimulus-related changes; however, in order to describe the pre-stimulus power changes related to and that precede (and distinguish) high and low self-related stimuli, we use the term ERSP. The ERSP does then still refer to changes related to stimuli but those that precede (rather than occur during or follow) the presentation of the actual stimuli by distinguishing between low and high self-related stimuli. (b) Experimental paradigm: after a 10–14 s fixation cross (pre-stimulus duration), subjects were presented with well-matched and selected (see "Methods") stimuli from the IAPS for 3 s. This was followed by a fixation cross and subsequent assessment of the stimuli as high or low self-related. Assessment of a given stimulus was followed by 1–2 s blink period.
ERSP, event-related spectral perturbation; MRS, magnetic resonance spectroscopy; PACC, perigenual anterior cingulate cortex; IAPS, International Affective Picture System; RT, reaction time.

extended infomax ICA were performed to obtain 64 ICs from the stimulus locked epoch in each participant. For each IC, an equivalent current dipole was estimated (DIPFIT 2.2, EEGLAB plug-in using Fieldtrip toolbox functions; Robert Oostenveld). ICs representing the typical physiological artifacts and electrode artifacts were identified by visual inspection of their time course data, multitrial event-related potential (ERP) image plots, the power spectrum, scalp topography, and dipole. On average, three ICs of stimulus-locked epoch were rejected from each participant's data. The remaining ICs were back-projected onto the scalp electrodes to obtain artifact-free EEG data. After completion of these artifact rejection analyses, each type of data epoch was divided into experimental conditions.

ERP analyses

For ERP extraction, data were filtered with a low-pass filter of 15 Hz and were baseline corrected using data from −100 ms to 0 ms relative to stimulus onset, that is, the presentation or perception of the stimulus (rather than the judgment). Data for high self- and low self-conditions were averaged across trials.

ERSP analyses

Event-related spectral perturbation (ERSP) is the degree to which spectral power differs from mean baseline power as a function of time and frequency. For ERSP calculation, the Morlet wavelet was used. 99 log-spaced frequencies ranging from 1 to 100 Hz were calculated every 1 ms starting from −3000 ms prior to and ending up to 3000 ms following stimulus onset (baseline from −1900 ms to −1700 ms). Wavelet cycle was increasing from 2 Hz, at the lowest frequency measured, 0.08 Hz, to 10 Hz at the highest, 100 Hz (Delorme & Makeig, 2004). To compare the difference between the high self- and low self-condition, we focused alpha band (8–9 Hz) in ERSP. Since several studies during self- versus other-judgment self-reference showed the activity at Cz (Geng, Zhang, Li, Tao, & Xu, 2012; Mu & Han, 2010), we here also focused on ERSP at Cz.

We performed cluster-based permutation test (Cohen, 2014) to avoid the issue of multiple comparisons in the large time-frequency space. First, we calculated *t*-vale for each pixel data of time-frequency window (−1000 to 0 ms, 8–9 Hz) at Cz, and those were thresholded using uncorrected parametric *p*-value ($p < .05$). Then, bwconncomp Matlab function was applied to identify clusters in the thresholded map, and the sum of *t*-value in each cluster was calculated. To generate probability distribution of the sum of *t*-value under null hypothesis, the 2000 times iterations of the following three steps were conducted: first, the condition label (self vs. non-self) was randomly shuffled. Second, we calculated *t*-value for each pixel data, and those were thresholded using uncorrected parametric *p*-value ($p < .05$). Third, we collected the biggest sum of the absolute *t*-value in the cluster. The distribution generated by the iterations was used to calculate the critical value.

MRS data acquisition and analysis

Single-voxel 1H MR spectra were acquired in a separate session (in randomized sequence with EEG) during the resting state using a 3T whole body MRI system (Skyra, Siemens Medical Solutions, Erlangen, Germany) using a 32-channel head coil (PRESS, TR = 2 s; TE = 40 ms; bandwidth = 2000 Hz; sample points = 2048; averages = 256). Voxels were prescribed on a high-resolution T1-weighted 3D data set (MPRAGE, TR = 2 s; TI = 1.1 s; TE = 4.8 ms; flip angle = 7; field of view = 256 × 256 × 192 mm; spatial resolution = 1 × 1 × 1 mm). One voxel of 20 × 10 × 20 mm was placed on the bilateral PACC, while a second was placed on the left DLPFC cortex (20 × 20 × 20 mm) in order to control for the regional specificity of the PACC effects. So as to account for visual effects, we also placed a voxel (20 × 20 × 20 mm) on the OCC. And, one additional voxel was placed on the THA (15 × 15 × 20 mm).

Because of the crucial role played by the PACC during self-related processing in the CMS, we concentrated our correlation analysis on this region, while other regions were used as controls. For each region, additional non-water-suppression scan without presaturation of water signal was acquired using four averages for automatic phase correction.

Spectra were analyzed using fully automatic LCModel software version 6.1.0 (www.s-provencher.com/pages/lcmodel.shtml). Metabolite concentrations of *N*-acetyl aspartate, total creatine (tCr) including creatine and phosphocreatine, total choline (tCho), myo-inositol (mI), glutamate (Glu), glutamine (Gln), and the combination of glutamate and glutamine (Glx) were obtained. Evaluation of the spectral quality was based on the line width at full-width at half maximum (FWHM) and the signal to noise ratio as provided by LCModel.

For individual metabolites, a standard deviation of the fitting error, Cramér–Rao lower bound (CRLB), was reported. Expressed in concentration percentage, CRLB can function as an indicator of the reliability of metabolic concentration quantification. The CRLB of each metabolite is commonly used to quantify the goodness of fit of the LCModel. Spectra with FWHM line widths larger than 8 Hz, and quantification results with a CRLB higher than 20%, were excluded from further analysis. The measurements for two subjects in the PACC and one subject in the DLPFC were discarded for these reasons (PACC: $n = 16$; DLPFC, OCC < THA). Metabolite concentrations are given as their ratio to the measured tCr concentration. As a slight interdependence, due to a spectral overlap in their resonances, results for glutamate and glutamine, these were quantified together. Recall that this combined concentration ratio of glutamate/glutamine to tCr is herein referred to as Glx. Because the LCModel quantifies glutamate and glutamine separately, individual glutamate and glutamine can be also subjected to further analysis associated with Glx.

Statistical analysis

ERP was averaged over a 1000 ms epoch separately for high self-condition and low self-condition. Baseline was corrected using the mean amplitude during the 200 ms pre-stimuli. A negativity was measured as the mean amplitude between 150 and 300 ms.

A positivity was measured as the mean amplitude between 300 and 400 ms. ERP data were then compared using paired sample *t*-tests. Using Pearson's correlation, the relation was calculated between pre-stimulus (−600 ms to −400 ms) ERSP/alpha power (8–9 Hz) difference between high self-condition and low self-condition—and PACC glutamate/creatine. For each participant, differences in pre-stimulus power were calculated by subtracting the low self-condition from the high self-condition. Because we hypothesized that glutamate in the PACC would mediate elevated pre-stimulus alpha power at frontal regions, we have focused on 14 frontal channels (Fp1,Fpz,Fp2,AF3,AF4,F7,F5,F3,F1,Fz,F2,F4,F6,F8) and applied false discovery rate (FDR) *p*-value correction for the correlation analyses.

RESULTS

Behavioral data

The mean number of pictures judged as high self and low self were, respectively, 21.04 pictures ($SD = 7.35$) and 24.96 pictures ($SD = 7.20$). A paired *t*-test revealed that no significant difference was found ($t(26) = -1.41$, $p = .17$) between high self and low self. The mean reaction time (RT) for the high self-condition was 1101.77 ms ($SD = 269.68$); for low self, 1182.69 ms ($SD = 314.31$). A paired *t*-test revealed that RTs for high self were shorter than for low self ($t(26) = -2.77$, $p = .01$). In accord with available ratings (Libkuman et al., 2007; Northoff et al., 2009; Schneider et al., 2008), we also compared high and low self-related stimuli as judged by our participants with regard to potential differences in emotional valence, and arousal; comparisons yielded no significant differences or correlations with subject ratings. That there were no such differences or correlations suggests that differences in assessment between high and low self-related stimuli were dependent upon participants' subjective preferences rather than upon objective features of the stimuli themselves.

Comparison between high and low self-related stimuli in ERP and ERSP (EEG)

First, we analyzed the ERPs for the perception period. ERPs during this period for pictures that were subsequently rated as high self were compared with those pictures that were rated as low self. A comparison of high to low self-relatedness, as can be seen in Figure 2, yielded differential ERPs between 150 and 400 ms—increased negativity between 150 and 300 ms ($t(20) = -2.82$, $p < .05$ in Fz); comparison also yielded delayed and reduced positivity at 300–400 ms—($t(20) = -1.35$, $p < .05$ in Cz). Since

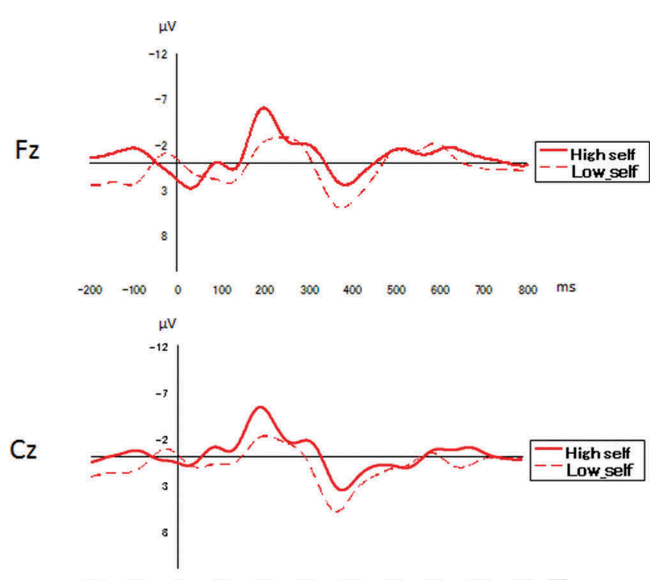

Figure 2. Event-related potentials (ERP) during high and low self-related stimuli. The figure illustrates the ERP for high and low self-related stimuli at Fz and Cz. The curves and analysis reveal marked difference between high and low self-related stimuli, during the 150–400 ms period.

we controlled our stimulus set for valence, arousal, and dominance (see "Methods" section), ERP and subsequent ERSP differences between high and low self-related stimuli must reflect the degree of self-relatedness assigned to the stimuli by subjects (see Figure 2a and 2b).

Based on these results, we calculated ERSP at Cz for the perception periods of high and low self-related stimuli. The ERSPs evidenced a significant difference between high and low self-related stimuli in the lower alpha frequency range, 8–9 Hz, and theta frequency range, 4–7 Hz (see Figure 3a). Most notably, alpha power changes were visible not only during the stimulus-related activity itself, for example, during presentation/perception of the stimulus but also during the pre-stimulus period (preceding the presentation, e.g., perception of the stimulus) at around −600 to −400 ms prior to the onset of the stimulus presentation (see the box in Figure 3b). Cluster-based permutation test yielded significant differences (cluster t-value sum = 141.72, df = 20, cluster count = 57, corrected $p < .05$) in lower alpha (8–9 Hz) between high and low self in ERSP around −500 ms pre-stimulus at Cz (see Figure 3b). This finding was further confirmed by the topographic plot for that time period (see Figure 3c). We also excluded spillover effects from preceding stimuli: we compared high versus low self-relatedness judgment as sorted by the preceding judgment. We did not find any significant difference in ERSP alpha power between high self-relatedness (−0.20 dB) and low self-relatedness (0.18 dB) of the preceding judgment at −600 to −400 ms, ($t(20)$ = −0.09, uncorrected $p > .05$ at Cz).

Collectively, these results demonstrate that the ERSP was significantly stronger in the lower alpha range (8–9 Hz) prior to the onset of stimulus presentation, for example, perception in those stimuli that were evaluated as high self, by comparison to those evaluated as low self. Thus, it seems that the degree of pre-stimulus alpha power can predict subjects' perception (and subsequent assessment) of stimuli as high or low self-related. And,

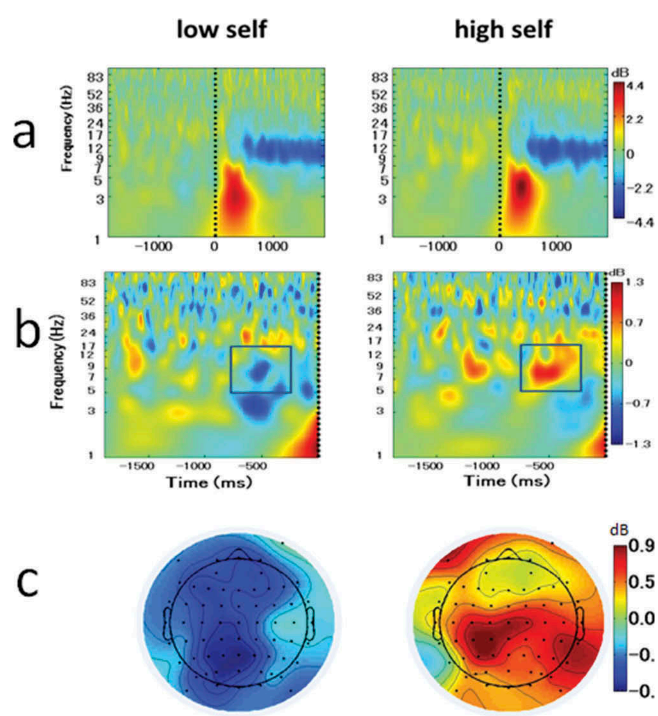

Figure 3. Event-related spectral perturbations (ERSP) during high and low self-related stimuli. The figure illustrates the ERSP for high and low self-related stimuli at Cz for stimulus onset (a) and the pre-stimulus period (e.g., prior to stimulus presentation or perception) (b) as well as the topographic maps of ERSP/alpha power for −600 to −400 ms prior to the presentation of those stimuli that were subsequently perceived (and assessed) as high and low self-related stimuli (c). Both exhibit low and high self-related stimulus conditions. Note that the post-stimulus onset (e.g., during stimulus presentation or perception) increase in ERSP in the alpha range (8–9 Hz) and theta range (4–7 Hz) at around 0–200 ms during high-self-related stimuli was larger than that during low self-related stimuli (a). These post-stimulus data are complemented by a pre-stimulus (e.g., prior to stimulus presentation or perception) increase in alpha during high self-related stimuli, at about −600 to −400 ms (b).

perception, in turn, is accompanied by higher or lower levels of post-stimulus alpha power.

Prediction of ERSP changes (EEG) by glutamate (MRS)

First, we obtained reliable spectra for glutamate in all four regions. We then investigated how the levels of glutamate (Glu/Cr as obtained in MRS) in the PACC (as controlled for by DLPFC, OCC, and THA) were related to the pre-stimulus ERSP changes that predicted high and low self-differentiation. In order to understand that relationship, we entered the concentration of Glu/Cr in PACC as a regressor when calculating the topographic ERSP high and low self-map at −600 to −400 ms. This yielded a significant positive relationship between PACC Glu/Cr and low alpha (8–9 Hz) pre-stimulus (−600 to −400 ms) high–low self-difference at Cz and in the frontal regions (see Figure 4: $r = 0.72$, uncorrected $p = .00227$, FDR corrected $p < .05$): the higher the subject's resting state concentration of glutamate in the PACC, the larger its pre-stimulus (−600 to −400 ms) low alpha (8–9 Hz) power/ERSP difference between high and low self (see Figure 4a).

Most importantly, the correlation with glutamate was specific for pre-stimulus (e.g., prior to the presentation or perception of the stimulus) alpha power since glutamate did not correlate with the post-stimulus onset changes in alpha power. The correlation was also regionally specific since neither did glutamate in the other regions (DLPFC, THA, and OCC) correlate with pre-stimulus alpha power (see Duncan et al., 2014).

To further illustrate the findings, we selected anterior frontal electrodes (F4, F5, F6, and F7) and correlated their respective pre-stimulus alpha power (−600 to −400 ms, −400 to −200 ms, −200

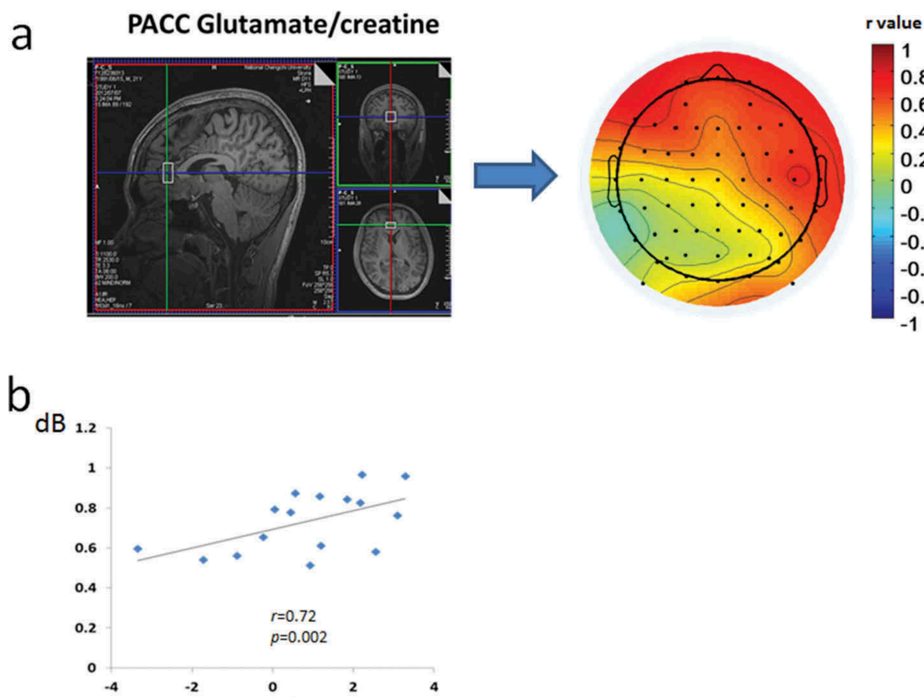

Figure 4. Glutamatergic modulation (MRS) of pre-stimulus event-related spectral perturbations (ERSP) during high and low self-related stimuli. The figure illustrates how the pre-stimulus (e.g., prior to stimulus presentation or perception) ERSP are related to glutamate concentration (set against creatine/Cr) in the PACC, in a topographic map (a) and a single channel (b). By plotting the concentration of glutamate in PACC (a, on the left) against ERSP of all channels at about −600 to −400 ms, we obtained the following topographic map (a, on the right). The deeper the red color, the more the PACC glutamate concentration influenced the pre-stimulus (e.g., prior to stimulus presentation or perception) ERSP at around −600 to −400 ms; this influence was observed especially in frontal and central regions, thereby corresponding to the anatomical location of the PACC. (b) The correlation of the PACC glutamate concentration with the degree of pre-stimulus (−600 to −400 ms) (e.g., prior to stimulus presentation or perception) ERSP in a single channel, F7: the higher the subject's PACC concentration of glutamate, the higher its pre-stimulus (e.g., prior to stimulus presentation or perception) ERSP at −600 to −400 ms, and the more likely the subsequent stimulus will be assessed by the subject as high self-related. Each dot in the graph corresponds to one subject.

to 0 ms, 0 to 200 ms, and 200 to 400 ms) with PACC glutamate concentration. This analysis yielded significant correlations between PACC glutamate and pre-stimulus alpha differences between high and low self for all of the pre-stimulus time windows at F7, F5, and F3 (r = 0.38–0.59; p = .000–.03): the higher the subject's PACC glutamate concentration, the larger its pre-stimulus alpha ERSP difference between high and low self-related stimuli (see Figure 4b).

In sum, resting state concentration of glutamate in the PACC specifically predicts the pre-stimulus state alpha power (8–9 Hz) difference between stimuli that were subsequently perceived (and assessed) as high and low self-related. That is, a higher resting state concentration of glutamate leads to a stronger ERSP pre-stimulus alpha power difference between high and low self-related stimuli. This finding suggests that the level of resting state glutamate modulates pre-stimulus alpha power (prior to presentation or perception of stimuli) in a way relevant to subsequent information processing: viz., the assignment of different degrees of self-relatedness (e.g., high or low) to subsequently perceived stimuli.

DISCUSSION

This is the first combined EEG-MRS investigation of the neural and biochemical correlates of the relationship between resting state and self-related activity—the rest-self overlap. We first focused on whether pre-stimulus activity levels (as accounted for by ERSP in EEG), that is, preceding the presentation or perception of the stimulus, predicted the subjects' subsequent perception (and judgment) of the stimuli as high and low self-related. Second, we sought to determine whether pre-stimulus activity changes were modulated by glutamate resting state levels in the PACC. Our combined EEG-MRS study yielded three main results: (i) postonset stimulus-related ERP differences and power (ERSP) differences between high and low self-related stimulus' perception at approximately 150–400 ms; (ii) elevated pre-stimulus alpha power (ERSP) preceding the presentation, for example, perception of those stimuli that were perceived to be highly self-related; and (iii) glutamate resting state concentration in PACC that correlates with elevated pre-stimulus (i.e., prior to stimulus presentation or perception) alpha power for high self-stimuli, in a regionally (not in other regions like the DLPFC, OCC, or THA) and biochemically (only glutamate, no other substances) specific way.

ERP and alpha power (ERSP) differences between high and low self-related stimuli

The first main finding in EEG concerns the observation of postonset stimulus-related differences during stimulus presentation, for example, perception in both ERP and ERSP differences at around 150–400 ms between high and low self-related stimuli. The ERP showed increased negativity between 150 and 300 ms, which is followed by delayed and reduced positivity between 300 and 400 ms that characterizes high self-related stimuli as distinguished from those that exhibit low self-relatedness. ERSP yielded elevated power specifically in the lower alpha frequency range (8–9 Hz), during high self-related stimuli. Both ERP and ERSP findings are well in accord with previous EEG studies of self-relatedness (see Esslen, Metzler, Pascual-Marqui, & Jancke, 2008; Knyazev, 2013).

Pictures were grouped according to how they were assessed by participants: high or low self-related. Therefore, the ERP and ERSP differences between high and low self-related stimuli must be related specifically to the participants' subjective assessment (rather than to objective features of the stimuli). Moreover, we controlled for other stimulus-related features (e.g., emotional) as well as for task-related effects (e.g., effects of the perception period). Accordingly, it appears to be the case that observed post-stimulus ERP and ERSP differences specifically reflect the subjective component evoked during neural stimulus processing. This is a tentative hypothesis, however, one that requires future studies wherein objective and subjective components of stimulus processing are directly compared to one another.

Pre-stimulus alpha power during high self-related stimuli

In addition to the postonset stimulus-related effects, we also observed pre-stimulus differences prior to the presentation, for example, perception, between those stimuli assessed as high and those assessed as low self-related. More specifically, stimuli that were subsequently perceived and assessed to be high self-related showed elevated power, specifically in the alpha range, beginning at −600 ms. This finding concerning the impact on subsequent perception is compatible with other EEG studies, especially those that involve visual and auditory modalities or cognitive functions (for a review, see Sadaghiani et al., 2010).

This marks the first time that such pre-stimulus prediction has been found applicable to and extendable to participant attribution of self-relatedness. Baldly, elevated pre-stimulus alpha power prior to stimulus-onset, at approximately −600 ms to 0 ms, can be used to predict that subjects will perceive (and subsequently assess) the respective stimulus as high rather than low self-related. It follows then that subjective perception (and assessment) of stimuli as high or low self-related may depend not only upon the stimuli themselves and their objective features, but also on the subjects' prior state, for example, pre-stimulus alpha power that precedes the presentation, for example, perception of the stimulus.

Collectively, our data underscore the special role of power changes, specifically in alpha, during pre-stimulus processing of self-relatedness. Power increases in alpha during stimulus-induced activity when comparing high versus low self-related stimuli have been reported by others (Justen et al., 2014; Knyazev, 2013; Mu et al., 2008). Our data, however, extend these findings: this is the first study that shows pre-stimulus alpha power can predict self-relatedness perception (and subsequent assessment). It seems to be the case that elevated, pre-stimulus alpha power disposes subjects' perception (and assessments) toward assigning a high degree of self-relatedness to the stimuli. In contrast, low level of pre-stimulus alpha power lets subjects perceive (and assess) the subsequent stimulus as low rather than high self-related.

But it remains unclear just what mechanisms enable alpha to play this distinctive role. Although it is well known that alpha is sensitive to changes in resting state activity level, as when shift from eyes open to eyes closed (Barry, Clarke, Johnstone, & Brown, 2009; Barry, Clarke, Johnstone, Magee, & Rushby, 2007; Chen, Feng, Zhao, Yin, & Wang, 2008; Nakao et al., 2013), the functional implications of this role in the resting state have not yet been fully explored. One such functional implication, however, may be indicated by our results—it seems to be a perfect candidate mechanism for neural mediation of the close relationship between resting state activity and self-relatedness, the rest-self overlap. Tentatively then, we propose the hypothesis that alpha power in the brain's resting state is a mechanism by means of which the resting state can select what is relevant for or important to any given person.

The hypothesis that resting state alpha is a mechanism for selecting high self-related stimuli accords well with what is known about the functional role of alpha in general. It has indeed been suggested that rhythmic alpha activity, through event-related synchronization and desynchronization, shapes the functional, timing, and spatial structure available for incoming stimuli, through mediation of activation processes and selective gating by specific networks (Jensen & Mazaheri, 2010; Klimesch, Sauseng, & Hanslmayr, 2007). According to this framework, the fact that our participants subjectively perceive (and assess) standardized stimuli as more or less self-related could result from extrinsic stimuli encountering a distinctive spatiotemporal constellation shaped by pre-stimulus (e.g., prior to stimulus presentation or perception) state alpha power and timing. Future studies utilizing MEG or other technologies might enable more precise investigation of the pre-stimulus alpha's spatiotemporal coordinates, including the mechanisms by means of which those coordinate modulate the degree of self-relatedness attributed to stimuli.

Glutamate modulates pre-stimulus alpha power

In addition to EEG, the subjects also underwent MRS to measure the resting state concentration of glutamate in different regions. We detected that glutamate resting state concentration in the PACC (but not in the DLPFC, OCC, or THA) predicted the degree of pre-stimulus (e.g., prior to stimulus presentation or perception) state alpha power (8–9 Hz) difference between high and low self-related stimuli: that is, the higher the glutamate resting state concentration in the PACC, the higher the pre-stimulus alpha power, and the more likely that the subsequent stimulus will be perceived and assessed as high (rather than low) self-related. This was observed for the whole brain, as shown by our topographical map correlation (Figure 4a) as well as for single anterior frontal electrodes in the pre-stimulus windows (Figure 4b). Most importantly, this correlation was biochemically, regionally, and neuronally specific: it applied to glutamate but not other metabolites; to the PACC, not other regions; and to pre-stimulus (e.g., prior to presentation or perception of the stimulus), not postonset (e.g., during stimulus presentation or perception) stimulus-related ERSP differences.

Glutamate has been demonstrated to modulate resting state measures like the BOLD amplitude in fMRI (Enzi et al., 2012), and the PACC functional connectivity to cortical and subcortical regions (Duncan et al., 2011, 2013; Falkenberg et al., 2012). These findings, however, left unresolved how glutamatergic modulation of resting state activity influences stimulus-induced activity, in general, and self-related stimuli, in particular. Our study is the first to demonstrate that glutamate specifically modulates pre-stimulus state alpha power as measured in EEG. This finding is not only in line with previous EEG investigations of glutamate (Lally et al., 2014), it also suggests that glutamate can influence indirectly, via pre-stimulus state, subsequent stimulus-induced activity: first, glutamate mediates pre-stimulus state activity and then resting state activity modulates stimulus-induced activity. This is unlike the case with GABA, which appears to influence directly stimulus-induced activity (Hayes et al., 2013; Wiebking et al., 2014). In sum, glutamate's influence on stimulus-related behavior, as, for instance, whether a stimulus is judged to be high or low self-related, is indirect, not direct.

As one of the main players, along with GABA, of the EIB, glutamate mediates predominantly the neural excitatory level. Our finding that glutamate mediates the level of pre-stimulus alpha power suggests that pre-stimulus alpha power is related to the excitatory level and, ultimately, the shift of the EIB toward elevated excitation. This finding, in conjunction with our observation that increased alpha power mediates high self-related stimuli, suggests that high levels of glutamatergic-mediated resting state excitation in the PACC incline or dispose subjects to assign high degrees of self-relatedness to subsequent stimuli. This is just a working hypothesis, however, one that requires more detailed investigation of intracranial data measuring firing rates and local field potentials, along with measurement and stimulation of glutamate.

Methodological limitations

We are not able to specify the neural substrate of early pre-stimulus differentiation. Although we are able to exclude spillover effects from preceding judgments, the exact neural mechanisms of pre-stimulus alpha increase remain unclear. These mechanisms may be related to purely spontaneous activity changes in the resting state and also in lower frequency bands like infra-slow frequency bands, because spontaneous activity of this type predominates, especially in CMS like the PACC (see Northoff, 2014a, 2014b; Raichle et al., 2001). In this context, it is intriguing to note that CMS have been associated with both self (Northoff et al., 2006; van der Meer, Costafreda, Aleman, & David, 2010) and the rest-self overlap (D'Argembeau et al., 2005; Qin & Northoff, 2011; Schneider et al., 2008; Whitfield-Gabrieli et al., 2011). But in order to better understand how self and lower frequency bands might be related, future studies that combine the recording of slow cortical potentials in EEG and fMRI during self-relatedness will be necessary. Only by conducting such studies can we further specify the neural mechanisms of elevated pre-stimulus alpha and of processing high self-related stimuli. And, as mentioned above, the use of higher resolution methods such as intracranial recordings will likely be necessary in order to identify the mechanisms whereby the interplay between glutamate concentration and pre-stimulus alpha power is realized.

Another limitation of this study is that we only measured the resting state concentration of glutamate. We did not conduct functional MRS while we did not conduct functional MRS (cf., Lally et al., 2014). A functional MRS study would have enabled us to measure glutamate levels while high and low self-related stimuli were being processed. Functional MRS would have enabled us to match glutamate and alpha power changes temporally.

Finally, we did carefully select our stimuli so as to exclude differences between high and low self-related stimuli, with respect to dominance, valence, and arousal. Nevertheless, we remained unable to control for other possible factors like reward. High self-related stimuli may exhibit a higher degree of reward than those that exhibit low self-relatedness because self appears to be related to distinctive activity levels in the reward system (de Greck et al., 2008, 2009, 2010). Hence, future EEG and MRS studies may be necessary in order to directly compare self-relatedness and reward, as well as to determine how these are modulated by glutamate.

CONCLUSION

This is the first direct investigation of the rest-self overlap in that we investigated the neural and biochemical mechanisms of the relationship between resting state and self-related processing. We demonstrated that the degree of pre-stimulus (e.g., prior to stimulus presentation or perception) changes in alpha power (ERSP) can be used to predict whether subsequent stimuli will be perceived (and assessed) as high or low self-related. Moreover, though conclusions are necessarily tentative, these pre-stimulus (e.g., prior to stimulus presentation or perception) state changes appear to be related to glutamate resting state concentration in the PACC. Taken together, these findings are the first to reveal temporal-neuronal (e.g., alpha power) and biochemical (e.g., glutamate) mechanisms that might mediate the rest-self overlap. Results of this investigation enhance understanding the neuro-biochemical mechanisms involved in the generation of self-relatedness. But the investigation's importance extends beyond just the issue of self-relatedness. These data also reveal some of the mechanisms—viz., alpha power and glutamatergic-mediated neural excitation—by means of which the pre-stimulus resting state (e.g., prior to stimulus presentation or perception) can influence subsequent stimulus processing. Of most importance, our study suggests that these mechanisms have significant psychological consequences, as is the case with the assignment of high or low self-relatedness to stimuli. In a word, these mechanisms partially explain what matters to self, and why.

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