Behavioral/Cognitive

Regional Excitatory–Inhibitory Balance Relates to Self-Reference Effect on Recollection via the Precuneus/Posterior Cingulate Cortex–Medial Prefrontal Cortex Connectivity

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Self-related representation can enhance perception and memory—a phenomenon known as the self-referential effect (SRE). While SRE has been linked to the activation of the default mode network (DMN), including the precuneus/posterior cingulate cortex (Pcu/PCC) and the medial prefrontal cortex (mPFC), the underlying neurochemical processes of DMN activations remain unclear. The balance of excitation and inhibition (E/I balance) within brain circuits is crucial for cognition and may play a role in the SRE. We examine whether the ratio of glutamate/glutamine (Glx) to γ-aminobutyric acid (GABA) concentrations, measured by ^{1}H-magnetic resonance spectroscopy (^{1}H-MRS) as a proxy measure for E/I balance, is associated with DMN neural processes involved in self-referential encoding. Fifty-four healthy participants aged 7–35 (25 female) underwent MRS to measure levels of Glx and GABA in Pcu/PCC and completed an fMRI scan during an encoding task that involved self-referential and semantic judgments. We found that the self-related condition led to better subsequent memory and greater activation in the Pcu/PCC compared with the semantic condition. Activations in the Pcu/PCC were positively correlated with the Glx/GABA+ ratio. Task-dependent functional connectivity analysis revealed that connectivity between the Pcu/PCC and medial prefrontal cortex (mPFC) was positively associated with both the Glx/GABA+ ratio and the SRE effect on recollection accuracy. Furthermore, mediation analysis showed that a higher Glx/GABA+ ratio correlated with better SRE on memory recollection through increased Pcu/PCC–mPFC connectivity. Our study provides valuable insights into how neurochemical activity is associated with self-related cognition via functional connectivity of large-scale brain networks.

Key words: **γ-aminobutyric acid; ^{1}H-magnetic resonance spectroscopy; default mode network; glutamate/glutamine; self-referential effect**

Significance Statement

Self-related representation can enhance perception and memory—a phenomenon known as the self-referential effect (SRE). While SRE has been linked to the activation of the default mode network (DMN), the underlying neurochemical processes remain unclear. Our study found that SRE was associated with the ratio of glutamate/glutamine (Glx) and γ-aminobutyric acid (GABA) concentrations, a proxy measure of excitatory/inhibitory balance, through functional connectivity between key nodes of the DMN. These findings indicate the critical role of excitatory/inhibitory balance in self-related processes, which may provide new insights into psychiatric disorders characterized by impaired self-awareness.

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Introduction

Understanding the self is crucial for individual well-being and social cognition (Linville and Carlston, 1994; Keysers and Gazzola, 2007; Dinulescu et al., 2021). Self-related representation functions as an integration hub that enhances perception and memory (Sui and Humphreys, 2015), a phenomenon known as the self-reference effect (SRE). Atypical self-representation may fail to integrate and enhance information processing, as evidenced by diminished SRE on memory in autism (Grisdale et al., 2014) and schizophrenia (Harvey et al., 2011) with variations linked to social symptoms (Henderson et al., 2009). Studying neurochemical correlates of self-referential thinking in neurotypical individuals is key to understanding self-representation mechanisms and establishing baselines for comparison with related disorders.

Neuroimaging evidence suggests that default mode network (DMN) regions, such as the posterior cingulate cortex (PCC) extending to the precuneus (Pcu) and the medial prefrontal cortex (mPFC), are activated during self-referential process (Craik et al., 1999; Zysset et al., 2002; Fossati et al., 2003). Moreover, one study reported that self-related processes were driven via PCC activation and moderated by the mPFC (Davey et al., 2016). The activation of DMN, indicated by increased blood oxygen level-dependent (BOLD) signal, reflects increased neural activity (Logothetis et al., 2001). Synaptic excitation and inhibition, inseparable events that collectively influence the membrane potential and input resistance, fundamentally regulate neuronal activity (Isaacson and Scanziani, 2011). Changes in the BOLD signal are largely affected by changes in excitation–inhibition (E/I) balance within microcircuits (Logothetis, 2008). The E/I balance is primarily determined by glutamate (Glu) and γ-aminobutyric acid (GABA), the principal excitatory and inhibitory neurotransmitters, respectively. ^{1}H-Magnetic resonance spectroscopy (^{1}H-MRS) is a noninvasive MRI technique to measure Glu and GABA concentrations in the human brain in vivo (Puts and Edden, 2012). The ratio of Glu and GABA concentration could serve as a proxy measure for E/I balance (Ford and Crewther, 2016; Thomson et al., 2024b), reflecting available neurometabolite.

Generally, MRS studies have found that GABA concentration is negatively correlated with BOLD activation changes in the same region like the visual cortex (Muthukumaraswamy et al., 2009, 2012; Donahue et al., 2010), motor cortex (Stagg et al., 2011), and anterior cingulate cortex (ACC; Northoff et al., 2007). Although studies on Glu are relatively limited, they typically show a positive correlation with BOLD activation changes (Bednařík et al., 2015; Ip et al., 2017). Notably, higher regional GABA concentration in the PCC/Pcu was previously linked to increased deactivation of this region during working memory tasks, whereas higher Glu concentration was associated with reduced deactivation (Hu et al., 2013). Regional brain metabolite concentrations also influence intrinsic functional connectivity across large-scale brain networks (Stagg et al., 2014; Levar et al., 2019). Glu/GABA ratio correlated positively with DMN intranetwork connectivity (Kapogiannis et al., 2013). However, how Glu and GABA levels relate to DMN activation and connectivity during self-referential processes, as well as their link with enhanced SRE, remains unknown.

Glu/GABA ratio in the pregenual ACC has been linked to impaired cognitive self-awareness (Kühnel et al., 2020). A study found that increased mPFC Glu levels induced by psilocybin were linked to negatively experienced ego dissolution (Mason et al., 2020). These findings suggest that Glu or GABA concentrations in DMN regions are linked to self-related processes, particularly self-awareness. Based on these previous results, we hypothesized that Glu and GABA concentrations in DMN regions are linked to both their BOLD activation and connectivity to support self-referential processes and their facilitatory effect on memory.

Here, we aim to examine the association between Glu/GABA ratio, activation, and functional connectivity related to self-referential processing. We collected fMRI data during a self/semantic-judgment picture encoding task and acquired ^{1}H-MRS data to quantify Glu and GABA concentration in the Pcu/PCC region. We conducted a univariate general linear model and task-dependent connectivity analysis to investigate the correlation between activation in Pcu/PCC, Pcu/PCC–mPFC functional connectivity, and the Glu/GABA ratio. A mediation model was applied to examine how the Glu/GABA ratio is linked to the SRE on recollection via BOLD signal.

Materials and Methods

Participants. A total of 117 participants between 7 and 35 years old from the Johns Hopkins University community and the Baltimore area completed the MRS scanning. Among these participants, 10 were excluded due to data corruption caused by incorrect parameter settings during MRS acquisition, which rendered the data unsuitable for preprocessing. Additionally, all spectra were visually inspected by an experienced MRS data user (N.A.P.). Spectra with significant artifacts resulting from motion, scanner heating, or inhomogeneity of B0—leading to indistinguishable GABA/Glu peaks—were also excluded ($n = 21$). As a result, a total of 31 participants were excluded during the MRS data quality check. Of the remaining participants, six didn't complete the whole fMRI scanning. Three participants lacked field mapping images, and 23 had excessive head motion during the fMRI task, defined as a maximum movement greater than 3 mm, and more than one-third of the total scans were identified as outliers (see below, Image acquisition and preprocessing, for the definition of outliers). Ultimately, 54 participants (mean age = 18.30 ± 7.08; 25 female) had both fMRI and MRS data that met the quality criteria and were included in the final analyses. All participants had IQ scores above 96 on the Kaufman Brief Intelligence Test 2, indicating at least average performance. Each participant was a native English speaker and right-handed and had normal or corrected-to-normal vision, with no history of psychiatric or developmental disorders. This study was approved by the Johns Hopkins School of Medicine Institutional Review Board (Approval Number: IRB00151734), at the Kennedy Krieger Institute and Johns Hopkins University, with all participants providing informed consent prior to their involvement.

Encoding and memory recognition task. During the encoding task, participants were shown objects with one of the two backgrounds, beach or garden. Objects were selected from seven categories: animal, clothing, fruit, vegetable, toy, tool, and instrument. In the self-encoding condition, participants were asked to respond to the question: "Do you like this object or dislike/not care about it?" A positive response was indicated by a smiley cartoon face, while a negative response was represented by a neutral cartoon face. In the semantic-encoding condition, the question posed was "Is this object living or nonliving?" Agreement was indicated by a green leaf, and disagreement was indicated by a green leaf with a red "X" through it. We chose the semantic condition as a comparison because it engages meaningful encoding processes while it is less dependent on the internally generated thought processes mediated by the core DMN, thus allowing us to isolate self-referential contributions to memory. Meanwhile, we measured metabolite concentrations in core regions of the DMN that are closely associated with self-encoding. Participants were instructed that there were no "correct" answers; they were simply asked to make judgments based on their personal preferences. The number of images assigned to the self-encoding condition and

semantic-encoding condition was equal (80 each). The encoding task consisted of four sessions, each comprising 40 trials. During each trial, a fixation image was first displayed for 1–9 s, and then each encoding image was shown for 3 s. The duration of each session was 244 s. The completion of the entire encoding task required approximately 17 min. The self-encoding and semantic-encoding questions were randomly assigned to each trial, along with the beach and garden background images. All four background–question combinations were evenly balanced across the categories. Participants performed the encoding task inside an MRI scanner with an MRI-compatible button box allowing them to answer the questions in either condition by pressing the left ("like it"; "living") or right ("dislike/not care about it"; "nonliving") button. Before scanning, participants were given instructions and asked to perform practice trials to ensure understanding of the task.

After scanning, participants were asked to perform a surprise memory recognition task. In this task, 160 "old" images (objects without backgrounds), which had appeared in the encoding task, along with 80 "new" images (objects without backgrounds) were displayed in a pseudorandom order. These images were divided into three sessions. For each image, participants were asked whether they had seen this image in the scanner and if they remembered any additional details about the image or the experience of encoding it in the scanner. Consequently, they had three response options: "new," indicating they had never seen the image before; "remember," indicating they had seen the image in the scanner and remembered additional details; and "familiar," indicating they had seen the image in the scanner but did not remember any additional details about it. "Remember" refers to a detailed recollection, while "familiar" indicates a sense of knowing without the accompanying contextual details (Tulving, 1985). This remember/know paradigm has been used in previous studies of the SRE, demonstrating that self-referential facilitation for detailed recollection is greater relative to familiarity (Conway and Dewhurst, 1995; Lawrence and Chai, 2021). If participants chose "remember" or "familiar," they were further asked two source memory questions to test the quality of their memory: one regarding the background with which the object was shown and another concerning the questions (like/dislike, living/not living) that were associated with the image in the scanner. We did not analyze the encoding question/background as we are not focusing on source memory in this study.

Behavioral analysis. We categorized the trials into different conditions based on participants' responses: "hits," "misses," "false alarms," and "correct rejections." "Hits" refer to images that appeared in the encoding process and were correctly identified as "remember" or "familiar." "Misses" refer to images that appeared in encoding but were incorrectly identified as "new." "False alarms" refer to images that did not appear in encoding but were incorrectly identified as "remember" or "familiar." "Correct rejections" refer to images that did not appear in encoding and were correctly identified as "new." Images for which participants did not respond were categorized as "failed to respond." These "failed to respond" images were excluded from the total count when calculating the rate. Recollection accuracy for each encoding condition was calculated by subtracting the false alarm rate from the remember rate. We also calculated d', which quantifies the separation between the signal and noise distribution in standard deviation units. The present work was focused on remember trials rather than familiar because previous research shows a more robust SRE for recollection (remember trials; Zhu and Zhang, 2002; Lawrence and Chai, 2021; Sweatman et al., 2022).

The self-reference effect on recollection (SRE recollection scores) was determined by subtracting the recollection accuracy for semantic-encoding images from that of the self-encoding images, effectively quantifying the amount of memory facilitation afforded by self-referential versus semantic encoding.

Image acquisition and preprocessing. Whole-brain images were acquired on a 3 T Philips scanner with a 32-channel head coil. Functional images were obtained using an echoplanar imaging sequence [35 slices; repetition time (TR), 2,000 ms; time to echo (TE), 30 ms; flip angle, 75°; voxel size, 3 mm ×3 mm ×3 mm; field of view, 240 mm ×240 mm). High-resolution T1-weighted anatomical images were acquired using a magnetization-prepared rapid acquisition gradient-echo sequence (MPRAGE; slice thickness, 0.83 mm; in-plane resolution, 1 mm × 0.83 mm; TR, 7 ms; TE, 3.2 ms). Additionally, a B0 field map was derived for distortion correction using the double-echo gradient-recalled echo sequence (short echo time, 7 ms; long echo time, 10 ms).

Functional brain images were preprocessed using the CONN toolbox (www.nitrc.org/projects/conn, RRID:SCR_009550). All images were realigned to the first image, corrected for slice timing, coregistered to segmented T1-weighted images, and spatially normalized into the standard template of the Montreal Neurological Institute. Finally, images were smoothed using a 6 mm full-width at half-maximum Gaussian kernel. Data were inspected for artifacts and motion using ART (https://www.nitrc.org/projects/artifact_detect/). The images in which scan-to-scan displacement of composite motion >0.9 mm were defined as outliers. The composite motion was a scan-to-scan movement, representing, for each scan, the maximum scan-to-scan movement (distance in millimeters) observed across six control points placed at the center of the six faces of a bounding box encompassing the brain, which is equivalent to approximately half the value of the framewise displacement by Jenkinson et al. (2002).

Spectroscopy acquisition and preprocessing. While the signals of different metabolites often overlap and are not easily resolved with conventional spectroscopy, specifically tailored "editing" ^{1}H-MRS sequences can reliably isolate and detect the signals of GABA (Puts and Edden, 2012; Mullins et al., 2014; Harris et al., 2017).^{1}H-MRS data were acquired from a 27 cm^3 voxel (3 cm × 3 cm × 3 cm) manually placed over the precuneus/posterior cingulate cortex (Pcu/PCC, Fig. 1*A*). MRS was performed using GABA+ editing MEscher–GArwood Point RESolved Spectroscopy (MEGA-PRESS; Mescher et al., 1998): 320 transients (160 ON and 160 OFF); TE, 68 ms; TR, 2,000 ms; with editing pulses placed at 1.9 ppm in the edit-ON acquisitions and 7.46 in the edit-OFF acquisitions and VAPOR water suppression. MRS data included 2,048 data points. An interleaved unsuppressed water reference scan (Edden et al., 2016) was performed with the same parameters as the water-suppressed scans, using 16 averages. This approach was employed to address scanner drift and facilitate subsequent eddy current and phase corrections, as well as metabolite quantification. Glu can also be quantified from GABA-edited spectra, but cannot be separated from its precursor glutamine in most approaches and is thus often referred to as Glx (glutamate and glutamine).

Metabolite levels were estimated using Gannet 3.1, a software package optimized for the processing of edited MRS data (Edden et al., 2014). This included spectral preprocessing including 3 Hz exponential line broadening, zero-filling, frequency-and-phase correction of individual averages using the spectral registration method, averaging, and subtraction of the edited subspectra to yield GABA-edited difference spectra which were subsequently fit with default settings: a single Gaussian signal for the GABA peak (between 2.79 and 3.2 ppm), a double-Gaussian peak for the Glx double (between 3.4 and 4.1 ppm), and linear, cosine, and sine baseline terms to account for baseline distortions resulting from residual water or lipid signals. The concentrations of GABA and Glx were estimated relative to the unsuppressed water signal in institutional units and as a ratio relative to total creatine (e.g., GABA/tCr). Using tissue segmentation implemented in SPM12 (https://www.fil.ion.ucl.ac.uk/spm/software/-spm12/), the fractional tissue volumes for gray matter, white matter, and cerebrospinal fluid were determined for each voxel. Water-scaled GABA+ and Glx measurements were corrected for tissue fraction composition. It is important to note that the GABA signal includes coedited macromolecules and is therefore referred to as GABA+. Previous studies have shown that macromolecular concentrations in the cortex of healthy individuals are highly stable, suggesting that GABA+ levels might primarily reflect differences in GABA concentrations (Mader et al., 2002; Knight-Scott et al., 2003; Donahue et al., 2010). The ratio of Glx versus GABA+ concentration level (denoted as Glx/GABA+ ratio) was calculated.

Univariate general linear model analysis. To assess the task-related brain responses, we categorized trials from the encoding task into "remember-self," "remember-semantic," "familiar-self," "familiar-semantic," "miss-self," and "miss-semantic" based on the answers of the recognition task. The trials that failed to respond were also modeled to remove their effect. For each category, onset time and duration were

modeled and convolved with the canonical hemodynamic response function (HRF) in SPM12 (https://www.fil.ion.ucl.ac.uk/spm/software/spm12/). Six head motion parameters (translation and rotation), framewise displacement, and outliers were included in the model to regress out the effect of head movement confounds. We utilized an individual explicit mask defined from each subject's smoothed (6 mm full-width at half-maximum Gaussian kernel) anatomical image in the first level analysis. We adopted high-pass filtering with a cutoff of 1/128 Hz to remove high-frequency noise and correction for serial correlations using a first-order autoregressive model [AR(1)]. The contrast of interest, "remember-self" versus "remember-semantic," aimed to capture differences in brain activations related to successfully remembered trials between self-referential and semantic conditions, focusing on distinctions in memory processes.

Activation analysis with Glx/GABA+ ratio. We first conducted a whole-brain multiple regression analysis to examine the correlation between brain activation and the Glx/GABA+ ratio. For the remember-self versus remember-semantic contrast, we used the Glx/GABA+ ratio as the regressor of interest while controlling for age and sex in SPM12. Significant clusters were identified using a height threshold of $p < 0.001$ and an extent threshold of $p < 0.01$, employing 3dClustSim (Cox et al., 2017). The beta values were extracted from significant clusters, representing the extent of activation. A higher beta value indicates that this region exhibits a stronger response to the remember-self condition compared with the remember-semantic condition.

To further validate our results, we performed an ROI analysis. The Pcu/PCC region was defined using a mask derived from the Neurosynth platform (https://neurosynth.org). An association test map was obtained from an automatic meta-analysis using "self-referential" as the search term. We adopted a voxel size of >100 as the threshold to define the ROI. Beta values were extracted from the defined regions for the remember-self versus remember-semantic contrast. Subsequently, we conducted a partial correlation analysis between activity and the Glx/GABA+ ratio, controlling for age and sex.

Task-dependent functional connectivity analysis with Glx/GABA+ ratio. We used the Pcu/PCC region as a seed region defined from the Neurosynth mask to conduct the generalized psychophysiological interactions (gPPI) analysis (McLaren et al., 2012), utilizing the Generalized PPI Toolbox (https://www.nitrc.org/projects/gppi) based on SPM12 for task-dependent functional connectivity. The mean time series from the seed region was extracted and then deconvolved as physiological variables and multiplied with the task design vectors for task condition ("remember-self," "remember-semantic," "familiar-self," "familiar-semantic," "miss-self," and "miss-semantic"), which were the psychological variables. These resulting vectors were then convolved with a canonical HRF to form PPI regressors. Each task regressor, the mean-corrected time series of the seed, head movements, and outliers were also included in the GLM model to remove overall task-related activation and the effects of confounding variables. The contrast of interest was remember-self versus remember-semantic conditions.

Firstly, we conducted a whole-brain analysis using a one-sample *t* test on all individual gPPI maps with the Pcu/PCC as the seed region, to examine whether any clusters showed significant connectivity with the seed when comparing the remember-self and remember-semantic conditions. And then, we extracted the beta value of the mPFC region, also defined by the Neurosynth mask, from the contrast map. This value indicates the connectivity strength between the seed region and the mPFC in the remember-self condition compared with the remember-semantic condition. To assess the specificity of the Pcu/PCC–mPFC connectivity in relation to the Glx/GABA+ ratio, we conducted additional gPPI analyses using other clusters from the Neurosynth mask as seeds. We then calculated their connectivity strength to the mPFC and standardized the values using *z*-scores. The coordinates of these clusters are reported in Extended Data Table S1. Similarly, using partial correlation to control for age and sex, we calculated the correlation between task-dependent connectivity and the Glx/GABA+ ratio.

Mediation analysis. The mediation model was performed using the PROCESS macro (version 4.1 by Andrew F. Hayes) based on SPSS (version 24.0, International Business Machines). In this model, the Glx/GABA+ ratio was set as the independent variable (X), behavioral performance as the dependent variable (Y), and functional connectivity as the mediator variable (M), with sex and age included as covariates of no interest. Path "a" represents the effect of X on M (X → M), while b represents the effect of M on Y (M → Y) when controlling for X. The indirect effect is given by "ab," which reflects the mediated effect of X on Y through M. The direct effect means the effect of X on Y when controlling for M. Following the procedure for testing mediation effects (Zhao et al., 2010), we first examine whether the indirect effect is significant to determine the presence of mediation. Then, we assess whether the direct effect is significant to identify the type of mediation. The significance of all models was calculated using a 5,000 bias-corrected bootstrapping resampling approach to obtain a 95% confidence interval (CI). If the 95% CI did not include zero, the mediation was considered significant.

Results

Behavioral results: SRE on memory accuracy

The mean and standard deviation of participants' hit and false alarm rates, recollection accuracy, and d' for the self- and semantic-encoding conditions are included in Table 1. Self-encoding led to significantly higher recollection accuracy ($t_{(53)} = 11.524$, $p < 0.001$, Cohen's $d = 1.087$) compared with semantic encoding. SRE calculated from d' also show the same effect ($t_{(53)} = 11.369$, $p < 0.001$, Cohen's $d = 0.548$). These results indicate that self-related information enhances recollection performance, which aligns with our expectations.

Glx/GABA+ ratio related to brain activation during self-encoding

Considering the broad age range of our sample, we first investigated the effect of age on GABA+ and Glx concentrations extracted from a 27 ml voxel (3 cm × 3 cm × 3 cm) placed over the Pcu/PCC (Fig. 1*A*). After controlling for sex, a partial correlation analysis revealed that GABA+ and Glx concentrations were negatively associated with age ($r = -0.40$, $p = 0.003$; $r = -0.65$, $p < 0.001$, Extended Data Fig. S1). Although the Glx/GABA+ ratio showed a similar trend, the correlation was not statistically significant ($r = -0.17$, $p = 0.216$). Nonetheless, we controlled the effect of age in our subsequent analyses. Additionally, Glx and GABA levels are highly correlated ($r = 0.44$, $p = 0.001$).

We then investigated whether the Glx/GABA+ ratio was related to task-evoked brain activation during self-encoding versus semantic-encoding conditions. We first conducted a whole-brain group-level *t* test to compare the difference between the remember-self condition and the remember-semantic condition. DMN regions, such as the Pcu/PCC, mPFC, and angular gyrus, showed increased activation during the successful self-related encoding condition compared with semantic encoding (Fig. 2*A*). Conversely, the middle and superior temporal gyrus, precentral and postcentral gyrus, inferior and superior parietal lobule, and middle frontal gyrus showed greater activations in

Table 1. The means and standard deviations of hit and false alarm rates under the self and semantic conditions, separately for remember and familiar responses

	Hit		False alarm		Accuracy	
	% Remember	% Familiar	% Remember	% Familiar	Recollection (remember)	d' (remember)
Self	0.62 ± 0.21	0.25 ± 0.22	0.05 ± 0.06	0.04 ± 0.05	0.57 ± 0.21	2.50 ± 1.15
Semantic	0.42 ± 0.17	0.17 ± 0.14			0.37 ± 0.16	1.91 ± 0.98

Accuracy reflects the recollection accuracy based on remember responses, along with the corresponding d'.

the semantic compared with the self condition. These results suggest that DMN regions contribute to self-encoding, consistent with previous studies.

Next, whole-brain regression analysis was performed on individual contrast maps comparing remember-self versus remember-semantic trials, with the Glx/GABA+ ratio as the covariate of interest and controlling for age and sex. This analysis revealed a significant cluster in the Pcu/PCC region with a height threshold of $p < 0.001$ and an extent threshold of $p < 0.01$ using 3dClustSim (Fig. 2*B*). Activation of this cluster was significantly and positively correlated with the Glx/GABA+ ratio ($r = 0.61$, $p < 0.001$, Fig. 2*B*). We also found a smaller cluster in the right angular gyrus positively correlated with Glx/GABA+ ratio.

We conducted an ROI-based analysis to validate this result (Fig. 2*C*,*D*). Activation of the Pcu/PCC cluster, derived from an independent meta-analysis from Neurosynth using the search term "self-referential," was also significantly positively correlated with the Glx/GABA+ ratio ($r = 0.42$, $p = 0.002$) when controlling for age and sex. Both whole-brain regression analyses and ROI analyses demonstrate that a higher regional Glx/GABA+ ratio is associated with greater activation of the same Pcu/PCC regions during successful self-encoding compared with semantic encoding.

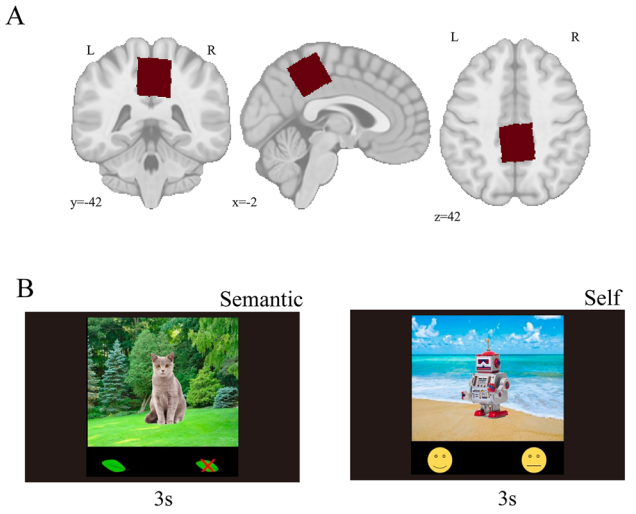

Figure 1. ***A***, Magnetic resonance spectroscopy (MRS) voxel placement. Example MRS voxel placement in the precuneus/posterior cingulate cortex (Pcu/PCC) for one single subject. ***B***, Self- and semantic-encoding task paradigm (Lawrence and Chai, 2021). Participants were asked to make judgments about objects under one of two conditions. In the semantic-encoding condition (left), the question was "Is this object living or nonliving?" In the self-encoding condition (right), they were asked, "Do you like this object or dislike/not care about it?"

Pcu/PCC–mPFC connectivity during self-encoding versus semantic-encoding: associations with Glx/GABA+ ratio and SRE

Given the critical role of the mPFC and PCC in self-related processes, we examined the relationship between task-dependent functional connectivity of Pcu/PCC–mPFC and the Glx/GABA+ ratio. We extracted the connectivity strength between Pcu/PCC and mPFC (Fig. 3*A*) from individual maps under the remember-self versus remember-semantic conditions. Partial correlation analysis revealed a positive relationship between the Glx/GABA+ ratio and Pcu/PCC–mPFC connectivity during the self-encoding process compared with the semantic-encoding process ($r = 0.42$, $p = 0.002$, Fig. 3*B*). To test the specificity of this correlation, we also examined the correlation between the connectivity of different seed regions, derived from the "self-referential" meta-analytic mask, to the mPFC and the Glx/GABA+ ratio. After correcting for multiple comparisons, we found no significant correlations from other seed regions, except for the Pcu/PCC–mPFC connection (Extended Data Table S2). We also examined the correlation between connectivity from the Pcu/PCC seed to other regions and found consistent results—only the Pcu/PCC–mPFC connection showed a significant correlation (Extended Data Table S3). This suggests that the significant positive correlation is driven by this specific pathway rather than the overall network connectivity strength. These

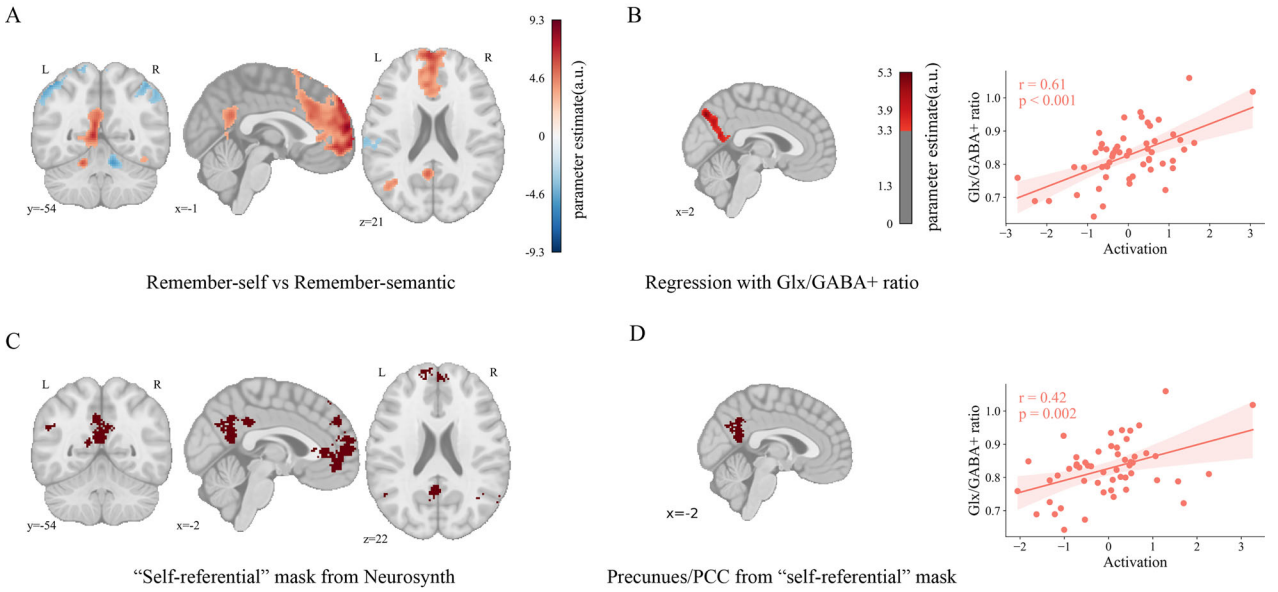

Figure 2. Glx/GABA+ ratio related to brain activation during self-encoding. ***A***, Group activation map for the remember_self versus remember_semantic contrast. ***B***, Whole-brain regression analysis revealed two significant clusters in the precuneus/posterior cingulate cortex (Pcu/PCC) and right angular gyrus associated with the Glx/GABA+ ratio, controlling for age and sex. The scatter plot shows that there was a significant positive association between Pcu/PCC activation and the Glx/GABA+ ratio during the "remember-self" versus "remember-semantic" condition. ***C***, Neurosynth mask with "self-referential" as the search term. ***D***, The activation in the Pcu/PCC region identified by the Neurosynth mask also showed a positive correlation with the Glx/GABA+ ratio.

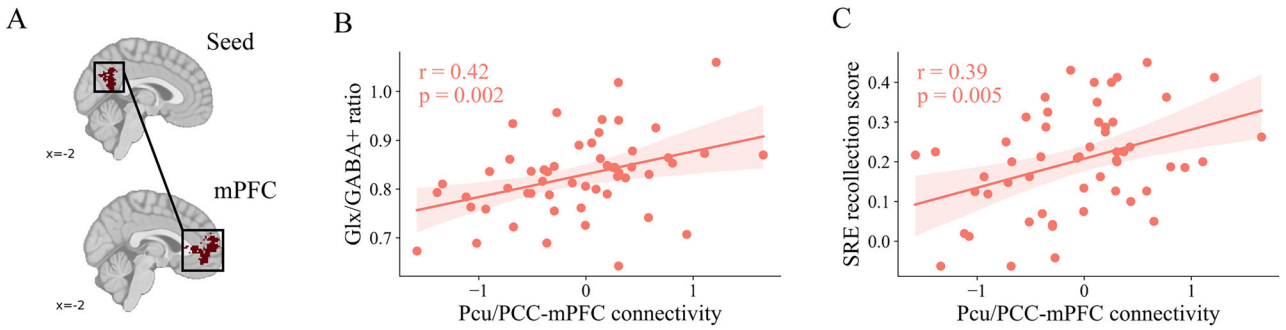

Figure 3. Connectivity between precuneus/posterior cingulate cortex (Pcu/PCC) and the medial prefrontal cortex (mPFC) associated with Glx/GABA+ ratio and self-reference effect (SRE) on recollection performance. ***A***, Task-dependent functional connectivity between the Pcu/PCC and mPFC during the "remember-self" versus "remember-semantic" conditions. ***B***, The Glx/GABA+ ratio showed a significant positive correlation with Pcu/PCC–mPFC connectivity. ***C***, Pcu/PCC connectivity was significantly positively correlated with the SRE on recollection performance.

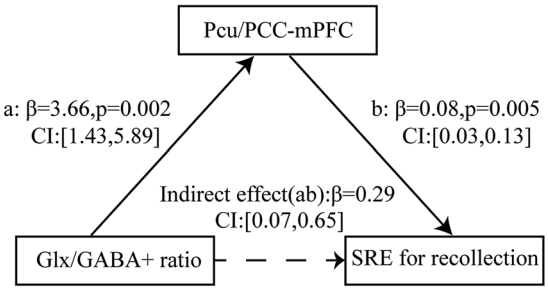

Figure 4. Mediation model. This model depicted the relationships among the Glx/GABA+ ratio, precuneus/posterior cingulate cortex (Pcu/PCC)–medial prefrontal cortex (mPFC) connectivity during the "remember-self" versus "remember-semantic" conditions, and the self-referential effect (SRE) on recollection scores. The indirect effect of the Glx/GABA+ ratio on SRE in recollection through Pcu/PCC connectivity was significant.

results suggest that a higher Glx/GABA+ ratio is associated with greater Pcu/PCC–mPFC functional connectivity during the self-related encoding process. Additionally, the group-level whole-brain analysis did not reveal any clusters that survived the commonly accepted threshold.

We further examined whether Pcu/PCC–mPFC connectivity contributes to the self-reference effect on memory recollection. We found a significant positive correlation between Pcu/PCC–mPFC connectivity and self-referential recollection accuracy ($r = 0.39$, $p = 0.005$, Fig. 3*C*) when controlling for age and sex. SRE recollection accuracy did not correlate with age ($r = 0.03$, $p = 0.838$). We calculated the correlations between Pcu/PCC–mPFC connectivity and recollection accuracy separately for self-encoding and semantic encoding and found that this effect was seemingly driven by self-related processing (self-encoding, $r = 0.39$, $p = 0.005$; semantic encoding, $r = 0.18$, $p = 0.204$; Extended Data Fig. S2). These results indicate that higher Pcu/PCC–mPFC connectivity during encoding is associated with a stronger self-reference effect on memory recollection.

Pcu/PCC–mPFC connectivity mediates the relationship between Glx/GABA+ ratio and recollection SRE

We investigated the relationships between Glx/GABA+ ratio, Pcu/PCC–mPFC connectivity, and behavioral performance using a mediation model to clarify how the Glx/GABA+ ratio affected SRE on recollection through Pcu/PCC–mPFC connectivity. There was no significant correlation between the Glx/GABA+ ratio and self-reference effect recollection score ($r = 0.08$, $p = 0.58$). We then tested an indirect pathway in which the Glx/GABA+ ratio contributes to the self-reference recollection score via the Pcu/PCC–mPFC functional connectivity with age and sex as covariates of no interest. We observed an indirect mediatory effect of the Glx/GABA+ ratio (indirect estimate = 0.29, 95% CI = 0.07 to 0.65, Fig. 4). The direct effect of the Glx/GABA+ ratio on the self-reference recollection score was not significant in our mediation model ($t = -0.73$, $p = 0.47$, 95% CI = −0.64 to 0.30), indicating that this is an indirect-only mediation model. These results collectively demonstrate that a higher Glx/GABA+ ratio is indirectly linked to the self-reference boost effect on memory recollection via Pcu/PCC–mPFC functional connectivity.

Discussion

Self-referencing during encoding can enhance subsequent memory performance. Our study investigated the neurochemical basis related to the neural processes underlying the SRE on memory recollection. We found that a higher Glx/GABA+ ratio, reflecting a greater availability of metabolites to exert excitation relative to inhibition in the Pcu/PCC, was associated with increased activation in Pcu/PCC and enhanced Pcu/PCC–mPFC functional connectivity involved in the self-encoding process. We also found that a higher Glx/GABA+ ratio is indirectly linked to the SRE on memory recollection via task-evoked Pcu/PCC–mPFC connectivity. Our study provides the first insights into how neurochemical activity is associated with self-related processing via activations and functional connectivity of the DMN.

Firstly, our activation results demonstrated that DMN regions were activated during self-encoding, which is consistent with previous studies (Craik et al., 1999; Zysset et al., 2002; Fossati et al., 2003). For semantic encoding, in addition to the semantic-related and language regions such as the superior and middle temporal gyrus, inferior and superior parietal lobule, and middle frontal gyrus (Alexander et al., 1989; Hart and Gordon, 1990; Dronkers et al., 2004; Binder et al., 2009), we also observed involvement of the postcentral and precentral gyri. This additional activation may reflect the rehearsal of sensory–motor experiences associated with specific word meanings(Reyes-Aguilar et al., 2023). And then, both the whole-brain regression analysis and the ROI analysis based on an independent meta-analytic mask suggest that a higher Glx/GABA+ ratio is associated with increased activation in the Pcu/PCC region during self-encoding. This is consistent with a previous finding that the concentration of Glx and GABA within a region is related to BOLD activation in the same areas involved in task modulation. Two studies reported that greater deactivation of the DMN during working memory tasks was correlated with higher GABA concentrations, lower Glu concentrations, and lower Glu/GABA ratio (Hu et al., 2013; Gu et al., 2019). We also identified a

smaller significant cluster in the right angular gyrus, which, although not the MRS sampling location, is a part of the DMN and shows a positive association with the Glx/GABA+ ratio. A systematic review has summarized converging evidence of negative associations between GABA levels and local brain activity, as well as positive associations between Glu levels and distal brain activity, outside the MRS sampling region (Kiemes et al., 2021). Our findings align with these previous studies on negative DMN activations and further contribute to the understanding of the positive activation of the DMN. DMN was first identified as a network commonly deactivated during a range of cognitive tasks requiring external orientation. Later studies have shown that the DMN is activated during internally oriented processes such as spontaneous self-related or social–cognitive processing and spontaneous autobiographical retrieval (Gusnard et al., 2001; Buckner et al., 2008; Schilbach et al., 2012; Fox et al., 2015). The deactivation of DMN is beneficial for externally oriented, goal-directed thinking and has been well-studied in both cognition and disease (Anticevic et al., 2012), as well as in its correlation with Glu and GABA (Northoff et al., 2007; Hu et al., 2013; Gu et al., 2019). However, the association of activation of DMN and Glx/GABA concentration has been less explored. Our study contributes to the current understanding of the relationship between regional metabolites and DMN activations by demonstrating a significant positive correlation between activation in the Pcu/PCC region—a hub of the DMN—and Glx/GABA+ ratio during self-referential processing, a core cognitive process supported by the DMN. This may suggest that if the extent to which a DMN region can exert excitatory activity relative to inhibitory activity is higher, it could be accompanied by the facilitation of self-encoding when subjects engage in internal processes.

We also found that subjects with a higher Glx/GABA+ ratio exhibited greater Pcu/PCC–mPFC connectivity during self-encoding. This finding complements the DMN activation results discussed above, suggesting that regional E/I balance is not only linked to neural activity within the same region but may also be associated with functional interactions between different regions. Previous studies have demonstrated a similar correlation between intrinsic connectivity and brain metabolite concentrations during resting states. GABA levels in the primary motor cortex have been found to negatively correlate with functional connectivity within the motor network (Stagg et al., 2014). Additionally, Glu levels in the mPFC positively correlate with functional connectivity between the mPFC and nucleus accumbens (Duncan et al., 2013), and Glu levels in the dorsal anterior cingulate cortex (dACC) positively correlate with connectivity between the dACC and midbrain (Schmaal et al., 2012). There is limited research on the relationship between GABA and Glu concentrations and task-induced functional connectivity. One study found that a higher Glu/GABA ratio in the Pcu/PCC was more strongly associated with greater connectivity between the DMN and the salience network during an *n*-back task (Gu et al., 2019). However, in this study, the task-evoked neural responses were regressed out, meaning that the resulting connectivity is independent of the specific task conditions (0-, 1-, 2-, and 3-back). Nevertheless, these previous studies have demonstrated a relationship between regional E/I balance and both the connectivity within the local network and with other networks. This suggests that the small-scale synchrony of microcircuits, which is influenced by E/I interactions, may scale up to larger-scale distributed brain networks (Isaacson and Scanziani, 2011; Rutishauser et al., 2012; Duncan et al., 2014). Our study further considers the effect of the task, providing new insights into the link between regional metabolite activity and large-scale distributed brain networks involved in self-related processes. Interestingly, we did not find any robust differences in connectivity changes between the remember-self and remember-semantic conditions at the group level. Given the correlation between E/I balance and connectivity, this lack of group-level difference may be masked by individual variability in connectivity that is associated with each participant's E/I ratio. Our results highlight that task-related functional connectivity is closely linked to brain metabolic levels and that both factors should be considered together when investigating cognitive processes.

Notably, we found that increased connectivity in the Pcu/PCC–mPFC pathway mediated the indirect relationship between the Glx/GABA+ ratio and the strength of the self-referential effect on recollection performance. This suggests that regional E/I balance within the DMN correlated with self-related processes through the functional interactions of distributed brain regions in the DMN. Some researchers suggest that, theoretically, self-awareness is regulated by dopamine through the mPFC/ACC via the GABA system (Lou et al., 2017; Mograbi et al., 2024). Our study takes the first step to investigate the neurochemical basis related to self-referential processing, providing empirical evidence—our combined fMRI-MRS study found that this processing might be affected by Glx and GABA signals via functional connectivity across key nodes of the DMN. Given the limitations of human studies, it is challenging to investigate self-related processes at a more microscopic level. Although our study is correlational and did not directly measure neurotransmitter changes at the cellular level during self-referential processes, it offers a potential neurochemical explanation for the observed effects. These results suggest that a higher E/I ratio (indicating a greater shift toward excitation from inhibition) is linked to increased Pcu/PCC–mPFC pathway engagement, which may enhance the encoding of self-related information and improve memory recollection.

SRE was diminished or absent in individuals with autism spectrum disorder (ASD) and schizophrenia (Harvey et al., 2011; Grisdale et al., 2014). This atypical self-related representation has been linked to social impairments and increased internalizing symptoms (Henderson et al., 2009; Burrows et al., 2017). Our findings in healthy individuals—demonstrating the neurochemical correlates of self-referential processing—may therefore provide a framework for understanding symptom mechanisms in disorders characterized by atypical self-concept. Notably, several therapeutic interventions targeting GABA and Glu systems have already been explored in autism (Purkayastha et al., 2015). Given that excitation/inhibition homeostasis is known to shape cognition (Zhou and Yu, 2018), and both ASD and schizophrenia exhibit E/I imbalance (Rubenstein and Merzenich, 2003; Howes and Shatalina, 2022), future studies should explicitly examine how modulating E/I balance may influence self-referencing and its downstream effects on social cognition in these population.

Our study has some limitations. Due to the simultaneous quality control of both fMRI and MRS images, the final sample size was reduced, which may explain why we didn't identify a significant correlation between the Glx/GABA+ ratio and age as previous studies (Thomson et al., 2024a). Different MRS processing pipelines may contribute to the inconsistency estimate of Glx/GABA+ (Craven et al., 2022) which suggests additional spectral modeling to validate reproducibility. Additionally, to extract accurate MRS signals, the size of the voxel we used was relatively

large, which exceeded the size of the fMRI ROI in our ROI analysis, potentially affecting the results of the association between the two modalities. Future studies could use more precise MRS ROIs and potentially investigate additional DMN regions. Although mediation analysis assumes causality, our study did not employ a longitudinal approach and cannot provide strong evidence for a causal link between the Glx/GABA+ ratio, functional connectivity, and behavioral performance. Finally, we investigate the neurochemical basis of SRE via key DMN nodes, but do not capture the broader role of E/I balance in more complex cognitive functions, which warrants further investigation across multiple additional brain regions and tasks.

References

Alexander MP, Hiltbrunner B, Fischer RS (1989) Distributed anatomy of transcortical sensory aphasia. Arch Neurol 46:885–892.

Anticevic A, Cole MW, Murray JD, Corlett PR, Wang XJ, Krystal JH (2012) The role of default network deactivation in cognition and disease. Trends Cogn Sci 16:584–592.

Bednařík P, Tkáč I, Giove F, Dinuzzo M, Deelchand DK, Emir UE, Eberly LE, Mangia S (2015) Neurochemical and BOLD responses during neuronal activation measured in the human visual cortex at 7 Tesla. J Cereb Blood Flow Metab 35:601–610.

Binder JR, Desai RH, Graves WW, Conant LL (2009) Where is the semantic system? A critical review and meta-analysis of 120 functional neuroimaging studies. Cereb Cortex 19:2767–2796.

Buckner RL, Andrews-Hanna JR, Schacter DL (2008) The brain's default network: anatomy, function, and relevance to disease. Ann N Y Acad Sci 1124:1–38.

Burrows CA, Usher L V, Mundy PC, Henderson HA (2017) The salience of the self: self-referential processing and internalizing problems in children and adolescents with autism spectrum disorder. Autism Res 10:949–960.

Conway MA, Dewhurst SA (1995) The self and recollective experience. Appl Cogn Psychol 9:1–19.

Cox RW, Chen G, Glen DR, Reynolds RC, Taylor PA (2017) FMRI clustering in AFNI: false-positive rates redux. Brain Connect 7:152–171.

Craik FIM, Moroz TM, Moscovitch M, Stuss DT, Winocur G, Tulving E, Kapur S (1999) In search of the self: a positron emission tomography study. Psychol Sci 10:26–34.

Craven AR, et al. (2022) Comparison of seven modelling algorithms for GABA-edited 1H-MRS: evaluation of data from 20 sites, with: FSL-MRS, Gannet, jMRUI (AMARES, QUEST), LCModel, Osprey and Tarquin. NMR Biomed 35:e4702–e4702.

Davey CG, Pujol J, Harrison BJ (2016) Mapping the self in the brain's default mode network. Neuroimage 132:390–397.

Dinulescu S, Alvi T, Rosenfield D, Sunahara CS, Lee J, Tabak BA (2021) Self-referential processing predicts social cognitive ability. Soc Psychol Personal Sci 12:99–107.

Donahue MJ, Near J, Blicher JU, Jezzard P (2010) Baseline GABA concentration and fMRI response. Neuroimage 53:392–398.

Dronkers NF, Wilkins DP, Van Valin RD, Redfern BB, Jaeger JJ (2004) Lesion analysis of the brain areas involved in language comprehension. Cognition 92:145–177.

Duncan NW, Wiebking C, Tiret B, Marjańska M, Hayes DJ, Lyttleton O, Doyon J, Northoff G (2013) Glutamate concentration in the medial prefrontal cortex predicts resting-state cortical-subcortical functional connectivity in humans. PLoS One 8:e60312.

Duncan NW, Wiebking C, Northoff G (2014) Associations of regional GABA and glutamate with intrinsic and extrinsic neural activity in humans-a review of multimodal imaging studies. Neurosci Biobehav Rev 47:36–52.

Edden RAE, Puts NAJ, Harris AD, Barker PB, Evans CJ (2014) Gannet: a batch-processing tool for the quantitative analysis of gamma-aminobutyric acid-edited MR spectroscopy spectra. J Magn Reson Imaging 40:1445–1452.

Edden RAE, Oeltzschner G, Harris AD, Puts NAJ, Chan KL, Boer VO, SchärM, Barker PB (2016) Prospective frequency correction for macromolecule-suppressed GABA editing at 3T. J Magn Reson Imaging 44:1474–1482.

Ford TC, Crewther DP (2016) A comprehensive review of the 1H-MRS metabolite spectrum in autism spectrum disorder. Front Mol Neurosci 9:14.

Fossati P, Hevenor SJ, Graham SJ, Grady C, Keightley ML, Craik F, Mayberg H (2003) In search of the emotional self: an fMRI study using positive and negative emotional words. Am J Psychiatry 160:1938–1945.

Fox KCR, Spreng RN, Ellamil M, Andrews-Hanna JR, Christoff K (2015) The wandering brain: meta-analysis of functional neuroimaging studies of mind-wandering and related spontaneous thought processes. Neuroimage 111:611–621.

Grisdale E, Lind SE, Eacott MJ, Williams DM (2014) Self-referential memory in autism spectrum disorder and typical development: exploring the ownership effect. Conscious Cogn 30:133–141.

Gu H, Hu Y, Chen X, He Y, Yang Y (2019) Regional excitation-inhibition balance predicts default-mode network deactivation via functional connectivity. Neuroimage 185:388–397.

Gusnard DA, Akbudak E, Shulman GL, Raichle ME (2001) Medial prefrontal cortex and self-referential mental activity: relation to a default mode of brain function. Proc Natl Acad Sci U S A 98:4259–4264.

Harris AD, Saleh MG, Edden RAE (2017) Edited ^{1}H magnetic resonance spectroscopy in vivo: methods and metabolites. Magn Reson Med 77: 1377–1389.

Hart J, Gordon B (1990) Delineation of single-word semantic comprehension deficits in aphasia, with anatomical correlation. Ann Neurol 27:226–231.

Harvey PO, Lee J, Horan WP, Ochsner K, Green MF (2011) Do patients with schizophrenia benefit from a self-referential memory bias? Schizophr Res 127:171–177.

Henderson HA, Zahka NB, Kojkowski NM, Inge AP, Schwartz CB, Hileman CM, Coman DC, Mundy PC (2009) Self-referenced memory, social cognition, and symptom presentation in autism. J Child Psychol Psychiatry 50:853–861.

Howes OD, Shatalina E (2022) Integrating the neurodevelopmental and dopamine hypotheses of schizophrenia and the role of cortical excitation-inhibition balance. Biol Psychiatry 92:501–513.

Hu Y, Chen X, Gu H, Yang Y (2013) Resting-state glutamate and GABA concentrations predict task-induced deactivation in the default mode network. J Neurosci 33:18566–18573.

Ip IB, Berrington A, Hess AT, Parker AJ, Emir UE, Bridge H (2017) Combined fMRI-MRS acquires simultaneous glutamate and BOLD-fMRI signals in the human brain. Neuroimage 155:113–119.

Isaacson JS, Scanziani M (2011) How inhibition shapes cortical activity. Neuron 72:231–243.

Jenkinson M, Bannister P, Brady M, Smith S (2002) Improved optimization for the robust and accurate linear registration and motion correction of brain images. Neuroimage 17:825–841.

Kapogiannis D, Reiter DA, Willette AA, Mattson MP (2013) Posteromedial cortex glutamate and GABA predict intrinsic functional connectivity of the default mode network. Neuroimage 64:112–119.

Keysers C, Gazzola V (2007) Integrating simulation and theory of mind: from self to social cognition. Trends Cogn Sci 11:194–196.

Kiemes A, Davies C, Kempton MJ, Lukow PB, Bennallick C, Stone JM, Modinos G (2021) GABA, glutamate and neural activity: a systematic review with meta-analysis of multimodal 1H-MRS-fMRI studies. Front Psychiatry 12:644315.

Knight-Scott J, Haley AP, Rossmiller SR, Farace E, Mai VM, Christopher JM, Manning CA, Simnad VI, Siragy HM (2003) Molality as a unit of measure for expressing 1H MRS brain metabolite concentrations in vivo. Magn Reson Imaging 21:787–797.

Kühnel A, et al. (2020) Impaired cognitive self-awareness mediates the association between alexithymia and excitation/inhibition balance in the pgACC. Psychol Med 50:1727–1735.

Lawrence R, Chai XJ (2021) Self-referential encoding of source information in recollection memory. PLoS One 16:e0248044.

Levar N, Van Doesum TJ, Denys D, Van Wingen GA (2019) Anterior cingulate GABA and glutamate concentrations are associated with resting-state network connectivity. Sci Rep 9:1–8.

Linville PW, Carlston DE (1994) Social cognition of the self.

Logothetis NK, Pauls J, Augath M, Trinath T, Oeltermann A (2001) Neurophysiological investigation of the basis of the fMRI signal. Nature 412:150–157.

Logothetis NK (2008) What we can do and what we cannot do with fMRI. Nature 453:869–878.

Lou HC, Changeux JP, Rosenstand A (2017) Towards a cognitive neuroscience of self-awareness. Neurosci Biobehav Rev 83:765–773.

Mader I, Seeger U, Karitzky J, Erb M, Schick F, Klose U (2002) Proton magnetic resonance spectroscopy with metabolite nulling reveals regional

differences of macromolecules in normal human brain. J Magn Reson Imaging 16:538–546.
Mason NL, et al. (2020) Me, myself, bye: regional alterations in glutamate and the experience of ego dissolution with psilocybin. Neuropsychopharmacology 45:2003–2011.
McLaren DG, Ries ML, Xu G, Johnson SC (2012) A generalized form of context-dependent psychophysiological interactions (gPPI): a comparison to standard approaches. Neuroimage 61:1277–1286.
Mescher M, Merkle H, Kirsch J, Garwood M, Gruetter R (1998) Simultaneous in vivo spectral editing and water suppression. NMR Biomed 11:266–272.
Mograbi DC, Rodrigues R, Bienemann B, Huntley J (2024) Brain networks, neurotransmitters and psychedelics: towards a neurochemistry of self-awareness. Curr Neurol Neurosci Rep 24:323–340.
Mullins PG, et al. (2014) Current practice in the use of MEGA-PRESS spectroscopy for the detection of GABA. Neuroimage 86:43–52.
Muthukumaraswamy SD, Edden RAE, Jones DK, Swettenham JB, Singh KD (2009) Resting GABA concentration predicts peak gamma frequency and fMRI amplitude in response to visual stimulation in humans. Proc Natl Acad Sci U S A 106:8356–8361.
Muthukumaraswamy SD, Evans CJ, Edden RAE, Wise RG, Singh KD (2012) Individual variability in the shape and amplitude of the BOLD-HRF correlates with endogenous GABAergic inhibition. Hum Brain Mapp 33: 455–465.
Northoff G, Walter M, Schulte RF, Beck J, Dydak U, Henning A, Boeker H, Grimm S, Boesiger P (2007) GABA concentrations in the human anterior cingulate cortex predict negative BOLD responses in fMRI. Nat Neurosci 10:1515–1517.
Purkayastha P, Malapati A, Yogeeswari P, Sriram D (2015) A review on GABA/glutamate pathway for therapeutic intervention of ASD and ADHD. Curr Med Chem 22:1850–1859.
Puts NAJ, Edden RAE (2012) In vivo magnetic resonance spectroscopy of GABA: a methodological review. Prog Nucl Magn Reson Spectrosc 60: 29–41.
Reyes-Aguilar A, Licea-Haquet G, Arce BI, Giordano M (2023) Contribution and functional connectivity between cerebrum and cerebellum on sublexical and lexical-semantic processing of verbs. PLoS One 18:e0291558.
Rubenstein JLR, Merzenich MM (2003) Model of autism: increased ratio of excitation/inhibition in key neural systems. Genes Brain Behav 2:255–267.
Rutishauser U, Slotine J-J, Douglas RJ (2012) Competition through selective inhibitory synchrony. Neural Comput 24:2033–2052.
Schilbach L, Bzdok D, Timmermans B, Fox PT, Laird AR, Vogeley K, Eickhoff SB (2012) Introspective minds: using ALE meta-analyses to study commonalities in the neural correlates of emotional processing, social & unconstrained cognition. PLoS One 7:e30920.
Schmaal L, Goudriaan AE, van der Meer J, van den Brink W, Veltman DJ (2012) The association between cingulate cortex glutamate concentration and delay discounting is mediated by resting state functional connectivity. Brain Behav 2:553–562.
Stagg CJ, Bachtiar V, Johansen-Berg H (2011) The role of GABA in human motor learning. Curr Biol 21:480–484.
Stagg CJ, et al. (2014) Local GABA concentration is related to network-level resting functional connectivity. Elife 3:e01465.
Sui J, Humphreys GW (2015) The integrative self: how self-reference integrates perception and memory. Trends Cogn Sci 19:719–728.
Sweatman H, Lawrence R, Chai XJ (2022) Development of self-referential effect on memory recollection. Child Dev 93:1848–1859.
Thomson AR, et al. (2024a) The developmental trajectory of 1H-MRS brain metabolites from childhood to adulthood. Cerebral Cortex 34:bhae046.
Thomson AR, Pasanta D, Arichi T, Puts NA (2024b) Neurometabolite differences in autism as assessed with magnetic resonance spectroscopy: a systematic review and meta-analysis. Neurosci Biobehav Rev 162:105728.
Tulving E (1985) Memory and consciousness. Canadian Psychology/ Psychologie canadienne 26:1.
Zhao X, Lynch JG, Chen Q (2010) Reconsidering Baron and Kenny: myths and truths about mediation analysis. J Consum Res 37:197–206.
Zhou S, Yu Y (2018) Synaptic EI balance underlies efficient neural coding. Front Neurosci 12:46.
Zhu Y, Zhang L (2002) An experimental study on the self-reference effect. Sci China C Life Sci 45:120–128.
Zysset S, Huber O, Ferstl E, Von Cramon DY (2002) The anterior frontomedian cortex and evaluative judgment: an fMRI study. Neuroimage 15:983–991.