

## ORIGINAL ARTICLE

# Association between Anterior Cingulate Neurochemical Concentration and Individual Differences in Hypnotizability

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## Abstract

Hypnosis is the oldest form of Western psychotherapy and a powerful evidence-based treatment for numerous disorders. Hypnotizability is variable between individuals; however, it is a stable trait throughout adulthood, suggesting that neurophysiological factors may underlie hypnotic responsiveness. One brain region of particular interest in functional neuroimaging studies of hypnotizability is the anterior cingulate cortex (ACC). Here, we examined the relationships between the neurochemicals, GABA, and glutamate, in the ACC and hypnotizability in healthy individuals. Participants underwent a magnetic resonance imaging (MRI) session, whereby T1-weighted anatomical and MEGA-PRESS spectroscopy scans were acquired. Voxel placement over the ACC was guided by a quantitative meta-analysis of functional neuroimaging studies of hypnosis. Hypnotizability was assessed using the Hypnotic Induction Profile (HIP), and self-report questionnaires to assess absorption (TAS), dissociation (DES), and negative affect were completed. ACC GABA concentration was positively associated with HIP scores such that the higher the GABA concentration, the more hypnotizable an individual. An exploratory analysis of questionnaire subscales revealed a negative relationship between glutamate and the absorption and imaginative involvement subscale of the DES. These results provide a putative neurobiological basis for individual differences in hypnotizability and can inform our understanding of treatment response to this growing psychotherapeutic tool.

**Key words:** magnetic resonance spectroscopy, hypnosis, individual differences, anterior cingulate cortex, MRI

## Introduction

Hypnosis is the oldest psychotherapeutic technique in Western medicine, commencing with the methods of therapeutic suggestion pioneered by Mesmer and his supporters in early

18th Century Europe. It has become a powerful evidence-based treatment approach for numerous disorders (Spiegel and Bloom 1983; Brom et al. 1989; Lang et al. 2000; Tefikow et al. 2013). Hypnosis is thought to involve an alteration of consciousness

accompanied by reduced peripheral awareness and heightened suggestibility (Spiegel and Spiegel 2004), which can induce changes in perception, emotion, thought, and behavior (Cojan et al. 2009). Specifically, hypnosis involves highly focused attention, referred to as absorption (Tellegen and Atkinson 1974), in combination with dissociation, the compartmentalization of experience (Elkins et al. 2015), and suggestibility, described as nonjudgmental behavioral responsiveness to instructions from others (Spiegel and Spiegel 2004).

Hypnotizability is variable between individuals; however, it is a stable trait throughout adulthood (Piccione et al. 1989). This suggests that neurophysiological factors may underlie interindividual differences in hypnotic responsiveness. There is now growing literature demonstrating differential brain activity and connectivity in individuals who are highly hypnotizable compared with those that are low using noninvasive neuroimaging methods such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) (Rainville et al. 1999b; Egner et al. 2005; Raz et al. 2005; Cojan et al. 2009; Deeley et al. 2012; Hoeft et al. 2012; Cojan et al. 2015; Halsband and Wolf 2015; Jiang et al. 2017; Landry et al. 2017). While activity in specific brain regions (e.g., anterior cingulate cortex, prefrontal cortex, and insula) is commonly reported across functional imaging studies of hypnosis, some discrepancies exist regarding the precise roles of these brain regions, which may be attributed to variations in hypnotic instructions, experimental context, study power, and/or other methodological sources (Rainville et al. 1999b; Halligan et al. 2000; Egner et al. 2005; Cojan et al. 2009). Despite this variability, in general, the literature supports a “top-down” view of hypnosis, whereby activity differences in frontal brain networks involved in attention, executive control, and cognitive monitoring contribute to interindividual variability in maintaining attentional focus towards relevant mental representations during hypnotic response (Landry et al. 2017).

One frontal brain region of particular interest in studies of hypnotizability is the anterior cingulate cortex (ACC). The ACC holds a central position in models of cognitive control, emotion, pain (Shackman et al. 2011), and volition (Darby et al. 2018). As such, evidence for its role in hypnosis, including hypnotic suggestions to reduce conflict processing (e.g., Stroop effect) (Nordby et al. 1999a; Raz et al. 2005) and pain affect (Rainville et al. 1997; Faymonville et al. 2000) is not surprising. Indeed, in a comprehensive systematic review examining brain correlates of hypnosis, the ACC was frequently shown to be involved in hypnosis; however, its precise role and associated activity was variable across studies due to the methodological considerations described above (Landry et al. 2017). In a previous fMRI study, Hoeft and colleagues (Hoeft et al. 2012) demonstrated increased functional connectivity between the dorsolateral prefrontal cortex and dorsal ACC (dACC) in high hypnotizables compared with lows at rest, suggesting an inherent coherency between specific frontal brain regions underlying variability in hypnotizability. In a follow-up fMRI study, Jiang and group (Jiang et al. 2017) reported decreased dACC and superior frontal gyrus activity during hypnosis in highly hypnotizable individuals, consistent with a previous report (Raz et al. 2005). In addition, hypnotic response was negatively associated with dACC activity for the high hypnotizable group, such that the higher the self-reported hypnotic intensity during the scan, the lower the dACC activity during hypnosis relative to rest (Jiang et al. 2017).

fMRI brain activity, as measured by the blood-oxygen-level-dependent (BOLD) signal has been shown to be coupled with neural activity (Logothetis et al. 2001), although many

physiological and biophysical factors also play a role (Ogawa et al. 1993). At the cellular level, neurochemical processes, including the cycling of gamma-aminobutyric acid (GABA) and glutamate, the major inhibitory and excitatory neurotransmitters of the central nervous system, regulate neuronal activity and are believed to directly impact BOLD contrast (Logothetis et al. 2001; Attwell and Iadecola 2002; Buzsáki et al. 2007). Previous groups have demonstrated that regional BOLD signals can be negatively associated with GABA concentration and positively associated with glutamate concentration as measured by magnetic resonance spectroscopy (MRS) (Northoff et al. 2007; Stagg, et al. 2011c; Hu et al. 2013; Duncan et al. 2014). MRS has also been used to demonstrate links between key neurochemicals and behavior in both healthy (Duncan et al. 2014; Cohen Kadosh et al. 2015; Yoon et al. 2016) and clinical (Harris et al. 2009; Foerster et al. 2012; Ford and Crewther 2016; Zunhammer et al. 2016; Ford et al. 2017; Lv et al. 2018) populations. To our knowledge, regional GABA and glutamate concentrations as they relate to hypnotizability have not previously been studied.

The goal of the current study was to examine GABA and glutamate concentrations in the ACC of individuals with varying levels of hypnotizability. Given previous findings of reduced ACC activity during hypnosis, our primary hypothesis was that there would be a positive correlation between GABA concentration in the ACC and hypnotizability level. Since it is possible that there may be coordinative effects of GABA and glutamate on brain activity (Hu et al. 2013), our secondary hypothesis was that there would be a negative relationship between ACC glutamate and hypnotizability level. Finally, we conducted exploratory analyses to examine potential relationships between GABA and glutamate concentrations and subscores of hypnotizability measures surrounding dissociation and the related construct of absorption (Tellegen and Atkinson 1974). Having a better understanding of these relationships can provide insight into the putative neurobiological basis for individual differences in hypnotizability and may inform our understanding of treatment response to this growing psychotherapeutic tool.

## Materials & Methods

### Overview

Participants completed one in-person study session whereby MRI scans were acquired, hypnotizability was assessed, and questionnaires were completed. MRI scan sessions included a high-resolution T1-weighted anatomical scan and an MRS scan to assess neurochemical concentrations in the ACC. Voxel placement for the MRS scan was determined via a coordinate-based meta-analysis, which revealed areas of the ACC most likely to be activated in functional neuroimaging studies of hypnosis. Each participant's level of hypnotizability was individually assessed by a trained rater using the Hypnotic Induction Profile (HIP), a standardized measure of hypnotic capacity (Spiegel et al. 1976; Spiegel 1977; Stern et al. 1978). Participants were provided instructions for the remaining questionnaires assessing components of hypnotizability and mood, which they completed in a quiet room without distractions.

### Coordinate-Based Meta-Analysis

To determine which brain region/subregion was most functionally relevant to individual differences in hypnotizability and inform voxel placement for magnetic resonance spectroscopy imaging, we employed a coordinate-based meta-analysis

(CBMA) using GingerALE version 3.0.2 ([www.brainmap.org/ale](http://www.brainmap.org/ale)). GingerALE implements activation likelihood estimation (ALE) meta-analyses to assess the colocalization of functional activations across studies (Turkeltaub et al. 2002, 2012; Laird et al. 2005; Eickhoff et al. 2009; Fox et al. 2014), while overcoming many limitations of individual studies such as low power/sample sizes, poor reproducibility, and heterogeneity in analysis pipelines (Samartsidis et al. 2017). Relevant activation foci included in the ALE were derived from a systematic search of PubMed using the key words, “fMRI”, “hypnosis”, “functional magnetic resonance imaging”, “PET”, or “positron emission tomography.” Given our strong a priori hypotheses regarding the involvement of the ACC from previous studies (Hoefl et al. 2012; Jiang et al. 2017) and the prevalence of ACC and frontal cortex findings in recent literature (Hoefl et al. 2012; Cojan et al. 2015; Halsband and Wolf 2015; Jiang et al. 2017), we specifically focused on activation foci in frontal brain areas to guide voxel placement. A functional imaging study was considered for inclusion if the following conditions were met: 1) fMRI or PET was used to assess brain function; 2) group analyses were performed (i.e., no case studies); 3) task-related activity related to hypnosis or resting-state activity in relation to hypnotizability was examined; 4) peak results for brain regions were explicitly reported using Talairach or Montreal Neurologic Institute (MNI) coordinates. For consistency, activation foci reported in Talairach space were converted to MNI using the `tal2mni` function in GingerALE. Review papers or papers that could not be obtained due to access restrictions or language restrictions were not included.

Using GingerALE, whole-brain probability maps were created across activation foci in MNI space. Probabilities were modeled by a 3D Gaussian function, which accounted for sample size by adjusting the Full-Width Half-Maximum (FWHM) for each study, such that larger sample sizes were smoothed with a tighter, taller Gaussian kernel (Eickhoff et al. 2009). GingerALE estimates the cumulative probability of at least one study reporting activation for a given locus, creating a statistically thresholded ALE map, with high values reflecting high probability estimates for activity at that locus (Morrison 2016). Using random effects algorithms, which support generalizability beyond the analyzed studies, the spatial relationship between foci of a given experiment was assumed to be fixed, and ALE results were assessed against the null distribution of random spatial association between experiments (Eickhoff et al. 2009). A cluster-wise inference threshold method was implemented as opposed to a false discovery rate strategy, which is no longer encouraged for ALE analyses (Eickhoff et al. 2012). Randomized data were simulated from the coordinates and a cluster-forming threshold was used to detect adjacent volumes that surpass the selected value. The cluster-forming threshold was set to  $P < 0.001$  (uncorrected), and the cluster-inference threshold was set to a conservative value of 0.01, as done by others (Landry et al. 2017).

## Participants

Twenty healthy right-handed individuals (10 women, 10 men; mean age  $\pm$  SD: 30.5  $\pm$  9.3 years) were recruited from Stanford University and the surrounding community. Sample size was predetermined based on the primary hypothesis that ACC GABA concentration would be positively associated with hypnotizability scores. In a previous study examining behavioral correlations with GABA concentration in the insula of individuals with fibromyalgia (Foerster et al. 2012), a positive correlation

coefficient of 0.63 was obtained. To achieve a power of  $1 - \beta = 0.80$  for a two-tailed correlation at level  $\alpha = 0.05$ , it was determined that 17 individuals were needed in line with several previous MRS studies examining associations with behavior and/or homologous brain regions (Levy et al. 2002; Foerster et al. 2012; Cohen Kadosh et al. 2015; Reckziegel et al. 2016; Lv et al. 2018; Puts et al. 2018). To account for potential errors related to spectral quality, twenty individuals were recruited. Three individuals were excluded due to high fit error, which was determined to be  $>12\%$  a priori (Puts et al. 2018). The final sample included in the analysis was 17 individuals (8 women, 9 men; mean age  $\pm$  SD: 31.3  $\pm$  9.8). All participants provided written informed consent, and Stanford University’s Human Subjects Research Institutional Review Board approved the study.

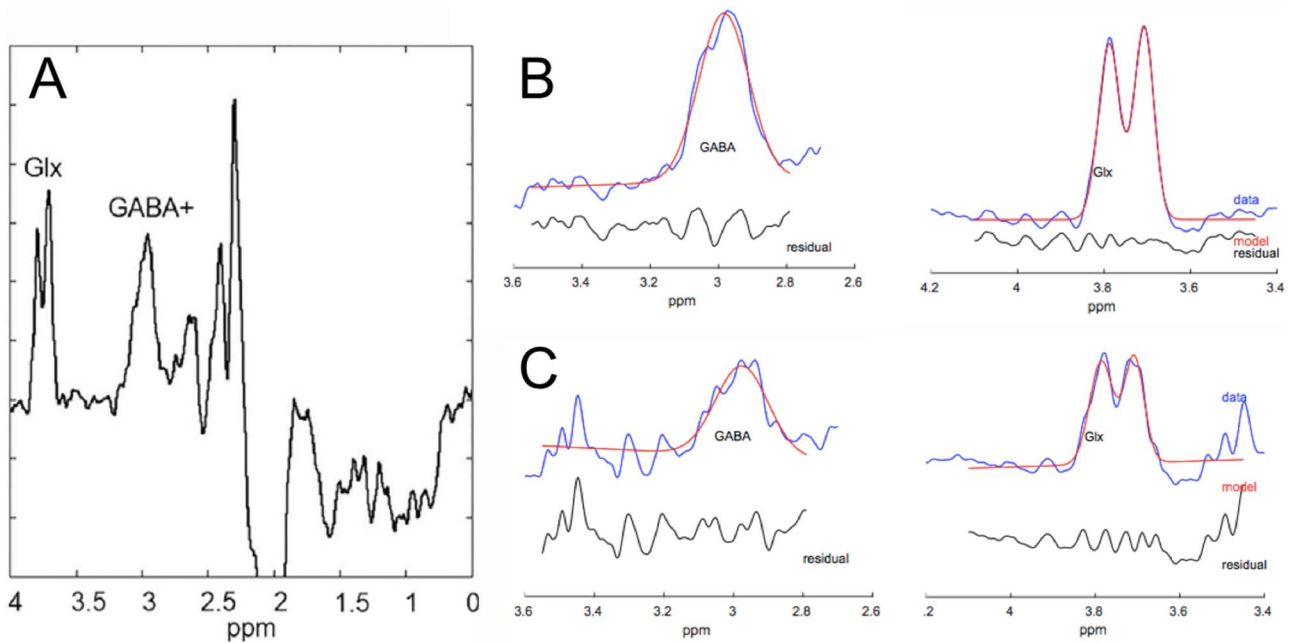
## MRI Scans

MRI scanning sessions were completed at the Stanford Center for Cognitive and Neurobiological Imaging. Images were acquired using a 3T GE Discovery MR scanner and 32-channel Nova head coil. For each participant, high-resolution T1-weighted 3D Bravo sagittal scans (0.9 mm<sup>3</sup> voxels) were acquired towards the start of the scanning session and used for accurate placement of the MRS voxels.

Single voxel in-vivo <sup>1</sup>H MRS scans were acquired using a MEGA-PRESS sequence (Mescher et al. 1998; Edden and Barker 2007) (editing pulses: 14 ms 180° Gaussian-weighted sinc pulses applied at 1.9/7.5 ppm with TE/TR = 68 ms/1500 ms, respectively) with a voxel of interest (VOI, 2.2  $\times$  2.2  $\times$  4 cm<sup>3</sup>) placed over the ACC, spanning significant clusters derived from the CBMA, with the corpus callosum as the inferior boundary. Volumes were shimmed at the start of each MRS scan. MEGA-PRESS uses a J-difference editing approach to measure GABA+ (GABA + homocarnosine + macromolecules) and Glx (glutamate + glutamine) relative to water (H<sub>2</sub>O) or creatine (Cr) (Fig. 1A). Therefore, relative values within the VOI are reported (Edden et al. 2014). MEGA-PRESS data were analyzed using Gannet software v.2.0 (Edden et al. 2014), an open-source software coded within Matlab (The Mathworks, Natick, USA).

## MRS Voxel Segmentation

Metabolite concentrations differ between brain tissue types, and because of the size of typical MRS voxels, it is often not possible to obtain “pure” gray matter voxels. These “partial volume” effects can confound the detection of metabolite concentrations due to individual differences in the relative concentrations of metabolites in different tissue types, for example, gray versus white matter (Tal et al. 2012). To account for potential confounds resulting from partial volume effects across subjects, we specifically computed the gray matter content within each participant’s MRS VOI. Specifically, MRS VOI information was extracted from each individual voxel prescription across MRS scans. This information was then used to create a 3D VOI mask aligned with the same matrix of the given participant’s high-resolution T1-weighted image. T1-weighted images were processed using the `recon-all` command of the FreeSurfer software suite (v.6.0; <http://surfer.nmr.mgh.harvard.edu>) (Fischl and Dale 2000), resulting in the segmentation of whole-brain gray matter, white matter, and cerebrospinal fluid tissue types. Next, gray matter within each of the 3D MRS VOIs was quantified by calculating overlap between FreeSurfer-defined gray matter and the 3D MRS VOI mask. Gray matter concentration was then included in a subsequent regression analysis.



**Figure 1.** (A) Representative edited spectrum of GABA+ and Glx using MEGA-PRESS. (B) “Good fit” examples from our cohort. GABA+ (left) and Glx (right) edited peaks using nonlinear least-squares fitting to estimate concentrations. (C). “Poor fit” examples of GABA+ and Glx. Since fit error percentages were >12%, the “poor fit” examples were excluded from further analysis.

## Hypnosis Assessment and Questionnaires

### Hypnotic Induction Profile (HIP)

A brief standardized measure of hypnotizability was used to assess subjective and behavioral responses to hypnotic suggestions involving: 1) dissociation; 2) levitation of a lowered hand; 3) a sense of involuntariness during elevation of the hand; 4) response to cut-off signal for instructions of lightness and movement; and 5) sensory alterations of floating, lightness, or buoyancy (Spiegel and Bridger 1970; Spiegel and Spiegel 2004). The HIP score ranges from 0 to 10, with scores from 0 to 3 indicating low hypnotizability, 4 to 6 indicating moderate hypnotizability, and 7 to 10 as high hypnotizability (Spiegel et al. 1976). High versus low hypnotizability on the HIP is associated with higher functional connectivity between the left dorsolateral prefrontal cortex and the dorsal ACC using fMRI (Hoeft et al. 2012). Additionally, the HIP is moderately and significantly correlated with the longer Stanford Hypnotic Susceptibility Scales at the same level (0.6) that single items from these scales are correlated with the total score (Orne et al. 1979; Frischholz et al. 1980).

### Dissociative Experiences Scale (DES)

It is a self-report scale to assess the degree to which subjects experience dissociation or changes in the normal integration of thoughts, feelings, and experiences into the stream of consciousness and memory (Bernstein and Putnam 1986). Specifically, the DES examines different types of dissociative experiences and the frequency by which they are experienced on a 0–100% scale in 10% increments. The DES is comprised of three subscales: 1) amnesic dissociation; 2) absorption and imaginative involvement; and 3) depersonalization and derealization (Bernstein and Putnam 1986). Scores on the DES have previously been shown to be associated with hypnotizability (Frischholz et al. 2015).

### Tellegen Absorption Scale (TAS)

It is a self-report questionnaire that measures absorption, which Tellegen and colleagues have described as the disposition for having episodes of attention that fully engage one’s representational (e.g., perceptual, motoric, imaginative, and ideational) resources to a unified representation of the attentional object (Tellegen and Atkinson 1974). More recently, absorption has also been described as the surrender of an “instrumental” set, which employs active, realistic, and effortful planning of behavior and adoption of an “experiential” set, characterized by an effortless, nonvolitional quality of involvement with objects of consciousness (Tellegen 1981). The TAS is a dichotomous scale, requiring a true or false response to items on nine subscales: 1) responsiveness to engaging stimuli; 2) responsiveness to inductive stimuli; 3) imagistic thought; 4) ability to summon vivid and suggestive images; 5) cross-modal experiences; 6) absorption in thoughts and imaginings; 7) vivid memories of the past; 8) episodes of expanded awareness; and 9) altered states of consciousness (Glisky et al. 1991). Scores on the TAS are significantly correlated with hypnotizability as measured by the HIP (Frischholz et al. 1987) and the Stanford Hypnotic Susceptibility Scales (Tellegen and Atkinson 1974; Tellegen 1981).

### Depression Anxiety Stress Scales (DASS-21)

It is a short form of the 42-item self-report measure of mental health focusing on three negative emotional states: depression, anxiety, and stress. Each of the three subscales is comprised of seven relevant items, rated on a 4-point severity/frequency scale that is summed to assess severity level in each of the emotional states (Lovibond and Lovibond 1995; Henry and Crawford 2005). Given the role of the ACC in negative affect (Shackman et al. 2011), this assessment was included to assess the potential contribution of negative emotional state to individual differences in ACC neurochemical concentrations.

## Data Analysis

### MRS Data Processing

Raw P files from MRS scans were submitted to analysis using Gannet software, a batch-processing tool for the quantitative analysis of GABA (Edden et al. 2014) and Glx. Estimates of the area under the edited spectra were provided using nonlinear least-squares minimization algorithms (Edden and Barker 2007). Overall fit error for each measure was calculated and if >12%, excluded from further analysis (Fig. 1B,C) (Puts et al. 2018).

### Associations with Behavioral Data

To assess relationships between neurochemical and behavioral measures, bivariate (Pearson) or Spearman's rho correlations, as appropriate, were carried out using R software version 3.3.3 (<https://www.r-project.org>). Relationships with GABA+ were examined to test our primary hypothesis that higher ACC GABA would be associated with higher hypnotizability. Relationships between GABA+ relative to water (GABA+/H<sub>2</sub>O) and creatine (GABA+/Cr) and HIP, DES, TAS, and DASS-21 total scores were examined. Given the multiple comparisons (eight in total), a false discovery rate (FDR) correction was applied at the  $P < 0.05$  level. Relationships between Glx relative to water (Glx/H<sub>2</sub>O) and creatine (Glx/Cr) were similarly examined with total scores of the behavioral measures to test our secondary hypothesis that lower ACC Glx would be associated with higher hypnotizability (significance set to  $P < 0.05$ , FDR corrected). Exploratory analyses of neurochemical excitability and questionnaire subscores were also conducted.

### Gray Matter Quantification

Gray matter within each participant's VOI was quantified and included as an independent variable in a stepwise linear regression model with HIP score as the dependent variable. Age and relevant neurochemical concentrations derived from correlation analyses above were additionally included as independent variables.

## Results

### Activation Likelihood Estimate

Analysis included 117 activation foci from frontal brain regions in 21 experiments (Table 1). Three significant ( $P < 0.01$ , cluster-level Family Wise Error) clusters were obtained. Two clusters were classified as ACC and one as medial frontal gyrus (MFG). The first ACC cluster was located in the right pregenual ACC (pgACC) (Brodmann Area (BA) 32; MNI:  $x = 8, y = 50, z = 2$ ) (Fig. 2, top), and the second cluster was located midline in the dorsal ACC (dACC) (BA 32; MNI:  $x = 0, y = 34, z = 24$ ) (Fig. 2, middle). The third cluster was located in the MFG adjacent to the ACC (BA 9; MNI:  $x = -2, y = 50, z = 8$ ). Based on the location of these clusters and our strong a priori hypotheses regarding the role of the ACC in hypnosis, MRS voxels of interest were positioned to span both the pgACC and dACC (Fig. 2, bottom).

### Neurochemical Concentrations and Hypnotizability

In accordance with our primary hypothesis, GABA+ ratios were positively correlated with hypnotizability as assessed by the HIP: GABA+/H<sub>2</sub>O and HIP ( $r = 0.635, P = 0.006$ ), GABA+/Cr and HIP ( $r = 0.488, P = 0.047$ ). Following FDR correction, only GABA+/H<sub>2</sub>O and HIP scores remained significantly correlated ( $q < 0.05$ ) (Fig. 2A). GABA+/H<sub>2</sub>O values for the participants that

**Table 1** Studies included in coordinate-based meta-analysis

| Study                        | Sample size | Imaging method | Rest/task <sup>a</sup> |
|------------------------------|-------------|----------------|------------------------|
| (Jiang et al. 2017)          | n = 57      | fMRI           | Task                   |
| (Hoeft et al. 2012)          | n = 24      | fMRI           | Rest                   |
| (Abrahamsen et al. 2010)     | n = 19      | fMRI           | Task                   |
| (Derbyshire et al. 2009)     | n = 13      | fMRI           | Task                   |
| (Raz et al. 2005)            | n = 32      | fMRI           | Task                   |
| (Schulz-Stübner et al. 2004) | n = 12      | fMRI           | Task                   |
| (Faymonville et al. 2000)    | n = 11      | PET            | Task                   |
| (Nusbaum et al. 2011)        | n = 14      | PET            | Task                   |
| (Halsband and Wolf 2015)     | n = 24      | fMRI           | Task                   |
| (Ludwig et al. 2015)         | n = 8       | fMRI           | Task                   |
| (McGeown et al. 2015)        | n = 29      | fMRI, MRI      | Rest + Struc           |
| (Burgmer et al. 2013)        | n = 19      | fMRI           | Task                   |
| (Müller et al. 2012)         | n = 16      | fMRI           | Task                   |
| (Deeley et al. 2012)         | n = 8       | fMRI           | Task                   |
| (Demertzi et al. 2011)       | n = 12      | fMRI           | Task                   |
| (Pyka et al. 2011)           | n = 19      | fMRI           | Task                   |
| (McGeown et al. 2009)        | n = 18      | fMRI           | Task                   |
| (Mendelsohn et al. 2008)     | n = 23      | fMRI           | Task                   |
| (Egner et al. 2005)          | n = 22      | fMRI           | Task                   |
| (Rainville et al. 1999b)     | n = 8       | PET            | Task                   |
| (Maquet et al. 1999)         | n = 9       | PET            | Task                   |

<sup>a</sup>Rest refers to resting-state scan while task refers to hypnosis task or induction done during scan. For studies including a task, a hypnosis condition was typically compared with a rest or control condition. Struc indicates that a study also assessed brain structure.

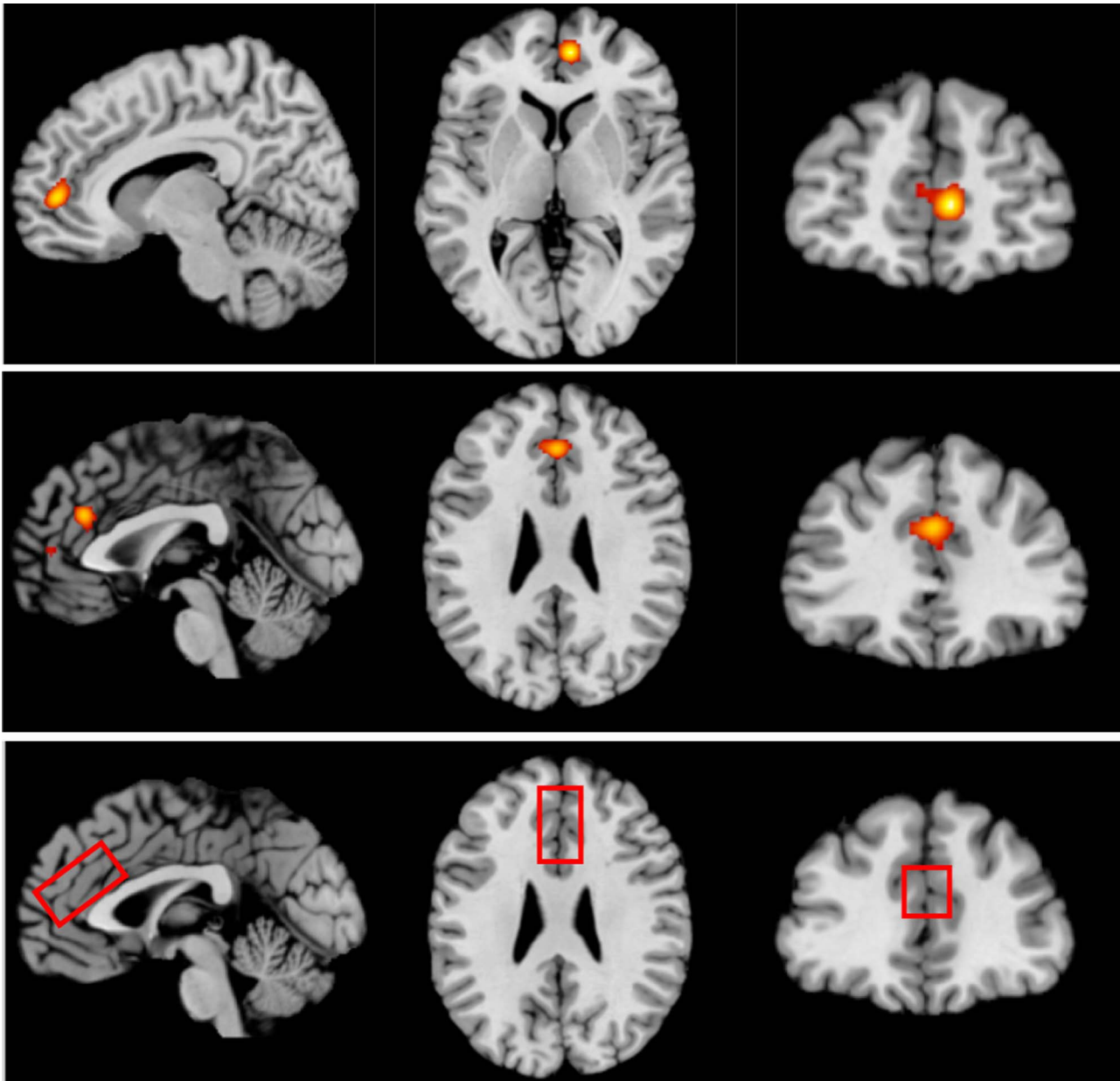
were excluded due to "poor fit" were in range of those included ( $P = 0.25$ ). A stepwise linear regression model with GABA+/H<sub>2</sub>O, VOI gray matter, and age as predictor variables revealed that neither proportion of gray matter (Fig. 3) nor age were significant predictors of hypnotizability and only GABA+/H<sub>2</sub>O values significantly predicted HIP scores (accounting for 36% of variance). No significant relationships between GABA+ ratios and DES, TAS, and DASS-21 total scores were obtained ( $P > 0.05$ ).

With regard to Glx, no correlations were detected between Glx ratios and total scores on the HIP or other questionnaires examined ( $P > 0.05$ ). However, an exploratory analysis of questionnaire subscales revealed a negative relationship between the absorption and imaginative involvement subscale of the DES and Glx/Cr, such that the lower the Glx/Cr concentration, the greater the absorption and imaginative involvement ( $r = -0.58, P = 0.011$ ) (Fig. 3B).

## Discussion

We examined the association between neurochemical concentrations in the ACC and variability in hypnotizability in healthy adult participants. Our results demonstrate a significant positive association between ACC GABA (GABA+) and hypnotic responsiveness such that the more highly hypnotizable an individual, the greater the GABA concentration. This association was independent of age and ACC gray matter within the MRS voxel. Additionally, an exploratory analysis revealed a negative association between ACC glutamate (Glx) and the absorption and imaginative involvement subscale of the DES.

GABA and glutamate are key constituents of the inhibition/excitation balance in the brain and can be readily measured using MRS (Duncan et al. 2014). Previous groups

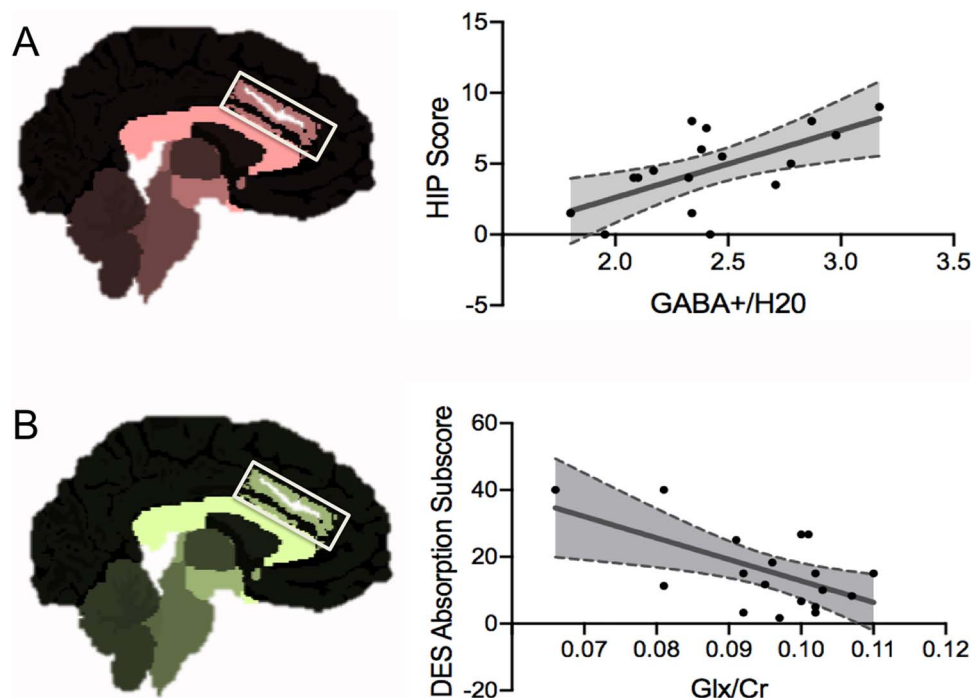


**Figure 2.** Results of the activation likelihood estimate revealed two regions of the ACC that are consistently involved in functional neuroimaging studies of hypnosis. One cluster was located in the pregenual ACC (top panel) and the other in the dorsal ACC (middle panel). The bottom panel shows the placement of the ACC voxels for the MRS scan.

have demonstrated a negative relationship between regional BOLD signals and GABA concentration across a variety of tasks (Northoff et al. 2007; Stagg et al. 2011c; Hu et al. 2013; Duncan et al. 2014). In line with these studies, we report higher GABA concentration with increasing hypnotizability, spanning the same ACC regions with decreased activity during hypnosis in high hypnotizables (Raz et al. 2005; Jiang et al. 2017). One explanation for this finding is that individuals that are more highly hypnotizable have greater pools of extracellular GABA in the ACC, supporting a more tonic, neuromodulatory role (Stagg et al. 2011a). This would allow certain individuals to more readily enter a hypnotic state characterized in part by decreased ACC activity. In agreement, it has been suggested that

MRS measures of GABA concentration more closely represent extracellular GABA, as evidenced by noninvasive transcranial magnetic stimulation paired pulse methods and ultrahigh-field MRS (Dyke et al. 2017). However, since MRS measures total GABA within a cortical region and cannot distinguish distinct functional pools of intracellular and extracellular GABA (Stagg et al. 2011b), it is not possible to completely rule out the contribution of phasic vesicular GABA to these signals.

The literature supports a “top-down” view of hypnosis, whereby activity differences in frontal brain networks involved in processes such as attention, executive control, and cognitive monitoring contribute to interindividual variability in maintaining attentional focus towards relevant mental



**Figure 3.** (A) There was a significant positive correlation between ACC GABA concentration (red brain) and hypnotizability as measured by the HIP ( $R=0.64$ ,  $P=0.006$ , FDR-corrected). (B) An exploratory analysis revealed a negative association between ACC glutamate (green brain) and the absorption and imaginative involvement subscale of the DES ( $R=-0.58$ ,  $P=0.011$ ). Note that both brain images show representative voxel segmentation with quantified gray matter within white boxes. Shaded areas on graphs represent 95% confidence intervals.

representations during hypnotic response (Landry et al. 2017). Our results provide additional support for this hypothesis, as interindividual differences in GABA concentrations in the ACC were related to hypnotizability. This finding provides a putative neurophysiological means by which individuals may vary in attentional processes involved in hypnotizability. Evidence for the contributions of other brain regions/networks to hypnotizability has been reported. However, the ACC specifically may act as a hub within these networks, allowing for information integration (Shackman et al. 2011) and directed attention facilitated by reduced conflict processing. The highly focused attention typical of hypnosis would be facilitated by a decrease in conflict monitoring, which is related to dissociation, the compartmentalizing of experience such that unrelated or conflicting thoughts, memories, or perceptions are less likely to impinge on processing focal attention. This is typical of hypnotic analgesia, for example, in which response to administered pain stimuli is reduced by decreasing activity in the dACC (Rainville et al. 1997; Rainville et al. 1999a) as well as somatosensory cortex (Spiegel 1989). Thus, the interaction of the ACC with other brain regions such as the DLPFC can further explain specific aspects of hypnotizability such as dissociation, as discussed by others and in more detail below (Jiang et al. 2017).

Our previous findings emphasized inhibition of dACC activity in hypnosis (Jiang et al. 2017). Both Egner (Egner et al. 2005) and Dienes and Hutton (Dienes and Hutton 2013) propose that hypnosis involves inhibition of higher level cortical function, specifically in the DLPFC; however, increased rather than decreased dACC activity associated with hypnosis was reported (Egner et al. 2005). As such, a bottom-up, rather than a top-down, model of hypnotic experience was proposed, arguing that awareness of intention is inhibited through salience network overriding of

executive control. Woody and colleagues (Woody and Farvolden 1998) attempt to reconcile such differences using the concept of dissociated control, citing Bowers' idea that: "in hypnosis lower levels of control of behavior may become relatively independent of the higher, executive level of control" (Woody and Sadler 1998). Hypnotic phenomena occur because higher order assessment of intention is inhibited—the hand movement, for example, occurs without awareness of intending to make the movement. But in the hypnotic induction, does the DLPFC, functionally more connected to the dACC among high hypnotizables, (Hoeft et al. 2012) inhibit both itself and the dACC, or does the dACC inhibit the DLPFC? We found that entry into the hypnotic state is characterized by reduction in dACC but not left DLPFC activity (Jiang et al. 2017).

An additional question is can inhibition of the salience network facilitate dissociation of the thought from the act? Why would "more" conflict monitoring "enhance" dissociation and a sense of involuntariness when a subject is instructed that his/her hand will float up in the air? It would seem that inhibiting salience activity would enhance dissociation of thought from act by allowing executive evaluation of only one aspect of experience—the motion without the experience of intention. However, the Egner study involved hypnosis during a Stroop task (Egner et al. 2005), which is designed to stimulate conflict monitoring. We (Nordby et al. 1999b) and others (Raz et al. 2002, 2006, 2007) have shown that hypnotic instruction can override the Stroop interference effect via reducing activity in the ACC. The Egner study used but did not try to reduce Stroop conflict monitoring, which may be why hypnosis appeared to increase ACC activity. Our earlier study provided hypnotic instructions to activate pleasant memories and emotions (Jiang et al. 2017) and so facilitated absorption and dissociation rather than

conflict detection. Dienes and Hutton (Dienes and Hutton 2013) applied low frequency repetitive transcranial magnetic stimulation (rTMS) to the left DLPFC to inhibit its function, and the hypnotic suggestions were typical (magnetic hands, arm levitation, rigid arm, and taste hallucination) and not likely to stimulate conflict monitoring. So inhibition of the DLPFC should have likewise inhibited dACC activity, as in our previous studies.

Additionally, since the ACC is a central hub for several brain networks (e.g., salience and central executive) involved in higher order cognitive functions, hypnosis may involve inhibition of salience evaluation, executive function, or more likely coordination between the two. The higher levels of GABA observed in the ACCs of high hypnotizables may indicate a greater capacity to reduce salience network activity when executive control activity is reduced—shared soothing rather than top-down inhibition.

Interestingly, we did not find an overall relationship between glutamate and hypnotizability as measured by the HIP. As some previous studies reported an inverse relationship between GABA and glutamate in relation to fMRI BOLD activity (Northoff et al. 2007; Stagg et al. 2011c; Hu et al. 2013; Duncan et al. 2014), we secondarily hypothesized that ACC glutamate concentration would decrease with increasing hypnotizability. Notably, behavioral associations with GABA, but not glutamate, have been reported previously (Reckziegel et al. 2016). In the current study, the lack of relationship between glutamate and HIP scores may reflect cognitive state at the time of scanning. MRS scans were acquired at rest (i.e., participants were not given a hypnotic induction); however, decreased ACC activity was demonstrated during a state of hypnosis (Jiang et al. 2017). It is possible that the relationship between glutamate and HIP scores would become evident if MRS scans were acquired during hypnosis as opposed to rest. Evidence for brain states reflecting contrasting dynamics of GABA and glutamate concentrations comes from MRS work in the occipital cortex during visual processing (Kurcyus et al. 2018). Others, however, have demonstrated a link between resting-state GABA and glutamate in predicting task-induced activity changes (Stagg et al. 2011a; Hu et al. 2013). In accordance with these studies, increased GABA at rest was indicative of higher hypnotizability in our cohort and also in line with increased functional connectivity at rest between the left DLPFC and dACC in high hypnotizables compared with low (Hoeft et al. 2012). As discussed above, one putative mechanism by which higher concentrations of ACC GABA and connectivity between the left DLPFC at rest can underlie higher hypnotizability is via top-down control by the DLPFC over the dACC to decrease its activity. In the study by Dienes and group, inhibitory rTMS applied to the left DLPFC enhanced both behavioral and subjective hypnotic responses (Dienes and Hutton 2013). Therefore, inhibition of the ACC via the DLPFC (Gratton et al. 2013) may underlie enhanced hypnotizability.

An alternative explanation for the lack of association between glutamate and HIP scores is that interindividual differences in glutamate concentration may be associated with aspects of hypnotizability but not total HIP score. In an exploratory analysis, we specifically examined subscales of dissociation (DES) and absorption (TAS), which revealed a negative relationship between glutamate and the absorption and imaginative involvement subscale of the DES. Dissociation is a disintegration between psychological elements with an absorptive/imaginative component involving directed and focused attention to tasks or representational systems (Spiegel and Spiegel 2004). An example of an absorption item on the DES is, “Some people find that when they are watching

television or a movie they become so absorbed in the story that they are unaware of other events happening around them” (Bernstein and Putnam 1986). In a study by Soffer-Dudek and colleagues, dissociative absorption was related to decreased coherence between frontal-occipital regions as measured by electroencephalography (EEG) connectivity (Soffer-Dudek et al. 2019). These effects were more pronounced in the slow-wave bands (theta and delta), which have been related to complex functions such as mental imagery, particularly over long-range connections (von Stein and Sarnthein 2000). Replication of these findings using other measures of hypnotizability that emphasize different aspects such as imagery vividness (Pekala and Maurer 2015) might help clarify the findings.

A novel aspect of our study was the use of a quantitative meta-analysis to inform MRS voxel placement over the ACC. The literature supports a role for the ACC in hypnosis given its central position in models of cognitive control and conflict processing. Given our strong a priori hypotheses regarding GABA and glutamate concentrations in the ACC, we specifically probed the literature for functional imaging coordinates related to hypnosis in frontal brain regions. Recent meta-analytic analyses examining whole-brain activation foci in hypnosis have been published elsewhere (Landry et al. 2017). Across studies, two clusters in the ACC were shown to be significantly involved in hypnosis, in addition to one adjacent medial frontal gyrus cluster. MRS voxels were prescribed to span both of these ACC clusters. While this approach helps support generalizability beyond the analyzed participants, the ACC is a functionally diverse cortical region. Still our voxel placement included ACC regions relevant to hypnosis and these regions may correspond to different aspects of hypnotic response depending on the hypnotic instructions provided between studies. Future studies may elect to examine subregions of the ACC separately, particularly with ultrahigh-field MRS, to enhance signal-to-noise ratios in smaller voxels.

Additionally, the current study employed a voxel segmentation procedure to account for differences in gray matter within MRS ACC voxels. This step was included since metabolite concentrations differ between brain tissue types (Tal et al. 2012), and it is often not possible to obtain “pure” gray matter voxels. Variation in the proportion of gray matter within voxels could influence resulting metabolite concentrations. Our results indicated that the proportion of gray matter within ACC voxels did not contribute to differences in hypnotizability as measured by the HIP, further supporting a role for ACC GABA concentration rather than differences in the amount of gray matter assessed. Since our study was conducted in healthy individuals and ACC voxels were placed midline to include both hemispheres, the proportion of gray matter may be less variable than in clinical populations or in brain regions where single hemisphere prescriptions are required (e.g., DLPFC). Additionally, voxel placement was guided by the results from activation likelihood estimate clusters and reliable anatomical landmarks such as the corpus callosum, which helped to consistently place voxels between participants. This procedure would be highly beneficial for studies including clinical populations and/or examining brain regions with less consistent landmarks for voxel placement.

Given the utility of hypnosis as a growing clinical tool, it is important to understand interindividual differences in hypnotizability. We provide a major step towards understanding the role of the ACC and regional neurochemical concentration variability in underlying interindividual differences in hypnotizability. Future studies may expand upon these findings by



examining ACC subregions using ultrahigh-field MRS and by examining neurochemical plasticity related to adjunctive procedures to enhance hypnotizability, including noninvasive brain stimulation.

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## Notes

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