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Report

Individual Differences in Subconscious Motor Control Predicted by GABA Concentration in SMA

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Summary

Subliminal visual stimuli affect motor planning [1], but the size of such effects differs greatly between individuals [2, 3]. Here, we investigated whether such variation may be related to neurochemical differences between people. Cortical responsiveness is expected to be lower under the influence of more of the main inhibitory neurotransmitter, GABA [4]. Thus, we hypothesized that, if an individual has more GABA in the supplementary motor area (SMA)—a region previously associated with automatic motor control [5]—this would result in smaller subliminal effects. We measured the reversed masked prime—or negative compatibility—effect, and found that it correlated strongly with GABA concentration, measured with magnetic resonance spectroscopy. This occurred specifically in the SMA region, and not in other regions from which spectroscopy measurements were taken. We replicated these results in an independent cohort: more GABA in the SMA region is reliably associated with smaller effect size. These findings suggest that, across individuals, the responsiveness of subconscious motor mechanisms is related to GABA concentration in the SMA.

Results and Discussion

Differences between people have long been studied at the level of personality or intelligence, but people also differ in much more basic neural processes, even ones that are subconscious and automatic (e.g., Figure 7 in [2], Figure 5 in [3]). In the study of such low-level phenomena, behavior across a group of individuals is usually averaged, and differences are treated as unwanted noise (random variation). However, this approach overlooks the inescapable fact that a component of the measured differences may reflect stable individual traits, no matter how low level the mechanism (see Figure S1 available online). Such basic traits may also hold essential clues into how individual differences translate into mental disorders. To our knowledge, no explanation has ever been provided for individual differences in automatic mechanisms operating at the threshold of conscious awareness, even though they potentially offer a cleaner index than measures of conscious behavior. Recent advances in magnetic resonance spectroscopy (MRS) allow us to ask whether these traits might be predicted by differences in neurotransmitter concentration in specific brain regions [6–13].

We studied reversed masked priming by using a standard paradigm [14, 15]. Participants must respond to arrows pointing left or right by pressing different buttons, and each target arrow is preceded by a very brief and backward-masked prime arrow (Figure 1A). Prior to the main priming procedure, the primes were set to be below the threshold of conscious perception determined for each participant by using a staircase discrimination task. Nevertheless, these prime stimuli influenced responses to the target arrows.

When the time between prime and target was very short, responses were facilitated by primes pointing in the same direction as targets (mean, 21 ms; $p < 0.017$). This is known as the positive compatibility effect (PCE), and is taken as an index of subliminal activation by the prime [1]. However, when the target was presented slightly later, responses were relatively delayed for targets pointing in the same direction as primes (mean 26 ms; $p < 0.008$). This reversed masked prime effect is known as the negative compatibility effect (NCE), and is taken as an index of an automatic inhibitory mechanism that is triggered to suppress the initial subliminal motor activation evoked by the primes [16–19]. Importantly for our study, this mechanism has been linked with a specific brain area, the supplementary motor area (SMA): the NCE has been reported absent in patients with very specific lesions in this region [5], and in healthy participants, the behavioral NCE is accompanied by fMRI modulation in the SMA [20].

Participants varied considerably in the size of their NCE (range, −45 to −8 ms), and this is a robust trait: we found a high correlation between measurements taken in the same person several weeks apart (Figure S1). We tested whether this individual variation is correlated with subtle differences in resting brain chemistry in the SMA. Neuronal activity in all cortical regions reflects a complex interplay between excitatory and inhibitory synapses. The latter mainly employ the neurotransmitter gamma-aminobutyric acid (GABA), and we predicted, therefore, that the size of the NCE might be related to the level of GABA concentration in the SMA, given that the SMA is thought to play an important role in the NCE [5, 20].

Furthermore, opposing predictions can be made depending on the exact role of the SMA: if the main role of the SMA in reversed priming is to be the site of inhibition, then we would predict that more GABA would be associated with more inhibition, and thus a larger NCE. If, on the other hand, the SMA is more involved upstream, with eliciting the inhibition process, we would predict smaller NCEs in those participants with higher GABA concentration in the SMA, because more GABAergic inhibition within a region would make that region less responsive [4] (for example, the GABA agonist muscimol is commonly used to temporarily deactivate a region in animal research, e.g., [21]).

Using edited MR spectroscopy [6, 8], we measured GABA concentration from a $(3\ cm)^3$ region of dorsal medial frontal cortex, including, but not limited to, both right and left SMA

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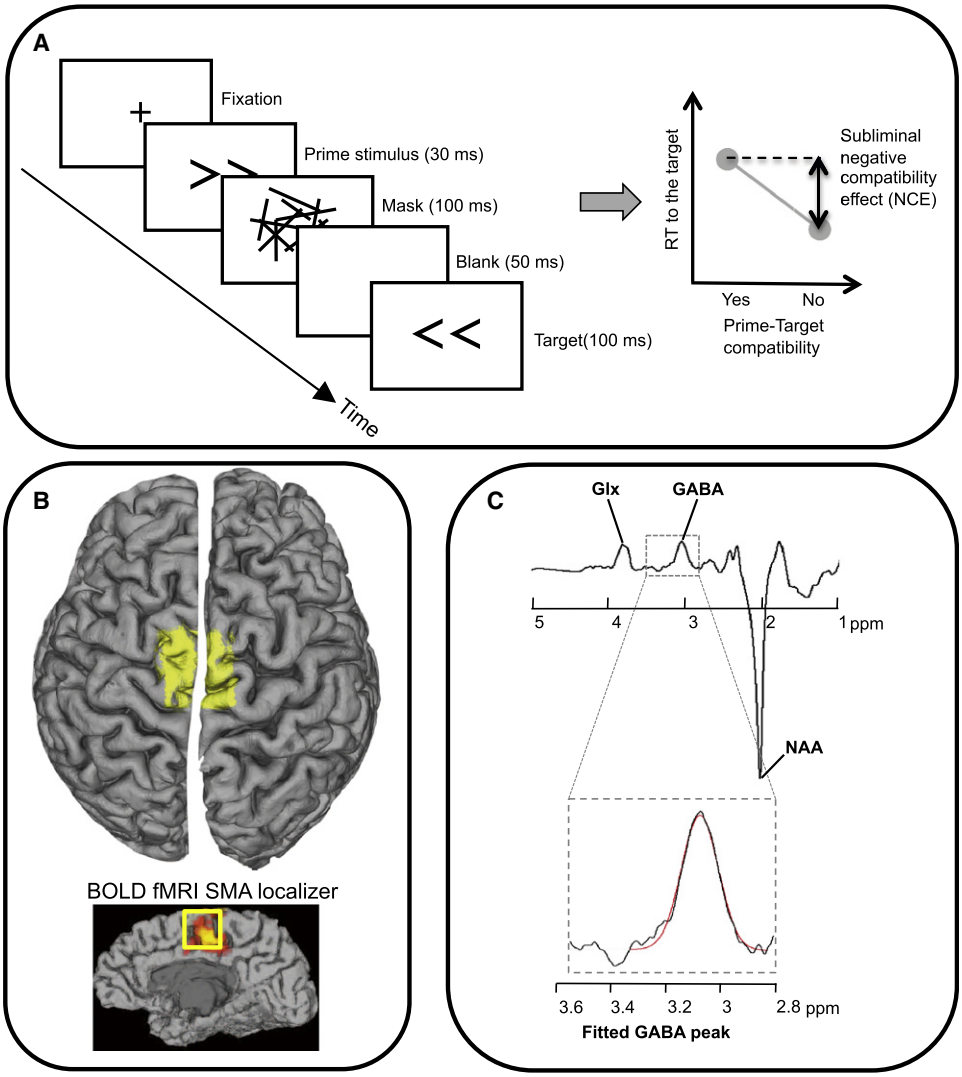

Figure 1. Methodology for Masked Priming and GABA Spectroscopy

(A) Target arrows were preceded by masked primes presented below the threshold for conscious discrimination. For the stimulus timing illustrated, responses tend to be slower when prime and target are the same (compatible) than when they are not (right-hand illustration). This is the measure of subliminal suppression, and the magnitude differs between individuals.

(B) The MRS voxel (yellow, $[3\ cm]^3$ voxel) was placed over the anatomical location of SMA. As a check on voxel placement, for two participants, we acquired a functional localizer for the SMA by using fMRI (see Experimental Procedures and bottom sagital view).

(C) Edited MR spectra allow the quantification of GABA concentration by extracting the area under the GABA peak [6, 8, 9, 49] (glutamine/glutamate, Glx, and N-acetyl-aspartate, NAA, peaks are also marked). The peak will also contain coedited macromolecules. See Experimental Procedures and Figure S2 for more details and individual spectra.

(we refer to this as the SMA region [Figures 1B and 1C]; see Figure S2 for individual GABA peaks within the spectra). This correlated well with the magnitude of the NCE, such that participants with higher GABA concentration in this region had smaller NCEs ($r = 0.77$; $p < 0.005$ uncorrected; $n = 12$; bootstrap 95% confidence interval, $r = 0.51–0.93$ [Figure 2A, left]). We replicated this result in a separate cohort of 13 subjects ($r = 0.62$; $p = 0.025$; bootstrap 95% confidence interval, $r = 0.11–0.85$ [Figure 2A, right]). In both groups, therefore, the magnitude of the NCE was inversely related to GABA concentration in SMA.

In the same participants, we also measured GABA concentration in other regions that have been associated with controlling the interaction between visual stimuli and action plans: dorsolateral prefrontal cortex, parietal cortex (both cohorts), anterior cingulate, and inferior frontal gyrus (first cohort) [22–25]. In these regions, GABA concentration did not correlate with the NCE (Figure 2B; see also Figure S3). Thus, our data show regional specificity for the relationship between GABA and subconscious motor suppression.

We also found that the NCE correlates behaviorally with positive priming (the PCE, first cohort, $r = -0.8$, $p < 0.005$; second cohort, $r = -0.5$, $p < 0.05$ one-tailed [Figures 3A and 3B]). People with smaller NCEs tend also to have smaller PCEs, which rules out the possibility that smaller NCEs simply reflected difficulty in overturning large initial positive priming phases. Rather, it suggests that, in some people, both mechanisms are less responsive. However, GABA in the SMA region does not significantly correlate with the PCE (Figures 3C and 3D), and, thus, the association between PCE and NCE

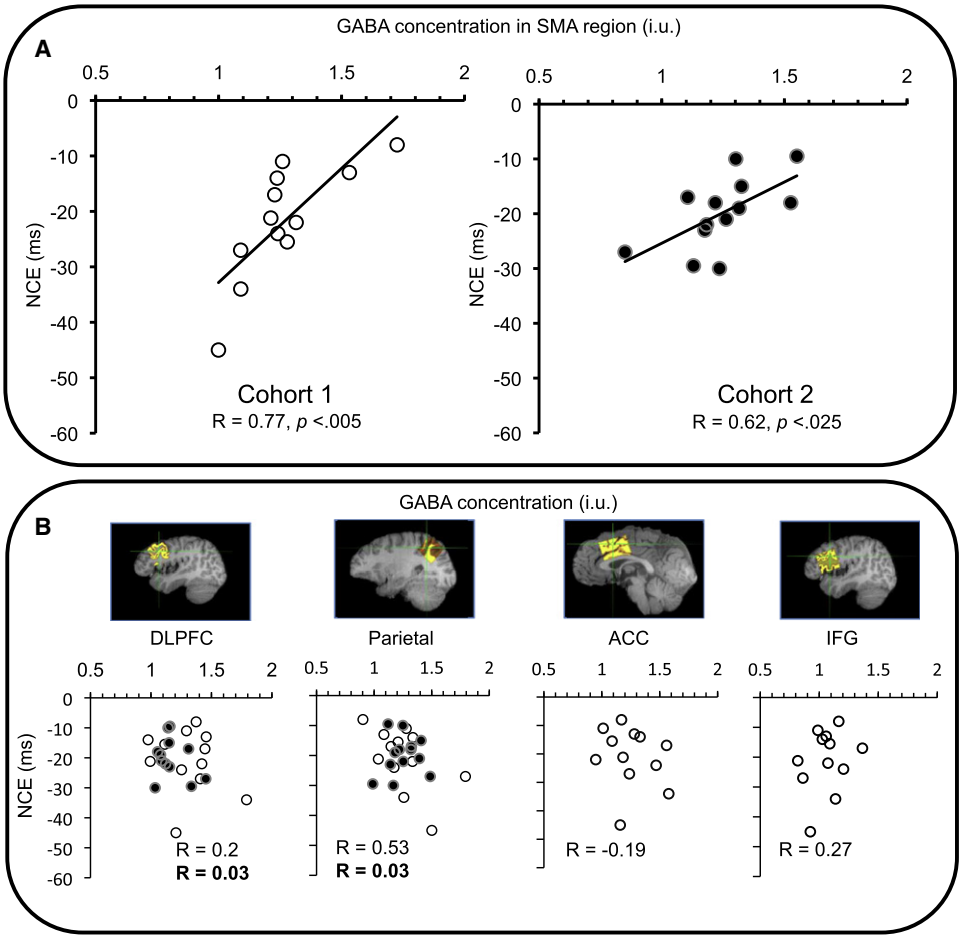

Figure 2. Subliminal Suppression Correlates with GABA in the SMA Region

Higher GABA concentration in the region around human SMA predicts smaller NCE across individuals (A). This result was replicated in a second cohort (right). (B) There was no correlation between the NCE and GABA concentration in dorsolateral prefrontal cortex (DLPFC), parietal cortex, anterior cingulate cortex (ACC), or inferior frontal gyrus (IFG). Positioning of these MRS voxels is shown for one participant (yellow rectangles on inset brains). Note that, although the word cortex is included in some labels (to follow standard abbreviations for these regions), all voxels necessarily included both gray and white matter. Filled symbols and bold R values reflect measurements from the second cohort. GABA concentration measurements are stated in institutional units (i.u.). All p values are given two-tailed, but uncorrected for multiple comparisons; the main relationship of interest between the NCE and the SMA was specified a priori [5], but even if it had not been (and the first p value is corrected), the replication demonstrates that the relationship is robust.

must arise elsewhere. This is consistent with previous research, in which lesions in the locality of the SMA disrupted the NCE, but a PCE was present [5].

We tested whether the correlation between the NCE and GABA in the SMA region might arise due to other individual factors: age, prime visibility, overall speed of responding, error rate, and gray matter volume. It did not; there were no significant correlations of either the NCE or GABA in SMA with any of these factors, and, when controlling for them, the correlation between SMA GABA and the NCE remained (Figure 4).

What, then, is the cause of the relationship between a person's NCE and GABA in their SMA region? The direction of the relationship implies that SMA is involved in the *production* of suppression rather than being the site where it occurs. The intuitive expectation might be that more GABA is associated with more inhibition, and, thus, a larger NCE. This relationship would be consistent with suppression *within* the SMA. However, directional expectations are complicated, because the SMA is part of a network with other regions. If it is involved upstream, in the eliciting of inhibition rather than the implementation of inhibition, then lowering the responsiveness of this region with more baseline GABA would be predicted to lessen its functional effect, reducing the NCE.

The latter prediction is consistent with the deactivating effect of GABA agonist muscimol, and also with the absence of the NCE in patients in which the area is deactivated by actual lesions [5]. It is also consistent with two MRS studies measuring GABA in primary motor cortex: lowered cortical excitability following theta burst stimulation was associated with increased GABA concentration [4], and motor learning, which is thought to increase cortical excitability, was associated with lower GABA levels [26]. Thus, the direction of correlation we found suggests that GABA levels in the SMA have a greater influence on the production of the suppression process creating the NCE than its implementation. The site of inhibition may be basal ganglia [27].

The relationship does not reflect general differences in caution or arousal, because neither the NCE nor SMA GABA correlated with overall speed or accuracy (Figure 4). Nor is it explained by any factor common to all sensorimotor tasks containing elements of response compatibility, conflict, or

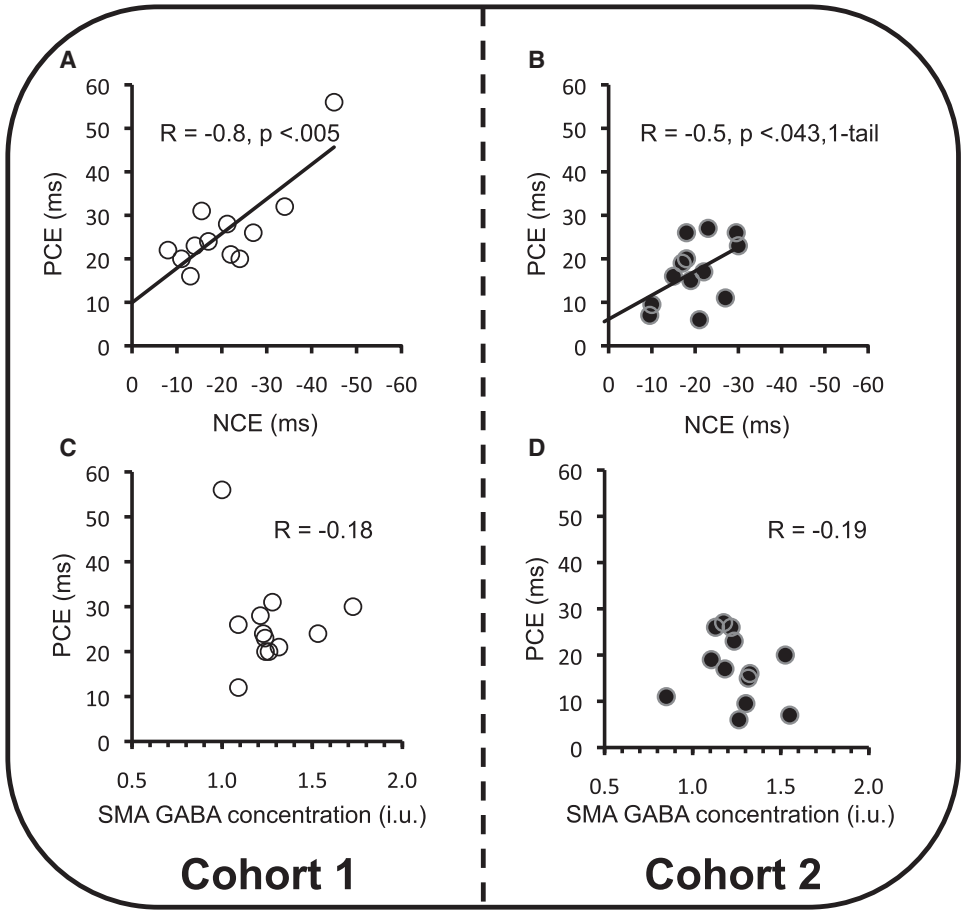

Figure 3. Correlations of the PCE with the NCE and GABA in the SMA

(A and B) Higher PCE (subliminal activation) predicts higher (more negative) NCE (subliminal suppression). Further analyses of previously published data [3] also revealed strong correlations between NCE and PCE (experiment 1, $r = -0.69$ [$p < 0.013$]; experiment 2, $r = -0.72$ [$p < 0.008$]; and experiment 3, $r = -0.63$ [$p < 0.03$]). Thus, it seems a general and robust phenomenon that the magnitudes of the PCE and NCE are correlated across individuals. However, although there is weak correlation in both cohorts between the PCE and GABA concentration in the SMA region (C and D), this was not significant (even across cohorts), and is presumably just mediated by the correlations between NCE and GABA and between NCE and PCE. Thus, it appears that the common factor between NCE and PCE does not lie with GABA in the SMA.

inhibition, because neither SMA GABA nor the NCE correlated with other tasks that we have measured, including the Simon task [28], the Eriksen flanker task [29], and the STOP task [30] (Figure S4).

In the Simon task [28], participants made left or right responses to the identity of letters appearing on the left or right of fixation. The location of the letter is irrelevant, but there is an automatic spatial compatibility effect such that responses tend to be faster when the stimulus appears on the same side as the required response. The fact that this "Simon effect" does not correlate behaviorally with the NCE (or PCE), or with GABA in the SMA region, indicates that individual differences in these two phenomena reflect dissociable traits. Similarly, in the Eriksen flanker task [29], participants respond to a central arrow, which is flanked by irrelevant arrows that also cause a compatibility effect: responses tend to be faster when the flankers point in the same direction as the target. Although recent evidence suggests some shared mechanism between subliminal suppression and the control of flanker interference [31], individual differences in the flanker effect appear dissociable from individual differences in the NCE, and do not reflect SMA GABA concentration.

In the STOP task [30, 32], participants made speeded button presses to a shape cue, but, on a subset of trials, a second stimulus was presented that instructed them to withhold their response. The interval between go and stop signals is modulated to find the interval at which participants successfully stop on 50% of the stop trials. This "stop signal reaction time" varied between participants, but, importantly, did not correlate with the NCE or with GABA in the SMA region.

Thus, we find some specificity in the relationship between SMA GABA and functional inhibitory mechanisms, but this is not to say that SMA GABA only influences the NCE. In general, we argue that control of specific functions will be subject to influence by the GABA level in areas of the brain that are causally involved in that function. Thus, GABA concentration in SMA presumably affects other functions for which SMA plays a critical role.

It is not yet known why natural differences in baseline GABA concentration occur, and what factors create their regional specificity (Figure S3; see also [33]). The differences in MRS signal that we measured probably reflect different densities of GABA interneurons or synapses. Abnormalities in GABAergic inhibition have been associated with a number of

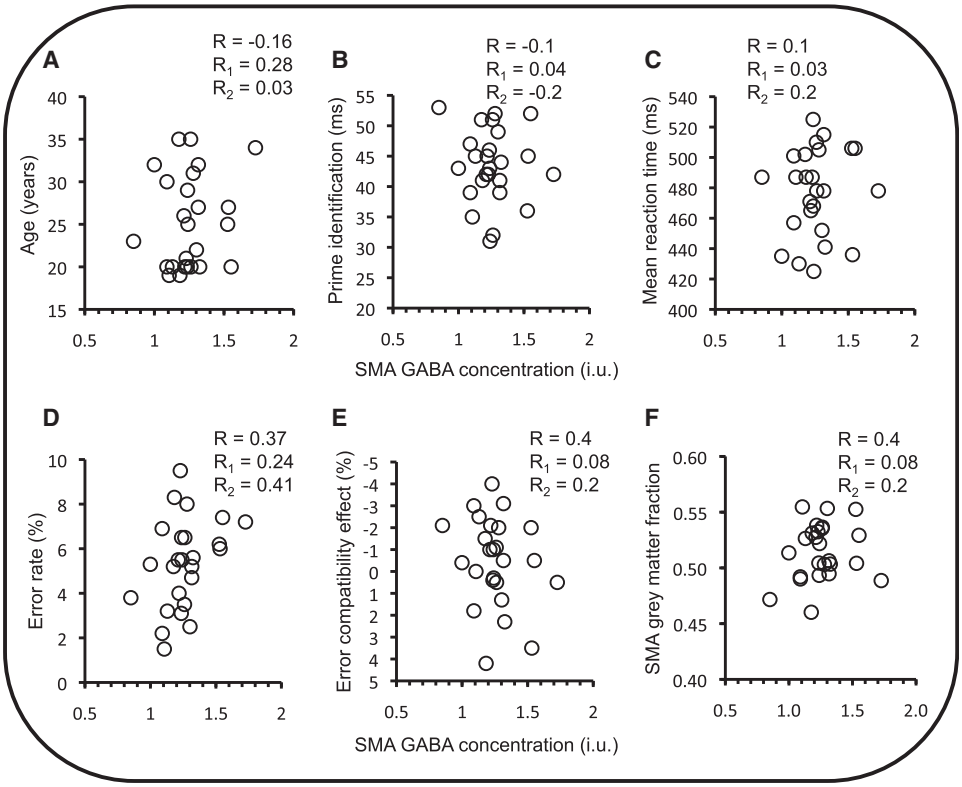

Figure 4. GABA in SMA Region Does Not Correlate with Other Potential Mediating Factors

(A) shows age, (B) shows prime identification, (C) shows mean reaction time, (D) shows error rate, (E) shows error compatibility effect, and (F) shows fraction of GM in SMA MRS voxel. R values are the correlation coefficient obtained putting both cohorts together; R1 and R2 values are the coefficient obtained for cohort 1 and 2 separately. There was also no significant correlation of any of these factors with the NCE (all $|R|$, $|R_1|$, or $|R_2| < 0.44$; $p > 0.16$). Most importantly, when these factors were controlled for, the (partial) correlation (R_p) between the NCE and GABA in the SMA region remained. When controlling for the amount of gray matter (GM), $R_{1p} = 0.8$ ($p < 0.003$) and $R_{2p} = 0.53$ ($p < 0.04$) (one-tailed). Similarly, when controlling for age, $R_{1p} = 0.77$ ($p < 0.005$), $R_{2p} = 0.62$ ($p < 0.035$); for average speed, $R_{1p} = 0.84$ ($p < 0.001$), $R_{2p} = 0.61$ ($p < 0.03$); for prime visibility, $R_{1p} = 0.8$ ($p < 0.003$), $R_{2p} = 0.55$ ($p < 0.03$) (one-tailed); and for error rate, $R_{1p} = 0.75$ ($p < 0.008$), $R_{2p} = 0.51$ ($p < 0.045$) (one-tailed). Note that, as a neurotransmitter, the concentration of GABA is expected to be higher in GM than in white matter, so one might predict a correlation between GM volume and GABA. However, the GM proportion in the voxel was very similar across participants (i.e., it was well controlled for), so there was little opportunity for a correlation to be revealed. GM proportion ranged from 49% to 54% in cohort 1, and from 46% to 55% in cohort 2. The essential point is not whether GM correlates with GABA, but that this relationship does not account for the correlation of GABA with the NCE.

clinical conditions, including schizophrenia, epilepsy, attention deficit/hyperactivity disorder, obsessive-compulsive disorder, depression, and bipolar disorder [34–40], but the relationship between symptoms and pathophysiology remains little understood.

The ability to relate specific and even subconscious traits to GABA in specific brain regions in healthy individuals promises to inform the study of such disorders, where there is no clear division between healthy and clinical populations. Moreover, our finding that differences in GABA concentration are regionally specific (as opposed to globally correlated) underlines the importance of targeting specific brain regions in clinical GABA MRS studies [41, 42], rather than inferring global changes from measurements of one region [43, 44].

In sum, we have found that individual variation in an automatic motor mechanism operating at the threshold of conscious awareness is reliably correlated with GABA concentration specifically in a region of medial frontal cortex, but not in other frontal regions or parietal cortex. This result promises that we can begin to understand differences in people's basic behavior in terms of the neurochemistry of specific brain regions.

Experimental Procedures

Overview

In the first experiment, we acquired (over two MR sessions per participant) MRS measurements from a $(3\ cm)^3$ voxel around the SMA, as well as an anatomical MRI scan and further MRS measurements from voxels in the parietal lobe, dorsolateral prefrontal cortex (DLPFC), inferior frontal gyrus (IFG), and the anterior cingulate cortex (ACC). Note that, in MRS, we acquire an average spectrum from a single predefined volume (it is not an imaging-like technique), and, thus, measurements for each volume were taken separately (12 min each). On a separate occasion (not in the scanner), each participant was tested in the masked priming tasks, Simon task, Eriksen flanker task, and STOP task.

The aim of the second experiment was simply to test, in a second, independent, cohort, the robustness of the relationship found between GABA and behavior in the first experiment. There was one MR session per participant, consisting of an anatomical MRI scan followed by three MRS measurements from voxels in the SMA region, DLPFC, and parietal cortex. On a separate occasion, each participant was tested in the masked priming tasks and Simon task.

Participants

For the first experiment, 12 volunteers (all male, aged 21–32 years) were recruited within the School of Psychology, Cardiff University. For the second experiment, 13 volunteers were similarly recruited (all male, aged

19–35 years). All had normal or corrected-to-normal vision, no neurological history, and received payment for their time. All were naive to the purpose of the study. The local ethics committee approved all procedures.

Anatomical MRI

A 1 mm^3 isotropic resolution, T1-weighted anatomical MRI scan (FSPGR) was carried out to allow MRS voxel placement, and subsequent reconstruction of the cortical surface and segmentation of the MRS voxel. To segment the volume, we used both FAST (http://www.fmrib.ox.ac.uk/fsl/) and FreeSurfer (http://surfer.nmr.mgh.harvard.edu/), and these methods showed a high degree of correlation for gray matter volume ($r > 0.95$). In the reported results, gray matter estimates came from FreeSurfer.

MRS

In both experiments, GABA-edited MEGA-PRESS spectra [6, 8] were acquired from voxels positioned according to anatomical landmarks. The SMA voxel was placed symmetrically over the midline with its backward face anterior to the central sulci. All voxels, except in the ACC, were $(3\ cm)^3$, with one face of the cube aligned with the cortical surface. The ACC voxel was $2 \times 3 \times 4\ cm^3$ in order to restrict it mainly to the appropriate region. The order of MRS voxels was counterbalanced across participants. Note that the MRS voxel is chosen a priori, and must be large enough to ensure sufficient signal quality to investigate individual differences in GABA concentration. Each MRS measurement was preceded by several brief anatomical imaging acquisitions in different orientations to allow accurate voxel placement.

The field strength was 3 Tesla, and the following experimental parameters were used: echo time (TE) = 68 ms; repetition time (TR) = 1800 ms; 400 transients of 4096 data points were acquired in 12 min; 16 ms Gaussian editing pulses were applied either to the GABA spins at 1.9 ppm or at 7.5 ppm in an interleaved manner. Phased-array coil data were combined (using the first point of the unsuppressed water-free induction decay signal), and spectra were processed by locally written software. Three hertz exponential line broadening and a high-pass water filter were applied, and the MEGA-PRESS difference spectrum was produced. The edited GABA signal at 3 ppm and the unsuppressed PRESS water signal were integrated: the integral of the GABA peak was calculated automatically by using a linear fit of the baseline and a Gaussian fit to the peak itself (Figure S2); the water signal was fitted with a Lorentzian-Gaussian lineshape [45]. The GABA-fitted amplitude was scaled to account for the fraction of cerebrospinal fluid (CSF) within the voxel, and the water amplitude was scaled to account for the different water content in CSF and gray and white matter [46]. A concentration measurement in institutional units was derived from the ratio of the GABA and water signals by using a single scalar to adjust for the editing efficiency and the T1 and T2 relaxation times of water and GABA. The GABA peak will also contain signal from coedited macromolecules (e.g., cytosol), and this may contribute 30%–40% of the integrated area [47]. However, we have no reason to expect that these would differ between individuals or have an influence on sensorimotor behavior. Confidence that individual differences in our measure of GABA concentration reflect actual GABA differences can be drawn from recently reported association of this measurement with gamma frequency, BOLD signal, transcranial magnetic stimulation, and sensory tuning, all of which are well modeled by variation in GABA [4, 10–12, 48].

Functional Localizer

As a check on the placement of our main voxel of interest, for two participants we acquired a functional localizer for the SMA by using fMRI. A standard boxcar protocol was used with 15 s of sequential finger movements and 15 s of rest. We used a gradient echo EPI sequence taking 26 oblique-axial slices at 3 mm isotropic voxel resolution; 265 T2*-weighted volumes (TR = 1500 ms, TE = 35 ms, 90° flip angle, acquisition matrix = 64 × 64). Due to time constraints, this could not be done for all participants in the MRS sessions.

Masked Priming

Stimulus presentation was performed by a PC-controlled Cambridge Research Systems (CRS) Visage connected to a 21 inch Sony GDM-F520 Trinitron monitor. Stimulus presentation was synchronized with the screen refresh rate of 100 Hz, and timing was controlled and measured by the CRS clock and thus not subject to the errors produced by normal PC operating systems. Manual responses were collected with a CRS CB6 button box.

Participants had to make speeded responses with a left- or right-hand key press to left/right arrows (1° × 1°), which occurred in random order and within 4° of fixation. A fixation cross was visible at the center of the screen at the beginning of each trial. The primes were identical to either one or the other targets, but presented for a briefer duration determined by prior adaptive staircase procedure (described below), and appeared within 0.3° of fixation. In all conditions, the prime was immediately followed by a mask of 2° × 2°, presented for 100 ms and constructed of 35 randomly orientated lines, excluding any orientation closer than 5° to the orientations in the arrow stimuli. A new mask was constructed on each trial.

To be sure that the masked-prime stimuli were subliminal at the start of the priming blocks, we used a psychophysical adaptive staircase procedure to determine the presentation duration for which an individual could consciously report the direction of the prime (for similar method, see [19]). Note that, although we did not measure prime visibility again after the main task, the settings we used were similar to studies in which we have measured visibility afterwards, and, in our experience, prime discriminability does not grow during priming blocks (in which the participant is ignoring the prime). To measure the NCE, we set the delay between prime offset and target onset to 150 ms. To measure the PCE, we set this delay to 40 ms. A control experiment, as well as previous work, found these timings to provide robust and approximately maximal PCE and NCE effects [3]. There were 400 trials in each block (PCE and NCE).

Several weeks (2–8) after the first measurement, we assessed the repeatability of the NCE measurement by submitting participants to a further 200 trials of the same masked prime paradigm. Details of the other tasks that we measured can be found in the Supplemental Information.

Supplemental Information

Supplemental Information includes Supplemental Experimental Procedures and four figures and can be found with this article online at doi:10.1016/j.cub.2010.09.003.

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