

Dorsolateral Prefrontal γ -Aminobutyric Acid in Men Predicts Individual Differences in Rash Impulsivity

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Background: Impulsivity is a multifaceted personality construct associated with numerous psychiatric disorders. Recent research has characterized four facets of impulsivity: “urgency” (the tendency to act rashly especially in the context of distress or cravings); “lack of premeditation” (not envisaging the consequences of actions); “lack of perseverance” (not staying focused on a task); and “sensation seeking” (engaging in exciting activities). Urgency is particularly associated with clinical populations and problematic disinhibited behavior.

Methods: We used magnetic resonance spectroscopy to measure concentration of the inhibitory neurotransmitter γ -aminobutyric acid (GABA) in the dorsolateral prefrontal cortex (DLPFC) in two cohorts of 12 and 13 participants.

Results: We find that variation in trait urgency in healthy men correlates with GABA concentration in the DLPFC. The result was replicated in an independent cohort. More GABA predicted lower urgency scores, consistent with a role in self-control for GABA-mediated inhibitory mechanisms in DLPFC.

Conclusions: These findings help account for individual differences in self-control and thus clarify the relationship between GABA and a wide range of psychiatric disorders associated with impaired self-control.

Key Words: Externalizing, γ -aminobutyric acid receptor α -2 (GABRA2), inhibition, neurochemistry, personality, self-control, stop-signal, urgency

The ability to flexibly regulate one’s behavior in a changing environment is key to adaptive social life. Failure in this regulation is salient in psychiatric disorders, where impulsivity is the second commonest symptom in the DSM (1,2). However, impulsivity is an umbrella term comprising several facets, which have been clarified in the UPPS model as: Urgency (or “rash impulsivity”), the tendency to act rashly in response to distress or other strong emotions and urges; Premeditation (lack of), the tendency to envisage the consequences of an act before engaging in it; Perseverance (lack of), the ability to remain focused on a difficult task; Sensation Seeking, the tendency to engage in exciting activities (3).

Of these four traits, urgency has been most strongly linked to problematic levels of alcohol consumption, smoking, gambling, binge eating, illicit drug use, aggression, and risky sexual behavior (4,5). High levels of urgency represent one extreme of wide natural variation in this trait, and the UPPS model is an example of how it is fruitful to understand human behavior and its maladaptive variants along a continuum (6). Thus, identifying the neurobiological bases of individual variation in urgency might be of key importance for understanding the pathophysiology of psychiatric disorders.

Building from previous focus on serotonin and dopamine (2,7,8), there is now increasing interest in the role of γ -aminobutyric acid (GABA) ergic neurotransmission in impulsivity. Variation in GABA

receptor genes has been associated with problematic levels of alcohol use, obesity, and drug use as well as bipolar spectrum disorders, conduct problems, and distress regulation (9–16). Notably, Dick *et al.* (16) found that the GABA receptor subunit α -2 gene is involved in the predisposition to alcohol dependence through a generalized “externalizing” pathway, a concept that captures a range of disinhibited behaviors that commonly co-occur—including aggression, aspects of impulsivity, antisocial behavior, and drug abuse (17)—forming a coherent spectrum of personality and psychopathology. Research connecting externalizing psychopathology and personality traits (18) has shown that externalizing liability is a normally distributed dimension of risk, with urgency having the largest loading on the general externalizing factor (5,19). Thus, we predict that, given that genetic variation in GABA transmission has been linked to general externalizing and that urgency is the best personality trait marker of the general externalizing liability, variation in GABA levels would be related to the urgency facet of impulsivity.

Any relationship between GABA and urgency might be specific to particular brain regions. Several studies have related general impulsivity to activity or gray matter thickness in the lateral prefrontal cortex (20–23). Increased delay discounting of rewards might reflect a general vulnerability to externalizing (24), and transcranial magnetic stimulation disruption of dorsolateral prefrontal cortex (DLPFC) leads to such enhanced discounting (25). Increased externalizing traits in undergraduate subjects are related to reduced amplitude of the error-related negativity (26) brain response, a signal that is abolished after lesions of lateral prefrontal cortex (27). Variation in urgency is linked to the ability to adaptively regulate emotions and cravings (5), and recent research links DLPFC to this aspect of control (e.g., [28]). Moreover, individual variation in emotion regulation abilities has also been linked to DLPFC function (29). In addition, magnetic resonance spectroscopy (MRS) and postmortem studies show alterations in GABA in DLPFC for psychiatric disorders linked with heightened emotional dysregulation and poor self-control, including cocaine addiction, depression, and schizophrenia (30–32). Hence, DLPFC would be a strong candidate area in which a relationship between urgency and GABA levels might be manifest.

There are also reasons to propose the inferior frontal gyrus (IFG)

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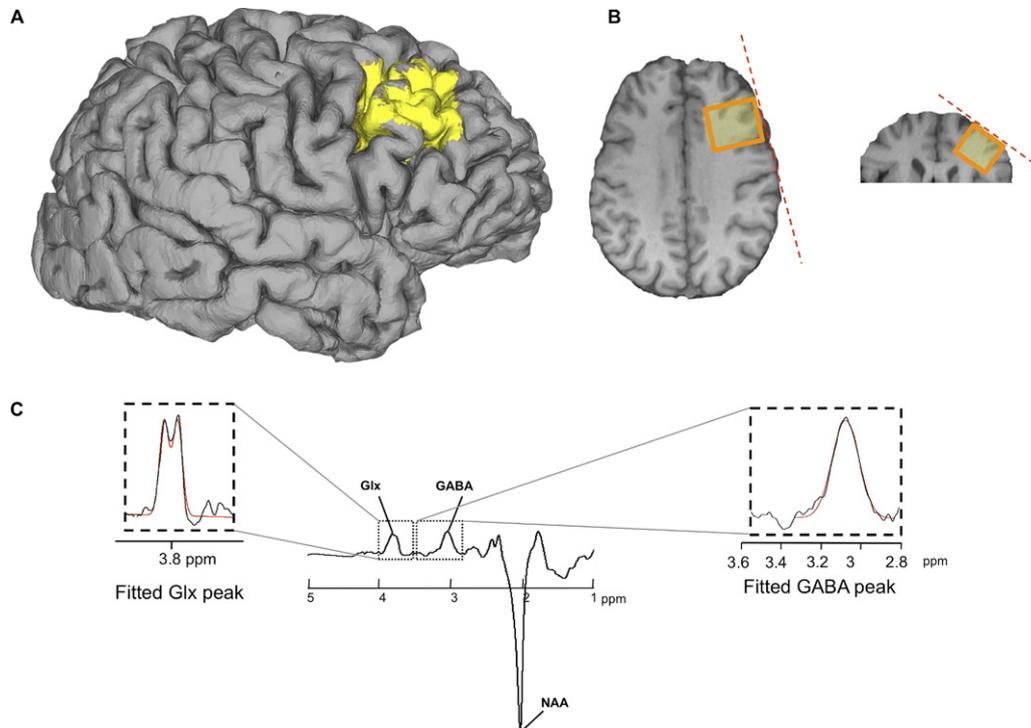


Figure 1. Methodology for spectroscopy. **(A,B)** The magnetic resonance spectroscopy voxel (yellow, 3 cm × 3 cm × 3 cm voxel) was placed over the anatomical location of the dorsolateral prefrontal cortex. Edited magnetic resonance spectra **(C)** allow the quantification of γ -aminobutyric acid (GABA) concentration by extracting the area under the GABA peak (39–41,68). In a similar way, we extracted a measure of glutamate + glutamine (Glx) (also marked is the *N*-acetylaspartate peak [NAA]). The GABA peak will contain signal from co-edited macromolecules, but although we do not know the exact contribution, we do not expect any individual differences in macromolecules to drive any correlation with our behavioral measures.

or the anterior cingulate cortex (ACC) as candidate areas for a GABA-urgency relationship. The IFG, for example, has been strongly linked with response inhibition in the stop-signal task (33), and variation in response inhibition has been suggested to be an important mechanism underlying externalizing vulnerability (34). The ACC, together with DLPFC, is thought to be a neural generator of the error-related negativity (35). Furthermore, Matsuo *et al.* (36) found that gray matter volume in rostral ACC was correlated with impulsivity (as measured by the Barrat Impulsiveness Scale [37]).

Advances in MRS (38–41) allow us to investigate individual differences in GABA concentration in specific regions of the human brain. This approach has proved successful in discovering group differences in regional GABA concentration between psychiatric and control cohorts (e.g., [32,42]) and more recently in relating specific behavioral and physiological measures in healthy participants to individual differences in regional GABA levels, even in the small cohort size of typical magnetic resonance (MR) studies (43–48). In frontal cortex in particular, higher GABA concentration measured in the region of the frontal eye fields was correlated with lower eye movement distractibility (i.e., better control) (49), leading us to predict that the likely direction of any association between frontal GABA and impulsivity would be higher GABA concentration and lower impulsivity (better control).

In this study we take a two-step approach. First, we explored whether resting GABA levels in any of the three candidate brain regions (DLPFC, IFG, and ACC) were related to urgency or indeed any of the other three impulsivity facets. Second, having identified a correlation between urgency and GABA in DLPFC, we aimed to test whether this would replicate in a second cohort. We also include data from two control regions, the parietal cortex and supple-

mentary motor area (SMA), which were measured in the same participants for the purpose of a different study (46).

Methods and Materials

Overview

In the first experiment, with edited MR spectroscopy (38,40), we measured GABA concentration from a 3 cm × 3 cm × 3 cm region of the right DLPFC, including but not limited to a sub-region of the middle frontal gyrus (we refer to this as the DLPFC region) (Figures 1A,B). The voxel size is dictated by signal-to-noise ratio; smaller voxels have been used previously for group averages but not for individual differences (e.g., [42,50,51]). We also acquired (over two MR sessions/participant) MRS measurements from voxels in the IFG, the ACC, the parietal lobe, and the SMA, as well as an anatomical magnetic resonance imaging (MRI) scan. The SMA and parietal voxels are included here as control voxels, although the primary purpose for their measurement was for a different study (investigating the relationship between masked priming and GABA in SMA, for which the prefrontal voxels served as control) (46). Note that in the present GABA-edited MRS protocol we acquire an average spectrum from a single predefined volume, and thus measurements for each volume were taken separately (12 min each). On a separate occasion, each participant completed the UPPS questionnaire and was then tested on the stop-signal task (participants also performed other tasks for the purpose of the priming study; neither the impulsivity data nor stop-signal relationships have been published before).

The aim of the second experiment was to test in an independent cohort the robustness of the relationship found between GABA and

urgency scores in the first experiment. There was one MR session/participant consisting of an anatomical MRI scan followed by MRS measurement from the DLPFC voxel. Parietal and SMA MRS voxels were again included in this session for the purpose of the priming study (46) and are presented here as control regions. On a separate occasion, participants completed the UPPS questionnaire and were tested in the stop-signal task (as well as the priming study tasks).

Participants

For the first experiment, 12 volunteers (21–32 years of age, mainly Caucasian) were recruited within the School of Psychology, Cardiff University. For the second experiment, 13 volunteers were similarly recruited (19–35 years of age, mainly Caucasian). Because menstrual cycle might affect GABA levels (52,53) and because there are gender differences in impulsivity (54), all the participants were men in order to remove these potential sources of variance. All had normal or corrected-to-normal vision, had no neurological or psychiatric history, and were right-handed. They received payment for their time. Participants were aware that the purpose of the scan was spectroscopy and that they would complete a personality questionnaire and performance tasks, but no further specification was given as to the nature of the hypotheses. The local Research Ethics Committee approved all procedures.

Structural MRI

A 1-mm³ isotropic resolution, T1-weighted anatomical MRI scan (fast spoiled gradient echo) 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 ($r > .95$). In the reported results, gray matter estimates came from FreeSurfer.

MRS

The GABA-edited MEscher–GARwood-Point RESolved Spectroscopy (MEGA PRESS) spectra (38,40) were acquired on a General Electric 3T-HDx MRI scanner (GE Healthcare, Waukesha, Wisconsin) from voxels positioned according to anatomical landmarks. For each participant, the DLPFC voxel was placed in the right middle frontal gyrus (i.e., between the superior and inferior frontal sulci, with the posterior surface of the voxel aligned with the precentral sulcus), with oblique localizing slices to match edges of the voxel to the cortical surface of the subject (Figure 1A). We placed a voxel of similar dimensions directly inferior to this voxel in the IFG (between the inferior frontal sulcus and the horizontal ramus), again matching the edge of the voxel to the cortical surface of the subject. The anterior cingulate voxel was placed over the midline and between the cingulate and the pericallosal sulci; this voxel was 3 cm × 2 cm × 4 cm—reducing the inferior-superior dimension helped avoid including part of the insula and corpus callosum. The parietal voxel was positioned in the right superior parietal lobule aligned with the cortical surface, whereas the SMA voxel was placed on the midline with its posterior surface aligned with the central sulci (for more information see 46).

The following experimental parameters were used: echo time = 68 msec; repetition time = 1800 msec; 400 transients of 4096 data points were acquired in 12 min; 16-msec Gaussian editing pulses were applied either to the GABA spins (1.9 ppm) or symmetrically about the water peak (7.5 ppm) in an interleaved manner. A further eight transients were acquired, without water suppression, as an internal concentration reference. Phased-array coil data (8 channels) were combined (with 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 water signal were integrated: the integral of the GABA peak was calculated automatically with a linear fit of the baseline and a Gaussian fit to the peak itself. The water signal was fitted with a Lorentzian-Gaussian lineshape (55). A Gaussian model was chosen for the GABA peak rather than a doublet, because empirically we rarely find a clear doublet with this protocol (45,46,56), but the integral derived is very consistent whichever fitting model is used ($r > .95$). The reason a doublet does not appear is complex. The pseudo-doublet has a small center-peak (Figure 3 in Waddell *et al.* [57]), the size of which will depend on sequence parameters such as refocusing bandwidth and refocusing slice profile. There is also likely to be a contribution from macromolecules, which is unknown and will depend on sequence parameters. The extent to which any pseudo-doublet splitting is filled in will therefore depend on these factors and the underlying line-width of the signals (approximately 12 Hz in this study). In other studies with a Siemens MEGA-PRESS (Siemens, Erlangen, Germany) implementation, a doublet appears in, at most, one-half of edited spectra (Figure 5 in Edden and Barker [40,48]).

The GABA integral was scaled to account for the fraction of cerebrospinal fluid within the voxel, and the water signal was scaled to account for the different water content in cerebrospinal fluid and gray and white matter (58). 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 (59) and GABA. Because T1 and T2 values for GABA are not available in the literature, they were estimated from the range for other metabolites (60–62). Note that this scalar adjustment changes only the absolute concentration values reported and not the relative values between individuals. We also obtained a combined measure of glutamate and glutamine levels, by fitting the glutamine/glutamate (Glx) peak (Figure 1C) with a Gaussian doublet centered on 3.75.

Measuring Impulsivity

After completing behavioral tasks of cognitive and automatic motor control (masked-priming, stop-signal, Simon tasks) (46), participants were administered the UPPS impulsive behavior scale. This scale was derived by Whiteside and Lynam (3) from a combined analysis of the five-factor model of personality (63) and a total of 21 subscales across 10 impulsivity measures (e.g., the Barratt Impulsiveness Scale-11) (37). This resulted in a fourfold division of impulsivity into facets of: Urgency, Premeditation (lack of), Perseverance (lack of), and Sensation Seeking (hence “UPPS”). Example statement for urgency include: “It is hard for me to resist acting on my feelings”; and “When I am upset I often act without thinking.” Representative questions for the other facets include: “I usually think carefully before doing anything” (Premeditation); “I finish what I start” (Perseverance); and “I would enjoy water skiing” (Sensation seeking). The UPPS scales have excellent reliability (Cronbach α approximately .9) (3) and have been validated, for example, against interview-based impulsivity assessments (4). The UPPS items are assessed on a scale ranging from 1 (agree strongly) to 4 (disagree strongly), and the UPPS is scored such that higher scores represent higher levels of impulsivity.

Results

The mean scores and their SDs in each subscale are given in Table 1. These were similar across the two cohorts (all $p > .07$) and

Table 1. Mean Scores of the 4 Subscales of the UPPS Impulsivity Measurement

	(Feeling of) Urgency	(Lack of) Premeditation	(Lack of) Perseverance	Sensation (seeking)	Age (yr)
Cohort 1	24 (4.5)	20.7 (4.1)	17.8 (3.7)	32.9 (4)	27 (1.3)
Cohort 2	23.7 (5.6)	20.9 (3.2)	19.8 (6.1)	33.3 (5)	22.7 (1.4)

Mean scores (and SD) obtained on the 4 subscales of the Urgency, Premeditation (lack of), Perseverance (lack of), and Sensation Seeking (UPPS) impulsivity measurement. Values are total scores from each of the UPPS scales. Number of items/scale: Urgency: 12 items; Premeditation: 11 items; Perseverance: 10 items; Sensation Seeking: 12 items.

comparable to those reported in similar populations of university staff and students.

The main result for the first cohort was a correlation between GABA concentration in DLPFC and urgency, such that participants with higher GABA concentration scored lower on this factor (Pearson's $r = -.70$, Spearman's $\rho = -.77$) (Figure 2A). There was also a correlation of DLPFC GABA with perseverance ($r = -.58$). However, with our sample size, these correlations are not significant after correcting for multiple comparisons (5 areas \times 4 impulsivity facets). Therefore we tested for replication in a second independent cohort, using the results of the first cohort to specify planned comparisons. The correlation between DLPFC GABA and urgency was replicated (Pearson's $r = -.67$, $p = .013$, 1-tailed, corrected for 2 comparisons, Spearman's $\rho = -.78$, $p = .0015$) (Figure 2B). We also performed bootstrapping to check whether just one or two points drove the correlations. This involved taking n random samples from within our data, with replacement (where n is the number of participants), computing the correlation coefficient r , and repeating 10,000 times to find the 95th percentile value of r (i.e., the value for which 95% of the values produced in bootstrapping were greater or equal to this value). If a correlation is driven by just one or two points, because in many of the iterations these would be left out, near zero r values would occur more than 5% of the time. Thus if the 95th percentile r value were near zero or crossed it, it would indicate the correlation is not robust. The Bootstrap 95th percentile values for R for the

Pearson's r for cohorts 1 and 2 were $-.31$ and $-.33$, respectively, indicating they are robust to subsampling.

This relationship did not generalize to the Glx peak in the spectrum (glutamate+glutamine) [Figure 2A insert]; 1st cohort: $r = -.15$, $p > .05$, [Figure 2B insert]; 2nd cohort: $r = -.3$, $p > .05$). The Glx correlated with neither GABA (1st cohort: $r = .39$, $p > .20$; 2nd cohort: $r = .37$, $p > .23$) nor any impulsivity subscale (1st cohort: all $r < .39$, all $p > .2$; 2nd cohort: all $r < .22$, all $p > .45$). However, note that the Glx peak is not a pure measure of glutamate, because glutamate cannot be unambiguously separated from glutamine with this technique at a 3-T field strength; therefore this absence of correlation cannot be taken to mean that individual differences in glutamate play no role.

The GABA concentration in the DLPFC did not correlate with Premeditation or Sensation-seeking, and the correlation with Perseverance found at first did not replicate in the second cohort (Figures S1A and S1B, top rows, in Supplement 1). This stresses the importance of an independent replication when evaluating correlations obtained with small samples and multiple possible comparisons. We found, in terms of regional specificity, no evidence that any of the impulsivity traits correlated with GABA measures taken from voxels in the other two candidate regions (IFG and ACC) or with the other two regions for which we obtained measurements with these cohorts (SMA and parietal).

We tested whether the correlation between urgency and GABA

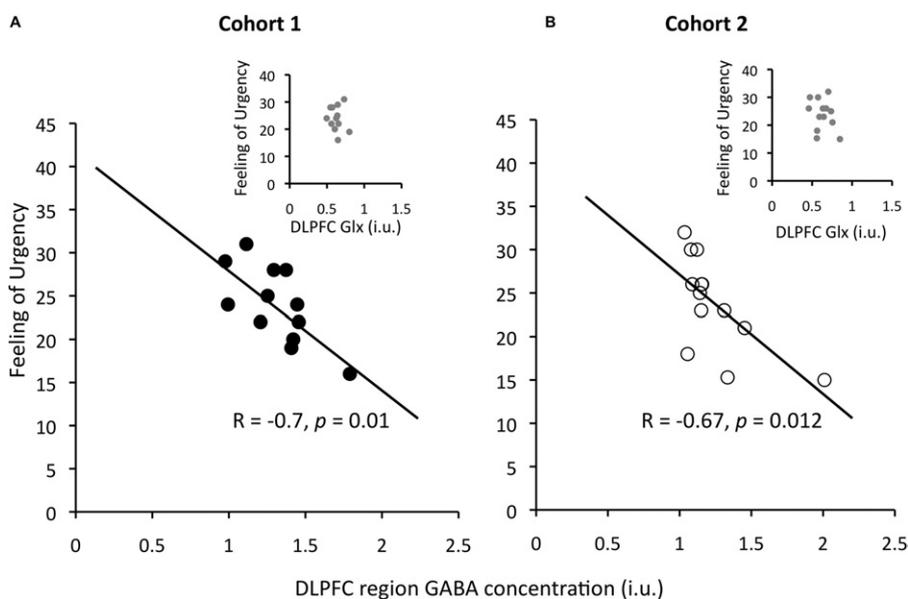


Figure 2. Urgency correlates with γ -aminobutyric acid (GABA) in the dorsolateral prefrontal cortex (DLPFC) region. Higher DLPFC GABA predicted lower urgency score across individuals (A). This result was replicated in a second cohort (B). The GABA concentration measurements are stated in institutional units (i.u.). The p value for cohort 2 is given one-tailed and corrected for two comparisons, because there were two planned tests of replication that arose from cohort 1. Inserts show that the relation observed for GABA levels did not hold for glutamate+glutamine (Glx).

in the DLPFC region might arise due to other individual factors such as age or gray matter fraction in the voxel. It did not; there were no significant correlations of either the urgency scores or DLPFC GABA with these factors (Figures S2A and S2B in Supplement 1), and when we controlled for them, correlations between DLPFC GABA and urgency remained strong or even improved (controlling for the gray matter fraction: 1st cohort: $r_{\text{partial}} = -.77, p < .005$; 2nd cohort: $r_{\text{partial}} = -.69, p < .012$; controlling for age: 1st cohort: $r_{\text{partial}} = -.70, p < .016$; 2nd cohort: $r_{\text{partial}} = -.68, p < .014$). We also tested whether the correlation might be related to irregular sleep patterns, tobacco, alcohol, drug use, or weight in our participants (for the 15 participants who provided this information). There was no relationship with any of these factors. None of the participants was taking any medication at the time of the study.

Because externalizing vulnerability has been linked to impaired response inhibition (34), we also tested whether results of the stop-signal task, an experimental measure of response inhibition, correlated with DLPFC GABA (and with urgency). We did not find any consistent relationship between GABA and either stopping ability (Figure S2C in Supplement 1) or overall response speed (1st and 2nd cohorts: all $r < .08, p > .8$). It is worth noting that performance in the stop task itself has previously been more strongly related to IFG and pre-SMA than to DLPFC (64–67), but we found no significant correlation between stopping and IFG GABA (1st cohort: $r = .24, p > .4$) or between stopping and GABA in our voxel centered on the SMA, which contained part of the pre-SMA (1st cohort: $r = .21, p > .5$). We also did not find a relationship between stopping ability and any of the components of impulsivity.

Discussion

The neurochemical balance in different brain regions has long been thought instrumental in the regulation of personality traits and psychiatric disorders, but it is not straightforward to link genetic or pharmacological data implicating particular neurotransmitter systems with particular brain regions (e.g., [8]). Employing MRS offers a way to fill this gap, enabling us to report here that individual differences in GABA concentration in a specific region (DLPFC) were reliably related to a specific personality trait (urgency). It is worth emphasizing that the correlation did not arise from general GABA concentration over the whole brain—there was no correlation with the other frontal and parietal areas we measured, although low signal-to-noise in edited MRS techniques might have contributed to absence of detection of correlations in these regions. Previous reports have found no evidence for correlation of GABA concentration between brain regions (46,49,68). Thus, on current data, it seems that having high GABA concentration in DLPFC does not necessarily mean that a person will have high GABA concentration in other brain regions, underlining the importance of targeting specific brain regions in clinical GABA MRS studies (32,69,70).

Recently, a series of genetic studies have linked variation in GABAergic neurotransmission with a variety of co-occurring disorders characterized by emotional dysregulation and poor self-control (9–11,14–16), thought to reflect a coherent externalizing spectrum (18). Our results support the utility of a dimensional approach to personality–psychopathology relations (e.g., [6]). The results also link GABAergic neurotransmission with the role of DLPFC in self-control (e.g., [28,29,71]). The exact mechanism by which differences in DLPFC GABA level would influence self-control ability is unknown. Our findings are consistent with the view that DLPFC neurons adapt their properties to robustly maintain information that is relevant to current goals (72). In the context of such “adaptive

coding” in the control of working memory, GABAergic inhibition has been posited as the mechanism for adjusting the focus of DLPFC neurons to the task at hand, leading to increased robustness of goal-representations in the face of distraction (e.g., from rewards or stressors) (73). Similarly, Sawaguchi (74) found that GABA continuously and preferentially suppresses neuronal activity via GABA-A receptors to limit the population of prefrontal neurons activated by a particular behavior, consistent with adaptive selectivity. This process might have parallels with the role of GABAergic inhibition in tuning the response properties of visual cortex neurons, sharpening orientation selectivity, for example (56,75). Thus it is plausible that higher GABA concentration can lead to more robust adaptive coding of goals in DLPFC, providing more effective integration of salient motivational information with current task goals, thus promoting adaptive behavior (76).

The details of the relationship between GABAergic neurotransmission in DLPFC and functional inhibition of behavior are likely to be complex. The DLPFC is part of a network involving loops through striatum and thalamus as well as numerous connections to other cortical and subcortical areas relevant for controlling behavior. Similarly, the roles of dopamine and serotonin are yet to be clarified (7,8,23) and are likely to interact with the role of GABA (77,78). Moreover, the reasons why people might differ in MRS measures of regional GABA concentration and how this relates to variation in receptor genes remain unknown. Also unknown is the contribution that macromolecules make to the GABA measurement: they are likely to make a significant contribution to the absolute measures but are currently thought unlikely to drive the differences between individuals, which correlate with neurophysiological and behavioral differences that are readily explained by GABA variation but would be difficult to explain by macromolecule variation (43–45,47,48,56,79). Most likely, differences in our measure of GABA concentration will be related to the number of GABA interneurons or the number and type of synapses, and we do not yet know what implications this could have for the wiring of GABAergic and glutamatergic excitation–inhibition circuits across the different cell layers of the neocortex (80,81). Importantly, however, such regional individual differences should not be expected to mimic the effects of agonist/antagonist pharmacological agents, which disturb neurotransmission over larger parts of the brain and probably do not change the number of interneurons present. Even when regionally specific, pharmacological agents might not mimic natural variation: for example, GABA_A receptor agonists such as muscimol can be used to temporarily “deactivate” regions of cortex (e.g., 82), but deactivating DLPFC would be expected to reduce impulse control (25) and thus be associated with higher urgency. Our finding that higher GABA predicts lower urgency is opposite to this prediction and shows that natural variation in GABA should not simply be considered analogous to more or less cortical deactivation.

Our findings also imply that neither GABA nor impulsivity have a simple relationship with response inhibition as measured by the stop-signal reaction time alone. We found no correlation between either GABA or impulsivity and the stop-task in our samples. Although correlation between impulsivity and the stop-task has been reported previously (83,84); other studies have not replicated this (e.g., 85). The findings of Young *et al.* (34) are informative in this respect. They found that the relationship between externalizing disinhibitory traits and response inhibition is better captured at the level of a latent response inhibition variable, measured across several “inhibition” tasks, than by any single task. Overall, these results suggest that DLPFC GABA is more related to a higher-level trait indexed by urgency than specific to the performance in the stop-

signal task, although such conclusion based on absent correlations must be only tentative.

In sum, we have found that that one facet of impulsivity, urgency—a quantitative trait linked at high levels with several clinically problematic externalizing, disinhibitory conditions—correlates with the concentration of GABA measured in DLPFC, a region implicated in self-control. We hope that these results as well as future research using regionally specific MRS in humans will help to bridge the gap between the regional specificity provided by imaging studies and the biochemical data from genomic and pharmacological investigations.

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Supplementary material cited in this article is available online.

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