CNS Spectrums

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Neurochemistry of response inhibition and interference in gambling disorder: a preliminary study of γ-aminobutyric acid (GABA+) and glutamate–glutamine (Glx)

Original Research

Cite this article: Weidacker K, Johnston SJ, Mullins PG, Boy F, and Dymond S (2022). Neurochemistry of response inhibition and interference in gambling disorder: a preliminary study of γ-aminobutyric acid (GABA+) and glutamate–glutamine (Glx). *CNS Spectrums* **27**(4), 475–485.
https://doi.org/10.1017/S1092852921000316

Received: 13 January 2021
Accepted: 16 March 2021

Key words:
Gambling; MRS; GABA; response inhibition; response interference

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Abstract

Background. Neurobehavioral research on the role of impulsivity in gambling disorder (GD) has produced heterogeneous findings. Impulsivity is multifaceted with different experimental tasks measuring different subprocesses, such as response inhibition and distractor interference. Little is known about the neurochemistry of inhibition and interference in GD.
Methods. We investigated inhibition with the stop signal task (SST) and interference with the Eriksen Flanker task, and related performance to metabolite levels in individuals with and without GD. We employed magnetic resonance spectroscopy (MRS) to record glutamate–glutamine (Glx/Cr) and inhibitory, γ-aminobutyric acid (GABA+/Cr) levels in the dorsal ACC (dACC), right dorsolateral prefrontal cortex (dlPFC), and an occipital control voxel.
Results. We found slower processing of complex stimuli in the Flanker task in GD ($P < .001$, $\eta^2_p = 0.78$), and no group differences in SST performance. Levels of dACC Glx/Cr and frequency of incongruent errors were correlated positively in GD only ($r = 0.92$, $P = .001$). Larger positive correlations were found for those with GD between dACC GABA+/Cr and SST Go error response times ($z = 2.83$, $P = .004$), as well as between dACC Glx/Cr and frequency of Go errors ($z = 2.23$, $P = .03$), indicating general Glx-related error processing deficits. Both groups expressed equivalent positive correlations between posterror slowing and Glx/Cr in the right dlPFC (GD: $r = 0.74$, $P = .02$; non-GD: $r = .71$, $P = .01$).
Conclusion. Inhibition and interference impairments are reflected in dACC baseline metabolite levels and error processing deficits in GD.

Introduction

Gambling disorder (GD) is a psychiatric condition characterized by irritability and failing to stop gambling, recurrent thoughts about gambling and gambling as a coping mechanism, loss chasing, and hiding gambling behaviors from others or exploiting others for gambling money.[1,2] The health-harming behaviors indicative of GD are now widely recognized as a public health issue.[3,4]

Gambling disorder has long been associated with deficits in self-reported impulsivity[5,6] and impaired task performance on behavioral indices of impulsive behavior.[7,8] A range of cognitive-behavioral domains have assessed the broad construct of impulsivity, such as attentional inhibition, motor inhibition, discounting, decision-making, and reflection impulsivity.[9] As a result, observed deficits are heterogeneous across studies and individuals, and warrant further investigation into the contribution of different impulsivity-related subprocesses in GD.[5,10] This may include, for example, inhibitory control understood in terms of prepotent response inhibition and resistance to interference from distractors.[11,12] Disentangling the separate and/or combined influence of specific impulsivity-related processes in GD might aid understanding of the various trajectories that lead to excessive gambling behavior and enable future treatment development.

One subprocess, response inhibition or the ability to inhibit prepotent responses, is often assessed using the stop signal task (SST).[13] In the SST, a manual button press is required on most trials upon visual presentation of an arrow. The minority of arrow presentations are followed by an auditory stop signal, indicating the requirement to withhold the prepotent button press. Importantly, the time at which the auditory stop signal is delayed in respect to the visual arrow, the stop signal delay (SSD), is adjusted in a stepwise manner, which is used to compute the stop signal response time (SSRT).

A second subprocess, response interference or resistance to interference from distractors, is commonly assessed using the Eriksen Flanker task.[14] Similar to the SST, a central arrow is presented and the direction it faces determines the required button press. In the Flanker task, the central task-relevant stimulus is either flanked by congruent (C) or incongruent (IC) arrows and presentation of IC flankers induces response competition which increases response times and error rates.[14]

Although response interference using the Flanker task has, to the best of our knowledge, not yet been studied in populations with GD, previous research on problem gambling and response inhibition using the SST has produced mixed results. Inhibition-related variables, such as the SSD and SSRT, often do not dissociate between gambling and nongambling participants.[15-20] Similarly, response time on Go trials fails to distinguish between those with and without GD.[21,22] However, both prolonged response time and SSRTs are seen in participants with high gambling severity, whereas at-risk gamblers do not differ in their SST performance compared to nongambling participants.[17,23] Studies of response inhibition in GD show increased SSRTs with moderate to large effect sizes and increased Go response times during Go/No-go tasks with small to moderate effect sizes.[24] In addition to inhibition-related SST measures, only two SST studies, to date, have investigated error frequency and posterror slowing (PES) in gamblers. Lorains et al[18] found enhanced error responses on Go trials in a sample of treatment-seeking gamblers, whereas Lawrence et al[21] found no differences to controls when investigating a moderate to severe disordered gambling sample. However, it is noteworthy that both studies also investigated the effects of previous trial types (correct go, correct stop, and failed stop) on current, within-session Go responses. Usually, behavioral responses that are preceded by an error are slower compared to that are preceded by correct trials, which might reflect an adaptive mechanism to reduce future errors or increased salience of errors[25-27]; however, both studies found no differences between gamblers and nongamblers on PES.

Despite measuring purportedly different aspects of impulsivity, the neural networks recruited during the Flanker task and SST overlap. Indeed, a recent activation likelihood estimation meta-analysis compared the neural networks involved in cognitive inhibition, composed of Stroop and Flanker task data, to those involved in response inhibition, consisting of SST and Go/No-go tasks, and found overlap among task-based functional magnetic resonance imaging (fMRI) activity in dorsal anterior cingulate cortex (dACC), right-, but not left-hemispheric, dorsolateral prefrontal cortex (dlPFC) and the left anterior insula.[28] In a Go/No-go version of the Flanker task, interference-related dACC activation correlated positively with response times and error rates during the IC condition, while the number of inhibition errors correlated negatively with response inhibition-related activity in the right, but not left-hemispheric, dlPFC activity.[29]

Functional abnormalities of the overlapping brain areas supporting response inhibition and response distractor interference have been reported in disordered gambling. For example, a recent SST fMRI study assessed high-frequency poker players and revealed increased dACC activity during successful response inhibition compared to nongambling controls in the absence of SSRT differences.[15] However, it is likely that gambling-related abnormalities in the dACC extend beyond neural activation. In a previous work conducted with the present sample of males with GD, we showed that baseline glutamate–glutamine (Glx) levels in the dACC negatively correlate with gambling severity.[30] This supports related findings showing that medication acting on glutaminergic transmission reduces gambling severity.[31,32] It is noteworthy that optimal response inhibition and interference task performance is assumed to depend on optimally balancing excitatory and inhibitory neurometabolites, such as glutamate and γ-aminobutyric acid (GABA).[33] Consistent with this, correlations between levels of these metabolites and behavioral performance have been reported previously. For instance, percentage of inhibition errors correlate negatively with GABA levels in the dACC,[34] as does self-reported impulsivity, which additionally correlates negatively with γ-aminobutyric acid (GABA+; + indicates contributions from unsuppressed macromolecules) levels in the right dlPFC.[35] Similarly, Chowdhury et al[20] reported a positive correlation between GABAergic transmission in the motor cortex and SSRTs. Interestingly, despite the absence of group differences in SST performance, Chowdhury et al[20] also found evidence for reduced $GABA_A$ receptor activity and increased glutamate receptor activity in a GD sample compared to nongamblers and at-risk gamblers, respectively. Additionally, exogeneous dopamine administration reduced prefrontal $GABA_A$ receptor availability less in treatment-seeking problem gamblers compared to healthy volunteers.[36]

In terms of distractor interference, one previous investigation into the relationship between response time differences between IC and C Flanker trials and metabolite levels in the medial/dorsal ACC found no correlation with Glx, while GABA was unassessed.[37] Little is known about the role of GABA in response interference in GD compared or non-GD populations. It is possible, however, that GABAergic processes are involved during Flanker task interference control: Faßbender et al[38] investigated the effects of Lorazepam, a benzodiazepine binding to the $GABA_A$ receptor and thereby enhancing GABA release, on Flanker performance and reported increased error rates as well as response times when dosage was increased. On the other hand, performance on the related interference Stroop task where the distracting stimulus dimension is dominant,[12] did not significantly correlate with glutamate or GABA in the dACC or parieto-occipital cortex.[34]

In sum, the existing evidence reveals conflicting findings on the range and type of impulsive deficits in GD, although little is known about the underlying neurochemistry of impaired response inhibition and interference. The present preliminary investigation therefore sought to undertake a combined behavioral and MRS study utilizing GD and non-GD samples. Baseline GABA+/Cr and Glx/Cr were assessed in the dACC, right dlPFC (given its' role in Flanker as well as SST tasks[28,29] and self-reported impulsivity[35]) and an occipital control voxel and then related to performance indices of response inhibition, using the SST, and distractor interference, using the Flanker task.

Methods

Participants

Twenty-six right-handed male participants were allocated into GD and non-GD groups based on their past year gambling severity scores on the *Problem Gambling Severity Index* (PGSI)[39]. This resulted in $n = 12$ in the GD group (ie, PGSI score > 8; $M = 15.2$, SD = 5.1; $M_{age} = 36.3$, SD = 9.5) and 14 age-matched, non-GD participants (ie, PGSI score < 1; $M = 0.071$, SD = 0.027; $M_{age} = 35.7$, SD = 8.7). The study was approved by the Department of Psychology Ethics Committee, Swansea University, and all participants provided signed informed consent. All methods were carried out in accordance with relevant guidelines and regulations (Declaration of Helsinki). Further data corresponding to the demographics and

MRS measures of this sample are reported in Weidacker et al.[30] In brief, we previously reported significant negative correlations for the GD sample between Glx/Cr in two locations, the dACC as well as occipital voxel, and gambling severity in terms of the PGSI[39] as well as the DSM-5[2] scores for problematic gambling behavior. Further, no significant between-group differences were found regarding MRS measures, but the GD group scored significantly lower on full scale intelligence (FSIQ; assessed with the Wechsler Abbreviated Scale of Intelligence[40] subtests for Matrix Reasoning and Vocabulary) and higher on attention deficit hyperactivity disorder (ADHD) symptoms (assessed with the World Health Organization Adult ADHD Self Report Scale version 1.1; ASRS[41]) compared to the non-GD group. Assessed with the Alcohol, Smoking, and Substance Involvement Screening Tests version 3,[42] GD participants scored also significantly higher on alcohol usage. Importantly, age, other substance use, such as for tobacco, cannabis, cocaine, and amphetamine, as well as the presence of Axis 1 disorders (assessed with the MINI International Neuropsychiatric Interview version 5.0.0[43]) were not statistically different between the groups[30]. Due to the significant between-group differences relating to ASRS and FSIQ scores, Pearson correlations were performed to assess the necessity of including them as covariates; none of the correlations with Flanker and SST variables reached significance ($|r| < 0.35$, Ps > .08), revealing no indication for inclusion.

Assessments

Gambling severity

The PGSI[39] assesses the severity of gambling problems via nine items, on a Likert scale from *never* (=0; 92.9% of the non-GD group), *sometimes* (=1; 7.1% of the non-GD group [1 participant scored 1]), *most of the time* (=2) to *almost always* (=3). All GD participants were categorized as *problem gamblers* (>8 on the PGSI). The PGSI has high internal consistency (Cronbach's α = 0.90) and adequate validity for both GD and non-GD groups.[44,45]

The *Diagnostic and Statistical Manual of Mental Disorders 5* (DSM-5)[2] states nine criteria for problematic gambling behavior leading to significant past year distress categorized as *mild* (4-5 criteria apply; 33.3% of the gamblers), *moderate* (6-7; 25%), or *severe* gambling problems (8-9, 41.7%).

The *South Oaks Gambling Screen* (SOGS)[46] assesses gambling risk via 20 items. Participants were characterized as *no problems* (=0; 92.9% of the non-GD group), *some problems* (1-4; 7.1% of the non-GD group [1 participant scored 1]), or *probable pathological gambling* (>5; 100% of the GD group).

Procedure

Prescreening for eligibility utilized the PGSI, SOGS, and DSM-5 as well as magnetic resonance exclusion criteria and participants were invited to the Imaging Center at Swansea University upon meeting the inclusion criteria (ie, PGSI score ≤1 or >8, right handedness, and safety criteria for scanning). The behavioral and MRS assessments took place on separate days (mean number of days between testing sessions = 15.7). Before MRS testing, participants' blood alcohol levels were measured with single use breathalyzers (none of the participants had consumed alcohol before testing). Behavioral tasks were administered in a counterbalanced order across participants.

Flanker task

The Flanker task was presented using Psychtoolbox[47] in combination with MATLAB R2010b (Mathworks Inc., Natick, MA). In the 200 stimuli Flanker task, either congruent (C; 70%) arrows (eg, > > > > > >) or incongruent (IC; 30%) arrows (eg, > > > < > > >) were presented. Participants were instructed to press as fast and accurately as possible in the direction where the middle arrow pointed to (button Z on the keyboard for middle arrows pointing to the left; button M for middle arrows pointing to the right) while ignoring all arrows on the sides. Within each stimulus type (C and IC), arrows pointing to the right and left were presented in equal proportions. The presentation of stimuli was pseudo-randomized with the restrictions to not have an IC trial presented at the first trial, exclude the possibility of two IC trials in a row, and to have between two and five C trials in between IC trials. In the intertrial interval, a centered fixation cross was presented, with randomized durations between 900 and 1200 ms, in steps of 50 ms. Before the start of the experimental task, 30 practice stimuli were shown to make participants familiar with the arrow design and task requirements. During this practice part, feedback was presented when response times exceeded 750 ms ("Please try to press faster"), upon wrong button presses ("Wrong direction"), and following correct button presses ("Well done!").

Stop signal task

The SST was presented using Psychtoolbox[47] in combination with MATLAB R2010b (Mathworks Inc.). In the SST, one arrow is presented centrally per trial and the participants are asked to press the button corresponding to the direction the arrow is pointing to (right pointing arrows required the button M, left pointing arrows the button Z on the keyboard) as fast and accurately as possible. On the minority of trials, an auditory stop signal is presented following the visual arrow, in these trials the participants are asked to inhibit their already initiated motor response as quickly as possible. The experiment was programmed in three experimental blocks with a self-paced break in between blocks, per block 100 stimuli were presented (30% of stop trials). Stimulus presentation was pseudo-randomized with the only restriction to prevent two consecutive stop trials. Within each stimulus type (stop, go), left and right arrows were presented equally often. In between trials, a centered fixation cross was presented with randomized durations between 900 and 1200 ms, in steps of 50 ms. The SSD, the delay between the visual presentation of the arrow and the auditive stop signal, was initially set to 250 ms at task begin. Thereafter, each correct withholding of button presses in response to stop trials decreased the SSD by 50 ms (minimum was set to 50 ms), incorrectly pressing a button at stop trials increased the SSD by 50 ms. Before the start of the experimental task, 40 practice stimuli (12 stop trials) were presented. One participant was excluded from the non-GD group due to recording issues.

MR acquisition

MR was acquired using a 3-T Siemens Magnetom Skyra scanner (Siemens Medical Solutions, Erlangen, Germany; software version VD13) in combination with a 32-channel head coil. The MPRage sequence was used to obtain a T1-weighted image with the following parameters: repetition time (TR = 2200 ms), echo time (TE = 2.45 ms), inversion time (TI = 900 ms), flip angle (8°), 192 slices, and 1-mm slices.

Single voxel MRS was based on the MEGA-PRESS MRS package[48] (provided by the University of Minnesota under a C2P agreement). The following voxel of interests (VOIs) were acquired in sequence: the dorsal ACC (30 × 30 × 20 mm), the right dlPFC (30 × 20 × 20 mm), and occipital, between the calcarine fissure and the parieto-occipital sulcus (20 × 30 × 25 mm). GABA+ was utilized as an edited estimate of gabaergic concentration (ie, concentration/level of GABA) in the absence of macromolecule suppression and acquired with the following parameters: TR = 1800 ms, TE = 68 ms, 200 averages (per ON and OFF spectra), 1024 complex data points, editing pulse frequency = 1.90 ppm (4.70 ppm center frequency), editing pulse bandwidth = 52 Hz, offset frequency set to 3.00 ppm (reflecting the offset, relative to water, of the carrier frequency of the slice-selective pulses). Higher-order shimming was performed manually to reduce local field inhomogeneities in each VOI and VAPOR was used for water suppression. No outer voxel suppression was applied. See Figure 1 for voxel locations overlap and Figure 2 for corresponding mean and individual spectra per group. Recommended minimum reporting details for the MRS details are also included in Appendix 1 as set out in the Minimum Reporting Standards for in vivo Magnetic Resonance Spectroscopy (MRSinMRS): Experts' Consensus Recommendations.[49] Five participants produced no adequate MRS data for any of the three MRS voxels during acquisition (eg, hardware failure, excessive motion, and inadequate shimming) and were therefore excluded prior to this report.

Spectral quantification

MRS quantification was conducted via GANNET 3.0.[50] (Baltimore, MD) in MATLAB on Siemens .rda files (averaged spectra) using the standard processing steps, inbuilt models and assumptions for this software (details at http://www.gabamrs.com). The edited spectrum was based on the subtraction of the "ON" and "OFF" spectra following alignment of subspectra based on the spectral registration algorithm.[51] The GANNET pipeline models GABA+, Glx, and the creatine (Cr) reference as a single-Gaussian, doublet, and singlet, respectively. Data are reported as a raw ratio of area under the fitted curve referenced to Cr (aligned with our previous report on this sample), for each metabolite, and does not account for differential proton densities, metabolite-specific relaxation properties, or tissue make up. In addition to GABA+/Cr and Glx/Cr, we utilized the GABA+/Glx ratio for MRS-related analyses in line with our previous report on this sample. While cerebrospinal fluid (CSF) correction is not necessary when using Cr as reference,

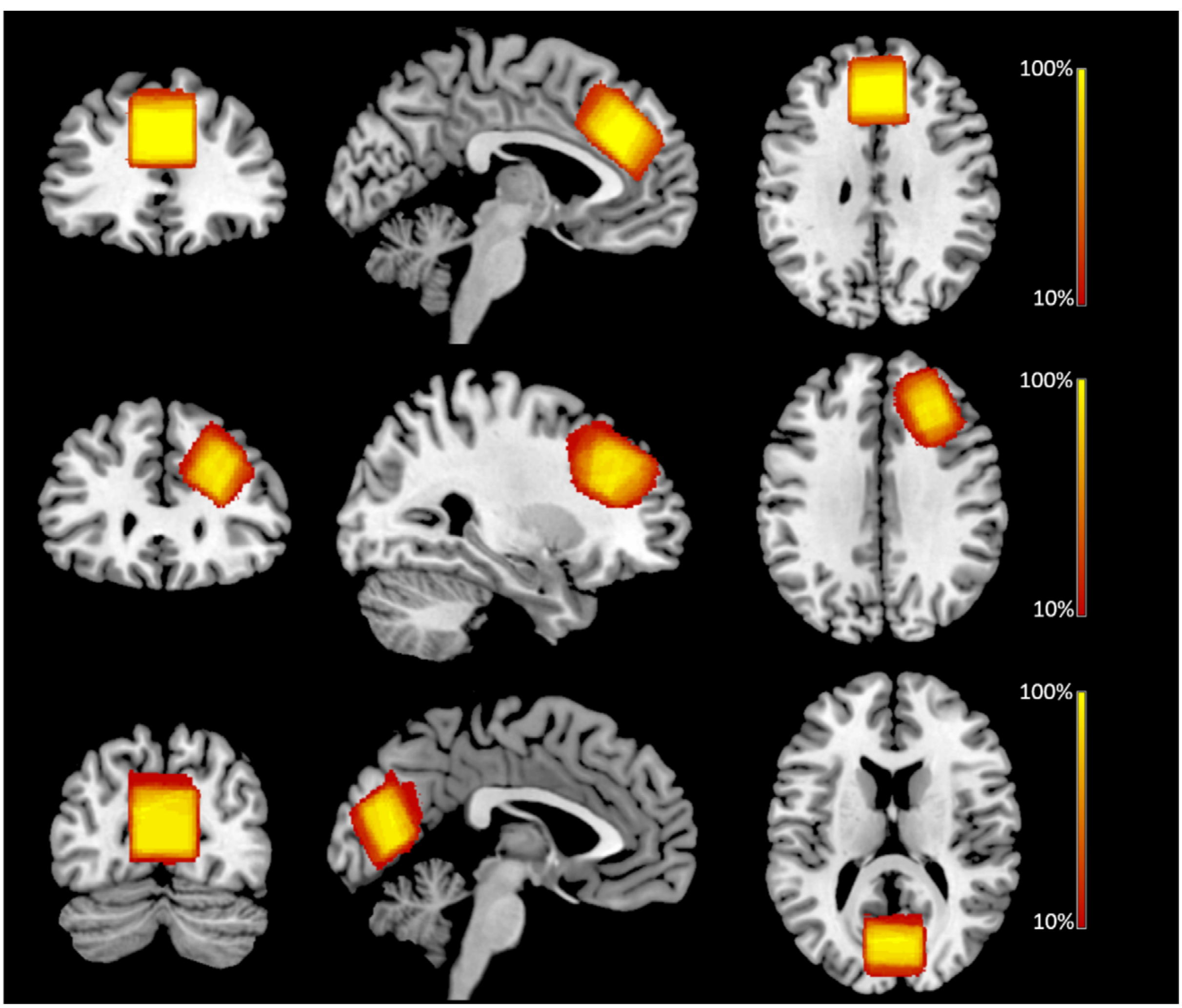

Figure 1. Voxel locations for the dACC, dlPFC, and occipital voxels. Percentage overlap across all participants (from 10% to 100%) per location is shown. Each participant's voxel location was transformed into MNI space before calculating the percentages. dACC, dorsal anterior cingulate; dlPFC, right dorsolateral prefrontal cortex; POC, posterior occipital cortex.

https://doi.org/10.1017/S1092852921000316 Published online by Cambridge University Press

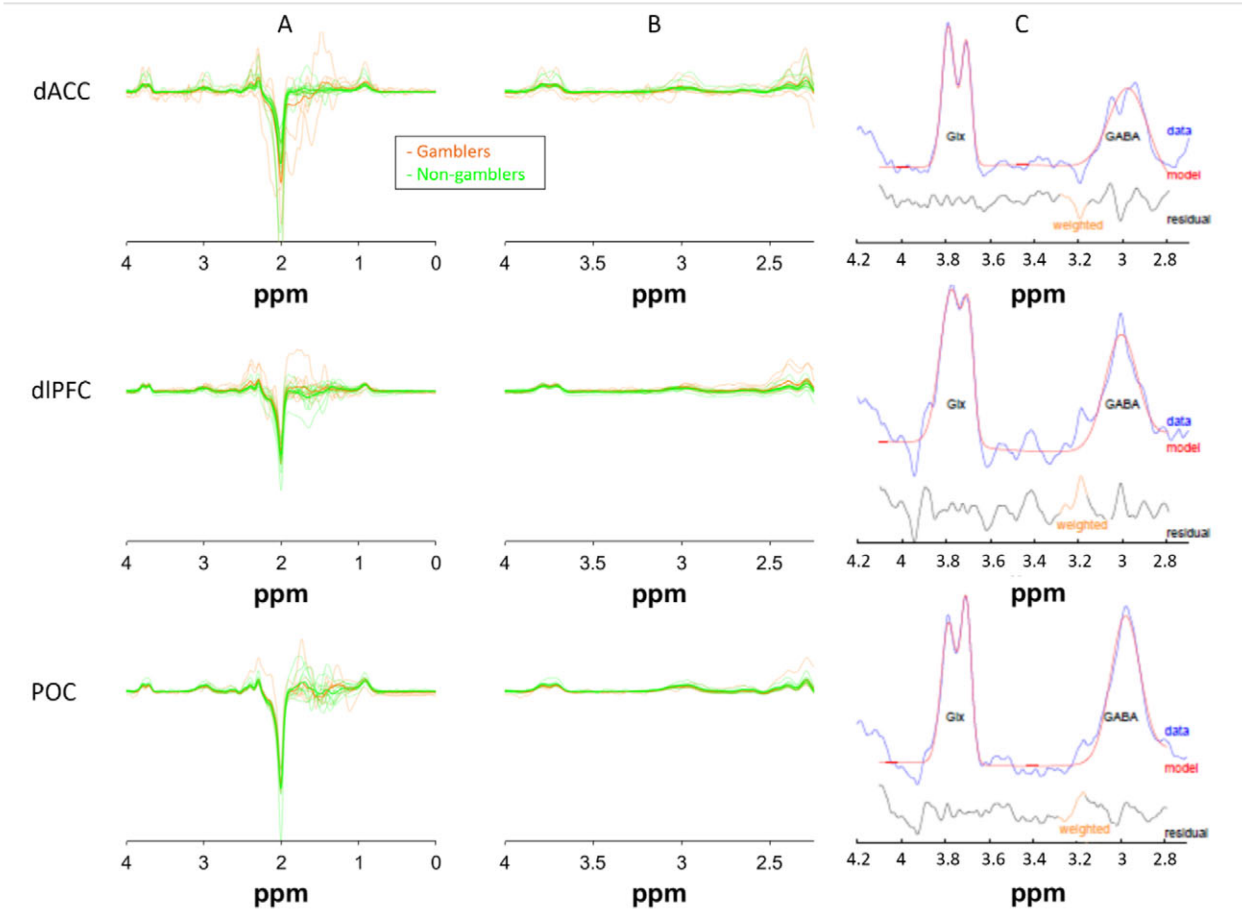

Figure 2. Spectra and example model fit for the dACC, dlPFC, and occipital MRS voxels. The first column (A) shows the individual MRS spectra (from 0 to 4 ppm), the second column (B) shows only the critical signal region (from 2.25 to 4 ppm). Both (A) and (B) are color coded with orange representing participants with and green representing participants without gambling disorder. The respective group average MRS plots are added as a thicker line following the same colour coding. The third column (C) shows an example GannetFit output per MRS voxel. dACC, dorsal anterior cingulate; dlPFC, right dorsolateral prefrontal cortex; MRS, magnetic resonance spectroscopy; POC, posterior occipital cortex.

gray matter (GM) contribution may however be of influence and is therefore controlled for in all MRS-related analysis via partial Pearson correlations using GM fraction of the respective MRS voxel, GM/(GM + CSF + white matter), as covariate. Per voxel, GM tissue fractions were obtained using unified segmentation[52] of the T1-weighted image in SPM12 (https://www.fil.ion.ucl.ac.uk/spm/). Within each voxel (eg, dACC), task performance indices (eg, SST Go error RTs) were correlated with MRS measures (eg, dACC GABA+/Cr) and corrected for GM contribution (eg, GM in dACC MRS voxel) using partial Pearson correlations. However, producing visual representations (scatterplots) of partial Pearson correlations included a few more steps. First, both variables in a correlation pair were corrected for GM contribution by performing linear regressions (eg, linear regression 1: predicting dACC GABA+/Cr from dACC GM; linear regression 2: predicting SST Go error RTs from dACC GM) and saving the corresponding residuals. These residuals are fully corrected for GM contribution and were used to create the corresponding scatterplot per significant correlation, and are as such simply a visual representation of a partial Pearson correlation, correcting for GM contribution.

From the 26 participants included in this report, individual MRS voxels were discarded due to inadequate MRS voxel acquisition during scanning, for example, due to excessive motion, inadequate shimming, hardware/recording issues (applies to two dACC, one dlPFC, and four occipital voxels), bad model fit (applicable to one dACC voxel), presence of subtraction artifact (one dACC and one occipital voxel), phase issues (one dlPFC and two occipital voxels), and presence of truncation artifact (one occipital voxel). GANNET Model fit was assessed based on visual inspection and full-width at half-maximum (FWHM) within three SDs from the group mean per metabolite (eg, within the dACC: GABA+, Glx). Due to excessive FWHM, one additional occipital voxel was excluded from analyses concerning GABA+. Data were included from 9 participants in GD and 13 in non-GD for the dACC voxel, leading to mean (and SDs) of the signal-to-noise ratios (SNR) for Glx of 21.77 (14.99) and 29.10 (11.96) and for GABA+ of 15.54 (10.69) and 18.65 (8.30), respectively for GD and non-GD. For the right dlPFC voxel, 11 GD and 13 non-GD participants were included, with SNRs for Glx equalling 18.61 (8.47) and 22.13 (7.27) and for GABA+ of 12.77 (5.09) and 16.35 (5.24). For the occipital voxel, 8 GD and 10 (Glx) or 9 (GABA+) non-GD participants were included, leading to SNRs for Glx of 18.14 (6.23) and 19.12 (5.45) and SNRs for GABA+ of 19.44 (6.76) and 19.38 (5.90), respectively. The mean FWHM (and corresponding SDs) of included dACC MRS data equalled 14.42 (2.35) and 16.32 (3.15) for Glx, and 16.50 (6.16) and 20.43 (3.18) for GABA+, respectively for GD and non-GD. FWHMs for included dlPFC MRS data equalled 14.51 (1.92) and 15.11 (3.21) for Glx, and 16.55 (4.15) and 19.18 (4.25) for GABA+, respectively for GD and non-GD. FWHMs for included occipital MRS data equalled 13.99 (1.21)

https://doi.org/10.1017/S1092852921000316 Published online by Cambridge University Press

and 14.95 (1.12) for Glx, and 20.55 (4.01) and 21.76 (3.71) for GABA+, respectively for GD and non-GD. The mean Gannet fit error (SD) for included dACC MRS data equalled 8.29 (9.66) and 5.36 (1.71) for Glx/Cr, and 9.42 (5.71) and 8.40 (3.75) for GABA+/Cr, respectively for GD and non-GD. The mean Gannet fit error (SD) for included dlPFC MRS data equalled 6.60 (3.09) and 5.96 (2.09) for Glx/Cr, and 8.93 (3.44) and 8.16 (3.69) for GABA+/Cr, respectively for GD and non-GD. The mean Gannet fit error (SD) for included occipital MRS data equalled 6.58 (2.99) and 6.02 (1.42) for Glx/Cr, and 6.47 (3.75) and 5.63 (1.60) for GABA+/Cr, respectively for GD and non-GD.

Statistical analysis

Flanker task

First an rmANOVA was conducted on correct response times with group as between-subject factor and trial type (C vs IC) as within-subjects factor. For error processing, two separate one-way ANOVAs were conducted with group as between-subject factor, the first on IC error response times, the second on error percentages. We confined the error analyses to IC trials (% $M = 9.04$, SD = 8.92, range = 0-40), since few participants made errors in C trials (% $M = 0.77$, SD = 0.88, range = 0-3.57). One participant per group made no IC errors and both were therefore excluded from the error response time analyses.

PES analyses were based on correct trials preceding and following IC errors as suggested for calculating robust PES.[53,54] The functional role of PES, the observation that trials following an error produce longer response times compared to trials being preceded by a correct trial[25] is under debate with arguments for reducing future error responses or being a result of the increased salience of errors among others.[26,27] Earlier investigations into PES and gambling behavior were based on only posterror response times, termed the traditional method to calculate PES.[54] Comparing approaches to PES calculation however showed that the traditional method is affected by global changes in attention and motivation, therefore underestimates PES, and is outperformed by the robust method which compares posterror responses to pre-error responses.[53] These trial types were subjected to an rmANOVA as within-subject factors, adding group as between-subject factor, and the resultant sample size was 11 for GD and 13 for the non-GD group.

The Flanker variables (response time differences between IC and C trials, percentage and response times of IC error trials and PES) were correlated to dACC, dlPFC, and occipital MRS variables (Glx/Cr, GABA+/Cr, and GABA+/Glx ratio) using partial Pearson correlation coefficients, correcting for GM content within each voxel, first using all participants and thereafter separately per GD and non-GD. The derived significant partial correlation coefficients were statistically compared following Fisher's r to z transformation. As this was an exploratory study, data are reported using exact P values without correction.

Stop signal task

The mean SSD was calculated as the average of SSDs stemming from successful stop trials and trials with premature responses (button presses that occurred before the stop signal). The probability of responses occurring when a stop signal was presented was calculated as inverse of % correct stop trials. To estimate SSRT, the go response time that matches this probability within the distribution of response times to go trial (including wrong trials and imputing the response times of missed go trials with the maximum of that distribution) was selected, and mean SSD was subtracted from it.

The SST exclusion criteria were as follows: SSRTs indicating waiting for the stop signal (eg, negative SSRT, applicable to one GD participant), probabilities outside the rage of 24.4% to 75% (not met by participants in this study), response time was higher at unsuccessful stop trials compared to the mean of the go trial distribution (not applicable to these participants), and recording issues (applicable to one non-GD participant). Applying these criteria resulted in a behavioral sample comprised of 11 GD and 13 non-GD participants. Calculations of mean SSD, probability, and SSRT are in line with recent suggestions on the use of the integration method for SST studies.[55]

Group-differences were assessed using separate one-way ANOVAs with group as between-subjects factor on response times to correct Go trials, % errors to Go trials (% $M = 2.82$, SD = 3.71, range = 0-17.14), SSDs, and SSRTs. Error response times for choice errors (Go: pressing the wrong direction) and inhibition failures (Stop: pressing during stop trials) were analyzed using an rmANOVA with trial type (Go vs Stop) as within- and group as between-subjects factor. Posterror slowing was analyzed as described above for the Flanker task, making use of trials preceding and following failed inhibition errors, in an rmANOVA with group as between-subject factor. Two GD participants did not make errors to Go targets and were therefore not incorporated in the associated response time analyses. The MRS variables were correlated to the SST variables (response times to correct go, wrong go and wrong stop trials, percentages go errors, PES, SSD, and SSRT) in the same manner as outlined for the Flanker task. Given the additional outlier criteria applied to the SST, the correlations between SST variables and dACC MRS measures were based on 8 GD (7 for Go error response times) and 12 non-GD participants, whereas correlations between dlPFC MRS measures and SST task-data were based on 10 GD and 12 non-GD participants, and correlations between POC MRS measures and SST performance were based on 8 GD and 9 (Glx) or 8 (GABA+) non-GD participants.

Across tasks, significant rmANOVA results are accompanied by η^2_p as effect size, while Cohen's d is used for independent-sample t tests. G*Power 3.1.9.2[56] was used for sensitivity analysis and the smallest detectable effect size d for between-group effects equalled 1.20, given our SST sample sizes, a two-sided α of 0.05 and 80% power. Regarding t tests, Levene's Test for Equality of Variances was performed and corrected statistics are reported when applicable. Multivariate normality (of all three variables within a partial Pearson correlation) was ascertained using Chi-square generalized distance plots obtained via the software Statgraphics (Version 18, Statistical Graphics Corporation, Rockville, MD) and all variables included in significant correlations fell within the 95% confidence interval, consistent with the hypothesis of an underlying multivariate normal distribution.

Results

Demographics

As expected, the GD and non-GD groups differed significantly on PGSI scores, $t(11.05) = 10.19$, $P < .001$, $d = 4.01$, SOGS scores, $t(11.12) = 11.68$, $P < .001$, $d = 4.59$, and number of endorsed DSM-5 criteria, $t(11) = 12.45$, $P < .001$, $d = 4.90$ (see Weidacker et al[30] for further details).

Response interference (Flanker task)

An rmANOVA on response times across trial types revealed a main effect of trial-type ($F(1,24) = 87.03$, $P < .001$, $\eta^2_p = 0.78$), group ($F(1,24) = 6.09$, $P = .02$, $\eta^2_p = 0.20$) and a non-significant interaction between group and trial type ($F(1,24) = 3.92$, $P = .06$). Response times to IC trials were significantly slower ($M = 535.27$, SD = 108.30) compared to C ($M = 424.80$, SD = 73.70) trials, regardless of gambling status. Gamblers had significantly longer response times ($M = 521.40$, SD = 105.52) compared to the non-GD group ($M = 444.58$, SD = 46.22) when averaged across trial type.

No significant effects of group were found when analyzing the IC error response times ($F(1,23) = 2.32$, $P = .14$) and the percentage of IC errors ($F(1,25) = 1.82$, $P = .19$). An rmANOVA on trials preceding and following IC errors revealed significant posterror slowing ($F(1,22) = 11.88$, $P = .002$, $\eta^2_p = 0.35$), but no significant main effect of group ($F(1,22) = 11.11$, $P = .30$) or interaction between group and trial type ($F(1,22) = 0.01$, $P = .93$).

Correlations between response interference and MRS measures

Analyzing associations between dACC MRS variables and Flanker variables did not reveal significant correlations in the whole sample ($|r_s| < 0.38$, $P_s > .12$). When assessing the correlations within the GD group, dACC Glx/Cr was significantly positively correlated with the proportion of IC errors ($r = 0.92$, $P = .001$), the remaining correlations were not statistically significant ($|r_s| < 0.69$, $P_s > .05$). Within the non-GD group, this correlation, between dACC Glx/Cr and proportion of IC errors, was not significant ($r = 0.02$, $P = .94$), as were the remaining correlations ($|r_s| < 0.27$, $P_s > .40$). Using Fisher's r to z transform, the difference between the correlation coefficient obtained for the relationship between dACC Glx/Cr and proportion of IC errors was significantly larger in GD compared to the non-GD group ($z = 3.03$, $P = .002$; see Figure 3).

In the dlPFC voxel, no correlations between MRS and Flanker variables were significant in the whole sample ($|r_s| < 0.25$, $P_s > .26$), the GD group ($|r_s| < 0.52$, $P_s > .12$) and the non-GD group ($|r_s| < 0.59$, $P_s > .05$). In the occipital voxel, no correlations were significant for the whole sample ($|r_s| < 0.35$, $P_s > .21$), the GD group ($|r_s| < 0.36$, $P_s > .48$), and the non-GD group ($|r_s| < .67$, $P_s > .05$).

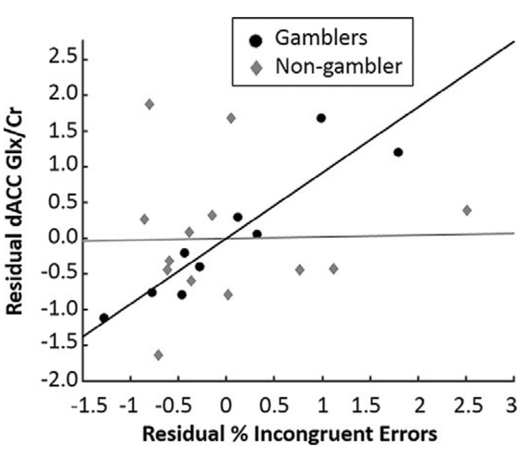

Figure 3. Scatterplot of the significant correlation (adjusted for gray matter content) between Glx in the dACC and percentage errors to incongruent trials in the Flanker task. This relationship is shown in black for gambling ($r = 0.92$, $P = .001$) and in gray for nongambling participants ($r = 0.02$, $P = .94$). dACC, anterior cingulate cortex. Lines represent the least squares fit to the data.

Response inhibition (SST)

Analyzing the effect of gambling status on correct response times to Go trials in the SST revealed no significant effect ($F(1,23) = 3.18$, $P = .09$). An rmANOVA on response times for choice errors for Go and inhibition errors on Stop trials produced a significant main effect of trial type ($F(1,20) = 34.25$, $P < .001$, $\eta^2_p = 0.63$), due to longer response times when performing errors of inhibition ($M = 379.09$, SD = 58.50) compared to the errors of choice ($M = 195.57$, SD = 47.26). The interaction between group and trial type ($F(1,20) = 0.63$, $P = .44$) as well as the main effect of group were not significant ($F(1,20) = 1.5$, $P = .23$). Further, the percentage of choice errors on Go trials did not differ significantly between groups ($F(1,23) = 1.80$, $P = .19$).

Analyzing the SST inhibition-related variables, mean SSDs ($F(1,23) = 2.71$, $P = .11$) and SSRTs ($F(1,23) = 1.42$, $P = .25$) revealed no significant group differences between GD and non-GD groups. An rmANOVA on posterror slowing revealed no significant main effect of trial type ($F(1,22) = 3.94$, $P = .06$), group ($F(1,22) = 1.65$, $P = .21$), or interaction between them ($F(1,22) < 0.01$, $P = .99$)

Correlations between response inhibition and MRS measures

Analyzing associations between dACC MRS variables and SST variables did not reveal any significant correlations in the whole sample ($|r_s| < 0.39$, $P_s > .09$). When assessing the correlations within the GD group, the response times on choice (Go) errors correlated positively with GABA+/Cr ($r = 0.86$, $P = .03$) and the GABA+/Glx ratio ($r = 0.936$, $P = .006$). Both correlations were not significant in non-GD, with $r = -0.39$, $P = .24$ for the correlation between Go error response times and GABA+/Cr, and $r = -0.50$, $P = .12$ for the correlation with GABA+/Glx. Comparing the obtained correlation coefficients for the relationship between GABA+/Cr and Go error response times across groups revealed a significantly stronger correlation in GD compared to non-GD ($z = 2.83$, $P = .004$; see Figure 4A). Similarly, the correlation between Go error response times and the GABA+/Glx ratio was significantly larger in GD compared to non-GD ($z = 3.75$, $P < .001$; see Figure 4B). Further, the % Go errors correlated positively with dACC Glx/Cr ($r = 0.85$, $P = .015$) in GD, while this correlation was not significant in non-GD ($r = 0.02$, $P = .95$). The remaining correlations were not significant ($|r_s| < 0.58$, $P_s > .17$) in GD and none of the correlations was significant within the non-GD sample ($|r_s| < 0.50$, $P_s > .11$). Comparing the groups on their correlation coefficients obtained for the association between % Go errors and Glx/Cr revealed a significantly stronger correlation in GD compared to non-GD ($z = 2.23$, $P = .03$; see Figure 4C).

Analyzing the partial correlations between dlPFC MRS variables and SST variables in the whole sample, revealed a significant correlation between Glx/Cr and PES ($r = 0.69$, $P < .001$), all remaining correlations were not significant ($|r_s| < 0.37$, $P_s > .13$). The significant correlation between Glx/Cr and PES was confirmed in both, the GD ($r = 0.74$, $P = .02$) and non-GD group ($r = 0.71$, $P = .01$; see Figure 4D). Within the GD group, dlPFC Glx/Cr also correlated negatively with the percentage Go/choice errors ($r = -0.68$, $P = .04$), whereas this correlation was not significant in the non-GD group ($r = 0.14$, $P = .68$). When comparing correlation coefficients for the association between dlPFC Glx/Cr and the percentage Go/choice errors across groups, no significant difference was obtained ($z = 1.94$, $P = .05$). The remaining correlations were not significant within the GD ($|r_s| < 0.67$, $P_s > .10$) and non-GD groups ($|r_s| < 0.45$, $P_s > .18$).

https://doi.org/10.1017/S1092852921000316 Published online by Cambridge University Press

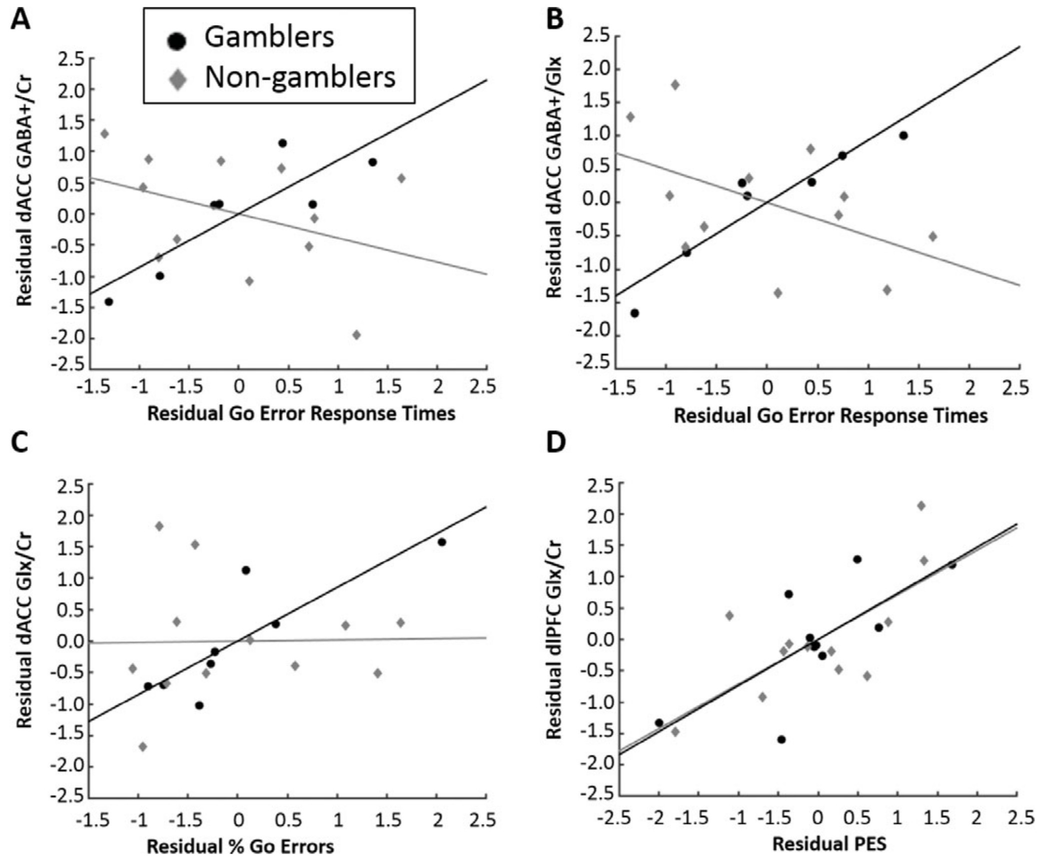

Figure 4. Scatterplot of the significant correlations (adjusted for gray matter content) obtained for the stop signal task. Data from gamblers are shown in black and data from nongamblers are depicted in gray. Lines represent the least squares fit to the data. (A) Positive, significant, correlation between Go error response times and dACC GABA+/Cr in gamblers ($r = 0.86$, $P = .03$); this correlation was not significant in nongamblers ($r = -0.39$, $P = .24$). (B) Positive, significant, correlation between Go error response times and ACC GABA+/Glx ratio in gamblers ($r = 0.936$, $P = .006$); this correlation was not significant in nongamblers ($r = -.50$, $P = .12$). (C) Positive, significant, correlation between % Go error responses, and dACC Glx/Cr in gamblers ($r = 0.85$, $P = .015$); this correlation was not significant in nongamblers ($r = 0.02$, $P = .95$). (D) Positive, significant, correlations between posterror slowing (PES) and dlPFC Glx/Cr in gamblers ($r = 0.74$, $P = .02$) and nongamblers ($r = 0.71$, $P = .01$). dACC, dorsal anterior cingulate cortex; dlPFC, dorsolateral prefrontal cortex; GABA+, γ-aminobutyric acid; Glx, glutamate–glutamine.

Assessing the significance of the partial correlations between occipital MRS and SST variables revealed no significant correlations in the whole sample ($|r_s| < .51$, $Ps > .06$), GD ($|rs| < .68$, $P_s > .22$), and non-GD ($|r_s| < 0.75$, $P_s > .05$).

Discussion

The present study is the first investigation of distractor interference and response inhibition performance in GD, with in vivo GABA+/Cr and Glx/Cr metabolic measurements obtained from three brain areas (dACC, right dlPFC, and an occipital control voxel). Gambling disorder individuals' behavioral performance evidenced prolonged response times in the Flanker task, regardless of stimulus congruency. On the other hand, SST performance did not suggest prolonged response times or inhibition deficits in those with GD. It is possible therefore that the complex stimuli used in the Flanker task might at least partially explain the reduced processing speed in GD that we observed. Despite error responses in the Flanker task not differentiating between groups, GD participants expressed a positive correlation between dACC Glx/Cr and the number of errors in response to IC targets, which was significantly larger than the correlation coefficient found within non-GD participants.

This is the first report of a positive correlation between dACC Glx/Cr and error rates on the Flanker task; the only previous related investigation focused on response times and Glx and found no significant association.[37] These different results suggest that dACC Glx/Cr may play a more prominent role in terms of error rates[57-59] compared to response times, in line with previous reports on increased glutamate-glutamine ratio levels in the dACC being associated with increased self-reported impulsivity as well as increased error rates on a Go/No-go task.[57] Similarly, decreased ACC Glutamate/Cr was previously associated with increases in cognitive control-related striatal activation when contrasting Stroop IC to C trials, and this activation in turn was correlated positively with error rates.[59] In sum, despite few behavioral differences between GD and non-GD on distractor interference measures, the metabolic differences suggest potentially abnormal dACC function related to error processing. This warrants further investigation of any associated striatal abnormalities in GD during interference-related errors.

Response inhibition, in terms of SST performance, has been subject to several investigations in GD, with individual studies finding heterogeneous results and meta-analyses indicating either no or moderate to large effects on SST response inhibition indices, respectively.[16,24] Previous research also supports the idea that response inhibition deficits in GD might emerge at higher gambling severity levels,[17,23] but this hypothesis was not supported by the present investigation which focused solely on participants with high gambling severity. However, due to the restrictive inclusion criteria, the current study suffers from a relatively small sample size and might therefore not be perfectly suited to identify smaller effects and should be a starting point for larger scale research.

Like previous investigations on SST-type tasks, PES was unaffected by the presence of GD in both the SST and Flanker tasks, despite both tasks producing significant PES. However, SST and Flanker PES seem to involve different neural aspects, only SST PES correlated positively with Glx/Cr levels in the right dlPFC, and no dissociation in the strength of correlation as a function of gambling addiction status was observed. Previous research on neural involvement during PES found a positive correlation between PES and left anterior midcingulate white matter, a region which supports connectivity to frontopolar and dorsolateral frontal brain regions.[60] However, dlPFC involvement in posterror slowing shows task-dependent variations[60] and might represent a subprocess of PES.[61] PES in terms of the Flanker task was found to be unaffected by Lorazepam and gamma-hydroxybutyrate, two GABA agonists working on different receptor types,[62,63] but PES was less pronounced in Flanker when compared to Stroop and Go/No-go tasks.[64] Within the Stroop task, Moeller et al[65] investigated the effect of methylphenidate on PES and reported enhanced PES following administration of the drug, which is thought to excite GABAergic interneurons as well as increase glutamate uptake.[66,67] As such, the finding that the neurochemical involvement in PES differs between Flanker and SST tasks might be due to task design and associated differences in pronunciation of PES. In the SST, it was notable that PES was positively associated with dlPFC Glx/Cr, regardless of gambling status.

Although our small samples of GD and non-GD showed consistent correlations between PES and dlPFC Glx/Cr levels, analysis of GD participants revealed additional associations between MRS measures and SST error processing indices that differed in directionality and significance to non-GD participants. Previous research on GD and error processing in the SST is limited, with Lorains et al[18] revealing enhanced Go error frequency in treatment-seeking problem gamblers, whereas Lawrence et al[21] found no between-group differences. The current investigation did not reveal behavioral differences in SST error processing, but did suggest between-group correlation differences between SST error processing and MRS measures. In the dACC, GABA+/Cr as well as the GABA+/Glx ratio correlated positively and significantly with Go error response times in GD, whereas both correlations were negative and did not reach significance in non-GD. Similarly, in GD, baseline dACC Glx/Cr correlated positively and significantly with the frequency of Go errors, a correlation which was also not significant in non-GD. This positive association between dACC Glx/Cr and SST Go errors in GD is resembles that found between dACC Glx/Cr levels and error rates for the Flanker task, perhaps indicating a general influence of baseline Glx on error processing deficits in GD.

In contrast to the Flanker task, response times in the SST did not depend on gambling status, but the positive correlations between Go error response times and dACC GABA+/Cr and the GABA+/Glx ratio indicated GD-specific abnormalities. Previous research with nongambling populations showed that enhancing GABA levels via agonists, such as Diazepam or Lorazepam, prolongs response times across tasks,[38,68] such as the positive association between baseline GABA+/Cr and SST response times found in the current investigation. Although GABA agonists induce widespread increases in cortical GABA, our investigation found the relationship between GABA+/Cr and response times significant within the dACC voxel. Previous neuroimaging research suggests hypo- or hyper-activation in the dACC during SST in GD and frequent poker players, respectively.[15,19] Together, this suggests that in GD dACC function may be affected and accompanied by neurochemical abnormalities, such as stronger associations between baseline GABA+/Cr and SST response times, as well as stronger correlations between Glx/Cr and error rates across interference and inhibition tasks.

Despite these promising findings on the relationships between MRS neurometabolites and task performance, the study has limitations. Since we recruited only GD participants with the highest severity level of gambling behavior (as indicated by PGSI scores) and age-matched controls, the presented research is based on small sample sizes regarding the per group correlations. We also provided a full investigation of all previously reported behavioral differences between GD and non-GD to enable a complete overview of the findings, this has the consequence of increasing the number of statistical tests conducted. The presented results were not corrected for multiple comparisons and exact P values are reported throughout to enable accurate judgement of the significance levels per investigation. Further, we assessed GABA+ and as such interpretation of findings should consider the contribution of macromolecules. Unfortunately, a not minor amount of MRS data had to be excluded due to reasons outlined earlier which further reduced the sample size and the acquired MRS data format almost certainly reduced data quality enhancement during postprocessing. Recent advances in edited MRS acquisition, such as the standardization of the MEGA-PRESS sequence across vendors,[69] and the increased functionality of quantification software in terms of analyzable data formats (TWIX, dicom) is likely of great benefit for future investigations.

Conclusion

In sum, this is the first evidence for distractor interference abnormalities in GD, with prolonged response times and associated neural differences specific to incongruent errors. Additionally, response inhibition did not differ statistically between GD and nongamblers. Neurochemically, GD expressed enhanced correlations between baseline dACC GABA+/Cr and Go error response times as well as between dACC Glx/Cr and frequency of Go errors in the SST and the frequency of IC errors in the Flanker task. Further, GD and non-GD participants expressed equivalently efficient PES in both response inhibition and distractor interference tasks, while neural involvement of baseline dlPFC Glx/Cr levels in the SST-based PES did not vary depending on gambling status.

Acknowledgments. S.D. is funded by Welsh Government through Health and Care Research Wales. The views expressed are those of the authors and not necessarily those of Health and Care Research Wales or Welsh Government. The authors thank the staff of the Imaging Center, Institute of Life Science, Swansea University for their assistance with data collection.

Funding. This work was supported by the International Center for Responsible Gaming (ICRG) and intra-mural funding from the Department of Psychology, Swansea University. The ICRG had no further role in study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Author Contributions. K.W. performed the recruitment, programming of the tasks, and data collection, analyzed the data, and drafted the manuscript. S.J.J. supported the data collection and MRS data acquisition. P.G.M. supervised the data analysis and supported the set-up of the scanning sequences. F.B. and S.D.

received the funding for this study. S.D. supported the design of the study and supervised the whole project. All authors supported the writing of the final manuscript.

Disclosures. The authors have nothing to disclose.

Supplementary Materials. To view supplementary material for this article, please visit http://doi.org/10.1017/S1092852921000316.

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