RUNNING HEAD: Impulsive Decision-Making and Gambling Severity

Impulsive decision-making and gambling severity: The influence of γ-amino-butyric acid (GABA) and glutamate-glutamine (Glx)

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Abstract

Discounting larger, delayed rewards for smaller, immediate rewards is a stable psychological trait known to be impaired in gambling disorder (GD). Neuroimaging with non-GD populations indicates involvement of anterior cingulate (ACC) and dorsolateral prefrontal cortex (dlPFC) in delay discounting. However, little is known about the role of intrinsic properties of brain functioning, such as neurotransmitter action, in impaired discounting in GD. Here, we used magnetic resonance spectroscopy to assess glutamate-glutamine (Glx) and γ-amino-butyric acid (GABA+) concentrations in the dorsal ACC (dACC), dlPFC and occipital cortex of human males with and without GD. Gambling symptom severity correlated negatively with Glx levels in the dACC and occipital voxels. Discounting of small and medium delayed rewards was negatively associated with GABA+ in the dACC, while the discounting of large delayed rewards was negatively associated with GABA+/Glx ratios in the dlPFC. Additionally, in GD, discounting of large delayed rewards was negatively correlated with occipital GABA+ levels. Overall, these findings show that high gambling symptom severity is associated with low levels of Glx and that dACC (GABA+), right dlPFC (GABA+/Glx), and occipital areas (GABA+) track the magnitude of delayed rewards during discounting.

Keywords: gambling disorder, γ-amino-butyric acid, glutamate-glutamine, delay discounting, magnetic resonance spectroscopy.

1. Introduction

Gambling disorder (GD) is a psychiatric condition and growing international public health concern (Wardle, Reith, Langham, & Rogers, 2019) leading to adverse harms across a range of domains (Browne et al., 2017; Downs & Woolrych, 2010; Shaw, Forbush, Schlinder, Rosenman, & Black, 2007). Disordered gambling is related to an increased risk of depression and suicide in men, and higher lifetime prevalence of psychiatric conditions in gamblers compared to non-gambling controls (Kessler et al., 2008; Sundqvist & Rosendahl, 2019).

Reward processing deficits are common in GD and the related impulsive control and substance use disorders (Clark, Boileau, & Zack, 2019), endowing tasks that reliably track impulsive behaviour a high transdiagnostic value. Impulsivity is a multi-faceted personality trait and is central to an understanding of GD and reward processing (Ioannidis, Hook, Wickham, Grant, & Chamberlain, 2019). Impulsive decision-making tasks like delay discounting tasks measure the preference for smaller, immediate rewards over larger, delayed rewards and thereby tap into the ability to delay gratification (Kirby & Marakovic, 1996). For instance, Kirby and Marakovic (1996) developed a delay discounting task, the Monetary Choice Questionnaire (MCQ), which estimates the discounting rate of a reward depending on the magnitude of the reward and the delay at which the reward will be received. In this task, participants choose between an immediate (lower) monetary reward and a delayed higher reward. In non-gambling adolescents, the discounting rate is higher (indicating higher impulsivity levels) compared to older adults, while discounting is indifferent between middle and older adulthood, suggesting a stable rate of discounting delayed rewards in non-gambling adults (Whelan & McHugh, 2009). Higher rates of discounting are seen in GD with and without concurrent substance abuse compared to controls (Albein-Urios, Martinez-González, Lozano, & Verdejo-Garcia, 2014; Andrade &

Petry, 2012; Ledgerwood, Alessi, Phoenix, & Petry, 2009; Michalczuk, Bowden-Jones, Verdejo-Garcia, & Clark, 2011; Miedl, Peters, & Büchel, 2012; Miedl et al., 2015; Petry, 2001; Petry & Casarella, 1999), while at moderate severity levels both increased discounting rates in gamblers (Cosenza, Griffiths, Nigro, & Ciccarelli, 2016; Dixon, Marley, & Jacobs, 2003) and no differences between gambling and non-gambling students (Holt, Green, & Myerson, 2003) have been found. Discounting also does not differ by type of preferred gambling activity (Sharman et al., 2019). Between-group differences in delay discounting may then at least partly depend on the severity of gambling problems, with those with the most severe forms of GD discounting delayed rewards more steeply than gamblers with fewer problems (Alessi & Petry, 2003).

Steeper discounting of delayed rewards in GD is accompanied by stable neural differences during delay discounting (Miedl et al., 2012, 2015). Delay discounting in healthy volunteers usually involves anterior cingulate (ACC), lateral prefrontal cortex and various subcortical structures such as dorsal striatum and insula (Wesley & Bickel, 2014). Similarly, single-cell recordings reveal neurons in the dorsolateral prefrontal cortex (dlPFC) are responsive to the subjective value of the delayed reward (Kim, Hwang, & Lee, 2008). According to the neural model of delayed discounting, the rate at which participants discount delayed rewards is linked to subcortical structures and cingulate cortex as well as prefrontal brain areas, reflecting the valuation and long-term planning processes (Frost & McNaughton, 2017). Additionally, areas within the occipital cortex (e.g., lingual gyrus and cuneus) show stronger activation when presented with immediate compared to delayed rewards and this activation difference correlates with steeper discounting (Wittmann, Leland, & Paulus, 2007). When comparing neural activity evoked by the delay discounting task between GD and non-GD volunteers, Miedl et al. (2015) found widespread differences

in cortical and subcortical brain regions involving the cingulate and medial/superior frontal gyrus. Of note, reduced dorso-prefrontal cortex activation has also been seen during decision making involving loss-chasing in GD, which correlates negatively with the duration of the disorder (i.e., sympton severity; Fujino et al., 2018).

To our knowledge, only one previous study has investigated the neurochemical substrates of inter-individual differences in delay discounting. Schmaal, Goudriaan, van der Meer, van den Brink, and Veltman (2012) measured glutamate-glutamine (Glx) concentrations in the left dorsal ACC (dACC) of healthy volunteers and found a negative correlation between delay discounting (measured as Area Under the Curve across different reward magnitudes) and Glx levels, which was partially mediated by increased functional connectivity between the dACC and reward-related midbrain structures. Evidence for glutaminergic abnormalities in GD stems mainly from pharmaceutical research revealing a positive effect of ligands increasing glutaminergic transmission on gambling behaviour (Olive, Cleva, Kalivas, & Malcolm, 2012). While Schmaal et al. (2012) only assessed Glx levels, research with rodents indicates a role for γ-amino-butyric acid (GABA) in the ACC. Highly impulsive rats express lower GABA binding in the ACC which correlates negatively with impulsive responding (Jupp et al., 2013). In humans, GABA is quantified using magnetic resonance spectroscopy (MRS) and as the corresponding signal contains additional contributions from macromolecules and homocarnosine, it is referred to as GABA+ (Rothman, Behar, Prichard, & Petroff, 1997). Our previous human research highlights the role of GABA+ in trait impulsivity. We observed a negative correlation between GABA+ concentrations in the dlPFC and impulsivity levels in two independent healthy samples (Boy et al., 2011), a finding consistent with altered neural activity in the dlPFC during impulsive decision-making. In GD, however, PET studies of GABA-A receptor availability have noted

that higher GABA-A binding in the amygdala is associated with higher impulsivity levels, an association which was absent in non-GD controls (Mick et al., 2017).

In sum, the evidence indicates abnormalities in delay discounting in GD related to symptom severity. Two cortical brain regions, the cingulate cortex and dlPFC, are most involved in discounting and differ in the extent of their recruitment in gamblers with a diagnosis of GD and non-gamblers without GD. While there is indirect evidence for the involvement of GABA and Glx levels in GD and direct evidence for an important role of glutaminergic dACC levels and delay discounting, to our knowledge no study has addressed the link between discounting impairments in GD and neurochemistry in the dACC and dlPFC. Moreover, it remains to be seen whether or not the previously observed negative correlation between dACC glutamate and reward discounting (Schmaal et al., 2012) extends to a different delay discounting task and measures.

The present exploratory MRS study investigated, for the first time, dorsal ACC, right dlPFC, and occipital GABA+ and Glx levels in small samples of GD and non-GD male volunteers. We first predicted that the dACC, dlPFC and occipital brain regions would be associated with discounting rates on the MCQ. Second, we expected a negative correlation between impulsivity (greater discounting) and dACC GABA+ concentration as well as GABA+ levels in the dlPFC. Finally, given that administration of medication that increases glutaminergic transmission results in a reduction of gambling behaviour (Olive et al., 2012), we hypothesized that Glx reductions would be related to increased gambling symptom severity.

2. Experimental procedures

2.1. Participants

Twenty-six, right-handed males were recruited and allocated to the GD or non-GD group based on gambling severity scores, resulting in *n* = 12 in the GD group (*Problem Gambling Severity Index* (PGSI) score > 8; *M* = 15.2, *SD* = 5.1; M_{age} = 36.3, *SD* = 9.5) and 14 age-matched, non-GD controls (PGSI score < 1; *M* = .071, *SD* = .027; M_{age} = 35.7, *SD* = 8.7). Participants' ethnicity was primarily White-European, both in the GD (91.7%) and the control groups (100%). All participants provided signed, informed consent to participate in the study, which was approved by the Department of Psychology Ethics Committee, Swansea University.

2.2. Assessments

2.2.1. Gambling severity. The *Problem Gambling Severity Index* (PGSI; Ferris & Wynne, 2001) consists of nine items assessing gambling severity, scored on a scale ranging from *never* (= 0; 92.9% of the controls), *sometimes* (= 1; 7.1% of the controls [1 participant scored 1]), *most of the time* (= 2) to *almost always* (= 3). Participants were categorized as *non-problem gambler* (= 0), *low problem gambler* (1-2), *moderate* (3-7), or *problem gambler* (> 8; 100% of the GD group). The PGSI has high internal consistency in terms of Cronbach's alpha (α = .90) and adequate validity for the GD and non-GD groups (Currie, Hodgins, & Casey, 2012; Orford, Wardle, Griffiths, Sproston, & Erens, 2010).

The *Diagnostic and Statistical Manual version 5 (DSM-5)* criteria for GD (American Psychiatric Association, 2013) state nine criteria for problematic gambling behaviour leading to significant distress assessed over a 12-month period and categorized as *mild* (4-5 criteria apply; 33.3% of the gamblers), *moderate* (6-7; 25%) or *severe* gambling problems (8-9,

41.7%). Comparison of DSM-5 to the DSM-IV criteria indicated equivalent internal consistency estimates (α = .73) (Petry, Blanco, Jin, & Grant, 2014).

The *South Oaks Gambling Screen* (SOGS; Lesieur & Blume, 1987) is a 20-item screening instrument for gambling risk. Participants were assigned to *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) categories. Validation of the SOGS revealed satisfactory reliability in the general population as well as in treatment seeking gamblers, α = .69 and .86, respectively, as well as high construct validity (Lesieur & Blume, 1987; Stinchfield, 2002).

2.2.2. Clinical and executive functioning assessments. The *MINI International Neuropsychiatric Interview (MINI)* version 5.0.0 (Sheehan et al., 1998) was administered, in a semi-structured interview format, assessing 17 Axis I psychiatric disorders according to the DSM-IV criteria (American Psychiatric Association, 1994).

The Alcohol, Smoking, and Substance Involvement Screening Tests (ASSIST) version 3.0 (World Health Organization, 2018) was used to assess frequency of usage of tobacco, alcohol, cannabis, cocaine, amphetamine type stimulants, inhalants, sedatives, hallucinogens, and opiates. The substance involvement scores are summed and then subdivided into *low-*, *moderate-* and *high*-risk levels per substance. Inhalants, sedatives, hallucinogenics and opiates were not consumed by any of the participants and are as such not listed in Table 1.

Participants' *full-scale intelligence (FSIQ)* was estimated based on the *Wechsler Abbreviated Scale of Intelligence* (WASI; Wechsler, 1999) subtests for Matrix Reasoning and Vocabulary.

Finally, the *World Health Organization Adult ADHD Self Report Scale (ASRS)* version 1.1 (Kessler et al., 2005) is an 18-item inventory scoring ADHD symptoms on a 5-point scale ranging from *never* (= 0), *rarely* (= 1), *sometimes* (= 2), *often* (= 3), to *very often* (= 4). Summed total scores were categorized into *unlikely to have ADHD* (0-16), *likely to have ADHD* (17-23) and *highly likely to have ADHD* (=> 24).

2.3. Procedure

Participants were first pre-screened for study eligibility using the PGSI, SOGS, and DSM-5 and magnetic resonance exclusion criteria. On meeting the inclusion criteria (i.e., PGSI score ≤ 1or > 8, right handedness, and safety criteria for scanning), participants were invited to the Imaging Centre at Swansea University where behavioural and spectroscopy assessments took place on separate days (mean number of days between testing sessions = 15.7). Before MRS testing, participants' blood alcohol levels were assessed with single use breathalysers (none of the participants had consumed alcohol before testing).

2.4. Delay discounting paradigm

A computerized version of the MCQ delay discounting task (Kirby & Marakovic, 1996) was presented using Psychtoolbox (Brainard, 1997) in combination with MATLAB R2010b (Mathworks Inc., Massachusetts, USA). The MCQ was 5 minutes duration and consisted of 27 binary choice trials between immediate and delayed rewards, relating to small, medium and large delayed rewards. The immediate rewards varied between £15 and £80, the delayed rewards between £25 and £85 and the delays varied between 7 and 186 days. Participants were instructed to pretend that the choice they make between immediate and delayed rewards relates to real monetary incentives. The locations (left vs. right) of the immediate and delayed rewards were counterbalanced across participants. Participants' choices were converted to *k* values using the hyperbolic function [V = A/(1+ *k*D)], where *k* is

the discount rate parameter, *D*, the delay in time, *A,* to the delayed rewards' magnitude, and *V*, to the magnitude of the immediate reward (Kirby & Marakovic, 1996).

2.5. MR acquisition

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

Single voxel MRS was conducted using the MEGA-PRESS MRS package developed by Marjańska et al. (2013) and provided by the University of Minnesota under a C2P agreement. GABA-edited MEGA-PRESS sequence parameters: TR = 1800 ms, TE = 68 ms, 200 averages, 1024 complex data points, offset frequency set to 3.00 ppm. Water suppression was achieved using VAPOR. Manual higher-order shimming was performed to reduce local field inhomogeneities in each voxel of interest (VOI). VOIs were placed in the dorsal ACC (30x30x20 mm), the right dlPFC (30x20x20 mm) and the occipital lobe, between the calcarine fissure and the parieto-occipital sulcus (20x30x25 mm; see Figure 1) without outer voxel suppression.

Insert Figure 1 About Here

2.6. Spectral Quantification

The MRS data was quantified using GANNET 3.0 (Baltimore, MD, USA), a MATLAB-based toolbox for the analysis of GABA data derived from the MEGA-PRESS sequence, using the standard processing steps, inbuilt models and assumptions for this software (details can be found at http://www.gabamrs.com). Given the absence of macromolecule suppression, GABA+ was utilized as an estimate of gabaergic concentration, from here on referred to as

GABA. Following phase and frequency correction, the 'ON' and 'OFF' spectra were subtracted to retrieve the edited spectrum for the quantification of GABA. Glx was estimated using the 'OFF' spectra. GANNET models the GABA peak as a single-Gaussian, Glx as doublet, and the creatine (Cr) reference as singlet. Measures of GABA and Glx are shown and analysed in institutional units (i.u.) referenced to Cr. Data is reported as a raw ratio of area under the fitted curve, for each metabolite, and does not take into account differential proton densities, relaxation properties for each metabolite, or tissue make up. (Note, the use of Cr as a reference avoids the need for CSF correction, as Cr content in the CSF is negligible). Grey matter (GM) and white matter volume may however influence the data, we therefore controlled for in each analysis. For the participants reported here, at least one of the neurotransmitters, GABA or Glx, was successfully fit, according to visual inspection and FWHM of the respective molecule falling within 3 *SDs* from the group mean (see Figure 1 for example spectra and model fit). These spectra inclusion criteria resulted in usable data from 9 participants in the GD group (gamblers) and 13 in the non-GD group (controls) for the dACC voxel, 11 gamblers and 13 controls for the right dlPFC voxel, and 8 gamblers and 10 (Glx) or 9 (GABA) controls for the occipital voxel.

2.7. Statistical Analysis

Where appropriate independent-sample *t*-tests, or Fisher's exact tests were used to compare groups on demographic variables. MCQ-based *k* values per reward type were compared between groups using the natural logarithmic transforms of the small, medium, and large *k*-values of the MCQ (less negative ln(*k*) values relate to higher untransformed *k* values and therefore to more delay discounting/impulsivity) in combination with a repeated-measures ANOVA with small, medium and large ln(*k*) values as within-subject factor and group as between-subjects factor. Significant effects were followed up with the

appropriate *t*-tests. Next, the groups were compared on the GABA/Cr, Glx/Cr and the GABA/Glx ratio, using a repeated-measures ANCOVA with GM fraction as covariate. In case of inequalities of variances across groups, corrected statistics are reported. To assess the relationship between gambling severity and metabolites, the MRS variables were correlated to PGSI, SOGS and DSM-5 total scores within the gambling group using partial Pearson correlation coefficients to covary out GM fractions. Thereafter, the MRS variables were correlated to the MCQ variables, ln(small *k*), ln(medium *k*), ln(large *k*), using partial Pearson correlation coefficients, correcting for GM fractions, first for all participants and thereafter separately per group. Obtained partial correlation coefficients were statistically compared following Fisher's *r* to *z* transformation. Given the preliminary and exploratory nature of the study, and the relatively small sample size, exact *p*-values are reported where possible and no correction for multiple comparisons was applied.

3. Results

3.1. Demographics

Demographic information is presented in Table 1. As expected, statistically significant differences were related to gambling severity. Gamblers scored lower on FSIQ than controls, while further group differences were present in terms of ADHD likeliness (in the GD group, 16.7% fell into the *unlikely* and 83.3% into the *highly likely* category, whereas all 14 in the non-GD group were *unlikely* to have ADHD). Groups differed in alcohol usage, with the GD group scoring higher than the non-GD control group. Importantly, the presence of other substance usage, age of the participants and presence of Axis 1 disorders were not statistically different between groups. Given the significant group differences on FSIQ and ASRS scores, Pearson correlations were carried out to assess the necessity of including them

as covariates; none of the correlations with MCQ variables reached significance (rs < .69, ps > .08), providing no indication for inclusion.

Insert Table 1 About Here

3.2. Delay discounting performance

Repeated-measures ANOVA on MCQ choices with small, medium and large ln(k) values as the within-subject factor revealed no significant interaction between group and reward magnitude (F(2, 48) = .12, p = .89), but a significant main effect of reward magnitude (F(2, 48) = 22.41, p < .001) with small rewards related to higher ln(k) values than medium (t (25) = 4.82, p < .001) and large rewards (t (25) = 6.27, p < .001). Similarly, medium rewards were associated higher ln(k) values than large rewards (t (25) = 2.49, p = .02). The main effect of group was not significant (F(1, 24) = 1.75, p = .20).

3.3. Between-group comparisons on MRS variables

Comparing the GABA/Cr, Glx/Cr and GABA/Glx ratios did not reveal significant differences between GD and non-GD groups in the dACC as indicated by a non-significant main effect of group (F(1,19) = .02, p = .89) and the non-significant interaction between group and metabolites (F(1,19.14) = .44, p = .52). Similarly non-significant were the main effect of group (F(1,21) = .15, p = .70) and the interaction between group and metabolites (F(1,21.11) = .60, p = .45) in the dlPFC and in the occipital voxel (main effect: F(1,14) = .02, p = .89; interaction: F(1,14.01) = .002, p = .97). However, the absence of significant between-group differences in MRS variables does not preclude the possibility that within-group differences in gambling severity are related to differing associations with MRS variables, which we assessed next.

3.4. Correlations between gambling scores and MRS measures

Partial Pearson correlation coefficients were computed to assess the relationship between gambling severity and MRS variables within the GD group while controlling for GM differences. In the dACC, Glx/Cr correlated negatively with symptom severity on the PGSI (r = -.73, p = .038) and DSM-5 (r = -.76, p = .029), with the remaining correlations not being significant (|rs|< .66, ps > .08). Comparing the correlation coefficients obtained from correlating gambling severity with GABA/Cr and Glx/Cr, respectively, revealed no significant differences for either PGSI (z = -1.28, p = .202) or DSM scores (z = -1.92, p = .055). Within the dlPFC, none of the MRS measures correlated significantly with any of the gambling severity measures (|rs| < .53, ps > .12). In the occipital voxel, Glx/Cr correlated negatively with the PGSI (r = -.86, p = .012) and the DSM 5 (r = -.79, p = .035) total scores. The remaining correlations were not significant (|rs|< .71, ps > .07). Comparing the correlation coefficients obtained for the occipital voxel across MRS variables did reveal significantly larger correlations between Glx/Cr and both PGSI (z = -.246, p = .014) and DSM scores (z = -2.58, p = .010) than with GABA/Cr. Figure 2 shows the adjusted scatterplots of the significant correlations between gambling severity and MRS measures (plotted are the standardized residuals of the linear regression predicting gambling severity scores from GM content on the x axis and the standardized residuals of the linear regression predicting MRS variables from GM content on the y axis), unadjusted scatterplots can be found in the supplement.

Insert Figure 2 About Here

For completeness, we also correlated ASRS and FSIQ with MRS measures. In the whole sample, dACC Glx/Cr correlated positively with ASRS total scores (r = .52, p = .016) while correcting for GM content. The remaining correlations were not significant (|rs| < .37, ps > .08).

3.5. Correlations between delay discounting and MRS measures

3.5.1. Whole sample. To assess the relationship between delay discounting (MCQ task) performance and MRS measures, partial (correcting for GM content) Pearson correlations coefficients were computed for the whole sample. Within the dACC, GABA/Cr correlated negatively with ln(*k*) values for small (r = -.51, p = .019) and medium (r = -.44, p = .048) delayed rewards. The remaining correlations were not significant (|*r*s|< .41, *p*s > .07). When comparing the significant correlation coefficients obtained for correlating the MCQ variables to dACC GABA/Cr to those assessing the correlation between MCQ variables and dACC Glx/Cr, no significant differences were found for small (z = -1.47, p = .142) and medium ln(k) values (z = -1.51, p = .130). Within the dlPFC voxel, significant negative correlations were obtained for the association between GABA/Glx ratio and ln(*k*) values for large (r = -.42, p = .046) delayed rewards. The remaining correlations were not significant (|*r*s|< .37, *p*s > .08). Within the occipital voxel, none of the MRS measures correlated significantly with MCQ variables (|*r*s| < .42, *p*s > .11).

Insert Figure 3 About Here

3.5.2. Within each group. Assessing the relationships between MRS measures and MCQ performance variables per group revealed no significant correlations for the dACC (|*r*s| < .59, *p*s > .07) and dlPFC (|*r*s| < .53, *p*s > .11). However, the occipital voxel's GABA/Cr concentration correlated negatively with ln(*k*) values for large delayed rewards within the GD group (r = -.77, p = .045). The remaining correlations were not significant (|*r*s|< .62, *p*s > .13). Comparing the significant correlation between large ln(*k*) values and GABA/Cr to those obtained for correlating large ln(*k*) and Glx/Cr revealed no significant differences (z = -1.95, p = .051). Figure 3 shows the adjusted scatterplots of the significant correlations between MCQ variables and MRS measures.

The results reported here are controlled for grey matter content; the uncorrected results and plots can be found in the Supplementary Materials. However, it is important to note that the addition/removal of the grey matter covariate did not alter the significance levels of findings described here.

4. Discussion

The present study is the first to relate both GABA and Glx levels in the dACC, right dlPFC and occipital cortex in male participants with and without GD to performance on a delay discounting task. We found that gambling symptom severity was related negatively to dACC and occipital Glx levels and that MCQ discounting rates were related to GABA levels depending on the delayed reward. Specifically, we found that the discounting rate of small and medium delayed rewards was negatively associated with GABA in the dACC, while discounting of delayed large rewards was negatively associated with GABA/Glx ratios in the right dlPFC. The GD participants showed an additional correlation between discounting of large delayed rewards and GABA in the occipital voxel, encompassing parts of the peri-calcarine cortex, lingual gyrus and cuneus. Taken together, these findings cast light on the role of impulse control-related neurotransmitters in impaired decision-making in GD.

Previous research on gambling severity and Glx levels focussed on the effect of glutamate-increasing medication on the reduction of gambling behaviour (Olive et al., 2012; Zack & Poulos, 2009). Grant, Kim, and Odlaug (2007), for example, administered N-acetylcysteine (NAC) to pathological gamblers and revealed a reduction in self-reported symptom severity. It is likely that gambling severity is associated with reduced glutamate levels in the extracellular environment, which overlaps with our findings from in vivo MRS of dACC and occipital Glx reductions at higher gambling severity. However, as MRS measurements rely on metabolite concentrations in intra and extracellular compartments

(Erecińska & Silver, 1990; Lehmann, Isacsson, & Hamberger, 1983) we cannot unequivocally determine the location of the reduced Glx levels observed in GD participants with high gambling severity scores.

The findings of an association between increased discounting and decreased GABA levels in dACC and occipital voxels, as well as decreased GABA/Glx ratio in the right dlPFC, are consistent with the cognitive neuroscience model of delay discounting (Frost & McNaughton, 2017). Simplified, the first system comprises occipital brain regions which perceive the visually presented gain. Wittmann et al. (2007), for instance, found the lingual gyrus to be differently activated depending on the delay at which the reward was received and that this difference in activation was enhanced if individual discounting rates were higher. Wittmann et al. also observed increased activation in the cuneus when participants choose the delayed reward over the immediate smaller reward in addition to a positive correlation between task related activation of the cuneus and *k* values. Importantly, the activation difference in the lingual gyrus and cuneus that was positively correlated with *k* was prominent when comparing shorter delays of less than 1 year to long delays > 1 year. In the present study, our occipital voxel encompassed the lingual gyrus as well as the cuneus, and when focussing on the magnitude of the delay and correcting for GM content, no significant correlations with MRS variables were obtained (see Supplement). When analysing the magnitudes of the delayed rewards, the GD group, whose behaviour was more skewed towards steeper discounting rates, showed a negative correlation between GABA+ and *k* values for large delayed rewards. This indicates that the occipital brain regions involved in delay discounting might not only be fine-tuned to the delay at which the reward will be received, as previously found (Prevost, Pessiglione, Metereau, Clery-Melin, & Dreher, 2010), but additionally to the magnitude of the reward, as reported here. Previous research

has shown that reduced GABA levels are related to increased impulsivity in rodents and humans (Boy et al., 2011; Jupp et al., 2013; Mick et al., 2017), but in the right dlPFC in humans and in the ACC and amygdala in rodents, respectively. As such, the present observation of an inverse relationship between GABA+ concentrations and impulsivity in the human occipital cortex is novel and may indicate metabolite abnormalities in early processing stages.

The dACC has previously been found to be more activated at higher discounting rates as measured by AUC (Shamosh et al., 2008), which mirrors our reported negative correlation between GABA+ in the dACC and discounting rates for small and medium sized delayed rewards. Similarly, rodent research found ACC lesions to alter choice behaviour in favour of smaller rewards away from investing significant effort to receive the reward (Walton et al., 2009). Further, metabolic activity in the ACC was higher when choices involved differences in response effort while reward magnitude was kept constant, indicating a role for the ACC in effort-based reward evaluation (Endepols et al., 2010; Walton et al., 2009). Monterosso et al. (2007) revealed enhanced ACC activation in humans during hard over easy choices. Based on our data, it can be assumed that large delayed rewards present an easier choice to make, since the subjective gain for delaying gratification is increased and as such less conflict is induced by the available choices. Small and medium-sized delayed rewards on the other hand are more similar in their subjective value to the immediate reward (making the choice more difficult) and further contain less effort in terms of delaying gratification and therefore might increase ACC involvement, which would at least partly explain the negative correlation found between dACC GABA levels and discounting rate of small and medium delayed rewards. Previous research similarly showed

an association between lower ACC GABA binding and more impulsive responding in a highly impulsive rat strain (Jupp et al., 2013).

Our findings with respect to right dlPFC showed a negative correlation between GABA/Glx and delay discounting of specifically large rewards. While we cannot unequivocally address the impact of delay on metabolites using the present delay discounting parameters, our results support primate research indicating stronger neuronal responses in the right dlPFC at higher reward magnitudes (Kim et al., 2008). The influence of dlPFC GABA on impulsivity in humans is well known (Boy et al., 2011), but the effect observed here relates to the ratio, as such increased discounting of large delayed rewards seems to depend on a balance of both, GABA and Glx. Previous research on the interaction between GABA and Glx and reward-related decision-making shows that the accuracy of subjective decisions between two options differing in reward magnitude and probability is governed by the interplay between GABA and glutamate; that is, high GABA and low glutamate are both related to choice accuracy (Jocham, Hunt, Near, & Behrens, 2012). Importantly, this association between GABA and glutamate is specific to a prefrontal area, ventromedial PFC, and absent in a parietal brain region, the intraparietal sulcus (Jocham et al., 2012). Thus, while previous research on the right dlPFC found GABA to be associated with self-reported impulsivity levels (Boy et al., 2011), impulsive decision-making might be more dependent on the interaction between GABA and glutamate in prefrontal brain areas.

The current investigation has several limitations. While the total sample size used is moderately large for MRS studies, the correlations with gambling severity are based on the GD group only and as such on a smaller sample size. Future research would benefit from exploring the association between gambling severity and metabolites with larger GD samples. No corrections for multiple comparisons were applied, and the current results are

therefore preliminary in nature and should be confirmed by subsequent research. An attempt to address this issue has been made by selecting minimal MCQ variables for this investigation. Additionally, while the dlPFC and dACC were chosen apriori based on previous research, the location of the occipital voxel contains parts of the lingual gyrus, the cuneus and the calcarine cortex, which might play different roles in delay discounting if investigated separately. Further, participants did not receive instructions on whether to open or close their eyes during the MRS session, which might induce random noise to our metabolite concentrations. It is known that occipital GABA levels increase when comparing eyes-closed to eyes-open, while Glx does not differ between these basic conditions (Kurcyus et al., 2018; Michels et al., 2012). Occipital Glx levels do, however, increase during visual stimulation (e.g., flickering checkerboard; Kurcyus et al., 2018), while other studies have failed to find differences in GABA and Glx in the dlPFC (Michels et al., 2012). Given this, it is likely that the present correlations between occipital Glx and gambling severity were less impacted than the reported correlation between occipital GABA and discounting of large delayed rewards in the GD group. The corresponding GABA-based occipital result should therefore be interpreted with caution until further replication.

In conclusion, the present study is the first to examine delay discounting and GABA and Glx levels in occipital, dACC and right dlPFC in GD. Higher gambling severity was linked with lower Glx levels in dACC and occipital brain regions. Our delay discounting findings further indicated that occipital brain regions respond to the magnitude of the delayed reward in GD and that dACC GABA concentrations were inversely related to discounting of small and medium-sized delayed rewards in the whole sample. Additionally, the GABA/Glx ratio in the right dlPFC was reduced for participants expressing higher discounting of large

delayed rewards, highlighting the importance of the neurochemical balance between GABA and Glx in prefrontal regions during reward-related decision-making.

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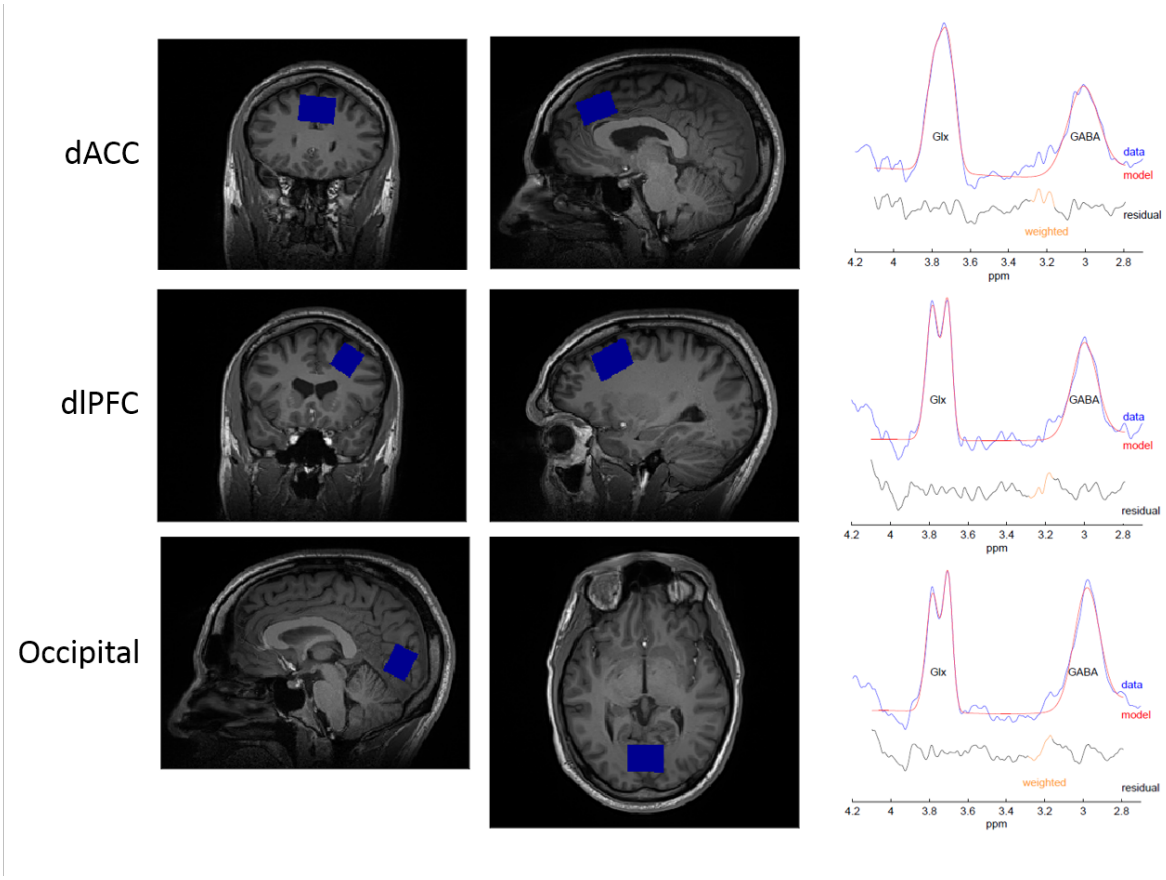

Figure 1. Voxel locations, example spectra and model fit for the dACC, dlPFC, and occipital voxels. dACC = dorsal anterior cingulate, dlPFC = right dorsolateral prefrontal cortex.

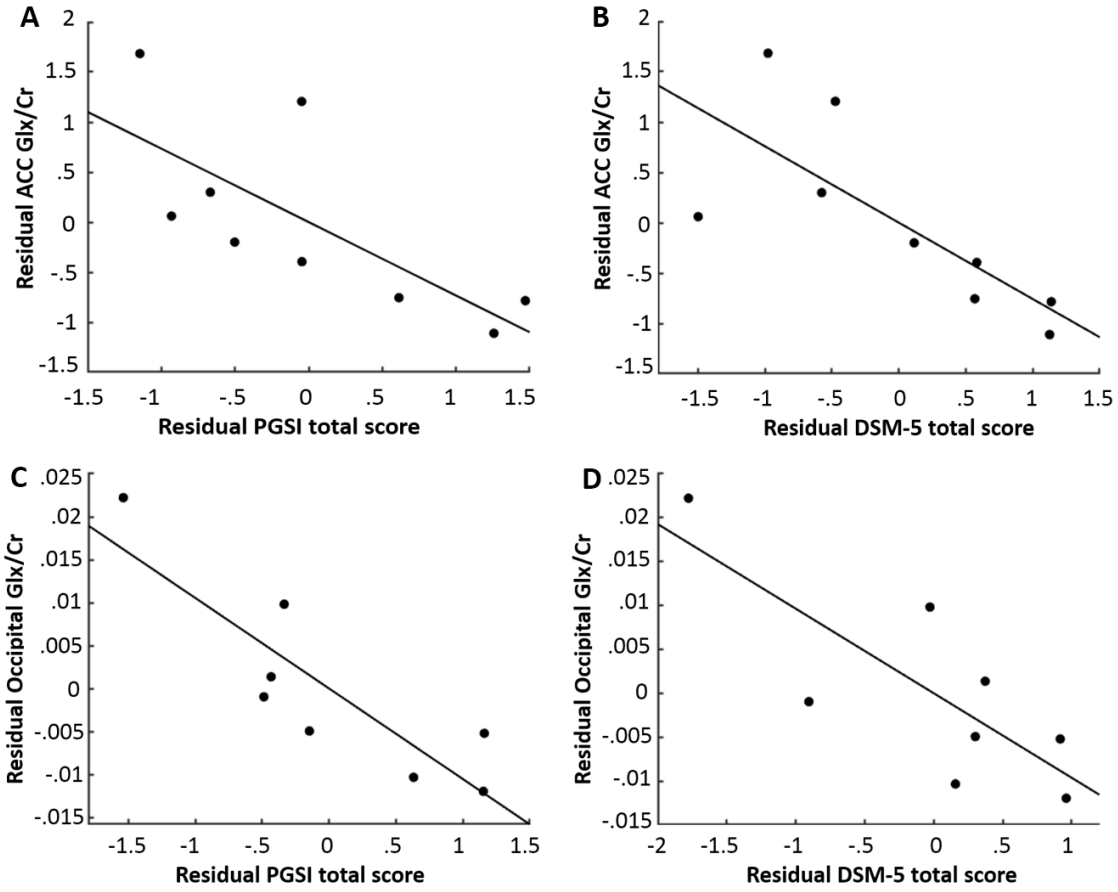

Figure 2. Scatterplots of the significant correlations (adjusted for grey matter content) between MRS variables and gambling severity measures in the GD group only. Scatterplots of the residuals for the correlation between (A) Glx in the ACC and PGSI total scores, (B) Glx in the ACC and DSM-5 total scores, (C) Glx in the occipital voxel and PGSI total scores, and (D) Glx in the occipital voxel and DSM-5 total scores. ACC = anterior cingulate cortex, PGSI = Problem Gambling Severity Index, DSM-5 = Diagnostic and Statistical Manual version 5 – gambling disorder.

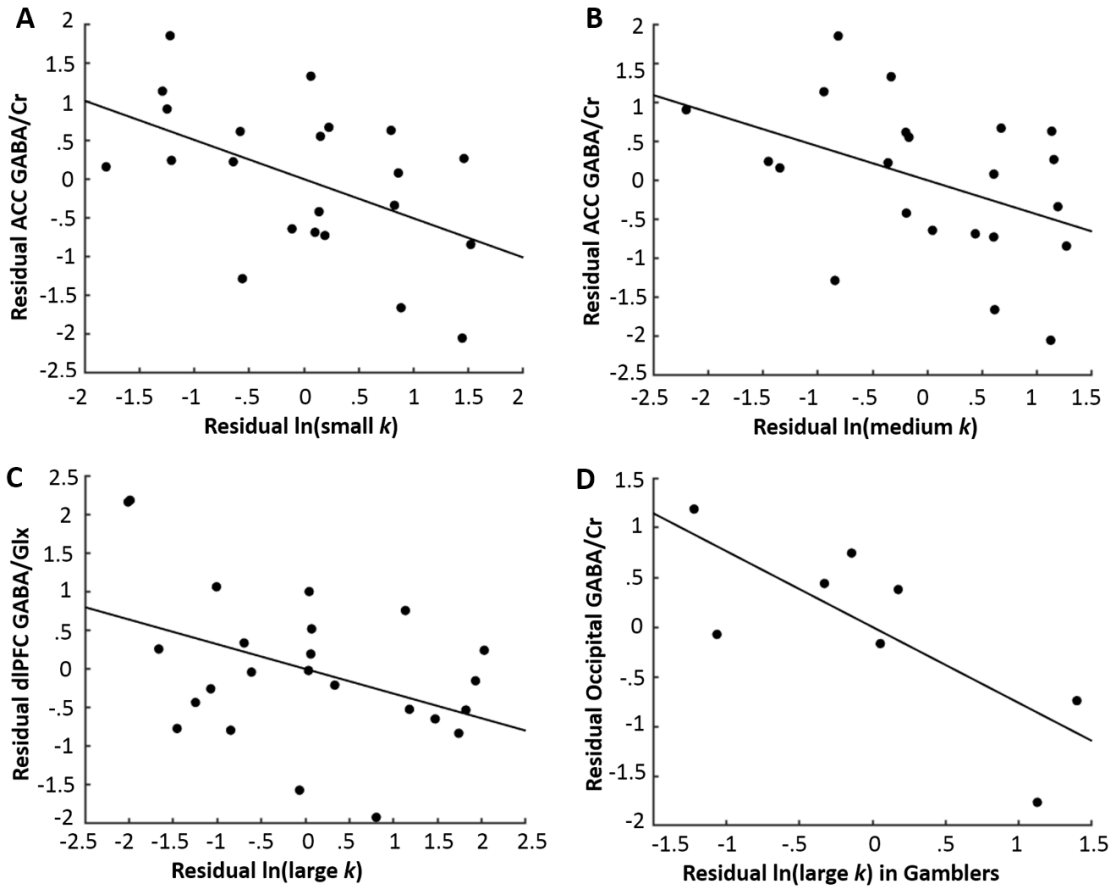

Figure 3. Scatterplots of the significant correlations (adjusted for grey matter content) between MRS variables and Monetary Choice Questionnaire variables in the whole sample (both GD and non-GD groups combined: A, B, C) and the GD group (D) as specified. Scatterplots of the residuals for the correlation between (A) GABA in the ACC and ln transformed *k* values, ln(small *k*), for small delayed rewards, (B) GABA in the ACC and ln(medium *k*), (C) GABA/Glx in the dlPFC and ln(large *k*), (D) GABA in the occipital voxel and ln(large *k*). ACC = anterior cingulate cortex, dlPFC = dorsolateral prefrontal cortex.

Table 1. Means, standard deviations (*SD*) or percentages and statistical comparisons across gamblers and controls based on descriptive information.

			Gamblers		Controls		Statistical Comparisons
			Mean	**SD**	**Mean**	**SD**	
Age			36.33	9.56	35.71	8.77	$t(24) = .172$, $p = .87$
FSIQ			102.50	5.15	116.43	8.40	$t(24) = 3.39$, $p < .05$
PGSI total			15.25	5.15	.071	.27	$t(11.05) = 10.19$, $p < .001$
SOGS total			11.25	3.31	.071	.27	$t(11.12) = 11.68$, $p < .001$
DSM-5 total			6.58	1.83	0	0	$t(11) = 12.45$, $p < .001$
Gambling onset (years)			19.33	7.28	na	na	
ASRS			43.75	23.15	3.43	5.04	$t(11.89) = 5.91$, $p < .01$
			58.3 %		42.9 %		FET $p = .63$
Axis 1 Disorders							
	Past/current MDE		41.7 %		57.1 %		FET $p = .35$
	Anxiety Disorders		0 %		7.1 %		FET $p = .54$
	Panic Disorder		8.3 %		7.1 %		FET $p = .72$
	PTSD		8.3 %		7.1 %		FET $p = .72$
	OCD		8.3 %		7.1 %		FET $p = .72$
ASSIST							
	Tobacco	low	66.7 %		71.4 %		FET $p = .82$
		moderate	33.3 %		21.4 %		
		high	0 %		7.1 %		
	Alcohol	low	33.3 %		78.6 %		FET $p < .05$
		moderate	58.3 %		21.4 %		
		high	8.3 %		0 %		
	Cannabis	low	91.7 %		85.7 %		FET $p = .56$
		moderate	8.3 %		14.3 %		
		high	0 %		0 %		
	Cocaine	low	91.7 %		100 %		FET $p = .46$
		moderate	8.3 %		0 %		
		high	0 %		0 %		
	Amphetamine	low	0 %		92.9 %		FET $p = .54$
		moderate	0 %		7. 1%		
		high	0 %		0 %		

Note. FSIQ=estimated full scale intelligence quotient based on *Wechsler's Abbreviated Scale of Intelligence*. PGSI = *Problem Gambling Severity Index*. SOGS = *South Oaks Gambling Screen*. DSM-5 = *Diagnostic and Statistical Manual of Mental Disorders – 5* (Gambling Disorder). In terms of comorbidities, several participants presented with more than one comorbid Axis 1 disorder. MDE = Major Depressive Episode, PTSD = Post traumatic stress disorder, OCD = Obsessive compulsive disorder, ASRS = Adult ADHD Self Report Scale, ASSIST = Alcohol, Smoking, and Substance Involvement Screening Tests, FET = Fisher's exact test. Reported statistics are based on individual

independent sample *t*-tests. For comparisons regarding ASSIST scores and Axis 1 Disorders, FETs were conducted.