Psychiatry Research: Neuroimaging 301 (2020) 111082

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

Reduced striatal GABA in unmedicated children with ADHD at 7T

Nicolaas A. Puts[a,b,c,*], Matthew Ryan[d], Georg Oeltzschner[a,b], Alena Horska[a], Richard A.E. Edden[a,b], E. Mark Mahone[d,e]

[a] Russell H. Morgan Department of Radiology and Radiological Science, The Johns Hopkins University School of Medicine, 600 N Wolfe St., Baltimore, MD 21287, United States
[b] F.M. Kirby Research Center for Functional Brain Imaging, Kennedy Krieger Institute, 707 N Broadway, Baltimore, MD 21205, United States
[c] Department of Forensic and Neurodevelopmental Sciences, Sackler Institute for Translational Neurodevelopment, Institute of Psychiatry, Psychology and Neuroscience, King's College London, 16 De Crespigny Park, London, SE5 8AB, United Kingdom
[d] Department of Neuropsychology, Kennedy Krieger Institute, 1750 E. Fairmount Ave., Baltimore, MD 21231 United States
[e] Department of Psychiatry and Behavioral Sciences, The Johns Hopkins University School of Medicine, 600 N Wolfe St., Baltimore, MD 21287, United States

ARTICLE INFO

Keywords:
ADHD
Neuroimaging
Ultra-high field
Glutamate
GABA
Magnetic resonance spectroscopy

ABSTRACT

Attention-deficit hyperactive disorder (ADHD) is characterized by inattention and increased impulsive and hypermotoric behaviors.Despite the high prevalence and impact of ADHD, little is known about the underlying neurophysiology of ADHD. The main inhibitory and excitatory neurotransmitters γ-aminobutyric acid (GABA) and glutamate are receiving increased attention in ADHD and can be measured using Magnetic Resonance Spectroscopy (MRS). However, MRS studies in ADHD are limited. We measured GABA and glutamate in young unmedicated participants, utilizing high magnetic field strength. Fifty unmedicated children (26 with ADHD, 24 controls) aged 5–9 years completed MRS at 7T and behavioral testing. GABA and glutamate were measured in dorsolateral prefrontal cortex (DLPFC), anterior cingulate cortex (ACC), premotor cortex (PMC), and striatum, and estimated using LCModel. Children with ADHD showed poorer inhibitory control and significantly reduced GABA/Cr in the striatum, but not in ACC, DLPFC, or PMC regions. There were no significant group differences for Glu/Cr levels, or correlations with behavioral manifestations of ADHD. The primary finding of this study is a reduction of striatal GABA levels in unmedicated children with ADHD at 7T. These findings provide guidance for future studies or interventions. Reduced striatal GABA may be a marker for specific GABA-related treatment for ADHD.

1. Introduction

Attention-deficit hyperactive disorder (ADHD)[1] typically presents as inattentive behavior as well as increased impulsive and hypermotoric behaviors.It is the most commonly diagnosed form of psychopathology in children under the age of six years (Armstrong and Nettleton, 2004). Symptoms associated with hyperactivity (including symptoms not included in the formal DSM-5 diagnosis of ADHD) are observed to be as high as 3–15% in community samples and 50% or higher among pediatric clinical referrals (Christophersen and Mortweet, 2001). Young children presenting with symptoms of ADHD are at significant risk for social, medical, and academic difficulties compared to children without ADHD (Greenhill et al., 2008; Lee et al., 2007; Palfrey et al., 1985). Earlier identification and better understanding of the neurobiological mechanisms of ADHD can potentially minimize the harmful impact of ADHD, and lead to more targeted behavioral and pharmacological treatments. Despite the high prevalence of ADHD and its major impact on patients, families, and communities, little is known about the underlying neurophysiology of ADHD.

The main inhibitory neurotransmitter γ-aminobutyric acid (GABA) and excitatory neurotransmitter glutamate are receiving increased attention in studies of ADHD. GABA acts predominantly via interneurons as well as striatal medium-sized spiny neurons located within both the striatum and cortex (Chesselet et al., 2007; Jahanshahi et al., 2015). There is evidence that GABA is involved in the neurophysiology of ADHD. For example, transcranial magnetic stimulation (TMS)

* Corresponding author at: Department of Forensic and Neurodevelopmental Sciences, Sackler Institute for Translational Neurodevelopment, Institute of Psychiatry, Psychology, and Neuroscience, King's College London, 16 De Crespigny Park, London, SE5 8AB, United Kingdom.
E-mail address: nicolaas.puts@kcl.ac.uk (N.A. Puts).

[1] *Abbreviations*: ADHD: Attention Deficit Hyperactive Disorder; GABA: γ-aminobutyric acid; MRS: Magnetic Resonance Spectroscopy; TMS: Transcranial Magnetic Stimulation; SICI: Short Interval Intracortical Inhibition; SNR: Signal to Noise; FWHM; Full Width Half Maximum; Glu/Gln: Glutamate/Glutamine; PANESS: Physical and Neurological Assessment of Subtle Signs; SES: Social Economic Status; ROI: Region of Interest; CRLB: Cramer Rao Lower Bounds.

https://doi.org/10.1016/j.pscychresns.2020.111082
Received 25 September 2019; Received in revised form 30 March 2020; Accepted 31 March 2020

measurements have shown reduction of short-interval intra-cortical inhibition (SICI) in children with ADHD (Gilbert et al., 2011). Several proton magnetic resonance spectroscopy (^{1}H MRS) studies have shown abnormal GABA levels in ADHD with both increases and decreases reported (Bollmann et al., 2015; Carrey et al., 2003; Edden et al., 2012; Ende et al., 2016). For a review, see (Schür et al., 2016). In addition, chronic ADHD medication (methylphenidate) has shown to alter GABA levels (Solleveld et al., 2017).

Altered glutamate levels are a potential indicator of impaired glutamate-glutamine cycling, and may lead to abnormal metabolic and excitatory neurotransmitter function. Although other mechanisms, including the dopamine/noradrenergic system (Russell et al., 2006), have been associated with ADHD, dysregulation of the reciprocal dopaminergic-glutamatergic modulation may be at the root of behavioral deficits in ADHD (Gross and Marshall, 2009; Russell, 2003; Volkow et al., 2004). Indeed, abnormal glutamate functioning in terminal areas of dopaminergic neurons has been linked to development of ADHD symptoms (Russell et al., 2006). An alternative hypothesis is that dysfunction in the glutamate-GABA circuitry disrupts the ability to inhibit context-inappropriate responses (MacMaster et al., 2003). Increased glutamate can have wide-ranging effects; it can cause a marked fall in neuronal membrane resistance and an increase in calcium permeability, leading to easier depolarization of themembrane and thus, an increase in cortical excitability (Courvoisie et al., 2004; Pavić et al., 2019; Zhang and Sulzer, 2003). In addition, reduced GABAergic inhibition my also lead to increased excitatory function and (circularly) reduced inhibition.

Despite these observations, there has been limited *in vivo* investigation of the link between specific neurotransmitter systems hypothesized to underlie symptoms of ADHD and actual behavioral symptoms, partly due to limitations in neuroimaging capabilities.^{1}H magnetic resonance spectroscopy provides a unique opportunity to measure brain chemistry in vivo. Glutamate and GABA can be measured using MRS, but the majority of previous studies on ADHD have had limited ability to resolve glutamatergic resonance at MRI field strengths of 3.0 Tesla or less and GABA can typically not be quantified reliably at 3T without the use of spectral editing techniques (Mullins et al., 2014; Puts and Edden, 2012), due to overlap with other, more concentrated metabolites in the spectrum. Most of the previous work has therefore predominantly focused on other metabolites, and those studies focused on GABA and glutamate make limited impact statements. Ultra-high field MRS allows for increased signal-to-noise, better regional specificity, and allows improved separation of glutamate and glutamine as well as the measurement of GABA without use of editing (Dou et al., 2013; Mekle et al., 2009; Snoussi et al., 2015; Tkac et al., 2001). Furthermore, due to increased signal-to-noise (SNR), 7T MRS allows for shorter scan times (preferential in difficult clinical cohorts). Unlike widely used spectral editing techniques, conventional unedited MRS is more robust to frequency drifts/shifts and sudden head movements. Few studies have employed ultra-high field imaging in pediatric populations, and (to our knowledge) only three studies have used MRS at 7T in children under an age of 10 years (Draper et al., 2014; Harris et al., 2015b; Mahone et al., 2018). There have currently not been any investigations of GABA and glutamate in children with ADHD at ultra-high field.

In this study, we aim to measure GABA and glutamate levels in the brains of children with ADHD. While there remains significant discussion as to which brain regions are predominantly affected, the majority of work has focused on frontal regions and interconnected subcortical regions (Carmona et al., 2009; Kates et al., 2002; Mostofsky et al., 2002; Shaw et al., 2007; Wellington et al., 2006). Indeed, recent studies have suggested that subcortical brain regions mature earlier than neocortical regions, and that the developmental trajectory of subcortical anomalies parallels the reduction of hyperactivity symptoms (Andersen, 2005; Mahone and Wodka, 2008; Muftuler et al., 2011). Furthermore, it is well known that cortical and subcortical regions are well-connected and provide a feedback-feedforward connectivity to engage and control behaviors (Akkal et al., 2007; Jahanshahi et al., 2015) which, when disrupted, could lead to symptoms associated with poorly controlled behavioral inhibition and executive function.Linking the circuits controlling motor behavior to the behavior itself is crucial in understanding the development of symptoms in children with ADHD. The striatum likely plays a crucial role in this process (Chevrier et al., 2019; Lu et al., 2019). It remains unclear, however, whether behaviors central to ADHD such as impaired behavioral inhibition, emerge due to anomalous striatal development and subsequent anomalous growth of the cerebral cortex (or vice versa).

Prior MRS studies of childhood ADHD have also had limited impact in understanding the complex neurochemistry of ADHD due to small sample size, comorbidities among study samples, assessment of predominantly boys, and study of children who have received varying levels of pharmacological treatment (Bollmann et al., 2015; Carrey et al., 2003, 2007; Edden et al., 2012; MacMaster et al., 2003; Moore et al., 2006; Perlov et al., 2009).

In this study, we address these issues by including only young, medication-naïve, non-comorbid participants, and by sampling adequate numbers of boys and girls from which to draw appropriate generalizations. Therefore, the proposed study will directly assess (in vivo) concentrations of neurotransmitters thought to underlie ADHD symptoms in young children (ages 5–9) who are just developing these symptoms, and before they have had pharmacological treatment. Prior to age 5, it is more difficult to characterize the behavioral features associated with ADHD or distinguish them from behaviors that occur in typically developing children, or to scan children reliably.

We employed a cross-sectional design of single voxel ^{1}H MRS obtained with short-echo time at 7.0 Tesla, along with neuropsychological assessment, to address the following goals: 1) measure frontal and striatal GABA and glutamate levels in medication-naïve children with ADHD, ages 5–9 years (compared to age- sex- and socioeconomic status [SES]-matched typically developing children); 2) examine relationships between GABA and glutamate levels in regions identified as abnormal in ADHD, and measures of behavioral inhibition, focusing on *reactive inhibition* (i.e., withholding a prepotent motor response, or stopping one that is underway), *selective inhibition* (i.e., unintended, age-inappropriate associated movements), and *proactive inhibition* (i.e. learning something within a new context; Castellanos et al., 2005; Mostofsky and Simmonds, 2008; Willcutt et al., 2008) 3) examine relationships between GABA and glutamate levels and severity of ADHD. As a secondary benefit, the increased spectral resolution of 7T MRS allows for improved separation of glutamine (Gln) and Glu. Gln is a potential indicator of abnormal Glu metabolism (e.g. (Rae, 2014)), and is an interesting secondary target for exploration. In light of the known involvement of the striatum on inhibitory control, and given that levels of GABA/Glu may exert an influence on inhibition/excitation balance, we hypothesize that behavioral inhibition is correlated with striatal glutamate and GABA concentrations. Given the involvement of frontal region in regulating these behaviors, we hypothesize that frontal GABA and glutamate concentrations add to the prediction of these behaviors more than non-frontal metabolite levels.

2. Methods

2.1. Participants

The current study was approved by the Institutional Review Board of the Johns Hopkins Medical Institutions. Parents or legal guardians of all participants provided informed, written consent and all participants provided assent prior to the study. Procedures for recruitment of participants, screening and diagnosis of ADHD, and inclusion of control participants are summarized below.

Participants were recruited from outpatient clinics at the Kennedy Krieger Institute, local schools, and pediatricians' offices, and from

flyers in the community. Children between ages 5 and 9 years were screened by initial parent telephone interview to obtain demographic information, educational and developmental history, and medication status. Potential participants were excluded if there was a history of Autism Spectrum Disorder, Intellectual Disability or speech/language disorder or reading disorder identified either through telephone screening or prior school assessment completed up to 1 year prior to recruitment, evidence of visual impairment or hearing loss, or history of other neurological disorder. To avoid confounding the impact of medication on metabolite levels under investigation, all children enrolled in the study were medication-naïve.

Following telephone screening, parents were interviewed about their child using a structured psychiatric interview (i.e., Diagnostic Interview of Children and Adolescents–Fourth Edition [DICA-IV]; (Constantino et al., 2003; Reich, 2000)). Modules included: ADHD; Conduct Disorder; Oppositional Defiant Disorder; Major Depressive Disorder; Bipolar Disorder; Dysthymic Disorder; Separation Anxiety Disorder; Panic Disorder; Generalized Anxiety Disorder; Specific Phobia; and OCD. Children with psychiatric diagnoses other than Oppositional Defiant Disorder and Specific Phobias (based on DICA-IV interview) were excluded.

ADHD-oriented behavior rating scales, including the Conners' Parent and Teacher Rating Scales–Revised (CPRS-R/CTRS-R) (Conners, 2008) were used to confirm diagnosis of ADHD. Inclusion in the ADHD group was based on the following criteria: (a) Positive ADHD diagnosis (any type) on DICA-IV, and, (b) T-scores greater than 65 on the DSM-IV Hyperactive/Impulsive or Inattentive scales of the CPRS-R or CTRS-R. Parents of TD participants completed the DICA-IV and CPRS-R; teachers completed the CTRS-R. TD participants with T-scores greater than 60 on either the DSM-IV Inattentive or Hyperactive/Impulsive scales of the CPRS-R or CTRS-R were also excluded. A total of 50 children (26 with ADHD, 24 typically developing controls—TD) were included in the present study (see Table 2 for demographics).

2.2. Performance-based assessment methods

All participants completed a brief assessment to examine neurocognitive functions associated with cognitive (executive) control, described below. Performance-based neuropsychological testing was completed during a single day as part of a specific research protocol (Table 1).

2.3. IQ measure

The Stanford Binet-Fifth Edition (Roid and Woodcock, 2000) was used to assess intellectual function in the sample. The Full Scale IQ score was used in analyses.

2.4. Neuropsychological measures of cognitive control

Three performance-based measures of inhibitory control were administered to each participant, emphasizing *reactive inhibition* (i.e., withholding a prepotent motor response, or stopping one that is underway—Conflicting Motor Response Test), *selective inhibition* (i.e., unintended, age-inappropriate associated movements—Physical and Neurological Assessment of Subtle Signs-(PANESS; (Camp et al., 1977), and *proactive inhibition* (i.e., involving an active cognitive decision—-commission errors from a computerized Go/No-go test). Measures were examined to measure functional impairment in cognitive control among children with ADHD, and to assess potential brain-behavior associations with GABA and glutamate.

2.5. Conflicting motor response test

Participants were told, "If I show you my finger, you show me your fist; if I show you my fist, you show me your finger." The examiner presented each of the two gestures 24 times in a fixed pseudo-random sequence. Participants were instructed to respond with the preferred hand as quickly as possible. The task therefore required the individual to inhibit the prepotent tendency to mimic the examiner. The variable of interest was total number correct (maximum score = =48), with higher scores indicative of better performance.

2.6. Motor overflow—PANESS

The revised PANESS (Denckla, 1985) is a quantified motor examination comprised of untimed and timed tasks. Untimed motor tasks include gaits on heels, toes, and sides of feet (and parallel overflow/postures); tandem gait forward/backward; standing/hopping on one foot; standing heel-to-toe with eyes closed; standing both feet together, arms outstretched with eyes closed (and choreiform). Timed tasks include a sequence of 20 toe taps, hand pats, and finger taps; 10 "heel-toe," 10 hand pronate-supinate and tongue side-to-side; and 5 sequences of finger appositions (left and right sides). *Overflow movements*, defined as co-movement of body parts not specifically needed to efficiently complete a task, are considered to represent failure of inhibition of prepotent movement. Overflow is documented during both gaits and timed activities. The total overflow score was used in analyses. Higher total scores indicate greater abnormality.

2.7. Commission errors

For this computerized go/no-go test, participants were seated in front of a screen that flashed green and red spaceships and were told to press the spacebar in response to green ships only. Cues appeared on screen for 300 msec. and were presented once every 1,800 msec. (fixed 1,500 msec. inter-stimulus interval). Cues were weighted towards green spaceships at a ratio of 3:1 and the task lasted 8 min. Commissions were defined as pressing the space bar after the presentation of a red ship. The total number of commission errors was used in analyses.

2.8. MRI and MRS procedures

All participants received mock scan training sessions to improve

Table 1
Behavioral and neuropsychological measures.

Test	i) Type	Measure of	Notes
Hollingshead Index	Parent report	Socioeconomic status	All participants
DICA-IV	Interview	Psychiatric diagnosis	All participants
YGTSS-modified	Parent report	Tic severity	TS group only
ADHD Rating Scale-IV	Parent rating	ADHD symptoms	Raw scores used
Full Scale IQ (SB-5)	Performance	Intellectual functioning	All participants
Conflicting Motor Response	Performance	Reactive inhibition	Total correct trials
PANESS - Overflow	Performance	Selective inhibition	Total overflow
Go/No-go Test - Commissions	Performance	Proactive inhibition	Number commission errors

Note: DICA-IV = Diagnostic Interview for Children and Adolescents-IV; PANESS = Physical and Neurological Assessment of Subtle Signs; SB-5 = Stanford Binet Intelligence Test, Fifth Edition. TS = Tourette syndrome; ADHD = Attention-deficit/Hyperactivity Disorder.

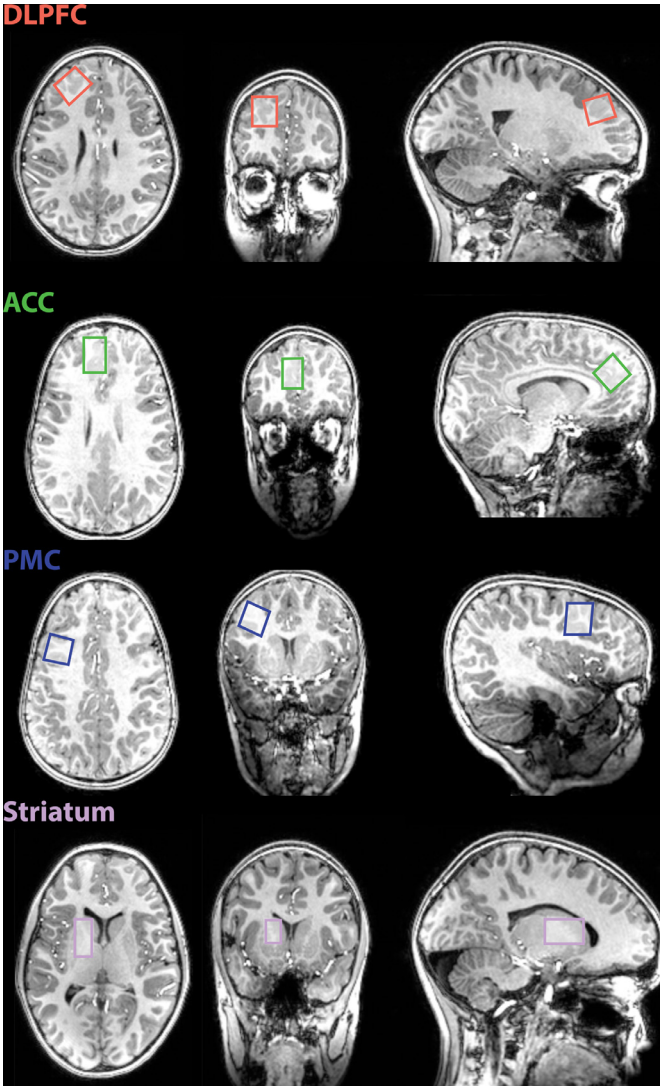

Fig. 1. Example voxel locations for DLPFC, ACC, PMC and Striatum.

comfort, decrease anxiety and train them to lie still. The mock scanner consists of an old MRI body and speakers that play recorded MRI sounds consistent with the sequences employed. Mock scan training was performed under the supervision of a trained Psychology Associate with over 5 years of experience. No sedation was used. Structural MRI and MRS were performed using a Philips 7T scanner 'Achieva' (Philips Healthcare, Best, The Netherlands) equipped with a quadrature transmit and 32-channel receive head coil (Nova Medical, Wilmington, MA). A high-quality T1-weighted MPRAGE structural brain image was acquired for planning of the MRS voxel locations. Before MRS data acquisition, shimming was performed up to 2nd order using a FASTMAP-based routine, and RF power was optimized on the localized voxel. The stimulated echo acquisition mode (STEAM)sequence was used for signal localization with the following parameters: TE/TM/TR/NS = 14 msec./26 msec./3000 msec./96 averages and VAPOR water suppression (Tkac et al., 1999). Spectra were acquired from four voxels: ventromedial prefrontal (VMPFC), dorsolateral prefrontal (DLPFC), premotor (PMC), and striatum. Voxel placement was performed using a documented procedure and images for reference (see **Fig. 1**).In addition, four water-unsuppressed averages were recorded per voxel, with the same acquisition settings. The ~8 ml($2 \times 2 \times 2$ cm^3) PMC voxel was placed in the left hemisphere, with the posterior face aligned to the pre-central sulcus, and the inferior face above the level of the corpus callosum. The ~8 ml($2 \times 2 \times 2$ cm^3) DLPFC voxel was placed in the left hemisphere, anterior to the premotor voxel, angulated so as to maximize GM content whilst avoiding the skull. The ~8 ml ($1.5 \times 3.5 \times 3$ cm^3) striatum voxel was placed in the left hemisphere, aligned in the sagittal plane with the principal axis of the striatum rotated to include predominantly putamen. The ACC voxel ($15 \times 20 \times 30$ cm^3) was placed on the midline with the anterior end of the voxel aligned with the anterior point of the ACC and rotated to align with the cortical curvature.

LCModel v6.3–0D (Provencher, 2001) was used for spectral analyses to quantify both GABA and glutamate using an in-house TE-specific simulated basis set including 21 metabolites and default parameters. Lipid and macromolecular basis functions with resonances from lipids (Lip09, Lip13a-d, Lip20) and macromolecules (MM09, MM12, MM14, MM17, MM20) were internally simulated by LCModel. . Only GABA and Glu were used for further analysis. GABA and Glu were measured as a ratio to total creatine (tCr = Cr + PCr) within each voxel. Only measurements with Cramér-Rao lower bound values ≤ 20% for the respective metabolite were included in subsequent analyses. The standalone Gannet 3.0 'CoRegStandAlone' module (Edden et al., 2014) was used for segmentation of the voxels ingray matter, white matter, and CSF, using SPM12 (Wellcome Department of Imaging Neuroscience Group, London, UK; http://www.fil.ion.ucl.ac.uk/spm).

2.9. Statistical analysis

Statistical analyses were performed in SPSS (IBM **SPSS** Statistics for Windows, IBM Corp., Armonk, N.Y., USA) and in R (R Core Team). First, demographics (age, SES, handedness, sex distribution) and neuropsychological variables were compared using ANOVAs for continuous variables and chi-square analyses for categorical variables. Second, data quality metrics (LCModel signal-to-noise ratio, linewidth, Cramér-Rao lower bound measures) were examined for distributions and group differences. Third, metabolite levels for each ROI were compared between groups separately for GABA and Glu, as well as Gln. The significance level for group comparisons of metabolite levels was set at alpha = 0.0125 (0.05/4, Bonferroni-corrected for the number of ROIs) for analyses of ROIs and neuropsychological tests. Differences in voxel tissue composition were assessed using two-sample T-tests with the significance threshold set at alpha = 0.0125 (0.05/4). Finally, the associations between regional metabolite concentrations and neuropsychological functions were examined within the ADHD group only for ROIs and neuropsychological functions showing group differences using Pearson R, with a significance level set to alpha = 0.05.

3. Results

3.1. Sample demographics

Demographic information is included in **Table 2**. After exclusion at recruitment/screening, the total sample included 26 children with ADHD (14 boys) and 24 TD controls (9 boys). The sample was primarily Caucasian (90%) and right-handed (88%). There were no significant differences between ADHD and TD groups in sex distribution ($X^2_{(1)} = 1.34$, $p = 0.247$), handedness ($X^2_{(1)} = 1.87$, $p = 0.349$), racial distribution ($X^2_{(2)} = 4.95$, $p = 0.084$), or age ($p = 0.376$). Conversely, the TD group had higher SES slightly above the significance threshold ($p = 0.052$), and FSIQ ($p = 0.001$), compared to the ADHD group. As such, both SES and FSIQ were used as covariates in subsequent group comparisons for neuropsychological variables as well as creatine ratios of GABA and Glu. Additionally, given the association between age and metabolite levels within the age range under investigation (Ghisleni et al., 2015), age was also added as a covariate for group comparisons of levels of GABA and Glu ratios.

Table 2
Demographics and neuropsychological data.

	TD (n = 24)			ADHD (n = 26)			p	η_p^2
	n	Mean	SD	n	Mean	SD		
Age	24	7.38	1.48	26	7.70	0.99	.376	.016
SES (Hollingshead Index)	23	58.39	8.69	26	52.17	12.48	.052	.078
CPRS Inattentive	21	49.57	9.25	26	77.92	11.81	< 0.001	.643
CPRS Hyperactive/ Impulsive	21	49.76	10.11	26	76.27	13.56	< 0.001	.551
FSIQ	24	113.04	9.57	26	101.92	12.43	.001	.205
Conflicting Motor Response*	23	40.65	5.48	25	36.04	5.38	.050	.087
Go/No-go Commissions	16	0.32	0.20	20	0.55	0.19	.011	.190
PANESS Total Overflow	21	5.62	3.69	24	11.21	8.60	< 0.001	.290

Note:.
* group comparisons (p, η_p^2) are controlling for SES and FSIQ.

3.2. Neuropsychological assessment

Results of performance-based neuropsychological assessment are also listed in Table 2. After controlling for SES and FSIQ, there were significant group differences for all three measures of inhibitory control (all $p < 0.01$), showing better performance among the TD group.

3.3. MRS acquisition

The MRI/MRS protocol of 45 min duration was well tolerated in both TD children and those with ADHD. Nevertheless, all four MRS voxels were not acquired in all children due to movement or child fatigue, resulting in some missing data. Two children completed a second scanning session to acquire remaining voxels. Table 3 summarizes the results for each voxel under investigation.

3.3.1. MRS results

Example spectra are shown in Fig. 2. Results of group comparisons for individual GABA and Glu concentrations across and within ROIs are listed in Table 3 along with group comparisons of quality metrics, and individual data points are shown inFig. 3. There were no significant group differences in signal-to-noise ratio, Cramér-Rao lower bound or linewidth within any of the 4 ROIs suggesting that group differences are not driven by group differences in MRS data quality (see also Table 3). Data quality metrics did not correlate with metabolite levels (all $p > 0.3$).

The ADHD group showed significantly reduced GABA/Cr in the striatum ($p = 0.010$, $\eta_p^2 = 0.176$), but not in ACC, DLPFC, or PMC regions (all $p > 0.34$). There were no significant group differences in any ROI for Glu/Cr levels. There were also no significant group differences in any ROI for Gln/Cr levels (ACC: $F(1,45) = 1.56$, $p = 0.218$, $\eta_p^2 = 0.033$; DLPFC: $F(1,38) = 0.92$, $p = 0.344$, $\eta_p^2 = 0.024$; PMC: $F(1,38) = 0.007$, $p = 0.935$, $\eta_p^2 < 0.001$; Striatum: $F(1,42) = 0.91$. $p = 0.345$, $\eta_p^2 = 0.021$). There were also no significant group differences in GM/WM/CSF for ACC, DLPFC, and striatum. GM and WM content differed significantly between groups for PMC (Table 4) but not for other voxels. To ensure the data weren't driven by differences in Cr, we tested whether tCr/NAA differed between groups for any of ROI, which it did not (LME covaried for SES, age, and FSIQ; ACC: $F(1,41) = 0.011$, $p = 0.918$, $\eta_p^2 < 0.001$; DLPFC: $F(1,32) = 0.354$, $p = 0.0.56$, $\eta_p^2 = 0.01$; PMC: $F(1, 36) = 0.27$, $p = 0.605$, $\eta_p^2 = 0.008$; Striatum: $F(1,36) = 1.113$, $p = 0.30$, $\eta_p^2 = 0.03$).

3.4. Brain/behavior correlations

Within the ADHD group, age was significantly associated with striatal GABA/Cr levels ($r = 0.578$, $p = 0.005$), and was subsequently controlled in subsequent brain-behavior correlations. Within the striatum in the ADHD group, reduced GABA/Cr was not significantly associated with performance on Conflicting Motor Exam ($r_p = -0.348$, $p = 0.200$), Go/No-go Commissions ($r_p = -0.148$, $p = 0.598$), or PANESS Total Overflow ($r_p = -0.102$, $p = 0.708$). Striatal GABA/Cr levels were not significantly correlated with ADHD symptom scores across groups (Inattention $r = -0.21$, $p = 0.17$; Hyperactivity/Impulsivity $r = -0.13$, $p = 0.40$) or separately in the ADHD group (Inattention $r = 0.23$, $p = 0.30$; Hyperactivity/Impulsivity $r = 0.25$, $p = 0.26$), or the TD group (Inattention $r = 0.07$, $p = 0.75$; Hyperactivity/Impulsivity $r = 0.14$, $p = 0.55$).

Table 3
GABA and Glu ratios in all ROIs for each group.

	TD (n = 24)			ADHD (n = 26)			p	η_p^2
	n	Mean	SD	n	Mean	SD		
GABA/Cr*								
ACC	23	0.393	0.061	24	0.371	0.042	.460	.013
DLPFC	19	0.354	0.087	19	0.483	0.669	.344	.028
PMC	20	0.383	0.774	21	0.357	0.051	.353	.025
Striatum	22	0.436	0.062	19	0.391	0.052	**.010**	**.176**
Glu/Cr*								
ACC	24	1.730	0.124	24	1.745	0.142	.402	.017
DLPFC	23	1.684	0.234	21	1.757	0.315	.290	.029
PMC	20	1.792	0.205	21	1.755	0.140	.514	.012
Striatum	22	1.369	0.325	20	1.405	0.121	.619	.007
SNR								
ACC	24	24.75	8.06	25	23.64	7.79	.626	.005
DLPFC	23	22.30	8.66	21	21.76	7.65	.828	.001
PMC	20	25.05	6.92	22	22.41	7.33	.238	.035
Striatum	22	17.55	6.23	22	17.86	6.71	.871	.001
FWHM								
ACC	24	0.023	0.008	25	0.026	0.013	.285	.024
DLPFC	23	0.024	0.007	21	0.044	0.055	.093	.066
PMC	20	0.022	0.003	22	0.029	0.020	.115	.061
Striatum	22	0.033	0.005	22	0.035	0.015	.607	.006
CRLB GABA								
ACC	23	9.79	6.45	24	9.42	2.65	.794	.002
DLPFC	19	14.91	13.16	19	14.00	9.62	.796	.002
PMC	20	10.05	2.46	21	12.82	8.78	.181	.044
Striatum	22	8.95	3.02	19	13.09	12.56	.141	.051
CRBL Glu								
ACC	24	3.17	2.26	24	5.40	12.65	.399	.015
DLPFC	23	3.70	1.84	21	4.05	3.43	.67	.004
PMC	20	3.00	0.79	21	4.18	4.93	.297	.027
Striatum	22	3.73	1.28	20	4.81	7.27	.496	.011

Note:.
* Results of group comparisons (p, η_p^2) are controlling for age, SES, and FSIQ. Bold-faced values are significantly different between the ADHD and TD groups at a significance level of 0.0125.

4. Discussion

In this study, 1H MRS was performed at the ultra-high field strength of 7T to quantify concentrations of GABA and glutamate in cortical and subcortical regions of unmedicated children with ADHD.

Our behavioral results support previous studies showing poorer behavioral inhibitory control in children with ADHD. Indeed, children with ADHD performed worse in all tasks related to inhibitory function. Concurrently, the MRS data show reduced GABA in striatum but not cortical regions, and no glutamate differences between cohorts, nor do these neurotransmitter levels correlate with behavioral outcome. However, we do show a correlation between GABA in striatum and age in the ADHD cohort.

There has been limited use of MRS in ADHD (Schür et al., 2016). Previous work has shown reduced GABA levels in motor cortical regions (Bollmann et al., 2015; Edden et al., 2012), whereas another study (Bollmann et al., 2015) found increased subcortical, but not cortical

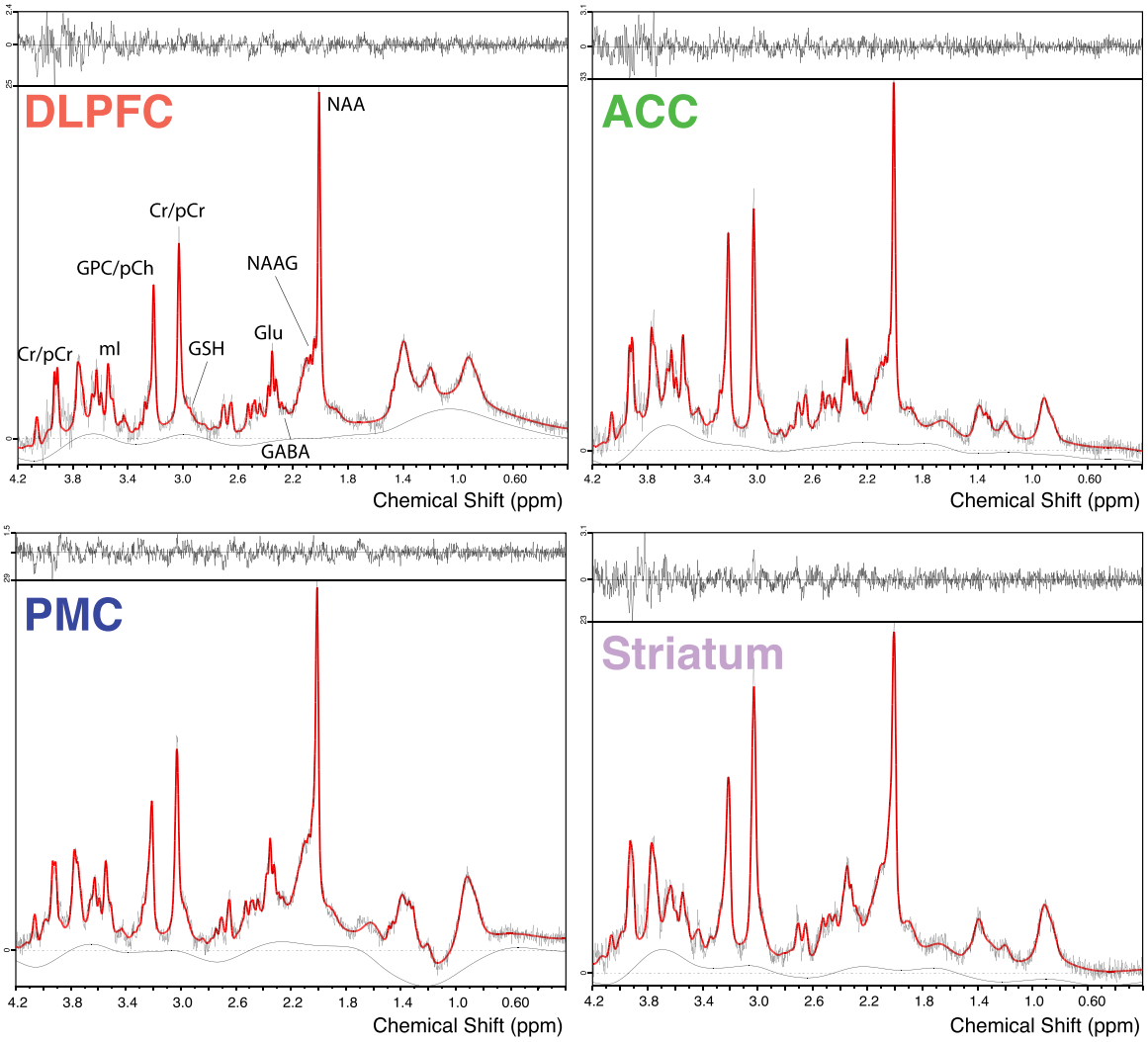

Fig. 2. Example spectra and residuals for all four regions.

GABA in adults, but not children, with ADHD. Ende et al. (2016) show reduced ACC GABA levels in young female adults with ADHD, suggesting that ACC regions may be affected later in life.

It is possible that frontal cortical regions do not exhibit neurotransmitter changes in early childhood, whereas phylogenetically earlier cortical regions might, and may be affected through development and therapy. Interestingly, Bollmann et al. (2015) also showed increased glutamine in children with ADHD whereas we did not, possibly reflecting a slightly later emergence of this abnormality, or as a response to treatment.Longitudinal approaches across cortical and subcortical regions in these cohorts are much needed.

As these primary cortical regions are more directly involved in motor output, it is possible that miscommunication between frontostriatal regions, mediated by altered striatal GABA, leads to predominantly altered motor function that is exemplified by differences in primary motor cortex.It is also important to note that GABA and glutamate have a complex relationship, both cortically, subcortically, and especially at a frontostriatal cortical network level. Indeed, subcortical dysfunction is well-known to affect cortical processing, and the interplay of GABAergic, glutamatergic, as well as other neurotransmitter systems especially at the subcortical level is not well known. It is well-established that the striatum is an important hub in the regulation of motor learning, motor planning, motivation, and reward, and it is therefore not surprising that our significant results show a decrease in GABA in striatum. Increased dopaminergic activity has been shown to affect motor learning and performance as well (Molina-Luna et al., 2009; Rioult-Pedotti et al., 2015).

Our finding that neither Glu nor Gln are different between cohorts suggests that the glutamate system in this particular cohort is intact. The glutamate system may be affected later in the disorder, with maturation, or as a response to treatment. Furthermore, given the higher GABA levels in subcortical regions, it is possible that we only find significantly reduced GABA levels in striatum due to higher GABA levels, and that noise in other regions is sufficiently high to mask group differences. However, given the substantial SNR at 7T this is unlikely (e.g., it is substantially higher than that at 3T regardless of lower SNR in striatum (Považan et al., 2020)). In addition, MRS signal from subcortical regions is often low, and indeed, our findings show the lowest SNR in the striatal voxel. Furthermore, it is important to note that the GM/WM ratio is different for the striatal voxel due to its anatomical location.

It is surprising that our results do not show a correlation between neurotransmitter levels in the striatum, where we do find significant group differences, and behavioral outcomes of motor inhibition or ADHD severity. In previous work, we found correlations between tactile and motor performance in ADHD (Puts et al., 2017), but as discussed above, these motor behaviors are most closely associated with primary motor cortex function. While it is well-established that the striatum is an important moderator of these motor behaviors, measuring up-stream control in the striatum might not reflect a linear relationship to what is

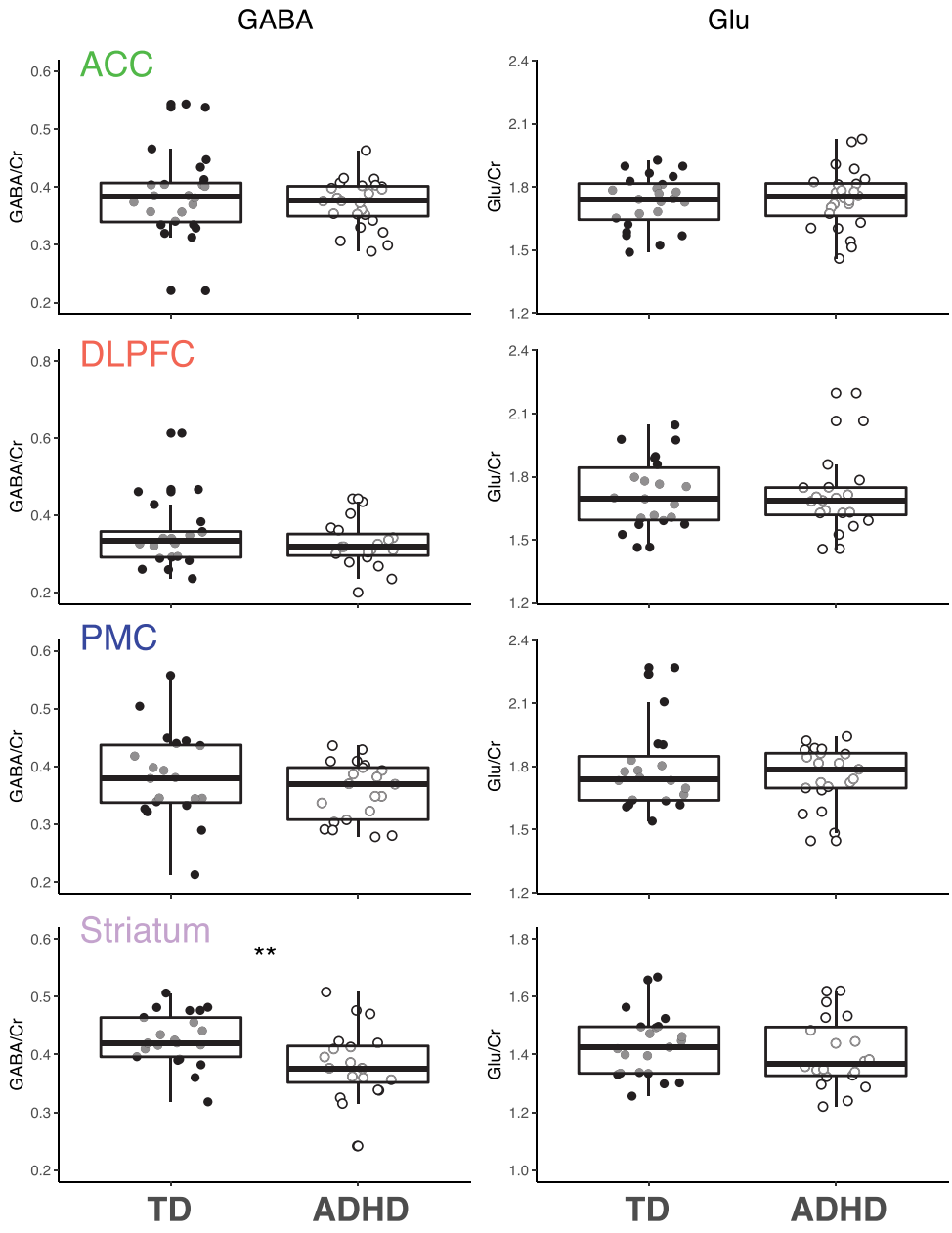

Fig. 3. Scatterplot and boxplots of GABA and Glu between groups for all regions of interest. *(** p = 0.01).*

Table 4
Proportion GM/WM/CSF.

	TD Mean	SD	ADHD Mean	SD	*p*
GM					
ACC	0.59	0.08	0.59	7.79	.57
DLPFC	0.60	0.09	0.60	0.04	.97
PMC	0.65	0.08	0.57	0.07	**.004**
Striatum	0.4	0.11	0.44	0.11	.28
WM					
ACC	0.38	0.1	0.38	0.1	.98
DLPFC	0.37	0.11	0.37	0.06	.92
PMC	0.31	0.08	0.40	0.07	**.002**
Striatum	0.59	0.11	0.53	0.11	.16
CSF					
ACC	0.025	0.028	0.05	0.03	.14
DLPFC	0.027	0.035	0.026	0.026	.84
PMC	0.04	0.02	0.025	0.017	.07
Striatum	0.004	0.004	0.016	0.04	**.32**

a predominantly primary motor output, whereas primary motor function likely correlates well with motor behaviors. The striatum is likely indirectly involved. In addition, given the ongoing development of these motor skills over the 5 – 9 age range, and the age-dependence of GABA levels, these associations may be stronger in older children. Additionally, the absence of correlations with ADHD severity was surprising, and we fail to link reduced striatal GABA with clinical manifestations of the disorder. It should be noted that, even at high fields, MRS remains a measurement technique with substantial variability, and that the assessment of ADHD symptomatology and diagnosis remain to be of subjective nature.

A limitation of MRS of GABA and Glu is that it likely predominantly measures presynaptic levels of these metabolites, which are mostly localized in the soma of neurons (Stagg et al., 2011). However, it is also possible that differences in ADHD not only lie in the presynaptic production and moderation of neurometabolites, but also, or rather, in the post-synaptic processes such as receptor function and density. Indeed, one study applying paired-pulse TMS showed reduced short-interval

cortical-inhibition in children with ADHD (Gilbert et al., 2011), a concept thought to reflect GABAA-receptor function, which has been since reproduced (Gilbert et al., 2019). It remains unclear how MRS measures of GABA relate to GABA-receptor function as these methodologies measure related, but not identical, mechanisms involved in cortical inhibition (Stagg et al., 2011). Additional MRS/TMS studies, or PET approaches, are required to investigate inhibitory dynamics.

In addition, previous work showed that chronic use of methylphenidate medication led to a decrease in GABA levels (Solleveld et al., 2017). It is possible that prior work showing differences in GABA reflected medication use rather than ADHD features of reduced GABA, while in this study we tested unmedicated children. In contrast, reduced striatal GABA may have been mediated somewhat by medication on those cohorts, leading to differences in cortical GABA. It is entirely possible that striatal GABA is a primal, early, marker of ADHD, with cortical differences occurring with longer disorder duration and/or medication use. Indeed, earlier striatal abnormalities are also seen in a spontaneously hypertensive animal model for ADHD (Hsu et al., 2010; Miller et al., 2014). Furthermore, we find a correlation between striatal GABA and age in the ADHD cohort. This may reflect abnormal, and reduced, maturation of subcortical systems that lead to hyperactive cortical processes. Longitudinal studies are required to track this effect in more detail.

The absence of cortical GABA differences here could be due to the different methodologies used. It is important to note that the measures of GABA and glutamate from this study may not be directly comparable to those acquired at lower field strength. The differences in technical approaches (field strength, voxel location) as well as clinical differences may have led to differences in the results found by various studies. MRS acquired using high field has shown to improve separation of metabolite signals compared to 3 T, however, much of the work at 3 T employed spectral editing, where the focus is on a specific neurotransmitter of interest. While 7T MRS allows for a higher spectral resolution and separation of signals, it is still not entirely obvious to what extent GABA and Glu can be measured reliably and accurately. Due to higher SNR, 7T MRS may allow for smaller effect sizes to be detected, and we may be more sensitive to region-specific changes in GABA levels in early childhood. Furthermore, conventional unedited 7T MRS usually requires shorter scan times, which mitigates the detrimental effect of movement and boredom in clinical pediatric cohorts. While there may be benefit of J-difference editing to measure GABA, it also relies on subtraction, which is highly sensitive to field instabilities and motion (Cui et al., 2018; Edden et al., 2016; Mikkelsen et al., 2017; Tapper et al., 2017), considerably more so than unedited MRS as employed here. While we did not find group differences in the data quality metrics reported (SNR, FWHM, or CRLB), and data quality was generally high. It is unlikely that differences in data quality contributed to the striatal group difference in GABA, it is important to note that movement, or frequency drift, can be an important factor in considering deviations in metabolite levels (see e.g.(Cui et al., 2018; Edden et al., 2016)). It should be noted that data quality (SNR and FWHM) were worse for the striatal voxel, this is common for MRS, in that field inhomogeneity is typically worse in subcortical region due to iron deposits and vicinity to ventricles, making shimming proves more difficult. That said, noisier data would make it more difficult to observe group differences, showing that the finding of reduced GABA in the striatum is perhaps quite robust. One ongoing debate in MRS research is the contribution of tissue, and the ratio used. Here, we used ratios relative to Cr, which is common, but it is important to ensure Cr does not differ between groups. For estimated concentrations using unsuppressed water, it is important to correct for tissue composition, taking tissue, and metabolite, specific relaxation into account as well (Gasparovic et al., 2006; Harris et al., 2015a; Mullins et al., 2014).

While real-time motion-tracking and frequency updates (Boer et al., 2012; Hess et al., 2011; Keating et al., 2010) are likely to reduce the impact of head motion and frequency, these technically demanding techniques are not available in standard implementations of MRS sequences. Post-hoc, the water frequency offset may indicate frequency shift indicative of movement. However, it is important that data are exported in a transient-by-transient fashion (not done here) such that post-hoc frequency and phase correction can be used optimally.

In addition to methodological considerations, it is well known that ADHD is also considered to have dopaminergic underpinnings (Gross and Marshall, 2009; Russell et al., 2006; Zhang and Sulzer, 2003) and indeed, this system is mostly associated with subcortical function. However, most key neurotransmitters, such as acetylcholine, dopamine, and serotonin are absent in proton MR spectra due to their very low concentrations and strongly coupled spectra.

In summary, this study shows reduced striatal, but not fronto-cortical, GABA levels in unmedicated children as measured at 7T. While this work is inconclusive as to the behavioral relevance of such reduced striatal GABA, it shows the importance of measuring GABA in unmedicated children with ADHD at 7T, and therefore these findings do provide guidance for future studies or interventions. Reduced striatal GABA may be a marker for specific GABA-related treatment approaches for ADHD, or an indication of treatment efficacy, with a variety of medications given the associations between dopamine and GABA (Hoerbelt et al., 2015; Lindefors, 1993).

Author contributions

Study concept and design was done by N.A.P., A.H, R.A.E.E., M.R and E.M.M., Data acquisition and analysis was done by N.A.P., A.H., G.O., R.A.E.E., M.R., A.H. and E.M.M., The manuscript was written by E.M.M., N.A.P., and R.A.E.E.

Declaration of Competing Interest

There are no conflicts of interest for any of the authors.

Acknowledgements

The project described was supported by award number R21MH092693 from the National Institute Of Mental Health. NAJP salary was supported through R00 MH107719.

References

Akkal, D., Dum, R.P., Strick, P.L., 2007. Supplementary motor area and presupplementary motor area: targets of basal ganglia and cerebellar output. J. Neurosci. 27, 10659–10673. https://doi.org/10.1523/JNEUROSCI.3134-07.2007.

Andersen, S.L., 2005. Stimulants and the developing brain. Trends Pharmacol. Sci. 26, 237–243. https://doi.org/10.1016/j.tips.2005.03.009.

Armstrong, M., Nettleton, S., 2004. Attention deficit hyperactivity disorder and preschool children. Semin. Speech Lang. 25, 225–232.

Boer, V.O., vd Bank, B.L., van Vliet, G., Luijten, P.R., Klomp, D.W.J., 2012. Direct B0 field monitoring and real-time B0 field updating in the human breast at 7 T. Magn. Reson. Med. 67, 586–591. https://doi.org/10.1002/mrm.23272.

Bollmann, S., Ghisleni, C., Poil, S.-S., Martin, E., Ball, J., Eich-Höchli, D., Edden, R.A.E., Klaver, P., Michels, L., Brandeis, D., O'Gorman, R.L., 2015. Developmental changes in gamma-aminobutyric acid levels in attention-deficit/hyperactivity disorder. Transl. Psychiatry 5, e589. https://doi.org/10.1038/tp.2015.79.

Camp, J.A., Bialer, I., Press, M., Winsberg, B.G., 1977. The physical and neurological examination for soft signs (PANESS): pediatric norms and comparisons between normal and deviant boys [proceedings]. Psychopharmacol. Bull. 13, 39–41.

Carmona, S., Haekzema, E.A., Gispert, J.D., Picado, M., Moreno, I., Soliva, J.C., Bielsa, A., Rovira, M., Hilferty, J., Bulbena, A., Casas, M., Tobena, A., Vilarroya, O., 2009. PE, Ventro-striatal reductions underpin symptoms of hyperactivity and impulsivity in attention-deficit/hyperactivity disorder. Biol. Psychiatry 101016jbiopsych05013.

Carrey, N., MacMaster, F.P., Fogel, J., Sparkes, S., Waschbusch, D., Sullivan, S., Schmidt, M., 2003. Metabolite changes resulting from treatment in children with ADHD: a 1H-MRS study. Clin. Neuropharmacol. 26, 218–221. https://doi.org/10.1097/00002826-200307000-00013.

Carrey, N.J., MacMaster, F.P., Gaudet, L., Schmidt, M.H., 2007. Striatal creatine and glutamate/glutamine in attention-deficit/hyperactivity disorder. Adolesc. Psychopharmacol. 17, 11–17.

Castellanos, F.X., Sonuga-Barke, E.J., Scheres, A., 2005. Varieties of attention-deficit/hyperactivity disorder-related intra-individual variability. Biol. Psychiatry 57,

1416–1423.
Chesselet, M.-F., Plotkin, J.L., Wu, N., Levine, M.S., 2007. Development of striatal fast-spiking GABAergic interneurons. Progress in Brain Research. pp. 261–272. https://doi.org/10.1016/S0079-6123(06)60015-0.
Chevrier, A., Bhaijiwala, M., Lipszyc, J., Cheyne, D., Graham, S., Schachar, R., 2019. Disrupted reinforcement learning during post-error slowing in ADHD. PLoS ONE 14, e0206780. https://doi.org/10.1371/journal.pone.0206780.
Christophersen, E.R., Mortweet, S.L., 2001. Treatments that work with children: empirically supported strategies for managing childhood problems. 10.1037/10405-000.
Conners, C.K., 2008. Conners 3. Multi-Health Systems, Inc, North Tonawanda, NY.
Constantino, J.N., Davis, S.A., Todd, R.D., Schindler, M.K., Gross, M.M., Brophy, S.L., Metzger, L.M., Shoushtari, C.S., Splinter, R., Reich, W., 2003. Validation of a brief quantitative measure of autistic traits: comparison of the social responsiveness scale with the autism diagnostic interview-revised. J. Autism Dev. Disord. 33, 427–433.
Courvoisie, H., Hooper, S.R., Fine, C., Kwock, L., Castillo, M., 2004. Neurometabolic Functioning and Neuropsychological Correlates in Children With ADHD-H: preliminary Findings. J. Neuropsychiatry Clin. Neurosci. 16, 63–69. https://doi.org/10.1176/jnp.16.1.63.
Cui, E.D., Maddock, R.J., Buonocore, M.H., Ozturk, M., Yoon, J.H., 2018. Quantifying the effects of head movement on magnetic resonance spectroscopy estimates of gamma-aminobutyric acid. bioRxiv 381699. 10.1101/381699.
Denckla, M.B., 1985. Revised Neurological Examination for Subtle Signs (1985). Psychopharmacol. Bull. 21, 773–800.
Dou, W., Palomero-Gallagher, N., van Tol, M.-J., Kaufmann, J., Zhong, K., Bernstein, H.-G., Heinze, H.-J., Speck, O., Walter, M., 2013. Systematic regional variations of GABA, glutamine, and glutamate concentrations follow receptor fingerprints of human cingulate cortex. J. Neurosci. 33, 12698–12704. https://doi.org/10.1523/JNEUROSCI.1758-13.2013.
Draper, A., Stephenson, M.C., Jackson, G.M., Pépés, S., Morgan, P.S., Morris, P.G., Jackson, S.R., 2014. Increased GABA contributes to enhanced control over motor excitability in Tourette syndrome. Curr. Biol. 24, 2343–2347. https://doi.org/10.1016/j.cub.2014.08.038.
Edden, R.A., Crocetti, D., Zhu, H., Gilbert, D.L., Mostofsky, S.H., 2012. Reduced GABA concentration in attention-deficit/hyperactivity disorder. Arch. Gen. Psychiatry 69, 750–753. https://doi.org/10.1001/archgenpsychiatry.2011.2280.
Edden, R.A., Puts, N.A., Harris, A.D., Barker, P.B., Evans, C.J., 2014. Gannet: a batch-processing tool for the quantitative analysis of gamma-aminobutyric acid-edited MR spectroscopy spectra. J. Magn. Reson. Imaging 40, 1445–1452. https://doi.org/10.1002/jmri.24478.
Edden, R.A.E., Oeltzschner, G., Harris, A.D., Puts, N.A.J., Chan, K.L., Boer, V.O., Schär, M., Barker, P.B., 2016. Prospective frequency correction for macromolecule-suppressed GABA editing at 3T. J. Magn. Reson. Imaging 44, 1474–1482. https://doi.org/10.1002/jmri.25304.
Ende, G., Cackowski, S., Van Eijk, J., Sack, M., Demirakca, T., Kleindienst, N., Bohus, M., Sobanski, E., Krause-Utz, A., Schmahl, C., 2016. Impulsivity and Aggression in Female BPD and ADHD Patients: association with ACC Glutamate and GABA Concentrations. Neuropsychopharmacology 41, 410–418. https://doi.org/10.1038/npp.2015.153.
Gasparovic, C., Song, T., Devier, D., Bockholt, H.J., Caprihan, A., Mullins, P.G., Posse, S., Jung, R.E., Morrison, L.A., 2006. Use of tissue water as a concentration reference for proton spectroscopic imaging. Magn. Reson. Med. 55, 1219–1226. https://doi.org/10.1002/mrm.20901.
Ghisleni, C., Bollmann, S., Poil, S.-S., Brandeis, D., Martin, E., Michels, L., O'Gorman, R.L., Klaver, P., 2015. Subcortical glutamate mediates the reduction of short-range functional connectivity with age in a developmental cohort. J. Neurosci. 35, 8433–8441. https://doi.org/10.1523/JNEUROSCI.4375-14.2015.
Gilbert, D.L., Huddleston, D.A., Wu, S.W., Pedapati, E.V., Horn, P.S., Hirabayashi, K., Crocetti, D., Wassermann, E.M., Mostofsky, S.H., 2019. Motor cortex inhibition and modulation in children with ADHD. Neurology 93, e599–e610. https://doi.org/10.1212/WNL.0000000000007899.
Gilbert, D.L., Isaacs, K.M., Augusta, M., Macneil, L.K., Mostofsky, S.H., 2011. Motor cortex inhibition: a marker of ADHD behavior and motor development in children. Neurology 76, 615–621. https://doi.org/10.1212/WNL.0b013e31820c2ebd.
Greenhill, L.L., Posner, K., Vaughan, B.S., Kratochvil, C.J., 2008. Attention deficit hyperactivity disorder in preschool children. Child. Adolesc. Psychiatr. Clin. ix 17, 347–366. https://doi.org/10.1016/j.chc.2007.11.004.
Gross, N.B., Marshall, J.F., 2009. Striatal dopamine and glutamate receptors modulate, methamphetamine-induced cortical Fos expression. Neuroscience 161, 1114–1125. https://doi.org/10.1016/j.neuroscience.2009.04.023.
Harris, A.D., Puts, N.A., Edden, R.A., 2015a. Tissue correction for GABA-edited MRS: considerations of voxel composition, tissue segmentation, and tissue relaxations. J. Magn. Reson. Imaging 42, 1431–1440. https://doi.org/10.1002/jmri.24903.
Harris, A.D., Singer, H.S., Horska, A., Kline, T., Ryan, M., Edden, R.A., Mahone, E.M., 2015b. GABA and Glutamate in Children with Primary Complex Motor Stereotypies: an 1H-MRS Study at 7T. AJNR Am. J. Neuroradiol. https://doi.org/10.3174/ajnr.A4547.
Hess, A.T., Dylan Tisdall, M., Andronesi, O.C., Meintjes, E.M., van der Kouwe, A.J.W., 2011. Real-time motion and B0 corrected single voxel spectroscopy using volumetric navigators. Magn. Reson. Med. 66, 314–323. https://doi.org/10.1002/mrm.22805.
Hoerbelt, P., Lindsley, T.A., Fleck, M.W., 2015. Dopamine directly modulates GABAA receptors. J. Neurosci. 35, 3525–3536. https://doi.org/10.1523/JNEUROSCI.4390-14.2015.
Hsu, J.-W., Lee, L.-C., Chen, R.-F., Yen, C.-T., Chen, Y.-S., Tsai, M.-L., 2010. Striatal volume changes in a rat model of childhood attention-deficit/hyperactivity disorder. Psychiatry Res. 179, 338–341. https://doi.org/10.1016/j.psychres.2009.08.008.
Jahanshahi, M., Obeso, I., Rothwell, J.C., Obeso, J.A., 2015. A fronto–s-triato–subthalamic–pallidal network for goal-directed and habitual inhibition. Nat. Rev. Neurosci. 16, 719–732. https://doi.org/10.1038/nrn4038.
Kates, W.R., Frederikse, M., Mostofsky, S.H., 2002. MRI parcellation of the frontal lobe in boys with attention deficit hyperactivity disorder or Tourette syndrome. Psychiatry Res. 116, 63–81.
Keating, B., Deng, W., Roddey, J.C., White, N., Dale, A., Stenger, V.A., Ernst, T., 2010. Prospective motion correction for single-voxel 1H MR spectroscopy. Magn. Reson. Med. 64, 672–679. https://doi.org/10.1002/mrm.22448.
Lee, S.S., Lahey, B.B., Owens, E.B., Hinshaw, S.P., 2007. Few Preschool Boys and Girls with ADHD are Well-Adjusted During Adolescence. Child Psychol. 36, 373–383. https://doi.org/10.1007/s10802-007-9184-6.
Lindefors, N., 1993. Dopaminergic regulation of glutamic acid decarboxylase mRNA expression and GABA release in the striatum: a review. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 17, 887–903. https://doi.org/10.1016/0278-5846(93)90018-N.
Lu, L., Zhang, L., Tang, S., Bu, X., Chen, Y., Hu, Xinyu, Hu, Xiaoxiao, Li, H., Guo, L., Sweeney, J.A., Gong, Q., Huang, X., 2019. Characterization of cortical and subcortical abnormalities in drug-naive boys with attention-deficit/hyperactivity disorder. J. Affect. Disord. 250, 397–403. https://doi.org/10.1016/j.jad.2019.03.048.
MacMaster, F.P., Carrey, N., Sparkes, S., Kusumakar, V., 2003. Proton spectroscopy in medication-free pediatric attention-deficit/hyperactivity disorder. Biol. Psychiatry 53, 184–187.
Mahone, E.M., Puts, N.A., Edden, R.A.E., Ryan, M., Singer, H.S., 2018. GABA and glutamate in children with Tourette syndrome: a 1H MR spectroscopy study at 7 T. Psychiatry Res. Neuroimaging 273, 46–53. https://doi.org/10.1016/J.PSCYCHRESNS.2017.12.005.
Mahone, E.M., Wodka, E.L., 2008. The neurobiological profile of girls with ADHD. Dev. Disabil. Res. Rev. 14, 276–284. https://doi.org/10.1002/ddrr.41.
Mekle, R., Mlynárik, V., Gambarota, G., Hergt, M., Krueger, G., Gruetter, R., 2009. MR spectroscopy of the human brain with enhanced signal intensity at ultrashort echo times on a clinical platform at 3T and 7T. Magn. Reson. Med. 61, 1279–1285. https://doi.org/10.1002/mrm.21961.
Mikkelsen, M., Barker, P.B., Bhattacharyya, P.K., Brix, M.K., Buur, P.F., Cecil, K.M., Chan, K.L., Chen, D.Y.T., Craven, A.R., Cuypers, K., Dacko, M., Duncan, N.W., Dydak, U., Edmondson, D.A., Ende, G., Ersland, L., Gao, F., Greenhouse, I., Harris, A.D., He, N., Heba, S., Hoggard, N., Hsu, T.W., Jansen, J.F.A., Kangarlu, A., Lange, T., Lebel, R.M., Li, Y., Lin, C.Y.E., Liou, J.K., Lirng, J.F., Liu, F., Ma, R., Maes, C., Moreno-Ortega, M., Murray, S.O., Noah, S., Noeske, R., Noseworthy, M.D., Oeltzschner, G., Prisciandaro, J.J., Puts, N.A.J., Roberts, T.P.L., Sack, M., Sailasuta, N., Saleh, M.G., Schallmo, M.P., Simard, N., Swinnen, S.P., Tegenthoff, M., Truong, P., Wang, G., Wilkinson, I.D., Wittsack, H.J., Xu, H., Yan, F., Zhang, C., Zipunnikov, V., Zöllner, H.J., Edden, R.A.E., 2017. Big GABA: edited MR spectroscopy at 24 research sites. Neuroimage 159, 32–45. https://doi.org/10.1016/j.neuroimage.2017.07.021.
Miller, E.M., Pomerleau, F., Huettl, P., Gerhardt, G.A., Glaser, P.E.A., 2014. Aberrant glutamate signaling in the prefrontal cortex and striatum of the spontaneously hypertensive rat model of attention-deficit/hyperactivity disorder. Psychopharmacology (Berl) 231, 3019–3029. https://doi.org/10.1007/s00213-014-3479-4.
Molina-Luna, K., Pekanovic, A., Röhrich, S., Hertler, B., Schubring-Giese, M., Rioult-Pedotti, M.-S., Luft, A.R., 2009. Dopamine in Motor Cortex Is Necessary for Skill Learning and Synaptic Plasticity. PLoS ONE 4, e7082. https://doi.org/10.1371/journal.pone.0007082.
Moore, C.M., Biederman, J., Wozniak, J., Mick, E., Aleardi, M., Wardrop, M., Dougherty, M., Harpold, T., Hammerness, P., Randall, E., Renshaw, P.F., 2006. Differences in brain chemistry in children and adolescents with attention deficit hyperactivity disorder with and without comorbid bipolar disorder: a proton magnetic resonance spectroscopy study. Am. J. Psychiatria 163, 316–318. https://doi.org/10.1176/appi.ajp.163.2.316.
Mostofsky, S.H., Cooper, K.L., Kates, W.R., 2002. Smaller prefrontal and premotor volumes in boys with ADHD. Biol. Psychiatry 52, 785–794.
Mostofsky, S.H., Simmonds, D.J., 2008. Response inhibition and response selection: two sides of the same coin. Neurosci 20, 751–761.
Muftuler, L.T., Davis, E.P., Buss, C., Head, K., Hasso, A.N., Sandman, C.A., 2011. Cortical and subcortical changes in typically developing preadolescent children. Brain Res. 1399, 15–24. https://doi.org/10.1016/j.brainres.2011.05.018.
Mullins, P.G., McGonigle, D.J., O'Gorman, R.L., Puts, N.A., Vidyasagar, R., Evans, C.J., Cardiff Symposium on, M.R.S. of G.,Edden, R.A., Cardiff Symposium on, M.R.S. of G., 2014. Current practice in the use of MEGA-PRESS spectroscopy for the detection of GABA. Neuroimage 86, 43–52. https://doi.org/10.1016/j.neuroimage.2012.12.004.
Palfrey, J.S., Levine, M.D., Walker, D.K., Sullivan, M., 1985. The emergence of attention deficits in early childhood: a prospective study. Behav. Pediatr. 6, 339–348.
Pavić, A., Holmes, A.O.M., Postis, V.L.G., Goldman, A., 2019. Glutamate transporters: a broad review of the most recent archaeal and human structures. Biochem. Soc. Trans. https://doi.org/10.1042/BST20190316. BST20190316.
Perlov, E., Philipsen, A., Matthies, S., Drieling, T., Maier, S., Bubl, E., Hesslinger, B., Buechert, M., Henning, J., Ebert, D., Tebartz Van Elst, L., 2009. Spectroscopic findings in attention-deficit/hyperactivity disorder: review and meta-analysis. World J. Biol. Psychiatry 10, 355–365. https://doi.org/10.1080/15622970802176032.
Považan, M., Mikkelsen, M., Berrington, A., Bhattacharyya, P.K., Brix, M.K., Buur, P.F., Cecil, K.M., Chan, K.L., Chen, D.Y.T., Craven, A.R., Cuypers, K., Dacko, M., Duncan, N.W., Dydak, U., Edmondson, D.A., Ende, G., Ersland, L., Forbes, M.A., Gao, F., Greenhouse, I., Harris, A.D., He, N., Heba, S., Hoggard, N., Hsu, T.-W., Jansen, J.F.A., Kangarlu, A., Lange, T., Lebel, R.M., Li, Y., Lin, C.-Y.E., Liou, J.-K., Lirng, J.-F., Liu, F., Long, J.R., Ma, R., Maes, C., Moreno-Ortega, M., Murray, S.O., Noah, S., Noeske, R., Noseworthy, M.D., Oeltzschner, G., Porges, E.C., Prisciandaro, J.J., Puts, N.A.J., Roberts, T.P.L., Sack, M., Sailasuta, N., Saleh, M.G., Schallmo, M.-P., Simard,

N., Stoffers, D., Swinnen, S.P., Tegenthoff, M., Truong, P., Wang, G., Wilkinson, I.D., Wittsack, H.-J., Woods, A.J., Xu, H., Yan, F., Zhang, C., Zipunnikov, V., Zöllner, H.J., Edden, R.A.E., Barker, P.B., 2020. Comparison of Multivendor Single-Voxel MR Spectroscopy Data Acquired in Healthy Brain at 26 Sites. Radiology. https://doi.org/10.1148/radiol.2020191037. 191037.

Provencher, S.W., 2001. Automatic quantitation of localized in vivo 1H spectra with LCModel. NMR Biomed. 14, 260–264.

Puts, N.A.J., Edden, R.A.E., 2012. In vivo magnetic resonance spectroscopy of GABA: a methodological review. Prog. Nucl. Magn. Reson. Spectrosc. 60, 29–41. https://doi.org/10.1016/j.pnmrs.2011.06.001.

Puts, N.A.J., Harris, A.D., Mikkelsen, M., Tommerdahl, M., Edden, R.A., Mostofsky, S.H., 2017. Altered tactile sensitivity in children with Attention Deficit Hyperactive Disorder. J. Neurophysiol. https://doi.org/10.1152/jn.00087.2017. jn.00087.2017.

Rae, C.D., 2014. A Guide to the Metabolic Pathways and Function of Metabolites Observed in Human Brain 1H Magnetic Resonance Spectra. Neurochem. Res. 39, 1–36. https://doi.org/10.1007/s11064-013-1199-5.

Reich, W., 2000. Diagnostic Interview for Children and Adolescents (DICA). J. Am. Acad. Child Adolesc. Psychiatry 39, 59–66. https://doi.org/10.1097/00004583-200001000-00017.

Rioult-Pedotti, M.-S., Pekanovic, A., Atiemo, C.O., Marshall, J., Luft, A.R., 2015. Dopamine Promotes Motor Cortex Plasticity and Motor Skill Learning via PLC Activation. PLoS ONE 10, e0124986. https://doi.org/10.1371/journal.pone.0124986.

Roid, G.H., Woodcock, R.W., 2000. Uses of Rasch scaling in the measurement of cognitive development and growth. J. Outcome Meas. 4, 579–594.

Russell, V.A., 2003. Dopamine hypofunction possibly results from a defect in glutamate-stimulated release of dopamine in the nucleus accumbens shell of a rat model for attention deficit hyperactivity disorder–the spontaneously hypertensive rat. Neurosci. Biobehav. Rev. 27, 671–682.

Russell, V.A., Oades, R.D., Tannock, R., Killeen, P.R., Auerbach, J.G., Johansen, E.B., Sagvolden, T., 2006. Response variability in Attention-Deficit/Hyperactivity Disorder: a neuronal and glial energetics hypothesis. Behav. Brain Funct. 2, 30. https://doi.org/10.1186/1744-9081-2-30.

Schür, R.R., Draisma, L.W.R., Wijnen, J.P., Boks, M.P., Koevoets, M.G.J.C., Joëls, M., Klomp, D.W., Kahn, R.S., Vinkers, C.H., 2016. Brain GABA levels across psychiatric disorders: a systematic literature review and meta-analysis of ^{1}H-MRS studies. Hum. Brain Mapp. 37, 3337–3352. https://doi.org/10.1002/hbm.23244.

Shaw, P., Eckstrand, K., Sharp, W., Sci, U.S.A., 2007. Attention-deficit/hyperactivity disorder is characterized by a delay in cortical maturation. Proc. Natl. Acad. Sci. 104, 19649–19654.

Snoussi, K., Gillen, J.S., Horska, A., Puts, N.A., Pradhan, S., Edden, R.A., Barker, P.B., 2015. Comparison of brain gray and white matter macromolecule resonances at 3 and 7 Tesla. Magn. Reson. Med. 74, 607–613. https://doi.org/10.1002/mrm.25468.

Solleveld, M.M., Schrantee, A., Puts, N.A.J., Reneman, L., Lucassen, P.J., 2017. Age-dependent, lasting effects of methylphenidate on the GABAergic system of ADHD patients. NeuroImage Clin. 15, 812–818. https://doi.org/10.1016/j.nicl.2017.06.003.

Stagg, Charlotte J., Bachtiar, V., Johansen-Berg, H., 2011a. What are we measuring with GABA Magnetic Resonance Spectroscopy? Commun. Integr. Biol. 4, 573–575. https://doi.org/10.4161/cib.16213.

Stagg, C.J., Bestmann, S., Constantinescu, A.O., Moreno Moreno, L., Allman, C., Mekle, R., Woolrich, M., Near, J., Johansen-Berg, H., Rothwell, J.C., 2011b. Relationship between physiological measures of excitability and levels of glutamate and GABA in the human motor cortex. J. Physiol. 589, 5845–5855. https://doi.org/10.1113/jphysiol.2011.216978.

Tapper, S., Tisell, A., Lundberg, P., 2017. How does motion affect GABA-measurements? Order statistic filtering compared to conventional analysis of MEGA-PRESS MRS. PLoS ONE 12, e0177795. https://doi.org/10.1371/journal.pone.0177795.

Tkac, I., Andersen, P., Adriany, G., 2001. In vivo 1H NMR spectroscopy of the human brain at 7 T. Magn. Reson. Med. 46, 451–456.

Tkac, I., Starcuk, Z., Choi, I.Y., Gruetter, R., 1999. In vivo 1H NMR spectroscopy of rat brain at 1ms echo time. Magn. Reson. Med. 41, 649–656.

Volkow, N.D., Wang, G.J., Fowler, J.S., Telang, F., Maynard, L., Logan, J., Gatley, S.J., Pappas, N., Wong, C., Vaska, P., Zhu, W., Swanson, J.M., 2004. Evidence that methylphenidate enhances the saliency of a mathematical task by increasing dopamine in the human brain. Am. J. Psychiatry 161, 1173–1180. https://doi.org/10.1176/appi.ajp.161.7.1173.

Wellington, T.M.M., Semrud-Clikeman, M., Gregory, A.L., Murphy, J.M., Lancaster, J.L., 2006. Magnetic resonance imaging volumetric analysis of the putamen in children with ADHD: combined type versus control. J. Atten. Disord. 10, 171–180. https://doi.org/10.1177/1087054705284242.

Willcutt, E.G., Sonuga-Barke, E.J.S., Nigg, J.T., Sergeant, J.A., 2008. Recent developments in neuropsychological models of childhood psychiatric disorders. Adv. Biol. Psychiatry 24, 195–226. https://doi.org/10.1159/000118526.

Zhang, H., Sulzer, D., 2003. Glutamate spillover in the striatum depresses dopaminergic transmission by activating group I metabotropic glutamate receptors. J. Neurosci. 23, 10585–10592. https://doi.org/10.1523/JNEUROSCI.23-33-10585.2003.