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Review

# Fronto-striatal glutamatergic compounds in compulsive and impulsive syndromes: A review of magnetic resonance spectroscopy studies

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ABSTRACT

Compulsivity and impulsivity are cross-disorder traits observed in autism spectrum disorders (ASD), attention deficit hyperactivity disorder (ADHD) and obsessive compulsive disorder (OCD). Aberrant fronto-striatal glutamatergic signalling is core to the understanding of compulsive and impulsive disorders. In this review, the glutamate (Glu) neurochemistry of fronto-striatal circuits in paediatric and adult ASD, ADHD and OCD, as described in 59 studies, is outlined from the perspective of proton magnetic resonance spectroscopy ($^1$H MRS). Despite the methodological inconsistencies between studies, two observations stand out that form possible hypotheses for future studies. Firstly, a possible increase in Glx (combination of Glu, glutamine and GABA) in the striatum across ADHD, OCD and ASD. Secondly, an increased Glx signal in the anterior cingulate cortex in paediatric ASD and ADHD but a lower Glx signal in adult ASD and ADHD. This suggests neurodevelopmental changes in fronto-striatal glutamatergic circuits across the lifespan. Future studies should incorporate more homogeneous samples, perform MRS at field strengths of at least 3 Tesla and provide much more precise and standardized information on methods to improve our understanding of fronto-striatal glutamatergic transmission in compulsive and impulsive syndromes.



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## 1. Introduction

Autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), and obsessive compulsive disorder (OCD) are rather common neurodevelopmental disorders with prevalence rates of about 1% for ASD, 5.3% for ADHD, and between 2 and 3% for OCD (Baird et al., 2006; Polanczyk et al., 2007; Ruscio et al., 2010). The aim of the current study is to review the role of glutamate (Glu) (and GABA) in fronto-striatal circuits in ASD, ADHD and OCD and to examine possible overlap and differences between these disorders based on their underlying traits. Before describing the methods and findings, we will elaborate more on the relationships between the three disorders.

While the origin of symptoms starts very early in life (ASD), in early childhood (ADHD) or in late childhood (OCD), many patients with these disorders have persistent symptoms and impairment well into adulthood (Bloch et al., 2009; Faraone et al., 2006). ASD is characterized by impairments in social interaction, both verbal and nonverbal communication, restricted and stereotyped interests and behaviours; ADHD by inattentiveness, impulsivity and hyperactivity, and OCD by repetitive thoughts, impulses or images (obsessions) and repetitive behaviours or mental acts (compulsions) that cause distress (Hanna, 1995; Perlov et al., 2009). Despite the fact that these disorders clearly differ by their defining characteristics, they also have a strong clinical overlap. Between 25 and 50% of patients with ASD show clinically impairing symptoms of impulsivity, inattentiveness and hyperactivity that pass the threshold for diagnosing ADHD (Rommelse et al., 2010). In turn, the prevalence of comorbid social dysfunction up to full ASD in ADHD children is between 20 and 50% (Rommelse et al., 2010). Both ASD and OCD show repetitive behaviours among their core features and comparison of ASD and OCD symptoms has shown more similarities than differences (Anholt et al., 2010). Elevated ADHD symptoms have been reported in up to 30% of patients with OCD. Conversely, 8% of children with ADHD demonstrate comorbid OCD symptoms (Geller et al., 2000). These findings suggest interrelatedness between ASD, ADHD and OCD. One study to date has examined ADHD and ASD symptoms within an adult OCD patient group, and reported an increase in ASD and ADHD symptoms in patients compared to non-affected controls (Anholt et al., 2010). Autism-related attention switching problems and ADHD inattention proved to be the most significant predictor for OCD symptom dimensions and severity. It can be assumed therefore that attentional problems reflect symptom overlap and a common etiological factor underlying ASD, ADHD, and OCD. However, no other studies so far have further characterized the relationship between ASD, ADHD, and OCD.

Contemporary neuroscience stresses the importance of endophenotypes to elucidate commonalities across disorders (Robbins et al., 2012). In this context, endophenotypes can be described as heritable objectively measurable traits associated with a disorder in the population. These can be well-defined behavioural or cognitive processes associated with deficits in defined neural circuits. These deficits are predicted to be present in first degree relatives, even when unaffected, to a higher degree than in the general population and may enable early detection of a possible disorder (Gottesman and Gould, 2003). If these endophenotypes are investigated across disorders, this would highlight commonalities between seemingly different pathologies. Possible endophenotypes for ASD, ADHD and OCD are the underlying mechanisms of the cross-disorder traits impulsivity and compulsivity. Impulsivity is defined as a predisposition towards rapid unplanned reactions to internal or external stimuli with diminished regard to the potentially negative consequences of these reactions (Chamberlain and Sahakian, 2007; Fineberg et al., 2010). Compulsivity on the other hand, is characterized by a repetitive, irresistible urge to perform certain behaviour, the experience of loss of voluntary control over this urge, the diminished ability to delay or inhibit thoughts and behaviours, and the tendency to perform repetitive acts in a habitual or stereotyped manner (Chamberlain and Menzies, 2009). Compulsivity and impulsivity have been associated with deficits in response inhibition and cognitive control (Dalley et al., 2011). Similarly, they are both evident in substance dependence. ASD and OCD both show compulsive symptoms, while ADHD is, initially, more impulsive. The impulsivity of ADHD patients places them at risk for developing substance use disorders. Addictive behaviour is at first associated with impulsivity, but becomes more related to compulsivity at later stages (Grant and Potenza, 2006; Koob and LeMoal, 1997). All three disorders thus show compulsivity-related symptomatology, though in different ways. ADHD is related to more addictive compulsive behaviour, ASD to stereotyped behaviour, and OCD to more anxiety-based obsessions and compulsions. The nature of the relationship between these different compulsive (and impulsive) disorders is less clear, particularly in terms of underlying mechanisms. The impulsivity seen in ADHD constitutes vulnerability for compulsive drug seeking but does not, for instance, contribute to anxiety-based compulsivity seen in OCD or stereotyped behaviour seen in ASD. However, it is known that the presence of one of these disorders often co-occurs with one or even both of the other disorders. Therefore, it could be argued that a construct shared by all three disorders may be that of altered value estimation. The compulsivity, reflecting fear, seen in OCD is overvalued in a similar way as the overvalue prescribed to stereotyped behaviour in ASD and to reward (and undervalue to possible consequences) in impulsivity and compulsivity in ADHD.

Neuroanatomical models posit the existence of separate but intercommunicating fronto-striatal circuits involved in behavioural regulation (Alexander et al., 1986). In these circuits, a striatal component may drive impulsive or compulsive behaviour while a frontal component exerts control over it. An imbalance within these fronto-striatal circuits can lead to impulsivity or compulsivity. In ASD and ADHD dorsal fronto-striatal circuits have been linked to cognitive control while connections between orbitofrontal cortex (OFC) and ventral striatum are associated with reward and motivation (Alexander et al., 1986; Langen et al., 2012). Repetitive behaviours common in ASD and OCD have been linked to executive functioning deficits in the frontal cortex and its connections to striatal regions as well (Thakkar et al., 2008). This suggests that the tendencies to perform impulsive behaviour (especially present in ADHD) or compulsive behaviour, like the repetitive acts among ASD and OCD, are driven by striatal brain areas. The loss of control or the deficit in behavioural inhibition involves prefrontal cortex regions regulating monoamines within fronto-striatal circuits (Chantiluke et al., 2014; Del Campo et al., 2013; Silvetti et al., 2013). Impulse control deficits

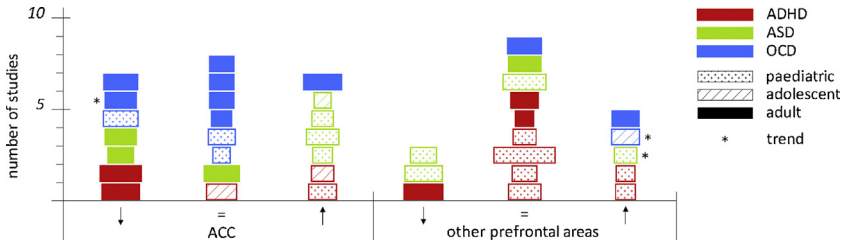


**Fig. 1.** Proton magnetic resonance studies of patients with attention deficit hyperactivity disorder (ADHD), autism spectrum disorders (ASD) and obsessive compulsive disorder (OCD) using a healthy comparison group. Measures of Glx (and Glu) by prefrontal brain area. The width of each study block is proportional to the square root of the total sample size (number of patients plus number of healthy controls). ACC, anterior cingulate cortex; ↓, decrease (patients < controls); = no difference (patients = controls) ↑, increase (patients > controls); *, trend towards increase or decrease.

usually involve aberrant dopaminergic functioning (Fineberg et al., 2010). Whether dopamine dysregulation reflects a primary deficit or is secondary to fronto-striatal glutamatergic deficits remains unclear. The glutamate-dopamine interaction is critical for the top-down control from prefrontal regions to the striatum (Arnsten, 2009). Fronto-striatal circuits such as those implicated in regulating compulsive and impulsive behaviour have a high glutamatergic receptor density (Monaghan et al., 1985). Glutamatergic receptors modulate the metabolism and function of fronto-striatal circuits by influencing synapse induction and elimination, cell migration, and ionotropic and metabotropic synaptic transmission. Dysregulation in dopamine associated with ASD, ADHD and OCD may therefore reflect abnormalities in glutamatergic functioning which in turn alters monoaminergic transmission (Carrey et al., 2007; Fatemi, 2008; Pittenger et al., 2011).

Additional insights in the neurobiology of ASD, ADHD and OCD and their overlap can be found by investigating the neurochemistry of the brain. Proton magnetic resonance spectroscopy ($^1$H MRS) allows for non-invasive in vivo quantification of specific neurometabolites such as *N*-acetylaspartate (NAA), creatine and phosphocreatine (tCr), choline (Cho), myo-inositol (mI), glutamate (Glu) and gamma aminobutyric acid (GABA). Glutamate and glutamine are together referred to as Glx. Although some studies of ASD, ADHD and OCD examined glutamatergic changes (Pittenger et al., 2011), most studies focus on monoamines. However, the role of neuronal Glu (even if glial and metabolic Glu transmission is discounted) remains highly relevant even though it is representing only a portion of total brain Glu as measured by $^1$H MRS (Pittenger et al., 2011). GABA is even less well studied, despite its dominant inhibitory role in the central nervous system.

Thus, the aim of the current manuscript is to review the role of glutamatergic compounds in fronto-striatal circuits in ASD, ADHD and OCD and to examine possible overlap and differences between these disorders based on their underlying traits. Further, we summarize the current knowledge on $^1$H MRS studies measuring Glu and Glu-related neurochemicals in regions encompassing the fronto-striatal circuits. Methodological issues explaining inconsistent findings and future study suggestions are also discussed.

## 2. Methods

With the key words "proton magnetic resonance spectroscopy" in combination with respectively "attention deficit hyperactivity disorder", "autism spectrum disorder" or "obsessive compulsive disorder" we searched the PubMed library (http://www.ncbi.nlm.nih.gov/pubmed) for studies in English using $^1$H MRS to compare Glu-related levels in patients with ASD, ADHD or OCD versus healthy subjects. Studies examining changes in glutamatergic levels after administration of medication or psychosocial treatment were also included. Both paediatric and adult studies were accepted, regardless of sample size. In addition, we only included studies examining brain regions in the fronto-striatal circuit or areas that have proven to be closely related to prefrontal and striatal brain regions, such as thalamus, amygdala and cerebellum (Durston et al., 2011). Due to the nature of Glu and the developmental changes within the fronto-striatal circuit, different patterns of the metabolite levels can be expected between children and adult patients (Pouwels et al., 1999). The findings of children and adult studies will be discussed separately where applicable. We abstained from performing a meta-analysis, since the underlying studies differ too much in design, selection of participants and methods, which makes it impossible to pool data in an appropriate matter (Crowther et al., 2010). However, we checked whether study results were dependent on sample size by comparing sample sizes of studies that did report differences in Glu or Glx signal to those that did not find differences.

## 3. Results

Fifty-nine studies examining glutamatergic levels with $^1$H MRS in ASD, ADHD, or OCD were included for further examination. Forty-three studies investigated either one of the three disorders (ADHD, ASD, OCD) compared to healthy controls; Sixteen examined changes after treatment administration in either ADHD or OCD. Sixteen studies compared Glu or Glx in ADHD patients versus healthy individuals (Table 1; Fig. 1), seven studied changes after treatment administration in ADHD (Table 2). Sixteen compared ASD with healthy individuals (Table 3; Fig. 1). Eleven studies compared OCD patients versus healthy controls (Table 4; Fig. 1) and nine studies examined glutamatergic changes after treatment in OCD (Table 5). Three of the ADHD and four of the OCD studies examining changes after treatment also included a healthy comparison group to assess differences in metabolite levels at baseline. No studies were found in which treatment changes in ASD were examined, possibly due to the fact that no specific pharmacological treatment is currently available for ASD core symptoms. An overview of the results from the studies comparing patients with healthy control subjects can be found in Figs. 1 and 2.

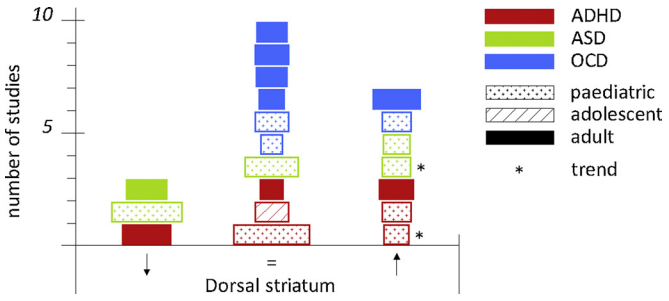


**Fig. 2.** Proton magnetic resonance studies of patients with ADHD, ASD and OCD using a healthy comparison group. Measures of Glx (and Glu) in the striatum. The width of each study block is proportional to the square root of the total sample size (number of patients plus number of healthy controls). Abbreviations as in Fig. 1.

**Table 1**
Proton magnetic resonance spectroscopy studies reporting glutamate (and GABA) differences between ADHD patients and healthy controls.

| References | Subjects | Comorbidities | Medication Status | Field strength | MRS Sequence | TR/TE/averages | Scan time | Coil type | Voxel size | Regions of interest | Quantification method | Reported results (calculated effect sizes, cohen's *d*) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Hesslinger et al. (2001) | 5 ADHD, 5 ADD, 5 HC<br>*Adults* | 3 avoidant and 1 antisocial personality | Psychotropic free | 2 T | PRESS | 3000/30/N.A | N.A | Quadrature headcoil | 2 × 2 × 2 cm | Left DLPFC<br>Left Striatum | Absolute concentrations | No differences between ADHD, ADD and HC |
| MacMaster et al. (2003) | 9 ADHD, 9 HC<br>*Children* | 6 ODD | Med free >48 h | 1.5 T | $^{1}$H MRS spin echo | 1500/135/256 | ~6.5 min per voxel | N.A | 4 $cm^3$<br>6 $cm^3$ | Right PFC<br>Left Striatum | Cr ratios | Increased Glx/Cr in Right PFC (1.47); trend for Left striatum ()<br>In controls positive correlation for age and Glx/Cr and in ADHD positive correlation for onset age and Glx/Cr |
| Courvoisie et al. (2004) | 8 ADHD, 8 HC<br>*Children* | None | Mostly stimulants (MPH) | 1.5 T | STEAM | 1600/20/128 | ~3.5 min | Standard MR headcoil | 2 × 2 × 2 cm | Bilateral frontal lobe (including SFG) | Cr ratios | Increased Glu/Cr in right frontal lobe (1.83) and left frontal lobe (1.57) |
| Sun et al. (2005) | 10 ADHD-C, 10 ADHD-I, 10 HC<br>*Adolescents* | 1 CD, 2 ODD, 3 Tic disorder | All med naïve | 1.9 T | PRESS | 1500/35.5/200 | ~5 min per voxel | Circularly polarized headcoil | 2 × 2 × 2 cm | Bilateral lenticular nuclei | Cr ratios | No differences between ADHD-C, ADHD-I and HC (left: – 0.36, right 0.17) |
| Moore et al. (2006) | 23 ADHD, 8 HC<br>*Children* | 8 ADHD + bipolar ODD | Amphetamine, Bupropion, atomoxetine etc | 1.5 T | PRESS | 2000/30/128 | ~4 min | N.A | 2 × 2 × 1.2 cm | Anterior cingulate | mI ratios<br>Cr ratios | Increased Glx/mI in ADHD (0.89) compared to both ADHD + bipolar and HC; same for Glx/Cr |
| Perlov et al. (2007) | 28 ADHD, 28 HC<br>*Adult* | Depression, Borderline, SUD and neurological disorders excluded | All med free > 6 months | 1.5 T | CSI PRESS | 1500/30/4 | 30 min in total | Quadrature headcoil | 16 × 16 voxels<br>6 × 11 × 1.5 VOI | Bilateral ACC | Cr ratios | Decreased Glx/Cr in Right ACC (−0.60) |
| Ferreira et al. (2009) | 10 ADHD-C, 9 ADHD-I, 12 HC<br>*Adult* | Dysthymia, ODD | Psychotropic med naïve | 1.5 T | PRESS | 1500/30/256 | 6:36 min per voxel | N.A | 16 × 16 voxels | Bilateral VMPFC<br>Bilateral pulvinar<br>Bilateral putamen<br>Bilateral head caudate | Cr ratios | Increased Glx/Cr in left putamen in ADHD-C compared to both ADHD-I (1.17) and HC (1.27) |
| Soliva et al. (2010) | 21 ADHD, 21 HC<br>*Children* | All axis I and neurological disorders excluded (ODD too) | All stimulants (MPH) | 1.5 T | PRESS | 2000/30/256 | ~ 8.5 min per voxel | N.A | 2 × 2 × 2 cm | Right DLPFC<br>Left cerebellar hemisphere | Absolute concentrations | No differences between ADHD and HC(cerebellum: 0.02) |
| Yang et al. (2010) | 15 ADHD, 22 HC<br>*Adolescents* | 6 ODD, 3 mood/anxiety disorder | 11 MPH, 1 bupropion | 1.5 T | PRESS | 1600/35/128 | ~3.5 min | N.A | 2 × 2 × 2 cm | Bilateral frontal lobe (ACG + MFG) | Absolute concentrations (i.u.)<br>CR + PCR ratios | No differences between ADHD and HC (left 0.71, right 0.04) |
| Perlov et al. (2010) | 30 ADHD, 30 HC<br>*Adults* | Depression, Borderline, SUD and neurological disorders excluded | All med free > 6 months | 1.5 T | CSI PRESS | 1500/30/4 | 30 min in total | Quadrature headcoil | 16 × 16 voxels<br>6 × 11 × 1.5 VOI | Bilateral cerebellar hemispheres | Cr ratios | Increased Glx/Cr in left cerebellar hemisphere (0.74) |
| Dramsdahl et al. (2011) | 29 ADHD, 38 HC<br>*Adults* | All axis I and neurological disorders excluded (epilepsy too) | 15 stimulants, 1 atomoxetine | 3 T | PRESS | 1500/35/N.A | N.A | 8 channel coil | 2 × 2 × 2 cm | Bilateral midfrontal region including ACC | Cr ratios | Decreased Glu/Cr in left midfrontal region ();<br>without comorbidity the difference with controls was larger<br>Negative correlation with inattentive symptoms |
| Arcos-Burgos et al. (2012) | 14 ADHD, 20 HC<br>*Adults* | ODD, CD<br>1 anxiety, 5 depression | All med naïve | 1.5 T | PRESS | 1500/30/3 | 6:05 and 10:23 min | 8 channel coil | CSI | 14 regions | Cr ratios | Increased Glx/Cr in right posterior cingulate |
| Edden et al. (2012) | 13 ADHD, 19 HC<br>*Children* | 5 ODD | 7 stimulants | 3 T | PRESS | 1800/68/N.A | 10 min | N.A | 3 × 3 × 3 cm | Motor cortex (hand knob) | Absolute concentrations (i.u.) | Decreased GABA in ADHD compared to HC |
| Tafazoli et al. (2013) | 13 ADHD, 13 HC<br>*Children* | Psychiatric and neurological excluded | 1 MPH, 2 amphetamines | 1.5 T | PRESS | 1500/30/4 | N.A | Quadrature headcoil | MRSI voxels | Bilateral middle frontal gyrus | Absolute concentrations (i.u.) | No differences between ADHD and HC (left −0.13, right −0,42) |
| Benamor (2014) | 102 ADHD, 38 HC<br>*Children* | PDD, psychosis and IQ < 70 excluded | 57 stimulants | 1.5 T | PRESS | 1500/30/128 | 40 min in total | N.A | 8 $cm^3$ | Bilateral PFC<br>Bilateral striatum<br>Left cerebellum | Cr ratios | Increased Glx/Cr in cerebellum (0.44) with highest levels in medication naive patients |
| Maltezos et al. (2014) | 40 ADHD, 20 HC<br>*Adults* | All axis I and neurological disorders excluded | 24 naïve, 16 MPH or dextramphetamine | 1.5 T | PRESS | 3000/30/N.A | 45 min in total | N.A | 2 × 2 × 2<br>2 × 2 × 1.5<br>1.6 × 2.4 × 2 | Left parietal (med)<br>Left basal gang (caudate/putamen)<br>Left DLPFC | Absolute concentrations | Decreased Glx in basal ganglia and in DLPFC (this did not survive correction) (−1,05)<br>No differences medicated/unmedicated |

ACC, anterior cingulate cortex; ACG, anterior cingulate gyrus; ADD, attention deficit disorder; ADHD, attention deficit hyperactivity disorder; ADHD-c, combined subtype; ADHD-I, inattentive subtype; CD, conduct disorder; CSI, chemical shift imaging; Cr, creatine; DLPFC, dorsolateral prefrontal cortex; GABA, gamma-aminobutyric acid; Glx, glutamate and glutamine; Glu, glutamate; HC, healthy controls; i.u., institutional units; MFG, middle frontal gyrus; mI, myo-inositol; MPH, methylphenidate; MRSI, magnetic resonance spectroscopic imaging; N.A, not applicable; ODD, oppositional defiant disorder; PDD, pervasive developmental disorder; PFC, prefrontal cortex; SFG, superior frontal gyrus; SUD, substance use disorder; T, tesla; TE, echo time; TR, repetition time; VMPFC, ventromedial prefrontal cortex; VOI, volume of interest. PRESS and STEAM are single voxel spectroscopy acquisition methods.

**Table 2**
Proton magnetic resonance spectroscopy studies reporting glutamate changes with treatment in ADHD patients.

| References | Subjects | Comorbidities | Treatment administered | Field strength | MRS sequence | TR/TE/averages | Scan time | Coil type | Voxel size | ROI(s) | Quantification method | Reported results (calculated effect sizes, cohen's *d*) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Jin et al. (2001) | 12 ADHD, 10 HC *Children* | Psychiatric or neurological disorder excluded | MPH (10 mg) | 1.9 T | PRESS | 1500/35.5/200 | ~5 min per voxel | Circularly polarized head coil | 2 × 2 × 2 cm | Bilateral globus pallidus | Cr ratios | No differences between ADHD and HC before and after treatment (left −0.1, right 0.41) |
| Carrey et al. (2002) | 4 ADHD *Children* | ODD | MPH and atomoxetine | 1.5 T | PRESS | 1500/135/256 | 10 min in total | N.A. | 7 $cm^3$<br>4 $cm^3$ | Left striatum<br>Right PFC | Cr ratios | Reduction of Glx/Cr in striatum (mean change 56.1%) after treatment |
| Carrey et al. (2003) | 14 ADHD *Children* | 3 ODD | MPH (10–15 mg), Dexedrine (2.5–15 mg), atomoxetine (20–30 mg) | 1.5 T | Long echo sequence | 1500/135/256 | 7 min per voxel | N.A. | 4 $cm^3$ | Left striatum<br>Right PFC | Cr ratios | Reduction of Glx/Cr (35%) in striatum after treatment (0.27) |
| Carrey et al. (2007) | 13 ADHD-C, 10 HC *Children* | Psychiatric or neurological disorder excluded | MPH (0.3–0.6 mg/kg) | 1.5 T | PRESS | 2000/30/256 | ~8 min per voxel | N.A. | 4 $cm^3$ | Left Striatum<br>Right PFC | Absolute concentrations | Baseline Glu/Glx increased in striatum. (0.92)<br>No reduction after treatment |
| Hammerness et al. (2012) | 10 ADHD, 12 HC *Adolescents* | None | MPH (up to 1.5 mg/kg) | 4 T | PRESS | 2000/30/128 | ~4 min | Proton volumetric headcoil | 2 × 2 × 2 cm | ACC | mI ratios | Baseline Glu, Gln, Glx increased (0.60, 0.46, 0.25), correlated with ADHD rating scale. Trend towards reduction after treatment |
| Wiguna et al. (2012) | 21 ADHD *Children* | None | MPH (20 mg long action p/d, 12 weeks( | 1.5 T | Unknown | 1000/30/N.A | N.A | Circularly polarized headcoil | 2 × 2 × 2 cm | Bilateral PFC | Cr ratios | Reduction Glu/Cr (15% in R, 14% in L PFC) (0.694) after treatment |
| Husarova et al. (2014) | 21 ADHD *Children* | Current MDD, anxiety, neurological disorders, learning disorders and tics excluded | 10 used MPH (18 mg for 5 days and then 36 or 54)<br>12 used ATX (0.5 mg for 5 days and then 12 or 1.4) | 1.5 T | PRESS | 3000/30/128 | ~6.5 min per voxel | N.A | 8 mL | Bilateral DLPFC and the white matter behind it | Absolute concentrations + Cr ratios | Increased WM Glx in the right hemisphere after MPH<br>Increased WM Glx in the left hemisphere after ATX (−0.74) |

ACC, anterior cingulate cortex; ADHD, attention deficit hyperactivity disorder; ADHD-c, combined subtype; ATX, atomoxetine; Cr, creatine; Glu, glutamate; Glx, glutamate and glutamine; HC, healthy controls; MDD, major depressive disorder ml, myo-inositol; MPH, methylphenidate; N.A, not applicable; ODD, oppositional defiant disorder; PFC, prefrontal cortex; T, tesla; TE, echo time; TR, repetition time; VMPFC, ventromedial prefrontal cortex; WM, white matter. PRESS is a single voxel spectroscopy acquisition method.

**Table 3**
Proton magnetic resonance spectroscopy studies reporting glutamate differences between ASD patients and healthy controls.

| References | Subjects | Comorbidities | Medication status | Field strength | MRS Sequence | TE/TR/averages | Scan time | Coil type | Voxel size | ROI(s) | Quantification method | Reported results (calculated effect sizes, cohen's *d*) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Friedman et al. (2003) | 45 ASD, 15 DD,13 HC *Children* | Neurological disorders, genetic syndromes excluded | Psychoactive excluded | 1.5 T | PEPSI | 2000/20 and 272/N.A | 20 min per volume | Receive only linear bird-cage coil | CSI | Frontal Striatum Thalamus | Absolute concentrations | No differences between ASD, DD and HC (overall −0.94, not specified per region) |
| Page et al. (2006) | 25 ASD, 21 HC *Adults* | Neurological disorders, genetic syndromes excluded | Psychotropic excluded | 1.5 T | PRESS | 3000/35/160 | ~8 min per voxel | N.A | 6 $cm^3$ 8 $cm^3$ | Amygdala-hippo-campal complex | Absolute concentrations and Cr ratios | Increased Glx in amygdala (0.92) |
| DeVito et al. (2007) | 26 ASD, 29 HC ♂ *Children* | Neurological disorders, genetic syndromes excluded | Stimulants, SSRI, risperidone, choline sterase inhibitor | 3 T | $^1$H MRSI sequence | 1800/135/N.A | 30 min in total | Quadrature RF headcoil | 0.8 × 0.8 × 0.9 cm | Grey and white matter in cerebrum | Absolute concentrations (i.u.) | Decreased Glx in grey matter (frontal (−0.15 left and −0.66 right), cerebellum |
| Hardan et al. (2008) | 18 ASD, 16 HC ♂ *Children* | Genetic and metabolic, TS, fragile X excluded | No information | 1.5 T | STEAM | 1600/20/4 | N.A | N.A | CSI | Bilateral thalamus | Absolute concentrations | Trend towards a decrease in left thalamus (-0.62) |
| O'Brien et al. (2010) | 22 Asperger, 22 HC *Adults* | Neurological disorders, genetic syndromes excluded | Psychotropic free | 1.5 T | PRESS | 3000/35/160 | ~8 min per voxel | Quadrature headcoil | 2 × 2 × 1.5 cm | Amygdala-hippocampal complex | Absolute concentrations and Cr ratios | No differences between Asperger and HC |
| Bernardi et al. (2011) | 14 ASD, 14 HC *Adults* | All axis I and neurological disorders excluded | All med free | 3 T | PRESS | 2000/30/1 per encoding step | N.A | N.A | 1 × 0.75 × 0.75 cm | ACC Thalamus | Absolute concentrations | Decreased Glx in ACC (−1.30) |
| Aoki et al. (2012) | 24 ASD, 25 HC ♂ *Adults* | Neurological disorders, brain injury, addiction excluded | All med free | 3 T | Unknown | 3000/15/136 | ~7 min | 8 channel coil | 2 × 2 × 2 cm | ACC | Unknown | No differences between ASD and HC |
| Harada et al. (2011) | 12 ASD, 10 HC *Children* | Authors do not report any exclusion criteria | Authors do not provide information on medication | 3 T | STEAM (MEGA) PRESS | 2500/68/256 | ~10.5 min per voxel | Birdcage headcoil | 3 × 3 × 3 cm | Lenticular nuclei Left frontal lobe | Absolute concentrations and ratios | Trend towards increased Glu/NAA in both regions (0.42 and 0.67) Decreased GABA in the frontal lobe |
| Bejjani et al. (2012) | 8 ASD, 10 HC<br>26 ASD, 16 HC *Children* | Medical and neurological disorders excluded | 1 fluoxetine 1 MPH<br>5 stimulants 1 atomoxetine Anti-depress + anti-psychotic | 1.5 T | PRESS | 1500/25/256 | ~6.5 min | Quadrature headcoil | 2.4–3.6 $cm^3$ 4 × 4 voxels<br>0.9 × 1.1 × 1.1 cm | pACC<br>pACC | Absolute concentrations | Increased Glx (1.03)<br>Increased Glx (0.98) |
| Joshi et al. (2013) | 7 ASD, 7 HC *Adolescents* | Yes (no information on which) | SSRI, stimulant, antidepressants and psychotics | 4 T | 2DJ PRESS | 2000/20 to 250/16 and 32 | ~7 min | N.A | 8 $cm^3$ 3.375 $cm^3$ | ACC | Absolute concentrations (i.u.) | Increased Glu in ACC (2.47) |
| Corrigan et al. (2013) | 53 ASD, 20 DD, 49 HC *Children* | Genetic, sensory and motor impairments, CVD excluded | Stimulants, antidepressants, antipsychotics and anticonvulsant | 1.5 T | PRESS | 2000/20/N.A | N.A | Birdcage RF headcoil (receive only) | 1 $cm^3$ | Anterior commisure Basal ganglia (GM and WM) | Absolute concentrations | Decreased Glx in WM in 3–4 year old ASD patients (−1.43) but no (longitudinal) differences across the three age groups (3–4, 6–7 and 9–10) |
| Kubas et al. (2012) | 12 ASD, 16 HC *Children* | Authors do not provide information on comorbidities | Authors do not provide information on medication | 1.5 T | PRESS | 1500/35/192 | ~5 min | N.A | | Frontal lobe (OFC) | Absolute concentrations (i.u.) | Decreased Glx (−1.07) Decreased GABA |
| Gaetz et al. (2014) | 17 ASD, 17 HC *Children* | Genetic, neurological, sensory and motor impairments excluded | 13 medication free, 2 SSRI's, 1 mood disorder treatment and 1 atypical antipsychotics | 3 T | MEGA PRESS | 1500/68/N.A | ~7 min per voxel | 32 channel coil (receive only) | 3 × 3 × 3 cm 4 × 3 × 2 | Motor Visual Auditory | Cr ratios | Decreased GABA in ASD in motor and auditory cortex |
| Horder et al. (2013) | 28 ASD, 14 HC *Adults* | Psychiatric or medical disorder affecting brain development excluded | Naïve | 1.5 T | PRESS | 3000/30/N.A | N.A | N.A | 2 × 2 × 1.5 1.6 × 2.4 × 2 | Left Basal ganglia Left DLPFC | Absolute concentrations (i.u.) | Decreased Glx in basal ganglia (−1.48) |
| Hassan et al. (2013) | 10 ASD, 10 HC *Children* | Neurological and metabolic disorders excluded | Authors do not provide information on medication | 1.5 T | PRESS | 1500/30/3 | N.A | N.A | 0.2 × 0.2 × 0.2 cm | Bilateral ACC Left striatum Left cerebellum Left frontal lobe | Absolute concentrations (i.u.) | Increased Glu in all regions (1.83 in striatum, 1.93 in ACC) |
| Tebartz van Elst et al. (2014) | 29 ASD, 29 HC *Adults* | Axis I excluded (except depression & anxiety) | SSRI's and neuroleptics | 3 T | PRESS | 3000/30/N.A | N.A | 12 channel coil | 2.5 × 1.6 × 2 2 × 2 × 2 cm | ACC Left cerebellum | Absolute concentrations (i.u.) | Decreased Glu and Glx in the ACC (−0.9) |

ACC, anterior cingulate cortex; ASD, autism spectrum disorder; CSI, chemical shift imaging; Cr, creatine; CVD, cardiovascular disease; DD, delayed development; DLPFC, dorsolateral prefrontal cortex; Glx, glutamate and glutamine; Glu, glutamate; GABA, gamma-aminobutyric acid; GM, grey matter; HC, healthy controls; i.u., institutional units; MPH, methylphenidate; MRSI, magnetic resonance spectroscopic imaging; N.A, not applicable; NAA, *N*-acetylaspartate; OFC, orbitofrontal cortex; pACC, pregenual anterior cingulate cortex; PEPSI, proton echoplanar spectroscopic imaging; SSRI, selective serotonin reuptake inhibitor; T, tesla; TE, echo time; TR, repetition time; TS, tuberous sclerosis; WM, white matter. PRESS and STEAM are single-voxel spectroscopy acquisition methods. ♂, male participants.

**Table 4**
Proton magnetic resonance spectroscopy studies reporting glutamate differences between OCD patients and healthy controls.

| References | Subjects | Comorbidities | Medication status | Field strength | MRS Sequence | TR/TE/averages | Scan time | Coil type | Voxel size | ROI(s) | Quantification method | Reported results (calculated effect sizes, cohen's *d*) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ebert et al. (1997) | 12 OCD, 6 HC *Adults* | Medical illness, schizoaffective and dementia excluded | 10 med free > 6 months, 2 clomipramine or fluvoxamine | 2 T | PRESS | 1500/30/256 | ~6.5 min per voxel | N.A | 2 × 2 × 2 cm | Bilateral anterior cingulate Right striatum | Relative to pCr/Cr | No differences between OCD and HC (striatum −0.35) |
| Bartha et al. (1998) | 13 OCD, 13 HC *Adults* | Schizoaffective disorders excluded | Med free > 6 wk | 4 T | STEAM | 1500/20/N.A | N.A | N.A | 1.5 × 2 × 1.5 cm | Left striatum (caudate + putamen) | Unknown | No differences between OCD and HC |
| Rosenberg et al. (2004) | 20 OCD, 14 MDD, 14 HC *Children* | 2 OCD anxiety, 1 ADD, 1 ODD, 1 dysthymia | All med naïve | 1.5 T | PRESS | 3000/30/512 | 60 min in total | N.A | 2 × 1.5 × 1 cm | ACC | Absolute concentrations (mmol) | Decreased Glx in OCD and MDD compared to HC (No difference between OCD and MDD) (−1.06) |
| Whiteside et al. (2006) | 15 OCD, 15 HC *Adults* | Substance abuse, medical/neurological/psychosis excluded | Stable doses of psychotropic medication | 1.5 T | PRESS | 2000/35/128 | ~4 min per voxel | N.A | 2 × 2 × 1 cm | Bilateral head caudate Bilateral OFC | Cr ratios | Increased Glx/Cr in right OFC (1.12) |
| Yücel et al. (2007) | 19 OCD, 19 HC *Adults* | All axis I disorders excluded | Stable doses of SSRI, venlafaxine etc | 3 T | PRESS | 3000/30/128 | ~6.5 min per voxel | N.A | 6.5 $cm^3$ | Dorsal ACC | Absolute concentrations (i.u.) | Trend towards decreased Glx in medicated patients |
| Starck et al. (2008) | 9 OCD, 16 HC *Adults* | Mild depression dysthymia 1 GAD | SSRI's, hypnotics etc | 1.5 T | PRESS | 2000/30/256 | ~8.5 min per voxel | Birdcage headcoil | 1.5 $cm^3$ 3.6 $cm^3$ 4 $cm^3$ | Right caudate Bilateral ACC | Absolute concentrations (i.u.) | No differences between OCD and HC Positive correlation between symptom severity and caudate Glx in OCD |
| Yücel et al. (2008) | 20 OCD, 26 HC ♀ *Adults* | All axis I disorders excluded | Stable doses of psychotropic medication | 3 T | PRESS | 3000/30/N.A | 30 min in total | N.A | 6.5 $cm^3$ | Bilateral dorsal ACC Bilateral rostral ACC | Absolute concentrations (i.u.) | Decreased Glx in bilateral rostral and left dorsal ACC in ♀ (−1.03) Correlation Glx and symptom severity |
| Bedard and Chantal (2011) | 13 OCD, 12 HC *Adults* | Active axis I disorders excluded | 2 med free, 11 SSRI, clompipramine or venlafaxine | 1.5 T | PRESS | 1500/30/128 | 45 min in total | Proton head coil | 8–9.6 $cm^3$ | Bilateral OFC Bilateral thalamus ACC | Relative to Cr | No differences between OCD and HC (ACC −0.45, left OFC −0.01, right OFC −0.6, right thalamus 0.44) |
| Simpson et al. (2012) | 24 OCD, 22 HC *Adults* | Tics (2) and MDD (4) | Med free > 10 wk | 3 T | PRESS | 1500/68/256 | ~6.5 min per voxel | 8 channel headcoil | 2.5 × 3 × 2.5 cm 1 × 2 × 4.8 cm | MPFCDLPFC | Brain water ratios (i.u.) | No differences between OCD and HC in Glx (MPFC 0.03, DLPFC −0.12) Decreased GABA in MPFC |
| Gnanavel et al. (2013) | 26 OCD, 15 unaffected relatives, 16 HC *Adults* | Axis I disorders excluded | Authors do not provide information on medication | 1.5 T | PRESS | 2000/30/256 | ~8.5 min per voxel | Phase-array headcoil | 1 × 1 × 1 cm | Caudate nucleus ACC Medial thalamus | Absolute concentrations | Increased Glx in caudate (3.81) and ACC (5.74) in OCD patients > unaffected siblings > HC |
| Weber et al. (2013) | 15 OCD, 18 HC (after dropout) *Adolescents* | Psychosis, Bipolar disorder, CD, substance or eating disorder excluded | Medication naïve | 3 T | PRESS | 2500/30/192 | ~8 min per voxel | 8 channel headcoil (receive only) | 2 × 2 × 2.5 | Bilateral PFC white matter next to ACC | Absolute concentrations | No differences between OCD and HC except for a trend towards increased Glx in the right PFWM (*p* .07) (0.37) |

ACC, anterior cingulate cortex; ADD, attention deficit disorder; CD, conduct disorder; Cr, creatine; DLPFC, dorsolateral prefrontal cortex; GABA, gamma-aminobutyric acid; GAD, generalized anxiety disorder; Glx, glutamate and glutamine; HC, healthy controls; i.u., institutional units; MDD, major depressive disorder; MPFC, middle prefrontal cortex; N.A, not applicable; OCD, obsessive-compulsive disorder; ODD, oppositional defiant disorder; OFC, orbitofrontal cortex; pCr, phosphocreatine; SSRI, selective serotonin reuptake inhibitor; T, Tesla; TE, echo time; TR, repetition time. PRESS and STEAM are all single-voxel spectroscopy acquisition methods. ♀, female participants.

**Table 5**
Proton magnetic resonance studies reporting glutamate changes with treatment in OCD patients.

| References | Subjects | Comorbidities | Treatment administered | Field strength | MRS sequence | TR/TE/averages | Scan time | Coil type | Voxel size | ROI(s) | Quantification method | Reported results (calculated effect sizes, cohen's *d*) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Moore et al. (1998) | 1 OCD *Children* | None | Paroxetine (10–20 mg/day) | 1.5 T | PRESS | 3000/30/512 | 27 min | N.A | 0.7 $cm^3$ | Head left caudate | Brain water ratios | Reduced Glx after 12 wk of treatment |
| Rosenberg et al. (2000) | 11 OCD, 11 HC *Children* | 4 anxiety, 1 dysthymia, 2 ODD | Paroxetine (10–60 mg/day, *M* = 45) | 1.5 T | PRESS | N.A/N.A/N.A | 60 min in total | Quadrature headcoil | 0.7 $cm^3$ | Head left caudate | Brain water ratios | Increased baseline Glx, reduction after treatment, correlated with symptoms |
| Bolton et al. (2001) | 1 OCD *Children* | None | Paroxetine (10–40 mg/day) | 1.5 T | PRESS | 3000/30/512 | 27 min | Quadrature headcoil | 0.7 $cm^3$ | Head left caudate | Brain water ratios | Reduced Glx after 12 weeks of treatment |
| Benazon et al. (2003) | 23 OCD *Children* | ODD, ADD, Dysthymia, GAD, SAD | CBT (12 weeks) | 1.5 T | PRESS | 3000/30/512 | 60 min in total | N.A | 0.7 $cm^3$ | Head left caudate | Brain water ratios | No changes after 12 weeks of CBT (−0.47) |
| Lazaro et al. (2012) | 11 OCD *Children* | All psychiatric and neurological disorders excluded | SSRI (20–60 mg/day) and behavioural counselling | 1.5 T | PRESS | 1500/35/N.A | N.A | Quadrature headcoil | 2 × 3 × 2 cm<br>2 × 2 × 2 cm | Anterior cingulate/ medial frontal lobe<br>Bilateral striatum | Absolute concentrations (mmol) | No changes after treatment (left striatum −0.09, right striatum −0.1, ACC −1.4) |
| O'Neill et al. (2012) | 5 OCD, 9 HC *Children* | Authors do not report any exclusion criteria | CBT | 1.5 T | PRESS | 1500/30/N.A | 90 min in total | Quadrature headcoil | 0.9 × 1.1 × 1.1 cm | pACC<br>Putamen<br>Thalamus | Absolute concentrations (i.u.) | No differences between OCD and HC before and after treatment |
| Whiteside et al. (2012) | 15 OCD, 15 HC *Children* | 5 GAD, 2 ADHD, specific phobia and depression | 16 sessions of BT, 2nd scan 4 months later | 1.5 T | PRESS | 2000/35/128 | 60 min in total | N.A | 4 $cm^3$ | Head caudate<br>pACC | Absolute concentrations and Cr ratios | No baseline differences between OCD and HC but reduced Glx in caudate after treatment (excluded ADHD patients) (1.71) |
| Zurowski et al. (2012) | 16 OCD, 9 HC, *Adults* | 1 ADHD, 2 mild depressive episode | CBT (3 months) | 3 T | PRESS | 3000/30/128 | ~6.5 min per voxel | 8 channel headcoil | 2 $cm^3$ | Right lateral OFC<br>Rostral ACC<br>Right ventral striatum | Absolute concentrations (i.u.) | No differences between OCD and HC before and after treatment |
| O'Neill et al. (2013) | 10 OCD *Adults* | All excluded except depression | CBT (4 weeks, daily) | 1.5 T | PRESS | 1500/30/N.A | N.A | Quadrature headcoil | 0.9 × 1.1 × 1.1 cm | pACC<br>aMCC | Absolute concentrations (i.u.) | Reduced Glx in left AMCC with CBT (1.14) |

ACC, anterior cingulate cortex; ADD, attention deficit disorder; ADHD, attention deficit hyperactivity disorder; aMCC, anterior middle cingulate cortex; BT, behavioural therapy; CBT, cognitive behavioural therapy; Cr, creatine; GAD, generalized anxiety disorder; Glx, glutamate and glutamine; HC, healthy controls; i.u., institutional units; N.A, not applicable; OCD, obsessive-compulsive disorder; ODD, oppositional defiant disorder; pACC, pregenual anterior cingulate cortex; SAD, separation anxiety disorder; SSRI, selective serotonin reuptake inhibitor; T, tesla; TE, echo time; TR, repetition time. PRESS is a single-voxel spectroscopy acquisition method.

Thirty of 59 studies examined paediatric patients and 24 examined adults. Five studies examined adolescents (mean ≥ 12 years). Twelve out of 43 studies that compared patients with healthy controls included patients who were medication naïve or medication free for at least six weeks. The 16 studies in which metabolite changes after treatment administration were studied examined the effects of the psychostimulant methylphenidate (MPH) or the noradrenaline reuptake inhibitor atomoxetine in ADHD, and selective serotonin reuptake inhibitors (SSRIs) or cognitive behavioural therapy in OCD. All studies excluded neurological disorders but only fourteen studies excluded all axis-I DSM-IV comorbidities.

In terms of the spectroscopy techniques utilized, only sixteen of 59 studies used field strengths ≥ 3 Tesla. Almost all studies used single voxel spectroscopy with point resolved spectroscopy (PRESS). Seventeen studies used internal references to tCr, tCho or mI as the main quantification method. Regions of interest (ROIs) were described in the papers with accompanying pictures in most cases but unfortunately no exact coordinates were provided. Tables 1–5 provide information on ROIs of the different studies.

### 3.1. Attention deficit hyperactivity disorder

Among the 16 studies comparing ADHD with healthy individuals, 11 investigated Glu or Glx in prefrontal regions. Six of these 11 studies did not report any differences between ADHD patients and healthy control individuals in dorsolateral prefrontal cortex (DLPFC) (Benamor, 2014; Hesslinger et al., 2001; Soliva et al., 2010), ventromedial prefrontal cortex (VMPFC) (Ferreira et al., 2009) and middle frontal gyrus (MFG)/anterior cingulate cortex (ACC) (Tafazoli et al., 2013; Yang et al., 2010). Three studies found increased Glx levels in the PFC (MacMaster et al., 2003), superior frontal gyrus (SFG) (Courvoisie et al., 2004) and ACC (Moore et al., 2006). These studies were all performed in children. Contrarily, three adult studies found decreased glutamatergic levels in the ACC (Dramsdahl et al., 2011; Perlov et al., 2007) and the DLPFC (Maltezos et al., 2014), although the result in this last study did not survive Bonferroni correction. In addition, one study reported decreased GABA levels in the motor cortex (PFC) in ADHD children (Edden et al., 2012). The study by Dramsdahl et al. and Edden et al. were performed at 3 T, all others at 1.5 T.

Six studies investigated striatal glutamatergic compounds. Three studies did not find any differences between ADHD patients and controls (Benamor, 2014; Hesslinger et al., 2001; Sun et al., 2005) and one adult study reported increased Glx levels in the left putamen (Ferreira et al., 2009). Another adult study found decreased Glx in the basal ganglia comprising the caudate and putamen (Maltezos et al., 2014)). One additional study reported increased Glx levels in the striatum approaching statistical significance after correcting for multiple comparisons (MacMaster et al., 2003). Additional findings were increased Glx levels in adult ADHD patients in the cerebellum (Perlov et al., 2010) and the posterior cingulate (Arcos-Burgos et al., 2012).

Three of seven studies that investigated glutamatergic changes after treatment also included a healthy comparison group. In two of them, baseline Glx was increased in ADHD compared to controls in the striatum (Carrey et al., 2007) and ACC (Hammerness et al., 2012). No Glx reductions were found after treatment with MPH, although one study found a trend towards post-treatment reductions at 3 T(Hammerness et al., 2012). The third study did not find differences between ADHD and controls in the globus pallidus (Jin et al., 2001). Four studies investigated glutamatergic changes after MPH or atomoxetine treatment and did not compare them with healthy controls. All but one of these studies found decreases in the striatum after treatment, with respectively 56.1% and 35% reductions (Carrey et al., 2002, 2003) and a PFC Glu reduction of 15% (Wiguna et al., 2012). The study by Husarova et al. (2014) found increased Glx in the white matter behind the DLPFC after treatment with MPH (right hemisphere) or atomoxetine (left hemisphere) (Husarova et al., 2014). All treatment studies except the one by Hammerness et al. (2012) were performed in paediatric ADHD cohorts.

### 3.2. Autism spectrum disorder

Sixteen studies discussed glutamatergic differences between ASD patients and healthy individuals. Twelve of sixteen examined regions within the PFC. In four of these 12 studies, no differences were found between ASD patients and healthy individuals in the ACC (Aoki et al., 2012) and DLPFC (Horder et al., 2013) and two other unspecified frontal regions (Friedman et al., 2003; Harada et al., 2011). Three childhood studies and one adolescent study demonstrated increased Glu and Glx levels in ASD in the ACC (Bejjani et al., 2012; Hassan et al., 2013; Joshi et al., 2013). Decreased levels of Glx were found in frontal grey matter (DeVito et al., 2007) in children, in the ACC in adults (Bernardi et al., 2011; Tebartz van Elst et al., 2014) and in the OFC in children (Kubas et al., 2012). Additionally, three studies found reduced GABA levels in several frontal areas (Gaetz et al., 2014; Harada et al., 2011; Kubas et al., 2012). Only four studies examined striatal glutamatergic levels. Three found no differences although in the study by Harada et al. (2011) a trend for elevated Glu was found in the lenticular nuclei (Corrigan et al., 2013; Friedman et al., 2003; Harada et al., 2011). One study found increased Glu in the striatum (Hassan et al., 2013).

Other areas examined in ASD were amygdala-hippocampal complex in which Glx increases were found in an adult ASD study (Page et al., 2006) but no differences were found in adults with Asperger syndrome (O'Brien et al., 2010). Further, no differences were reported in the thalamus (Bernardi et al., 2011; Friedman et al., 2003; Hardan et al., 2008); one study examining the cerebellum showed elevated levels of Glu in children with ASD (Hassan et al., 2013) while another found no differences between adult ASD patients and controls (Tebartz van Elst et al., 2014). Of all studies, seven used field strengths of 3 T and these studies were all able to find differences across ASD patients and controls (Bernardi et al., 2011; DeVito et al., 2007; Gaetz et al., 2014; Harada et al., 2011; Joshi et al., 2013; Tebartz van Elst et al., 2014) except for the study by Aoki et al. (2012).

### 3.3. Obsessive compulsive disorder

Among eleven studies comparing OCD patients with healthy control individuals, ten investigated prefrontal regions. In seven of these studies no differences were reported (Bedard and Chantal, 2011; Ebert et al., 1997; Simpson et al., 2012; Starck et al., 2008). These were all adult cohort studies investigating different PFC regions such as ACC, OFC, MPFC and DLPFC. Two studies found increased Glx in respectively the right OFC and the ACC in an adult patient group (Gnanavel et al., 2013; Whiteside et al., 2006). One adolescent study found no significant differences between patients and controls but a trend towards increased Glx in the right prefrontal white matter behind the ACC ($p$ .07) (Weber et al., 2013). Decreases in Glx were found in one adult study examining only female patients and one paediatric study in the ACC (Rosenberg et al., 2004; Yücel et al., 2008). One additional study found a trend towards decreased Glx in the dorsal ACC, but only in patients that were using SSRIs (Yücel et al., 2007). One study reported reduced GABA in the MPFC in an adult OCD group, while Glu differences were not found (Simpson et al., 2012). Five of 11 studies examined glutamatergic levels in the striatum of which one found increased Glx levels in the caudate nucleus in an adult sample (Gnanavel et al.,

2013). The other studies found no differences between patients and controls (Bartha et al., 1998; Ebert et al., 1997; Starck et al., 2008; Whiteside et al., 2006). In one study, a positive correlation between obsessive compulsive symptom severity, as measured by the Children's Yale-Brown Obsessive Compulsive Scale (CYBOCS), and Glx levels in the caudate was found (Starck et al., 2008).

In four of nine studies that examined glutamatergic changes after treatment, an additional control group was used. Three of these studies did not find any differences between OCD patients and controls in any region (O'Neill et al., 2012; Whiteside et al., 2012; Zurowski et al., 2012). One study found increased baseline Glx in the head of the left caudate nucleus that was reduced following treatment with paroxetine (Rosenberg et al., 2000). Of the five studies that did not include a control group, two examined the ACC (Lazaro et al., 2012; O'Neill et al., 2013). O'Neill et al. (2013) found reduced ACC Glx levels after four weeks of daily cognitive behavioural therapy (CBT). The study by Lazaro et al. (2012) examined both the effect of SSRIs and behavioural counselling but no differences were reported. Four of these five studies examined striatum as well. In two studies reduced Glx levels after 12 weeks of paroxetine treatment were reported (Bolton et al., 2001; Moore et al., 1998) and in the other two no changes were found after treatment with CBT or SSRIs (Benazon et al., 2003; Lazaro et al., 2012).

Studies that compared Glx levels in the ACC mainly found increased levels across ASD and ADHD in children and adolescent samples and decreases across adult samples. Since there were also several studies that did not report differences, we compared the sample sizes of positive versus negative studies with an independent samples *t* test. Children studies finding increases did not significantly differ in sample size from children studies finding no differences ($t$ (7) = .033, $p$ *.864*). Adult studies finding decreases also did not significantly differ from studies finding no differences ($t$ (9) = −2.146, $p$ *.585*). There were no adult studies finding increases and no children studies finding decreases (see Fig. 1).

In the striatum, the findings were more inconsistent. We therefore performed analysis of variance (ANOVA) to compare sample size across studies finding decreases, no differences and increases. No significant differences in sample sizes were found ($F$ (2,17) = 2.178, $p$ .144).

### 3.4. The relationship between Glx levels and behavioural measures

Several studies performed additional correlation analyses to examine the relationship between Glx levels and behavioural findings. In one ADHD children study a positive correlation was found between Glx levels in the frontal lobe (SFG) and memory disability (Courvoisie et al., 2004). Two adult studies found a negative correlation between Glx levels and inattentive symptoms in that lower Glx levels were paired with higher inattentiveness (Dramsdahl et al., 2011; Maltezos et al., 2014).

In ASD negative correlations were found between Glx levels in the ACC and basal ganglia and communication skills, with lower Glx leading to worse communication skills in adult patients (Horder et al., 2013; Tebartz van Elst et al., 2014). In addition, Hassan and colleagues found a strong correlation between blood and brain glutamate (Hassan et al., 2013).

In several OCD studies, correlations were found between Glx levels in frontal brain areas and symptom severity as measured by (C)YBOCS (Gnanavel et al., 2013; Whiteside et al., 2006; Yücel et al., 2008); a reduction in Glx after treatment with paroxetine correlated with a reduction in YBOCS severity scores as well (Rosenberg et al., 2000). These findings form interesting perspectives for future studies to further examine the relationship between ASD, ADHD and OCD in terms of their underlying traits.

### 3.5. Glx changes after treatment administration

Studies examining Glx changes after treatment were only performed in ADHD and OCD patients. Most studies performed in ADHD patients found, compared to controls, increased baseline levels of Glx in the striatum and ACC (Carrey et al., 2007; Hammerness et al., 2012) which tend to reduce after treatment with either MPH or atomoxetine (Carrey et al., 2002, 2003; Hammerness et al., 2012; Wiguna et al., 2012). One study, however, found increases in prefrontal white matter after treatment with MPH and atomoxetine (Husarova et al., 2014). All other studies were performed in grey matter.

In OCD, baseline Glx levels were mostly similar in patients and controls in PFC and striatum (O'Neill et al., 2012; Whiteside et al., 2012; Zurowski et al., 2012) but after treatment with paroxetine or behavioural therapy reductions in Glx levels were found (Bolton et al., 2001; Moore et al., 1998; O'Neill et al., 2013; Rosenberg et al., 2000; Whiteside et al., 2012). In one study, a reduction in Glx levels in the caudate nucleus was correlated with a significant reduction in symptom severity (Rosenberg et al., 2000).

Treatment studies show that in most cases Glx levels decrease after administration of either a drug or therapy. Almost all treatment studies were performed in children and unfortunately not always with a comparison group to see whether baseline Glx levels differ from Glx levels in control children. Future studies should take medication levels carefully into account because medication may influence metabolite levels significantly.

## 4. Discussion

The current review investigated 59 studies that examined Glu-related neurochemistry in ASD, ADHD and OCD patient groups compared to healthy controls or after treatment administration. Many studies were very heterogeneous; for example, only a few studies excluded all axis-I DSM-IV comorbidities. Most of the studies allowed for anxiety and mood disorders, which are known to influence neurochemistry themselves (Yildiz-Yesiloglu and Ankerst, 2006). In addition, only 16 of 59 used field strengths ≥3 Tesla and were thus able to report the less ambiguous Glu signal instead of the combined Glx signal. In addition, the interpretation of Glu levels in spectroscopy is problematic. Glu is present in both intra- and extra-cellular stores, not only in neurons but also in glia (influencing neurotransmission) as well as being a derivative of metabolic processes. This means that the measurement of Glu levels by MRS do not reflect one specific function (Pittenger et al., 2011). The combined Glx signal is even less informative. This should be taken into account when interpreting $^{1}$H MRS studies examining Glu, especially when they use lower field strengths, which have less spectral resolution to accurately measure Glx levels. All these issues make it difficult to detect differences between patients and healthy individuals. In addition to the heterogeneity, many studies were very explorative in nature because of the relatively new application of spectroscopy within these disorders.

Nevertheless, we were able to find some consistent findings across and between disorders within our study selection: (1) Possible increased Glx in the striatum across ADHD, OCD and ASD; (2) Increased Glx in the ACC in paediatric and adolescent ADHD and ASD; (3) Decreased Glx in the ACC in adult ASD and adult ADHD. These findings are discussed in greater detail below; because the studies performing $^{1}$H MRS in ASD, ADHD and OCD so far have been limited in their methodologies and sample selection, the

findings must be interpreted with caution. They nevertheless may form preliminary hypotheses for future testing.

### 4.1. Possible increased Glx in striatum across ADHD, OCD and ASD

Several studies showed increased Glx in striatal areas (Carrey et al., 2007; Ferreira et al., 2009; Gnanavel et al., 2013; Hammerness et al., 2012; Hassan et al., 2013; Rosenberg et al., 2000) which in ADHD seem to decline after treatment with MPH (Carrey et al., 2002, 2003), and in OCD with paroxetine (Bolton et al., 2001; Moore et al., 1998; Rosenberg et al., 2000). The findings must be interpreted with caution given that other studies failed to find differences between patient groups and controls (Bartha et al., 1998; Ebert et al., 1997; Friedman et al., 2003; Hesslinger et al., 2001; Jin et al., 2001; O'Neill et al., 2012; Sun et al., 2005; Whiteside et al., 2006, 2012; Zurowski et al., 2012) and that some studies even found decreases (Corrigan et al., 2013; Horder et al., 2013; Maltezos et al., 2014). Hassan et al. (2013), however, reported also increased blood Glu levels in paediatric ASD, a finding that was positively correlated with brain Glu. A previous study showed elevated serum Glu levels in autism as well (Shinohe et al., 2006).

There is evidence that the dorsal striatum (caudate and putamen) is involved in compulsivity, while the ventral striatum (mainly nucleus accumbens) is associated with impulsive behaviour (Fineberg et al., 2010). The fact that many studies did not find differences may be explained by their choice of striatal area, leading to a heterogeneous data set.

Ferreira et al. (2009) have suggested a relationship between dopamine, Glu and acetylcholine that results in elevated Glu levels in the striatum in ADHD patients. The striatum itself is, in fact, not glutamatergic. Striatal Glu is derived from afferent connections, metabolic pools and precursors into GABA (Pittenger et al., 2011). Tonic Glu activity in the PFC has an inhibitory effect on phasic Glu in the striatum. Because tonic Glu in frontal regions seems to be disturbed in ASD, ADHD and OCD, the phasic Glu in the striatum may be altered as well. Preclinical studies of glutamatergic neural activity suggest a parallel with brain glucose metabolism. Increased caudate Glx concentrations in OCD may be consistent with previous reports of increased glucose metabolism in the same brain region (Baxter et al., 1992). In paediatric ASD, increased caudate volumes have been reported that might influence the concentration of metabolites (Anagnostou and Taylor, 2011). Furthermore, increased striatal volumes seem to be correlated with OCD and repetitive symptom severity, a key symptom of both ASD and OCD that is representative of cognitive inflexibility (Hollander et al., 2005). In general, data suggest increased values of Glx in the dorsal striatum, given that many studies find these increased levels. Future studies should confirm this hypothesis by using larger and more homogeneous sample sizes.

### 4.2. Increased Glx in ACC in paediatric ADHD and ASD

Children and adolescents with ADHD and ASD demonstrate increased Glx levels in the ACC region (Bejjani et al., 2012; Hammerness et al., 2012; Hassan et al., 2013; Joshi et al., 2013; Moore et al., 2006). Although there are also studies that do not demonstrate this finding, sample size comparison showed no significant differences between studies that find no differences and the ones that do.

Glutamatergic transmission from the ACC is assumed to be involved in exerting control over the impulsive ventral striatum. Hammerness et al. (2012) reported a trend towards Glx reductions after MPH treatment in adolescents with ADHD with baseline increased Glx compared to controls. In addition, two studies found increased Glx levels in other prefrontal areas, such as the superior frontal gyrus (SFG) (Courvoisie et al., 2004; MacMaster et al., 2003). Several studies failed to find differences between paediatric patients and controls (Carrey et al., 2007; Friedman et al., 2003; Soliva et al., 2010; Tafazoli et al., 2013; Yang et al., 2010), which may result from inclusion of diverse PFC regions such as DLPFC (Soliva et al., 2010) and MFG (Tafazoli et al., 2013) which have different functionalities. It is possible that the difference in Glx levels between patients and controls may be ACC specific and may not generalize to other PFC regions but this needs to be further demonstrated. The study by Friedman et al. (2003) investigated preschool ASD children and found no differences in Glx. According to Joshi et al. (2013) school-aged children show elevated Glx levels because of stress-related release of Glu in the prefrontal cortex, which is not present at younger ages.

Abnormal Glu functioning in dopaminergic prefrontal areas may be involved in the pathophysiology of ADHD. Dopamine levels in the striatum are lower in ADHD patients, which co-occur with increased PFC Glu levels (Russell, 2003). MPH blocks dopamine reuptake, leading to an increase in dopamine levels following Glu-stimulated release in the nucleus accumbens (NAc) (Russell, 2003). Dopamine acting on inhibitory dopamine D4 receptors blocks Glu release from the PFC afferents to the NAc. Moore et al. (2006) suggest that reduced NAc dopamine levels in untreated paediatric ADHD patients could lead to increased Glu in the ACC.

Evidence from several studies also points to ACC involvement in ASD (Jiao et al., 2011), such as deficits in joint attention and social orienting (Mundy, 2003). Increased Glx levels in the ACC in paediatric ASD support this hyper-glutamatergic hypothesis in ASD (Fatemi, 2008). Excessive Glu levels in the brain of patients with ASD may be the result of decreased amounts of the enzymes glutamic acid decarboxylase (GAD) 65 and 67, which convert Glu into GABA (leading to an excitatory-inhibitory imbalance) and altered glial Glu regulation in ASD.

### 4.3. Decreased Glx in ACC in adult ASD and adult ADHD

In contrast to paediatric ASD and ADHD, adults mainly showed decreased Glx levels in the ACC (Bernardi et al., 2011; Dramsdahl et al., 2011; Perlov et al., 2007; Tebartz van Elst et al., 2014). The studies performed in OCD are less supportive of either increases or decreases because most adult studies were not able to find differences between patients and control participants (Bedard and Chantal, 2011; Ebert et al., 1997; O'Neill et al., 2012; Starck et al., 2008; Whiteside et al., 2012; Zurowski et al., 2012). Also in this comparison, no sample size differences were found across studies finding decreases and studies finding no differences. It also seems that studies finding differences across ASD and ADHD patients and controls are more represented by 3 T studies than studies finding no differences.

A glutamatergic deficit in the ACC region supports the postulate of impaired cognitive control in adult ADHD and the hypothesis of hypo-glutamatergic function. In children with ADHD hyper-glutamatergic functioning in the ACC was found. Metabolite levels change with age (Horska et al., 2002), which could be related to differences between paediatric and adult symptomatology. In adults, for example, the hyperactive symptoms seem less abundant than in children and inattention becomes more dominantly present (Faraone et al., 2006). According to Perlov et al. (2007), hyperactivity may be caused by excessive Glu transmission in the PFC which can be attenuated by NMDA Glu receptor antagonists. This suggests an overactive PFC in hyperactive children and may explain the lower levels of Glu in adults with ADHD, who seem to show less hyperactive symptoms. In adult ASD, decreased metabolism and smaller volumes of the ACC have been reported (Haznedar et al., 1997). Di Martino et al. (2009) reported in their review hypo-activation of the ACC in individuals with ASD during

fMRI measurements as well. In addition, in a very recent activation likelihood estimation (ALE) meta-analysis by Dickstein et al. (2013), hyper-activation in children with ASD in prefrontal regions compared to adults were reported.

An alternative explanation for the reversed pattern of adult ASD and ADHD patients compared to children is changes in synaptic pruning over time. Synaptic pruning refers to the regulatory process in which an overall number of neurons and connections is reduced (Iglesias et al., 2005). In normal development, pruning leads to a better connected brain, but there are hypotheses concerning excessive pruning, which may lead to clinical disorders such as schizophrenia (Keshavan et al., 1994). In children with ASD cortical grey matter seems to be increased compared to controls but it decreases with age, possibly reflecting the effects of excessive pruning.

Three studies reported reduced ACC Glx levels in OCD patients while other studies reported increases in Glx in the ACC and OFC. Because OCD is a very heterogeneous disorder with many different compulsive subtypes, one explanation may be that certain subgroups of OCD patients show reduced Glx levels based on mutations in genes affecting glutamatergic transmission (Brennan et al., 2013). Another cause of the different findings could be the variability in voxel location in the ACC. Differences across children and adults were not found in OCD although it may seem that Glu levels are normalized in adult OCD patients, given the fact that several studies did not find differences across OCD patients and controls in the ACC, even when studies were performed at 3 T (Simpson et al., 2012; Weber et al., 2013; Zurowski et al., 2012).

### 4.4. Glx changes in other brain regions

In addition to the general findings described in the previous sections involving ACC and striatum, other regions, like the cerebellum and amygdala, also showed elevated Glx levels in the patient groups, especially in ASD and to a lesser extent in ADHD (Benamor, 2014; Hassan et al., 2013; Page et al., 2006; Perlov et al., 2010). Studies examining other prefrontal areas than the ACC reported less consistent results.

Only five studies reported on levels of GABA and all found decreased levels in PFC areas (Edden et al., 2012; Gaetz et al., 2014; Harada et al., 2011; Kubas et al., 2012; Simpson et al., 2012). This finding was evident across all patient and age groups. According to Edden et al. (2012) altered GABA levels reflect deficits in inhibitory control of the PFC, which can be related to ASD, ADHD and OCD such that the PFC has a lack of control over the compulsivity or impulsivity regulated by the striatum.

Based on the studies described in the current review paper, it becomes clear that more work is needed in the field of spectroscopy. Studies that have been performed so far were very different in patient groups, specified regions of interest and $^{1}$H MRS techniques, which make it difficult to draw general conclusions. The most striking finding was the difference between ACC Glx levels in paediatric and adult ADHD and ASD, which gives us greater insight in the developmental trajectory of these disorders. Secondly, the similarities across OCD patients and adult ADHD and ASD may suggest that in childhood, ADHD and ASD are more alike, while they both become more compulsive when growing older and thus resembling OCD patients. Thirdly, ASD, ADHD, and OCD all show deficits in striatal areas that seem to be related to elevated Glx levels. The findings reported in this review show that ASD, ADHD and OCD indeed show similarities, but also differences that need more investigation. Studying the underlying mechanisms of impulsivity and compulsivity instead of the disorders separately may assist in improving their biological understanding and consequent clinical management.

### 4.5. Study limitations and challenges

Despite our general findings across the 59 studies, the existing spectroscopy literature in the compulsive and impulsive disorders ASD, ADHD and OCD remains limited and ambiguous. This is likely due to very small and heterogeneous study samples and varying methodologies. Samples differed, besides age, in illness severity, comorbidity and medication use, which can all influence neurochemistry on itself. In addition, only sixteen of 59 studies used field strengths of 3 Tesla and higher. With field strengths below 3 Tesla it is very difficult to unambiguously separate Glu from overlapping spectral peaks. This means that all these studies reported results on combined Glx signal, which is less specific. Glx is often treated as a reflection of the neurotransmitter Glu but it is actually a composite, something that should be kept in mind when interpreting Glx results. Several studies were however able to disambiguate the Glx signal in the separate Glu and glutamine spectra.

A number of studies quantified Glu concentrations as ratios with creatine or choline as internal references. This approach assumes that no Cr and Cho differences are present between patients and controls. There are however studies reporting differences in these metabolites between ASD, ADHD and OCD patients and controls (Colla et al., 2008; Mirza et al., 2006; Suzuki et al., 2010) suggesting that using these metabolites as internal references results in confounded findings, especially in comparing them with studies that use absolute concentrations. Furthermore, the choice of voxel location was very variable across studies, especially concerning the ACC. This makes it difficult to compare these results as well. In addition to the limitations of the reviewed studies, $^{1}$H MRS has its own limitations in terms of spectral and spatial resolution and the inability to distinguish between intra- and extra-cellular neuronal and glial and metabolic Glu levels. Despite these limitations, the assessment of glutamate-related metabolites is for now best done with relatively cheap, fast and non-invasive $^{1}$H-MRS.

The main limitation of current neuroscience is that disorder groups are examined separately. The existence of commonalities across ASD, ADHD and OCD is well known (Anholt et al., 2010) and one should take advantage of that in creating more clarity among the underlying mechanisms of these disorders.

### 4.6. Future directions

The aim of the current review was to highlight commonalities and differences between the developmental disorders ADHD, ASD, and OCD. Based on the disparities in the described studies it is very difficult to draw definitive conclusions upon this. What is clear from previous studies is that there indeed seem to be similarities across the three disorders and that it is worthwhile to examine their underlying traits. This may be particularly helpful in improving diagnosis further as these traits form an essential part of the disease dimensions as described in the NIMH Research Domain Criteria (RDoC) (Cuthbert, 2014). At present, DSM based diagnosis is dependent on subjective observations whereby experienced clinical personnel are key. Instead, biomarkers such as those from neuroimaging and neurochemistry studies may provide more objective criteria in time. Examining the neurobiology of underlying traits of psychiatric disorders using techniques such as MRS will shed more light on their commonalities and makes it possible to go beyond separate clinical diagnoses. Since patients can have similar diagnoses based on different criteria, subtyping of patients should not be based on diagnostic criteria alone (Robbins et al., 2012). Differences across younger and older patients, especially in the ACC, should also be further investigated because this may clarify developmental changes across the disorders based on possible underlying changes in the fronto-striatal circuit.

Methodologically, future studies should consider (i) resolving Glu signal instead of reporting Glx, e.g. by acquiring data at higher field strengths; (ii) using multiple voxels, for instance by performing MRS imaging; (iii) combining MRS with other neuroimaging techniques to assess neurochemistry simultaneously with structural or functional abnormalities; (iv) incorporating glutamatergic genotype data as it is well known that neurodevelopmental disorders are highly heritable (Manolio et al., 2008); and (v) longitudinal studies that might help in exploring the early onset of disorders and the developmental issues regarding ASD, ADHD and OCD as became evident from the comparison of children and adults in the current review.

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## References

Alexander, G.E., DeLong, M.R., Strick, P.L., 1986. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annu. Rev. Neurosci. 9, 357–381.

Anagnostou, E., Taylor, M.J., 2011. Review of neuroimaging in autism spectrum disorders: what have we learned and where we go from here. Mol. Autism 2, 4.

Anholt, G.E., Cath, D.C., van Oppen, P., Eikelenboom, M., Smit, J.H., van Megen, H., van Balkom, A.J., 2010. Autism and ADHD symptoms in patients with OCD: are they associated with specific OC symptom dimensions or OC symptom severity? J. Autism Dev. Disord. 40, 580–589.

Aoki, Y., Abe, O., Yahata, N., Kuwabara, H., Natsubori, T., Iwashiro, N., Takano, Y., Inoue, H., Kawakubo, Y., Gonoi, W., Sasaki, H., Murakami, M., Katsura, M., Nippashi, Y., Takao, H., Kunimatsu, A., Matsuzaki, H., Suchiva, K.J., Kato, N., Kasaki, K., Yamasue, H., 2012. Absence of age-related prefrontal NAA change in adults with autism spectrum disorders. Transl. Psychiatry 2, e178.

Arcos-Burgos, M., Londono, A.C., Pineda, D.A., Lopera, F., Palacio, J.D., Arbelaez, A., Arbelaez, A., Acosta, A.T., Vélez, J.I., Castellanos, F.X., Muenke, M., 2012. Analysis of brain metabolism by proton magnetic resonance spectroscopy ($^1$H-MRS) in attention-deficit/hyperactivity disorder suggests a generalized differential ontogenic pattern from controls. Atten. Deficit Hyperact. Disord. 4, 205–212.

Arnsten, A.F., 2009. Stress signalling pathways that impair prefrontal cortex structure and function. Nat. Rev. Neurosci. 10, 410–422.

Baird, G., Simonoff, E., Pickles, A., Chandler, S., Loucas, T., Meldrum, D., Charman, T., 2006. Prevalence of disorders of the autism spectrum in a population cohort of children in South Thames: the Special Needs and Autism Project (SNAP). Lancet 368, 210–215.

Bartha, R., Stein, M.B., Williamson, P.C., Drost, D.J., Neufeld, R.W., Carr, T.J., Canaran, G., Densmore, M., Anderson, G., Siddiqui, A.R., 1998. A short echo $^1$H spectroscopy and volumetric MRI study of the corpus striatum in patients with obsessive-compulsive disorder and comparison subjects. Am. J. Psychiatry 155, 1584–1591.

Baxter Jr., L.R., Schwartz, J.M., Bergman, K.S., Szuba, M.P., Guze, B.H., Mazziotta, J.C., Alazraki, A., Selin, C.E., Fernq, H.K., Munford, P., 1992. Caudate glucose metabolic rate changes with both drug and behavior therapy for obsessive-compulsive disorder. Arch. Gen. Psychiatry 49, 681–689.

Bedard, M.J., Chantal, S., 2011. Brain magnetic resonance spectroscopy in obsessive-compulsive disorder: the importance of considering subclinical symptoms of anxiety and depression. Psychiatry Res. 192, 45–54.

Bejjani, A., O'Neill, J., Kim, J.A., Frew, A.J., Yee, V.W., Ly, R., Kitchen, C., Salamon, N., McCracken, J.T., Toga, A.W., Alger, J.R., Levitt, J.G., 2012. Elevated glutamatergic compounds in pregenual anterior cingulate in pediatric autism spectrum disorder demonstrated by $^1$H MRS and $^1$H MRSI. PLoS ONE 7, e38786.

Benamor, L., 2014. (1)H-Magnetic resonance spectroscopy study of stimulant medication effect on brain metabolites in French Canadian children with attention deficit hyperactivity disorder. Neuropsychiatr. Dis. Treat. 10, 47–54.

Benazon, N.R., Moore, G.J., Rosenberg, D.R., 2003. Neurochemical analyses in pediatric obsessive-compulsive disorder in patients treated with cognitive-behavioral therapy. J. Am. Acad. Child Adolesc. Psychiatry 42, 1279–1285.

Bernardi, S., Anagnostou, E., Shen, J., Kolevzon, A., Buxbaum, J.D., Hollander, E., Hof, P.R., Fan, J., 2011. In vivo $^1$H-magnetic resonance spectroscopy study of the attentional networks in autism. Brain Res. 1380, 198–205.

Bloch, M.H., Craiglow, B.G., Landeros-Weisenberger, A., Dombrowski, P.A., Panza, K.E., Peterson, B.S., Leckman, J.F., 2009. Predictors of early adult outcomes in pediatric-onset obsessive-compulsive disorder. Pediatrics 124, 1085–1093.

Bolton, J., Moore, G.J., MacMillan, S., Stewart, C.M., Rosenberg, D.R., 2001. Case study: caudate glutamatergic changes with paroxetine persist after medication discontinuation in pediatric OCD. J. Am. Acad. Child Adolesc. Psychiatry 40, 903–906.

Brennan, B.P., Rauch, S.L., Jensen, J.E., Pope, H.G., 2013. A critical review of magnetic resonance spectroscopy studies of obsessive-compulsive disorder. Biol. Psychiatry 73, 24–31.

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 $^1$H-MRS study. Clin. Neuropharmacol. 26, 218–221.

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

Carrey, N., MacMaster, F.P., Sparkes, S.J., Khan, S.C., Kusumakar, V., 2002. Glutamatergic changes with treatment in attention deficit hyperactivity disorder: a preliminary case series. J. Child Adolesc. Psychopharmacol. 12, 331–336.

Chamberlain, S.R., Menzies, L., 2009. Endophenotypes of obsessive-compulsive disorder: rationale, evidence and future potential. Expert Rev. Neurother. 9, 1133–1146.

Chamberlain, S.R., Sahakian, B.J., 2007. The neuropsychiatry of impulsivity. Curr. Opin. Psychiatry 20, 255–261.

Chantiluke, K., Barrett, N., Giampietro, V., Brammer, M., Simmons, A., Murphy, D.G., Rubia, K., 2014. Inverse effect of fluoxetine on medial prefrontal cortex activation during reward reversal in ADHD and autism. Cereb. Cortex (Epub ahead of print).

Colla, M., Ende, G., Alm, B., Deuschle, M., Heuser, I., Kronenberg, G., 2008. Cognitive MR spectroscopy of anterior cingulate cortex in ADHD: elevated choline signal correlates with slowed hit reaction times. J. Psychiatr. Res. 42, 587–595.

Corrigan, N.M., Shaw, D.W.W., Estes, A.M., Richards, T.L., Munson, J., Friedman, S.D., Dawson, G., Artru, A.A., Dager, S.R., 2013. Atypical developmental patterns of brain chemistry in children with autism spectrum disorder. JAMA Psychiatry 70, 964–974.

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.

Crowther, M., Lim, W., Crowther, M.A., 2010. Systematic review and meta-analysis methodology. Blood 116, 3140–3146.

Cuthbert, B.N., 2014. The RDoC framework: facilitating transition from ICD/DSM to dimensional approaches that integrate neuroscience and psychopathology. World Psychiatry 13, 28–35.

Dalley, J.W., Everitt, B.J., Robbins, T.W., 2011. Impulsivity, compulsivity, and top-down cognitive control. Neuron 69, 680–694.

Del Campo, N., Fryer, T.D., Hong, Y.T., Smith, R., Brichard, L., Acosta-Cabronero, J., Chamberlain, S.R., Trait, R., Izquierdo, D., Regenthal, R., Dowson, J., Suckling, J., Baron, J., Aigbirhio, F.I., Robbins, T.W., Sahakian, B.J., Muller, U., 2013. A positron emission tomography study of nigro-striatal dopaminergic mechanisms underlying attention: implications for ADHD and its treatment. Brain 136, 3252–3270.

DeVito, T.J., Drost, D.J., Neufeld, R.W., Rajakumar, N., Pavlosky, W., Williamson, P., Nicolson, R., 2007. Evidence for cortical dysfunction in autism: a proton magnetic resonance spectroscopic imaging study. Biol. Psychiatry 61, 465–473.

Di Martino, A., Ross, K., Uddin, L.Q., Sklar, A.B., Castellanos, F.X., Milham, M.P., 2009. Functional brain correlates of social and nonsocial processes in autism spectrum disorders: an activation likelihood estimation meta-analysis. Biol. Psychiatry 65, 63–74.

Dickstein, D.P., Pescosolido, M.F., Reidy, B.L., Galvan, T., Kim, K.L., Seymour, K.E., Di Martino, A., Barrett, R.P., 2013. Developmental meta-analysis of the functional neural correlates of autism spectrum disorders. J. Am. Acad. Child Adolesc. Psychiatry 52, 279–289, e216.

Dramsdahl, M., Ersland, L., Plessen, K.J., Haavik, J., Hugdahl, K., Specht, K., 2011. Adults with attention-deficit/hyperactivity disorder – a brain magnetic resonance spectroscopy study. Front. Psychiatry 2, 65.

Durston, S., van Belle, J., de Zeeuw, P., 2011. Differentiating frontostriatal and fronto-cerebellar circuits in attention-deficit/hyperactivity disorder. Biol. Psychiatry 69, 1178–1184.

Ebert, D., Speck, O., Konig, A., Berger, M., Hennig, J., Hohagen, F., 1997. $^1$H-magnetic resonance spectroscopy in obsessive-compulsive disorder: evidence for neuronal loss in the cingulate gyrus and the right striatum. Psychiatry Res. 74, 173–176.

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.

Faraone, S.V., Biederman, J., Mick, E., 2006. The age-dependent decline of attention deficit hyperactivity disorder: a meta-analysis of follow-up studies. Psychol. Med. 36, 159–165.

Fatemi, S.H., 2008. The hyperglutamatergic hypothesis of autism. Prog. Neuropsychopharmacol. Biol. Psychiatry 32, 911.

Ferreira, P.E., Palmini, A., Bau, C.H., Grevet, E.H., Hoefel, J.R., Rohde, L.A., Anés, M., Ferreira, E.E., Belmonte-de-Abreu, P., 2009. Differentiating attention-deficit/hyperactivity disorder inattentive and combined types: a (1)H-magnetic resonance spectroscopy study of fronto-striato-thalamic regions. J. Neural Transm. 116, 623–629.

Fineberg, N.A., Potenza, M.N., Chamberlain, S.R., Berlin, H.A., Menzies, L., Bechara, A., Sahakian, B.J., Robbins, T.W., Bullmore, E.T., Hollander, E., 2010. Probing compulsive and impulsive behaviors, from animal models to endophenotypes: a narrative review. Neuropsychopharmacology 35, 591–604.
Friedman, S.D., Shaw, D.W., Artru, A.A., Richards, T.L., Gardner, J., Dawson, G., Posse, S., Dager, S.R., 2003. Regional brain chemical alterations in young children with autism spectrum disorder. Neurology 60, 100–107.
Gaetz, W., Bloy, L., Wang, D.J., Port, R.G., Blaskey, L., Levy, S.E., Roberts, T.P., 2014. GABA estimation in the brains of children on the autism spectrum: measurement precision and regional cortical variation. Neuroimage 86, 1–9.
Geller, D., Biederman, J., Faraone, S.V., Frazier, J., Coffey, B.J., Kim, G., Bellordre, C.A., 2000. Clinical correlates of obsessive compulsive disorder in children and adolescents referred to specialized and non-specialized clinical settings. Depress. Anxiety 11, 163–168.
Gnanavel, S., Sharan, P., Khandelwal, S., Sharma, U., Jagannathan, N.R., 2013. Neurochemicals measured by H-MR spectroscopy: putative vulnerability biomarkers for obsessive compulsive disorder. MAGMA (Epub ahead of print).
Gottesman, I.I., Gould, T.D., 2003. The endophenotype concept in psychiatry: etymology and strategic intentions. Am. J. Psychiatry 160, 635–645.
Grant, J.E., Potenza, M.N., 2006. Compulsive aspects of impulse-control disorders. Psychiatr. Clin. N. Am. 29, 539-X.
Hammerness, P., Biederman, J., Petty, C., Henin, A., Moore, C.M., 2012. Brain biochemical effects of methylphenidate treatment using proton magnetic spectroscopy in youth with attention-deficit hyperactivity disorder: a controlled pilot study. CNS Neurosci. Ther. 18, 34–40.
Hanna, G.L., 1995. Demographic and clinical features of obsessive-compulsive disorder in children and adolescents. J. Am. Acad. Child Adolesc. Psychiatry 34, 19–27.
Harada, M., Taki, M.M., Nose, A., Kubo, H., Mori, K., Nishitani, H., Matsuda, T., 2011. Non-invasive evaluation of the GABAergic/glutamatergic system in autistic patients observed by MEGA-editing proton MR spectroscopy using a clinical 3 Tesla instrument. J. Autism Dev. Disord. 41, 447–454.
Hardan, A.Y., Minshew, N.J., Melhem, N.M., Srihari, S., Jo, B., Bansal, R., Keshavan, M.S., Stanley, J.A., 2008. An MRI and proton spectroscopy study of the thalamus in children with autism. Psychiatry Res. 163, 97–105.
Hassan, T.H., Abdelrahman, H.M., Abdel Fattah, N.R., El-Masry, N.M., Hashim, H.M., El-Gerby, K.M., Abdel Fattah, N.R., 2013. Blood and brain glutamate levels in children with autistic disorder. Res. Autism Spectr. Disord. 7, 541–548.
Haznedar, M.M., Buchsbaum, M.S., Metzger, M., Solimando, A., Spiegel-Cohen, J., Hollander, E., 1997. Anterior cingulate gyrus volume and glucose metabolism in autistic disorder. Am. J. Psychiatry 154, 1047–1050.
Hesslinger, B., Thiel, T., Tebartz van Elst, L., Hennig, J., Ebert, D., 2001. Attention-deficit disorder in adults with or without hyperactivity: where is the difference? A study in humans using short echo (1)H-magnetic resonance spectroscopy. Neurosci. Lett. 304, 117–119.
Hollander, E., Anagnostou, E., Chaplin, W., Esposito, K., Haznedar, M.M., Licalzi, E., Wasserman, S., Soorya, L., Buchsbaum, M., 2005. Striatal volume on magnetic resonance imaging and repetitive behaviors in autism. Biol. Psychiatry 58, 226–232.
Horder, J., Lavender, T., Mendez, M.A., O'Gorman, R., Daly, E., Craig, M.C., Lythgoe, D.J., Barker, G.J., Murphy, D.G., 2013. Reduced subcortical glutamate/glutamine in adults with autism spectrum disorders: a [(1)H]MRS study. Transl. Psychiatry 3, e279.
Horska, A., Kaufmann, W.E., Brant, L.J., Naidu, S., Harris, J.C., Barker, P.B., 2002. In vivo quantitative proton MRSI study of brain development from childhood to adolescence. J. Magn. Reson. Imaging 15, 137–143.
Husarova, V., Bittsansky, M., Ondrejka, I., Dobrota, D., 2014. Prefrontal grey and white matter neurometabolite changes after atomoxetine and methylphenidate in children with attention deficit/hyperactivity disorder: a H-1 magnetic resonance spectroscopy study. Psychiatry Res. Neuroimaging 222, 75–83.
Iglesias, J., Eriksson, J., Grize, F., Tomassini, M., Villa, A.E., 2005. Dynamics of pruning in simulated large-scale spiking neural networks. Biosystems 79, 11–20.
Jiao, Y., Chen, R., Ke, X., Cheng, L., Chu, K., Lu, Z., Herskovits, E.H., 2011. Predictive models for subtypes of autism spectrum disorder based on single-nucleotide polymorphisms and magnetic resonance imaging. Adv. Med. Sci. 56, 334–342.
Jin, Z., Zang, Y.F., Zeng, Y.W., Zhang, L., Wang, Y.F., 2001. Striatal neuronal loss or dysfunction and choline rise in children with attention-deficit hyperactivity disorder: a $^{1}$H-magnetic resonance spectroscopy study. Neurosci. Lett. 315, 45–48.
Joshi, G., Biederman, J., Wozniak, J., Goldin, R.L., Crowley, D., Furtak, S., Lukas, S.E., Gönenç, A., 2013. Magnetic resonance spectroscopy study of the glutamatergic system in adolescent males with high-functioning autistic disorder: a pilot study at 4 T. Eur. Arch. Psychiatry Clin. Neurosci. 263, 379–384.
Keshavan, M.S., Anderson, S., Pettegrew, J.W., 1994. Is schizophrenia due to excessive synaptic pruning in the prefrontal cortex? The Feinberg hypothesis revisited. J. Psychiatr. Res. 28, 239–265.
Koob, G.F., LeMoal, M., 1997. Drug abuse: hedonic homeostatic dysregulation. Science 278, 52–58.
Kubas, B., Kulak, W., Sobaniec, W., Tarasow, E., Lebkowska, U., Walecki, J., 2012. Metabolite alterations in autistic children: a $^{1}$H MR spectroscopy study. Adv. Med. Sci. 57, 152–156.
Langen, M., Leemans, A., Johnston, P., Ecker, C., Daly, E., Murphy, C.M., Dell'acqua, F., Durston, S., Consortium, A.I.M.S, Murphy, D.G., 2012. Fronto-striatal circuitry and inhibitory control in autism: findings from diffusion tensor imaging tractography. Cortex 48, 183–193.
Lazaro, L., Bargallo, N., Andres, S., Falcon, C., Morer, A., Junque, C., Castro-Fornieles, J., 2012. Proton magnetic resonance spectroscopy in pediatric obsessive-compulsive disorder: longitudinal study before and after treatment. Psychiatry Res. 201, 17–24.
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.
Maltezos, S., Horder, J., Coghlan, S., Skirrow, C., O'Gorman, R., Lavender, T.J., Mendez, M.A., Mehta, M., Daly, E., Xenitidis, K., Paliokosta, E., Spain, D., Pitts, M., Asherson, P., Lythgoe, D.J., Barker, G.J., Murphy, D.G., 2014. Glutamate/glutamine and neuronal integrity in adults with ADHD: a proton MRS study. Transl. Psychiatry 4, e373.
Manolio, T.A., Brooks, L.D., Collins, F.S., 2008. A HapMap harvest of insights into the genetics of common disease. J. Clin. Invest. 118, 1590–1605.
Mirza, Y., O'Neill, J., Smith, E.A., Russell, A., Smith, J.M., Banerjee, S.P., Bhandari, R., Boyd, C., Rose, M., Ivey, J., Renshaw, P.F., Rosenberg, D.R., 2006. Increased medial thalamic creatine-phosphocreatine found by proton magnetic resonance spectroscopy in children with obsessive-compulsive disorder versus major depression and healthy controls. J. Child Neurol. 21, 106–111.
Monaghan, D.T., Yao, D., Cotman, C.W., 1985. L-[3H]Glutamate binds to kainate-, NMDA- and AMPA-sensitive binding sites: an autoradiographic analysis. Brain Res. 340, 378–383.
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. Psychiatry 163, 316–318.
Moore, G.J., MacMaster, F.P., Stewart, C., Rosenberg, D.R., 1998. Case study: caudate glutamatergic changes with paroxetine therapy for pediatric obsessive-compulsive disorder. J. Am. Acad. Child Adolesc. Psychiatry 37, 663–667.
Mundy, P., 2003. Annotation: the neural basis of social impairments in autism: the role of the dorsal medial-frontal cortex and anterior cingulate system. J. Child Psychol. Psychiatry 44, 793–809.
O'Brien, F.M., Page, L., O'Gorman, R.L., Bolton, P., Sharma, A., Baird, G., Daly, E., Hallahan, B., Conroy, R.M., Foy, C., Curran, S., Robertson, D., Murphy, K.C., Murphy, D.G., 2010. Maturation of limbic regions in asperger syndrome: a preliminary study using proton magnetic resonance spectroscopy and structural magnetic resonance imaging. Psychiatry Res. 184, 77–85.
O'Neill, J., Gorbis, E., Feusner, J.D., Yip, J.C., Chang, S., Maidment, K.M., Levitt, J.G., Salamon, N., Ringman, J.M., Saxena, S., 2013. Effects of intensive cognitive-behavioral therapy on cingulate neurochemistry in obsessive-compulsive disorder. J. Psychiatr. Res. 47, 494–504.
O'Neill, J., Piacentini, J.C., Chang, S., Levitt, J.G., Rozenman, M., Bergman, L., Salamon, N., Alger, J.R., McCracken, J.T., 2012. MRSI correlates of cognitive-behavioral therapy in pediatric obsessive-compulsive disorder. Prog. Neuropsychopharmacol. Biol. Psychiatry 36, 161–168.
Page, L.A., Daly, E., Schmitz, N., Simmons, A., Toal, F., Deeley, Q., Ambery, F., McAlonan, G.M., Murphy, K.C., Murphy, D.G., 2006. In vivo $^{1}$H-magnetic resonance spectroscopy study of amygdala-hippocampal and parietal regions in autism. Am. J. Psychiatry 163, 2189–2192.
Perlov, E., Philipsen, A., Hesslinger, B., Buechert, M., Ahrendts, J., Feige, B., Bubl, E., Hennig, J., Ebert, D., Tebartz van Elst, L., 2007. Reduced cingulate glutamate/glutamine-to-creatine ratios in adult patients with attention deficit/hyperactivity disorder – a magnet resonance spectroscopy study. J. Psychiatr. Res. 41, 934–941.
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.
Perlov, E., Tebarzt van Elst, L., Buechert, M., Maier, S., Matthies, S., Ebert, D., Hesslinger, B., Philipsen, A., 2010. H(1)-MR-spectroscopy of cerebellum in adult attention deficit/hyperactivity disorder. J. Psychiatr. Res. 44, 938–943.
Pittenger, C., Bloch, M.H., Williams, K., 2011. Glutamate abnormalities in obsessive compulsive disorder: neurobiology, pathophysiology, and treatment. Pharmacol. Ther. 132, 314–332.
Polanczyk, G., de Lima, M.S., Horta, B.L., Biederman, J., Rohde, L.A., 2007. The worldwide prevalence of ADHD: a systematic review and metaregression analysis. Am. J. Psychiatry 164, 942–948.
Pouwels, P.J., Brockmann, K., Kruse, B., Wilken, B., Wick, M., Hanefeld, F., Frahm, J., 1999. Regional age dependence of human brain metabolites from infancy to adulthood as detected by quantitative localized proton MRS. Pediatr. Res. 46, 474–485.
Robbins, T.W., Gillan, C.M., Smith, D.G., de Wit, S., Ersche, K.D., 2012. Neurocognitive endophenotypes of impulsivity and compulsivity: towards dimensional psychiatry. Trends Cogn. Sci. 16, 81–91.
Rommelse, N.N., Franke, B., Geurts, H.M., Hartman, C.A., Buitelaar, J.K., 2010. Shared heritability of attention-deficit/hyperactivity disorder and autism spectrum disorder. Eur. Child Adolesc. Psychiatry 19, 281–295.
Rosenberg, D.R., MacMaster, F.P., Keshavan, M.S., Fitzgerald, K.D., Stewart, C.M., Moore, G.J., 2000. Decrease in caudate glutamatergic concentrations in pediatric obsessive-compulsive disorder patients taking paroxetine. J. Am. Acad. Child Adolesc. Psychiatry 39, 1096–1103.
Rosenberg, D.R., Mirza, Y., Russell, A., Tang, J., Smith, J.M., Banerjee, S.P., Bhandari, R., Rose, M., Ivey, J., Boyd, C., Moore, G.J., 2004. Reduced anterior cingulate glutamatergic concentrations in childhood OCD and major depression versus healthy controls. J. Am. Acad. Child Adolesc. Psychiatry 43, 1146–1153.

Ruscio, A.M., Stein, D.J., Chiu, W.T., Kessler, R.C., 2010. The epidemiology of obsessive-compulsive disorder in the National Comorbidity Survey Replication. Mol. Psychiatry 15, 53–63.

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.

Shinohe, A., Hashimoto, K., Nakamura, K., Tsujii, M., Iwata, Y., Tsuchiya, K.J., Sekine, Y., Suda, S., Suzuki, K., Sugihara, G., Matsuzaki, H., Minabe, Y., Sugiyama, T., Kawai, M., Iyo, M., Takei, N., Mori, N., 2006. Increased serum levels of glutamate in adult patients with autism. Prog. Neuropsychopharmacol. Biol. Psychiatry 30, 1472–1477.

Silvetti, M., Wiersema, J.R., Sonuga-Barke, E., Verguts, T., 2013. Deficient reinforcement learning in medial frontal cortex as a model of dopamine-related motivational deficits in ADHD. Neural Netw. 46, 199–209.

Simpson, H.B., Shungu, D.C., Bender Jr., J., Mao, X., Xu, X., Slifstein, M., Kegeles, L.S., 2012. Investigation of cortical glutamate-glutamine and gamma-aminobutyric acid in obsessive-compulsive disorder by proton magnetic resonance spectroscopy. Neuropsychopharmacology 37, 2684–2692.

Soliva, J.C., Moreno, A., Fauquet, J., Bielsa, A., Carmona, S., Gispert, J.D., Rovira, M., Bulbena, A., Vilarroya, O., 2010. Cerebellar neurometabolite abnormalities in pediatric attention/deficit hyperactivity disorder: a proton MR spectroscopic study. Neurosci. Lett. 470, 60–64.

Starck, G., Ljungberg, M., Nilsson, M., Jönsson, L., Lundberg, S., Ivarsson, T., Ribbelin, S., Ekholm, S., Carlsson, A., Forssel-Aronsson, E., Carlsson, M.L., 2008. A $^{1}$H magnetic resonance spectroscopy study in adults with obsessive compulsive disorder: relationship between metabolite concentrations and symptom severity. J. Neural Transm. 115, 1051–1062.

Sun, L., Jin, Z., Zang, Y.F., Zeng, Y.W., Liu, G., Li, Y., Seidman, L.J., Faraone, S.V., Wang, Y.F., 2005. Differences between attention-deficit disorder with and without hyperactivity: a $^{1}$H-magnetic resonance spectroscopy study. Brain Dev. 27, 340–344.

Suzuki, K., Nishimura, K., Sugihara, G., Nakamura, K., Tsuchiya, K.J., Matsumoto, K., Takebayashi, K., Isoda, H., Sakahara, H., Sugiyama, T., Takei, N., Mori, N., 2010. Metabolite alterations in the hippocampus of high-functioning adult subjects with autism. Int. J. Neuropsychopharmacol. 13, 529–534.

Tafazoli, S., O'Neill, J., Bejjani, A., Ly, R., Salamon, N., McCracken, J.T., Alger, J.R., Levitt, J.G., 2013. $^{1}$H MRSI of middle frontal gyrus in pediatric ADHD. J. Psychiatr. Res. 47, 505–512.

Tebartz van Elst, L., Maier, S., Fangmeier, T., Endres, D., Mueller, G.T., Nickel, K., Ebert, D., Lange, T., Hennig, J., Biscaldi, M., Riedel, A., Perlov, E., 2014. Disturbed cingulate glutamate metabolism in adults with high-functioning autism spectrum disorder: evidence in support of the excitatory/inhibitory imbalance hypothesis. Mol. Psychiatry, 1–12.

Thakkar, K.N., Polli, F.E., Joseph, R.M., Tuch, D.S., Hadjikhani, N., Barton, J.J., Manoach, D.S., 2008. Response monitoring, repetitive behaviour and anterior cingulate abnormalities in autism spectrum disorders (ASD). Brain 131, 2464–2478.

Weber, A.M., Soreni, N., Stanley, J.A., Greco, A., Mendlowitz, S., Szatmari, P., Schachar, R., Mannasis, K., Pires, E., Swinson, R., Noseworthy, M.D., 2013. Proton magnetic resonance spectroscopy of prefrontal frontal white matter in medication naive children with OCD. Psychiatry Res. 222, 67–74.

Whiteside, S.P., Abramowitz, J.S., Port, J.D., 2012. Decreased caudate N-acetyl-l-aspartic acid in pediatric obsessive-compulsive disorder and the effects of behavior therapy. Psychiatry Res. 202, 53–59.

Whiteside, S.P., Port, J.D., Deacon, B.J., Abramowitz, J.S., 2006. A magnetic resonance spectroscopy investigation of obsessive-compulsive disorder and anxiety. Psychiatry Res. 146, 137–147.

Wiguna, T., Guerrero, A.P., Wibisono, S., Sastroasmoro, S., 2012. Effect of 12-week administration of 20-mg long-acting methylphenidate on Glu/Cr, NAA/Cr, Cho/Cr, and mI/Cr ratios in the prefrontal cortices of school-age children in Indonesia: a study using $^{1}$H magnetic resonance spectroscopy (MRS). Clin. Neuropharmacol. 35, 81–85.

Yang, P., Wu, M.T., Dung, S.S., Ko, C.W., 2010. Short-TE proton magnetic resonance spectroscopy investigation in adolescents with attention-deficit hyperactivity disorder. Psychiatry Res. 181, 199–203.

Yildiz-Yesiloglu, A., Ankerst, D.P., 2006. Review of H-1 magnetic resonance spectroscopy findings in major depressive disorder: a meta-analysis. Psychiatry Res. Neuroimaging 147, 1–25.

Yücel, M., Harrison, B.J., Wood, S.J., Fornito, A., Wellard, R.M., Pujol, J., Clarke, K., Phillips, M.L., Kyrios, M., Velakoulis, D., Pantelis, C., 2007. Functional and biochemical alterations of the medial frontal cortex in obsessive-compulsive disorder. Arch. Gen. Psychiatry 64, 946–955.

Yücel, M., Wood, S.J., Wellard, R.M., Harrison, B.J., Fornito, A., Pujol, J., Velakoulis, D., Pantelis, C., 2008. Anterior cingulate glutamate-glutamine levels predict symptom severity in women with obsessive-compulsive disorder. Aust. N. Z. J. Psychiatry 42, 467–477.

Zurowski, B., Kordon, A., Weber-Fahr, W., Voderholzer, U., Kuelz, A.K., Freyer, T., Wahl, K., Büchel, C., Hohagen, F., 2012. Relevance of orbitofrontal neurochemistry for the outcome of cognitive-behavioural therapy in patients with obsessive-compulsive disorder. Eur. Arch. Psychiatry Clin. Neurosci. 262, 617–624.