A Critical Review of Magnetic Resonance Spectroscopy Studies of Obsessive-Compulsive Disorder

Supplemental Information

Table S1. Proton Magnetic Resonance Spectroscopy Studies Reporting Neurochemical Differences Between OCD Patients and Healthy Controls

Authors	Subjects	Comorbidities	Medication Status	Field Strength	MRS Sequence*	Voxel Size	Tissue Segmentation	Region(s) of Interest	Neurochemicals Examined	Quantification Method	Reported Results
Ebert *et al.* (1997) (1)	12 OCD, 6 HC	SCZ and schizoaffective disorder excluded	10 med free > 6 months; 2 receiving stable dose of CMP or fluvoxamine	2 T	PRESS	2 X 2 X 2 cm	No	ACC; right striatum (caudate + putamen); right POC	tNAA, Glx, tCr, tCho, mI	tCr ratio	decreased tNAA/tCr in right striatum in OCD; decreased tNAA/tCr in ACC correlated with severity of illness
Bartha *et al.* (1998) (2)	13 OCD, 13 HC	1 OCD subject with MDD; 12 with pure OCD	All med free > 6 weeks	4 T	STEAM	1.5 X 2 X 1.5 cm	Yes	left corpus striatum (caudate + putamen)	tNAA, Glu, Gln, taurine, tCho, tCr	arbitrary units	decreased tNAA in left corpus striatum in OCD
Ohara *et al.* (1999) (3)	12 OCD, 12 HC	current MDD excluded	2 med naïve; 10 receiving stable dose of CMP or haloperidol	1.5 T	PRESS	2 X 2 X 2 cm	No	bilateral lenticular nuclei (contained lenticular nuclei, insula, caudate, and thalamus)	tNAA, tCr, tCho	tCr and tCho ratios	no significant differences were found in tNAA/tCr, tNAA/tCho, and tCho/tCr between OCD and HCs
Fitzgerald *et al.* (2000) (4)	11 pediatric OCD, 11 HC	5 OCD subjects with comorbid anxiety disorders; 6 subjects with pure OCD; many with subthreshold depression	All med naïve	1.5 T	multislice spin-echo	7.5 x 7.5 x 15 mm	No	right and left medial and lateral thalami	tNAA, tCr, tCho	tCr, tCho, and tCr+tCho ratios	decreased tNAA/tCho and tNAAt/Cr in left and right medial thalami in OCD
Rosenberg *et al.* (2001) (5)	11 pediatric OCD, 11 HC	5 OCD subjects with comorbid anxiety disorders; 6 subjects with pure OCD; many with subthreshold depression	All med naïve	1.5 T	multislice spin-echo	7.5 x 7.5 x 15 mm	No	right and left medial and lateral thalami	tNAA, tCr, tCho	absolute concentrations (mmol)	increased left and right medial thalamic tCho in OCD compared to HC
Russell *et al.* (2003) (6)	15 pediatric OCD, 15 HC	lifetime history of psychosis, bipolar disorder, MDD, PTSD, conduct disorder, Tourette's syndrome, eating disorders, and substance abuse/dependence excluded	All med naïve	1.5 T	multislice spin-echo	7.5 x 7.5 x 15 mm	Yes	right and left DLPFC	tNAA, tCr, tCho	absolute concentrations (mmol)	Increased tNAA in left, but not right, DLPFC in OCD compared to HC
Smith *et al.* (2003) (7)	27 pediatric OCD, 18 pediatric MDD, 18 HC	6 OCD subjects had comorbid anxiety disorders; 1 had dysthymia and comorbid anxiety disorder; 2 had ODD; 18 with pure OCD	All med naïve	1.5 T	multislice spin-echo	7.5 x 7.5 x 15 mm	No	right and left medial and lateral thalami	tNAA, tCr, tCho	absolute concentrations (mmol)	increased left and right medial thalamic tCho in OCD compared to MDD and HC
Rosenberg *et al.* (2004) (8)	20 pediatric nondepressed OCD, 14 pediatric MDD, 14 HC	2 OCD subjects had comorbid anxiety disorders; 1 had ADD; 1 had ODD; 1 had dysthymia; 15 had pure OCD	All med naïve	1.5 T	PRESS	2 x 1.5 x 1 cm	No	ACC	tNAA, Glx, tCr, tCho, mI	absolute concentrations (mmol)	decreased Glx in ACC in OCD and MDD; No differences in ACC Glx between OCD and MDD
Kitamura *et al.* (2006) (9)	12 OCD, 32 HC	any history of psychosis, depressive disorders, bipolar disorder, SCZ, PTSD, eating disorders, ADHD, PDD excluded	2 med free; 10 receiving stable dose of SSRI or CMP	3 T	PRESS	15 mm^3; 15 x 20 x 15 mm; 15 x 30 x 15 mm	No	ACC; basal ganglia; thalamus; frontal and parietal white matter	tNAA, tCr, tCho	tCr ratio	increased tCho/tCr in parietal white matter in OCD; parietal tCho/tCr correlated with OCD severity
Whiteside *et al.* (2006) (10)	15 OCD, 15 HC	current MDD, bipolar disorder, or SCZ excluded	7 med free; 8 receiving stable dose of either SSRI, CMP, mirtazapine, bupropion, trazodone, or clonazepam	1.5 T	PRESS	2 x 2 x 1 cm	No	left and right caudate head; left and right OFC	tNAA, Glx, tCr, tCho, mI	tCr ratio	increased Glx/tCr and tNAA/tCr in the right OFC; decreased mI/tCr in caudate head bilaterally
Mirza *et al.* (2006) (11)	27 pediatric OCD, 18 pediatric MDD, 18 HC	6 OCD subjects had comorbid anxiety disorders; 1 had dysthymia and comorbid anxiety disorder; 2 had ODD; 18 with pure OCD	All med naïve	1.5 T	multislice spin-echo	7.5 x 7.5 x 15 mm	No	right and left medial and lateral thalami	tNAA,tCr, tCho	absolute concentrations (mmol)	increased left and right medial thalamic tCr in OCD compared to MDD and HC
Mohamed *et al.* (2007) (12)	10 OCD, 10 HC	1 OCD subject with GAD; 9 had pure OCD	All receiving stable dose of SSRI	1.5 T	multislice spin-echo	15 x 8.6 x 8.6 mm	No	right and left thalamus; right and left basal ganglia	tNAA, tCr, tCho	tCr and tCho ratios	decreased tNAA/tCr in right basal ganglia in SSRI non-responders,; increased tCho/tCr in right thalamus in SSRI non-responders
Sumitani *et al.* (2007) (13)	20 OCD, 26 HC	all Axis I disorders, other than OCD, excluded	8 med naïve or med free; 8 receiving SSRI; 4 receiving SSRI + antipsychotic	1.5 T	STEAM	1.7 x 1.7 x 1.5 cm	Yes	bilateral ACC; left basal ganglia (caudate + putamen); left frontal lobe	tNAA, tCr, tCho	absolute concentrations	decreased tNAA in ACC in responders to SSRI + antipsychotic versus HC

Table S1. (continued)

Authors	Subjects	Comorbidities	Medication Status	Field Strength	MRS Sequence*	Voxel Size	Tissue Segmentation	Region(s) of Interest	Neurochemicals Examined	Quantification Method	Reported Results
Yücel *et al.* (2007) (14)	19 OCD, 19 HC	all Axis I disorders, other than OCD, excluded	8 med free, 11 receiving stable dose of SSRI, CMP, or venlafaxine	3 T	PRESS	6.5 cm^3	Yes	dorsal ACC	tNAA, Glx, tCr, tCho, mI	absolute concentrations (i.u.)	decreased tNAA in dorsal ACC in OCD vs. HC
Yücel *et al.* (2008) (15)	20 OCD, 26 HC	all Axis I disorders, other than OCD, excluded	8 med free; 12 receiving stable dose of SSRI, CMP, or venlafaxine	3 T	PRESS	6.5 cm^3	Yes	right and left dorsal ACC; right and left rostral ACC	tNAA, Glx, tCr, tCho, mI	absolute concentrations (i.u.)	decreased Glx in right and left rostral ACC and left dorsal ACC in female OCD patients; Glx correlated with symptom severity in female OCD patients; increased mI in right rostral and dorsal ACC in male and female OCD patients
Starck *et al.* (2008) (16)	9 OCD, 16 HC	several OCD subjects with mild depression or dysthymia; 1 OCD subject with GAD	1 med naïve; 5 receiving SSRI; 1 receiving CMP + quetiapine; 2 receiving hypnotics	1.5 T	PRESS	1.5 cm^3; 3.6 cm^3; 4.0 cm^3	No	right caudate (head + body); bilateral ACC; OCC	tNAA, Glu, Glx, tCho, mI, tCr	absolute concentrations (i.u.)	no significant differences in metabolites between OCD and HC; OCD symptom severity positively correlated with caudate tCr, Glx, Glu, and tCho as well as OCC mI; OCD symptom severity negatively correlated with OCC Glx
Atmaca *et al.* (2009) (17)	18 OCD, 18 HC	all current or past psychiatric disorders were excluded	All med free > 2 weeks	1.5 T	unclear from manuscript	10 x 10 x 2.4 mm	No	left and right hippocampus	tNAA, tCr, tCho	tCr and tCho ratios and absolute concentrations (mmol)	decreased tNAA/tCr, tNAA/tCho, and absolute tNAA in hippocampus in OCD versus HC; increased absolute tCho in hippocampus in OCD versus HC
Arnold *et al.* (2009) (18)**	16 pediatric OCD	lifetime history of psychosis, bipolar disorder, conduct disorder, Tourette's syndrome, and eating disorders excluded	All med naïve	1.5 T	PRESS	2 X 1.5 X 1 cm; 2 X 2 X 2 cm	No	ACC; POC	tNAA, Glx, tCr, tCho, mI	absolute concentrations (mmol)	decreased Glx in ACC, but not POC, was associated with the rs1019385 polymorphism of the *GRIN2B* gene
Fan *et al.* (2010) (19)	21 OCD, 19 HC	all comorbid psychiatric disorders were excluded	10 med naïve; 11 med free > 8 weeks	1.5 T	PRESS	2 x 2 x 2 cm	No	medial prefrontal cortex	tNAA, tCr, tCho, mI	tCr ratio	increased tNAA/Cr in medial prefrontal cortex in OCD versus HC
Bédard and Chantal (2011) (20)	13 OCD, 12 HC	all active (for at least 6 months prior to enrollment) Axis I disorders, except OCD, were excluded	2 med free; 11 receiving stable dose of SSRI, CMP, or venlafaxine > 3 months	1.5 T	PRESS	8.0 cm^3 to 9.6 cm^3	No	left and right OFC; left and right median temporal lobe; left and right thalami; ACC	tNAA, Glx, tCr, tCho, mI	tCr ratio	no significant differences in metabolites between OCD and HC in any ROIs; significant negative correlation between OCD symptom severity and mI/tCr in left orbitofrontal cortex
Besiroglu *et al.* (2011) (21)	30 OCD (15 with autogenous obsessions and 15 with reactive obsessions), 15 HC	current MDD, psychosis, bipolar disorder excluded; comorbid anxiety disorders were permitted as long as OCD was the primary diagnosis	All med free	1.5 T	PRESS	2 x 2 x 2 cm; 1.6 x 1.6 x 1.6 cm	No	right rostral ACC; right amygdala-hippocampal region	tNAA, tCr, tCho	tCr ratio and absolute concentrations (mmol)	decreased tNAA/tCr in right rostral ACC in OCD versus HC, which were more likely due to increased absolute tCr in ACC in OCD; increased tNAA/tCr in right amygdala-hippocampal region in OCD with autogenous obsessions, which was more likely explained by increased tNAA levels

ACC, anterior cingulate cortex; ADD, attention deficit disorder; ADHD, attention-deficit/hyperactivity disorder; CMP, clomipramine; DLPFC, dorsolateral prefrontal cortex; GAD, generalized anxiety disorder; Gln, glutamine; Glu, glutamate; Glx, glutamate plus glutamine; HC, healthy controls; i.u., institutional units; MDD, major depressive disorder; mI, myo-inositol; MRS, magnetic resonance spectroscopy; OCD, obsessive-compulsive disorder; OCC, occipital cortex; OFC, orbitofrontal cortex; PDD, pervasive developmental disorder; POC, parieto-occipital cortex; PRESS, point-resolved spectroscopy; PTSD, posttraumatic stress disorder; SCZ, schizophrenia; SSRI, selective serotonin reuptake inhibitor; STEAM, stimulated echo acquisition mode; T, Tesla; tCho, total choline; tCr, total creatine; tNAA, total *N*-acetylaspartate.

*Multislice spin-echo refers to multi-voxel, 2-dimensional chemical-shift imaging with multi-slice selection. Stated voxel dimensions with multislice spin-echo refer to nominal voxel size (FOV/sampling matrix). PRESS, STEAM and PROBE-P are all single-voxel acquisitions.

**This study did not include a healthy comparison group.

Table S2. Proton Magnetic Resonance Spectroscopy Studies Reporting Neurochemical Changes with Treatment in OCD Patients

Authors	Subjects	Comorbidities	Treatment Administered	Field Strength	MRS Sequence*	Voxel Size	Tissue Segmentation	ROI(s)	Metabolites Examined	Quantification Method	Reported Results
Moore *et al.* (1998) (22)	1 pediatric OCD	none	paroxetine	1.5 T	PRESS	0.7 cm^3	No	head of left caudate	tNAA, Glx, tCr, tCho, mI	ratio to brain water concentration (x 10^4/water)	decreased Glx in head of left caudate after 12 weeks of paroxetine treatment
Rosenberg *et al.* (2000) (23)	11 pediatric med-naïve OCD, 11 HC	lifetime history of psychosis, bipolar disorder, MDD, eating disorders, substance abuse/dependence, Tourette's disease, ADHD, conduct disorder, or autistic spectrum disorder excluded	paroxetine	1.5 T	PRESS	0.7 cm^3	No	head of left caudate	tNAA, Glx, tCr, tCho, mI	ratio to brain water concentration (x 10^4/water)	increased pre-treatment Glx in head of left caudate in OCD vs. HC; significant decrease in Glx in left head of caudate after 12 weeks of paroxetine treatment in OCD
Bolton *et al.* (2001) (24)	1 pediatric OCD	none	paroxetine	1.5 T	PRESS	0.7 cm^3	No	head of left caudate	tNAA, Glx, tCr, tCho, mI	ratio to brain water concentration (x 10^4/water)	decreased Glx in head of left caudate after 12 weeks of paroxetine treatment that persisted 3 months after medication discontinuation
Benazon *et al.* (2003) (25)	21 pediatric, treatment-naïve OCD	lifetime history of psychosis, bipolar disorder, MDD, eating disorders, substance abuse/dependence, Tourette's disease, ADHD, conduct disorder, or autistic spectrum disorder excluded	CBT	1.5 T	PRESS	0.7 cm^3	No	head of the left caudate	tNAA, Glx, tCr, tCho, mI	ratio to brain water concentration (x 10^4/water)	no significant changes in left caudate head in OCD after 12 weeks of CBT despite clinical improvement
Jang *et al.* (2006) (26)	13 med-naïve OCD, 13 HC	lifetime history of psychosis, bipolar disorder, substance abuse/dependence, Tourette's disease excluded	citalopram	1.5 T	^{1}H-MRSI PRESS	20 mm thick slab with voxel dimensions of 7.5 x 7.5 x 20 mm	Yes	prefrontal cortex, parietal cortex, ACC, PCC, frontal white matter, parietal white matter	tNAA	tCr and tCho ratios	decreased pretreatment tNAA/tCr in prefrontal cortex, frontal white matter and ACC in OCD vs. HC; significantly increased tNAA/tCr in prefrontal cortex and frontal white matter after 12 weeks of citalopram treatment in OCD
O'Neill *et al.* (2012) (27)	5 med-free pediatric OCD; 9 HC	authors do not report any exclusion criteria for comorbid Axis I disorders	CBT	1.5 T	^{1}H-MRSI PRESS	9 mm thick slab x 2	Yes	bilateral putamen, thalamus, and rostral ACC	tNAA, Glx, tCr, tCho, mI	absolute concentrations (i.u.)	increased pre-treatment tNAA in left rostral ACC in OCD vs. HC; tNAA and tCr in left rostral ACC significantly decreased and tCho in right thalamus significantly increased after 12 weeks of CBT
Lázaro *et al.* (2012) (28)	11 treatment-naïve pediatric OCD, 12 HC	all comorbid psychiatric and neurological disorders excluded	naturalistic treatment with SSRI + CBT	1.5 T	PRESS	2 x 3 x 2 cm; 2 x 2 x 2 cm	Yes	ACC/medial frontal lobe, left and right striatum	tNAA, Glx, tCr, tCho, mI	absolute concentrations (i.u.)	decreased pre-treatment tCho in left striatum in OCD vs. HC; No significant changes following 6 months of SSRI + CBT
Whiteside *et al.* (2012) (29)	15 adult OCD, 15 HC	exclusions included: lifetime history of SCZ, bipolar disorder, mental retardation, substance abuse or current MDD	CBT	1.5 T	single-voxel short TE PROBE-P	2 x 2 x 1 cm	Yes	left and right caudate head; left and right OFC	tNAA, Glx, tCr, tCho, mI	absolute concentrations (i.u.)	decreased pre-treatment tNAA in caudate and decreased tNAA and tCr in right OFC in OCD vs. HC; Significantly increased tNAA in left caudate head after 12 weeks of CBT

^{1}H-MRSI, proton magnetic resonance spectroscopy imaging; ACC, anterior cingulate cortex; ADHD, attention-deficit/hyperactivity disorder; CBT, cognitive behavioral therapy; Glx, glutamate plus glutamine; HC, healthy controls; i.u., institutional units; MDD, major depressive disorder; mI, myo-inositol; OCD, obsessive-compulsive disorder; OFC, orbitofrontal cortex; PCC, posterior cingulate cortex; PRESS, point-resolved spectroscopy; PROBE-P, proton brain examination; ROI, region of interest; SCZ, schizophrenia; SSRI, selective serotonin reuptake inhibitor; T, Tesla; tCho, total choline; tCr, total creatine; tNAA, total *N*-acetylaspartate.

*^{1}H-MRSI PRESS refers to multi-voxel, 2-dimensional chemical-shift imaging with PRESS volume excitation. Stated voxel dimensions with ^{1}H-MRSI PRESS refer to nominal voxel size (FOV/sampling matrix). PRESS and PROBE-P are single-voxel acquisitions.

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