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Frontal cortex myo-inositol is associated with sleep and depression in adolescents: a proton magnetic resonance spectroscopy study

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Abstract

Aim: This study used proton magnetic resonance spectroscopy (^{1}H MRS) to evaluate neurochemistry of the frontal cortex in adolescents with symptoms of sleep and depression.

Methods: 19 non-medicated adolescent boys (mean age 16.0y; n=9 clinical cases with depression/sleep symptoms and n=10 healthy controls) underwent ^{1}H MRS at 3T. MR spectra were acquired from the anterior cingulate cortex (ACC), the dorsolateral prefrontal cortex, and frontal white matter. Concentrations of N-acetyl aspartate, total creatine, choline-containing compounds, total glutamine plus glutamate, and myo-inositol (mI) were compared between the two subgroups and correlated with sleep and clinical measures in the total sample. Sleep was assessed with self-report questionnaires and ambulatory polysomnography recordings.

Results: Concentrations of mI were lower in both frontal cortical regions among the depressed adolescents as compared to healthy controls. No statistically significant differences in other metabolite concentrations were observed between the subgroups. Frontal cortex mI concentrations correlated negatively with depression severity, subjective daytime sleepiness, insomnia symptoms, and the level of anxiety, and positively with total sleep time and overall psychosocial functioning. The correlations between mI in the ACC and total sleep time as well as daytime sleepiness remained statistically significant when depression severity was controlled in the analyses.

Conclusion: Lower frontal cortex mI may indicate a disturbed second messenger system. Frontal cortical mI may thus be linked to the pathophysiology of depression and concomitant sleep symptoms among maturing adolescents. Short sleep and daytime sleepiness may be associated with frontal cortex mI independently from depression.

Introduction

Depression is tightly associated with disturbed sleep: so tightly that sleep disturbance is one of the diagnostic criteria of major depressive disorder [1]. The presence of symptoms of disturbed sleep has been linked with more severe forms of depression [2-4] and poorer depression treatment response [5]. The underlying neurobiological links between disturbed sleep and mood remain, however, obscure.

Adolescence is marked by increased incidence of depression and insomnia and dramatic changes in sleep patterns [6]. The trajectory of the maturational changes in sleep structure during adolescence matches temporally and topographically adolescent brain cortical maturation. Both the decrease in deep slow wave sleep and cortical grey matter reduction start from the occipital posterior regions and occur latest in the higher-order association areas of the frontal cortex [7-9]. Frontal cortex developmental processes continue until adulthood [10], making the frontal cortex vulnerable to aberrations in development still during late adolescence [11].

The prefrontal cortex (PFC), which is importantly involved in self-referential processing and regulation of mood states via its interactions with striatal and limbic structures, has been repeatedly implicated as a key brain region involved in the pathophysiology of depression across diverse age groups [12, 13]. In depressed adolescents, both structural and functional changes in the PFC have been reported: a trend towards decreased regional volumes, abnormal cortical thinning, and reduced activation in cognitive control and decision making tasks [13]. The structure and function of the PFC have likewise been observed to correlate with sleep habits [14-16], sleep loss [17, 18], and sleep pathologies [19-21].

Proton magnetic resonance spectroscopy (^{1}H MRS) allows to detect and measure *in vivo* several neurometabolites and thus to examine distinct neurochemical processes involved in the pathophysiology of depression. In depressed adolescents, ^{1}H MRS has revealed numerous but inconsistent findings in the frontal cortex. Both higher and lower levels of choline-containing compounds (Cho) have been reported in the medial frontal cortex and the left dorsolateral PFC (DLPFC) [22-24], higher myo-inositol (mI) levels have been observed in the DLPFC [24], and lower glutamate plus glutamine (Glx) and N-acetyl-aspartate (NAA) concentrations in the anterior cingulate cortex (ACC) have been found [13,25, 26]. The first and thus far the only attempt to study the link between sleep, mood, and frontal ^{1}H MRS neurochemistry in young people with affective disorders found that a later sleep midpoint is associated with altered glutamatergic processes in the ACC, independent of depression severity [27]. In that study, diurnal rhythm and motor activity was measured with actigraphy from a rather heterogeneous group of 15-33 year-old adolescents and young adults with an emerging unipolar or bipolar disorder [27].

MRS findings suggest that cellular health and neurotransmission might be impaired in the frontal cortical areas in adolescents with depression. Further, it seems possible that sleep would also affect the same neurometabolic processes. However, the findings still remain inconsistent for several reasons. Most notably, the number of subjects studied is typically small in ^{1}H MRS studies, and the samples have been heterogeneous in terms of age, pubertal status, gender, psychotropic medication use, and the presence of other psychiatric comorbidities. Further, methodological approaches and brain areas studied have been variable.

We hypothesized that frontal cortex ^{1}H MRS neurochemistry would be altered in depressed adolescents as compared to healthy controls. Further, we hypothesized that sleep symptoms would be associated with metabolite levels in a similar way than depressive symptoms. We studied this in a carefully evaluated and selected homogeneous sample of non-medicated adolescent boys and performed ^{1}H MRS in two frontal cortical regions (ACC, DLPFC), and additionally in frontal white matter (FWM; control region with no hypothesis of altered metabolism) with a 3 Tesla MR imager.

Materials and methods

Participants

A total of 20 non-medicated adolescent boys participated in the study. Ten of them were patients suffering from depressive and/or sleep symptoms recruited from the Helsinki University Central Hospital Department of Adolescent Psychiatry outpatient units, and ten were healthy controls recruited via advertisements for the hospital staff. Imaging data was not available for one adolescent in the patient group due to drop-out, leaving a total of 19 participants in the analyses presented. Written informed consent for study participation was received both from the participants and their parents or legal guardians and the study protocol was approved by the ethics committee of the Helsinki University Central Hospital.

Exclusion criteria for all participants included mental retardation, insufficient knowledge of Finnish language, current use of medication, age over 17.5 or under 14.5 years, chronic somatic illness, substance abuse/dependence, principal DSM-IV diagnosis other than depressive/sleep disorder, and any contraindications for brain MRI. All adolescents were free of psychotropic and other

medication during the whole study period. No structural pathologies were found in their brain anatomy according to brain MRI evaluated by a neuroradiologist (N.L.), and the presence of somatic conditions was ruled out based on blood samples. All subjects consumed less than three cups of coffee daily or the equivalent amount of other caffeinated products. Detailed subject characteristics are described in Table 1.

Psychiatric evaluation

The present and lifetime episodes of DSM-IV axis I disorders were assessed with the Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime version (K-SADS-PL), a semi-structured diagnostic interview [28]. All interviews were performed by the same clinician (A.S.U.) and confirmed in a diagnostic meeting with a senior clinician (M.M.). As part of the DSM-IV axial diagnostic procedure, the global assessment of functioning scale (GAF; numeric range of 0-100) was used according to DSM-IV guidelines to assess overall psychosocial functioning [1]. GAF has been previously used in studies among adolescents [29, 30].

Depression symptom severity was assessed with two different scales: the 21-item Beck Depression Inventory (BDI-21), and the Hamilton Depression Rating Scale (HDRS). The BDI-21 is a standardized 21-item self-rating questionnaire [31], which has been well studied also in adolescents [32, 33]. The subjects were asked to rate each of the symptoms on a 4-point scale ranging from 0 (Not at all) to 3 (Severely) according to the severity of the symptom (sum score range 0-63). The HDRS is a widely used and standardized 17-item depression severity scale, in which each of the depressive symptoms is rated by the clinician on a scale of 0-2 or 0-4 points (total sum score range 0-52) [34].

The HDRS has been originally developed for adults, but it has previously been successfully applied to study adolescents (e.g. [4, 35-37]).

To complement the psychiatric evaluation, subjects also filled in the Alcohol Use Disorder Identification Test (AUDIT) [38], and the Beck Anxiety Inventory (BAI) [39].

Assessment of sleep

Insomnia symptoms were assessed with Athens Insomnia Scale (AIS), a validated self-report questionnaire designed for quantifying sleep difficulties during the past month based on the ICD-10 criteria [40]. It consists of eight items rated on a scale of 0-3 (total sum score range 0-24) on sleep induction, awakenings during the night, final awakening, total sleep duration, sleep quality, daytime well-being, daytime functioning capacity, and sleepiness during the day.

Daytime sleepiness symptoms were measured with the Pediatric Daytime Sleepiness Scale (PDSS) [41], a self-rated sleepiness scale specially designed for use among school-aged adolescents. The PDSS consists of 8 items rated on a scale of 0-4 (total sum score range 0-32) related to frequency of falling asleep/drowsiness in class and while doing homework, daytime alertness, daytime tiredness/grumpiness, troubles waking up, falling back to sleep after being awakened, need for outside help to wake up, and thoughts of needing more sleep.

Sleep length and sleep efficiency referred to sleep period were assessed with ambulatory polysomnography performed in the adolescents' home environment for two consecutive nights. The recordings included electroencephalogram (EEG), electro-oculogram (EOG), and chin electro-myogram (EMG) recordings and was performed using standard guidelines (Embla, Flaga Hf.

Medical devices; EEG positions according to the International 10-20 system; derivations F4-M1, C4-M1, O2-M1 and backup derivations F3-M2, C3-M2, and O1-M2; sampling rate 200Hz). The recordings were scored manually in 30-s epochs by a certified sleep technologist blinded to the subgroup status of the subjects using standard criteria [42] and total sleep time and sleep efficiency (time asleep relative to sleep period) were calculated from the scorings. The average values of the two nights were used in the analyses.

Magnetic Resonance Spectroscopy

Proton Magnetic Resonance Spectroscopy (^{1}H MRS) was performed at 3.0 T clinical imager (Verio, Siemens, Erlangen, Germany) in the morning after the two nights of polysomnographic recordings, starting between 10:30 and 12 am. Patients lay in a supine position, and a 32 channel head coil was used in data collection. T2 weighted turbo spin echo images (repetition time (TR) of 3630 and echo time (TE) of 96 ms) were collected in transaxial, sagittal, and coronal planes in order to enable a careful positioning of MRS voxel and to screen possible anomalies. Automatic preparation and shimming procedure was followed by manual shimming before data acquisition. PRESS localization technique with TR of 10000/2000 ms, TE of 30/30 ms and 2/96 acquisitions were used to obtain unsuppressed reference spectra and water suppression spectra, respectively. Voxel sizes were kept constant for ACC (15x25x20), left DLPFC (25x15x15), and left FWM (15x15x15) in each subject.

LCModel v6.3 (http://s-provencher.com/pages/lcmodel.shtml) was used to assess the concentrations of N-acetylaspartate (NAA), total creatine (tCr), choline containing compounds (Cho), total glutamine plus glutamate (Glx), and myo-inositol (mI). Also, signal-to-noise ratio (SNR)

and full width at half maximum (FWHM) were determined from each spectra. The typical location of the ^{1}H MRS voxels and representative ^{1}H MR spectra are shown in Fig. 1.

Statistical analyses

Statistical analyses were performed with the IBM SPSS Statistics Version 22 software. Normality of the data was assessed with the Kolmogorov-Smirnov test of normality. Comparisons between subgroups were performed with one-way analysis of variance (ANOVA) or non-parametric independent samples Kruskal-Wallis tests in case of non-normal distribution of the data. To assess correlations between mI concentrations and clinical measures (TST, sleep efficiency, BDI-21 total score, HDRS, BAI, AIS, PDSS, GAF), correlation analyses using the Pearson's correlation analysis or the Spearman's non-parametric correlation analysis (in case of non-normal distribution of the data) were performed. Findings were considered statistically significant at the p <0.05 level.

Results

Participant characteristics

Participants were on average 16.0 ± 0.8 (mean ± SD) years old. The subgroups of cases and controls did not differ in terms of their age, body mass index (BMI), serum testosterone levels, alcohol use, or anxiety symptoms (one-way ANOVA n.s.; Table 1).

No axis-I diagnoses were found among the controls, and the cases were confirmed to suffer from depressive disorder (lifetime first depressive episode for 6, second episode for 2 of the subjects; mean length of current depressive episode 52 ± 52 weeks), except for one patient suffering only

from a circadian rhythm sleep disorder with minor mood symptoms. This non-depressed subject was discarded from the group comparisons, but his data was used in the correlational analyses of the total sample. None of the subjects suffered from bipolar disorder nor manifested psychotic features of depression. Comorbid anxiety disorder was present in one, and comorbid disruptive behavior disorder in one subject, while others did not have comorbid axis-I disorders.

Quality of the ^{1}H MRS spectra

Mean signal-to-noise ratios (SNR) for ACC, DLPFC, and FWM spectra were 46 ± 7.38 ± 6, and 21 ± 5, respectively. FWHMs for ACC, DLPFC, and FWM spectra were 4.5 ± 1.2 Hz, 5.7 ± 1.7 Hz, and 6.3 ± 2.3 Hz, respectively. There were no differences in ACC, DLPFC, and FWM spectral quality between control and patient groups measured by SNR or FWHM. Cramer-Rao lower bound values for myo-inositol quantification were 7% or below in each spectra. Because of technical failure or patient movement, MRS spectra could not be obtained in two cases in the DLPFC area, limiting total sample size to n=17 in the DLPFC, and in one case in the FWM, limiting total sample size to n=16 in the FWM.

Subgroup comparisons of metabolite concentrations

The concentration of myo-inositol was lower in cases vs. controls in both frontal cortical areas (ACC: $F(1,16) = 10.026$; $p = 0.006$; DLPFC: $F(1,14) = 5.381$; $p = 0.036$; One Way ANOVA; Fig. 2). No significant differences were observed in the concentrations of the other metabolites in either of

these two cortical brain areas or in any metabolite concentrations in FWM (One-way ANOVA or Independent Samples Kruskal-Wallis tests n.s.; Fig. 2).

Metabolites and clinical measures

In the total sample, myo-inositol levels in the ACC correlated negatively with depression severity (HDRS, BDI-21), level of anxiety (BAI), insomnia symptoms (AIS), daytime sleepiness symptoms (PDSS), and positively with total sleep time (TST; Fig. 3) and overall psychosocial functioning (GAF). Myo-inositol level in the DLPFC correlated negatively with depression severity (HDRS) and positively with total sleep time (TST). Other correlations of mI with clinical measures remained statistically non-significant. The results are presented in detail in Table 2.

In order to examine whether the significant associations between mI and sleep measures are confounded by depressive symptoms, we performed additional partial correlation analyses, in which depression severity was controlled for (partial correlation analyses; BDI-21 total score without sleep item as covariate). The correlations between mI in the ACC and TST (correlation coefficient $r = 0.582$; $p = 0.011$), and mI in the ACC and PDSS ($r = -0.543$; $p = 0.024$) remained significant. The correlations between mI in the DLPFC and TST ($r = 0.492$; $p = 0.053$), and between mI in the ACC and AIS ($r = -0.358$; $p = 0.145$) did not remain statistically significant.

The correlations of other metabolites with clinical measures are presented in the supplementary material Table 1. In summary, in these analyses tCr concentrations in the ACC correlated negatively with HDRS ($r = -0.482$; $p = 0.037$) and AIS ($r = -0.514$; $p = 0.024$; Pearson's correlation), while tCr concentrations in the DLPFC did not correlate with clinical measures. NAA, Cho, and Glx

concentrations did not correlate with any of the clinical measures in either frontal cortical area. In FWM, metabolite concentrations did not correlate with any of the clinical measures.

Discussion

The main finding of this study was that frontal cortex myo-inositol is lower in depressed adolescent boys as compared to healthy controls, and also correlates with sleep length and daytime sleepiness symptoms when severity of depression is controlled for. This implies that both poor sleep and depression may be linked to similar neurometabolic pathways in the frontal cortex. These metabolic alterations appear specific to the cortex since they were not observed in frontal white matter.

Myo-inositol is a naturally occurring glucose isomer which has a number of known roles in the brain. Myo-inositol was initially found in astrocytes, and was therefore proposed as a glia-specific marker [43]. It has, however, also been detected in neuronal cells [44]. It acts as an organic osmolyte involved in maintenance of cell volume, it is required for the synthesis of cell membrane phospholipids, and it acts as a precursor in the phosphatidylinositol (PI) second messenger system [45,46]. The PI cycle is activated following ligand binding to a number of cell surface receptors, including those for serotonin, glutamate, histamine, and dopamine, leading to increased second messengers inositol triphosphate (IP3) and diacylglycerol (DAG), which initiate different cascades of cellular events, including mobilization of intracellular calcium and activation of protein kinase C (PKC), which, in turn, have multiple downstream cellular effects [45,46]. The source of neuronal mI is primarily the recycling of PI cycle constituents, but some of the total mI is synthesized in brain from glucose and some transported from blood [47]. Our findings of lower myo-inositol in

depressed adolescents with sleep symptoms may point towards an imbalance in the second messenger signaling system.

Considering its widespread neurometabolic role, it is not surprising that altered myo-inositol concentrations have been previously detected in a variety of neurological, psychiatric and behavioural conditions, including e.g. head injuries, Alzheimer's disease, attention deficit-hyperactivity disorder (ADHD), obsessive-compulsive disorder, sleep disorders, as well as mood disorders in different age groups [48-55]. In particular, reduced cerebral mI concentration has been suggested as a neurochemical biomarker for depression: lower inositol has been reported in the CSF of depressed patients [56] as well as in postmortem frontal cortex of suicide victims and bipolar disorder patients [57]. Some ^{1}H MRS studies have observed lower cerebral mI concentrations in depressed patients as compared to controls [48,58-60]. On the contrary, bipolar disorder may be characterized by elevated frontal cortex mI concentrations and the anti-manic effects of lithium may be associated with a reduction of mI [61]. Further, electro-convulsive treatment (ECT) may increase mI concentrations [60]. These results are not, however, unanimous, as some studies have reported increased or non-different mI levels in depressed patients as compared to healthy controls [24, 62, 63]. Inositol is widely present in a range of foods (fruits, plants, meats, whole-grain cereals) and available as a dietary supplement. Currently evidence is unclear whether or not inositol is of benefit in the treatment of depression [64].

The results of the current study support earlier findings on decreased cortical myo-inositol in depression, particularly in the adolescent age group, and encourage further studies on the role of mI in depression and associated sleep symptoms. Understanding these pathophysiological

phenomena early in the course of depression would be crucial not only in furthering our scientific understanding of the links between poor sleep and mood, but also in developing targeted, effective, and hopefully even preventive interventions [6].

Less is known on the associations between mI and sleep. In healthy older people, poorer sleep quality and less efficient sleep correlated with higher hippocampal mI/tCr ratios, which were hypothesized by the authors to associate with hippocampal glial alterations [50]. The authors also pointed out, however, that their findings may reflect neurodegenerative/pathophysiological processes in this age group, similar to those seen in Alzheimer's disease [50, 52, 65, 66]. The contrast between the findings by Cross et al. (pointing towards higher mI in relation with poor sleep in older people) and our findings (pointing towards lower mI in relation with poor sleep in adolescents) may thus be at least partly explained by factors related to maturational or neurodegenerational processes. In addition, brain region specific factors may also contribute to the differences: mI concentration [46, 67] and neuronal activity during the sleep-wake cycle [68] differs between the hippocampi vs. frontal cortical areas. The study by Cross et al. concentrated on the hippocampi and did not yield results from the frontal cortex, and our study concentrated on frontal brain areas only. The frontal cortex (more specifically the ACC) was the region of interest in the study by Naismith et al. reporting an association between sleep midpoint and altered glutamatergic processes among young people with affective disorders. However, mI was not among the neurometabolites of interest in their study [27].

To the best of our knowledge, our study is the first to demonstrate an association between subjective and objective sleep measures and frontal cortex myo-inositol concentrations in a

sample of adolescent boys. Further, while our study reveals that depressed adolescents show lower cortical myo-inositol concentrations as compared to healthy controls, depression does not fully explain the associations of mI with sleep length and daytime sleepiness. Both sleep length and depression may thus affect the same neurometabolic pathways in the maturing frontal cortex of adolescents in an additive manner.

In addition to findings related to mI, we found that tCr concentrations in the ACC correlated negatively with depression severity and insomnia symptoms. tCr has conventionally been used as a reference metabolite, and very few studies with inconsistent findings have assessed tCr concentrations in psychiatric disorders [69]. However, tCr is not a constant compound in the brain, but plays a pivotal role in cell energy homeostasis, and thus lower tCr levels related to insomnia and depressive symptoms may indicate impaired energy metabolism [46]. The fact that no significant findings were detected in other MRS metabolites may be attributed to the small sample size, which may not allow us to detect subtle differences.

Important strengths of this study include the homogeneous nature of the sample in terms of gender and age, the lack of psychotropic and other medication use among the subjects, the use of polysomnography (the gold standard of sleep research) to determine sleep length, the detailed psychiatric evaluation of the participants, and the inclusion of a control group. Further, the patient and control groups were well matched for their age and hormonal status. Since antidepressive medication may at least region-specifically affect the brain MRS metabolic profile [70], we find the lack of psychotropic medication use a particular strength of our study.

Limitations of the study include most importantly the small sample size, which allows us to make only preliminary conclusions on the results. Further studies with larger sample sizes are needed especially to conduct more specific multi-variable analyses in subgroups. Further, as our study was cross-sectional, we cannot make definite inferences on causality: are shorter sleep and depressive symptoms actually causing a change in myo-inositol metabolism, or are the alterations in myo-inositol underlying the clinical phenotypes? This remains to be answered in longitudinal study designs. Excluding female participants from the sample on one hand limits the generalizability of the findings to adolescent girls, but on the other also excluded the potential effects of the menstrual cycle phase on sleep and brain metabolism [71, 72]. Boys and girls also differ from each other in terms of brain maturational changes during adolescence [73]. In addition, a limitation of this study is the lack of correction for partial volume effects. In theory, gray matter atrophy could lead to an increased CSF fraction inside the VOI and therefore decreased metabolite levels. Should this occur, a decrease in all metabolite levels and SNR would be expected, but we did not see differences between groups in any other metabolite nor SNR than mI.

Conclusion

Lower frontal cortex mI may point towards a disturbed second messenger system and be linked to the pathophysiology of depression and concomitant sleep symptoms among maturing adolescents. Short sleep and daytime sleepiness may be associated with frontal cortical mI independently from depression. Further studies are needed to explore the role of mI in depression and associated sleep symptoms in more detail.

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Conflicts of interest

No conflicts of interest.

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Table and figure legends.

Table 1.

Variable		Mean	SD	Range
Age (n=19)		**16.0**	**0.8**	**14.7-17.3**
	Cases (n=9)	15.8	0.9	14.7-17.3
	Controls (n=10)	16.2	0.7	14.8-17.2
BMI (n=19)		**20.9**	**2.8**	**16.8-27.6**
	Cases (n=9)	21.4	3.7	16.8-27.6
	Controls (n=10)	20.6	1.7	17.8-23.8
S-Testo (n=18)		**19.9**	**3.7**	**15.0-27.6**
	Cases (n=9)	20.4	3.9	15.0-26.3
	Controls (n=9)	19.4	3.6	15.3-27.6
BDI-21 (n=19)		**9.0**	**10.7**	**0-33**
	Cases (n=9)	15.8*	11.7	1-33
	Controls (n=10)	2.8*	4.0	0-12
HDRS (n=19)		**5.8**	**6.9**	**0-19**
	Cases (n=9)	11.9**	5.1	4-19
	Controls (n=10)	0.3**	0.7	0-2
BAI (n=18)		**5.3**	**5.2**	**0-18**
	Cases (n=8)	7.9	5.6	1-18
	Controls (n=10)	3.2	4.1	0-13

GAF (n=19)		**67.1**	**16.0**	**43-90**
	Cases (n=9)	51.6**	6.4	43-59
	Controls (n=10)	81.0**	4.6	75-90
AIS (n=19)		**5.8**	**5.9**	**0-18**
	Cases (n=9)	9.9*	6.0	1-18
	Controls (n=10)	2.1*	2.2	0-7
PDSS (n=18)		**15.5**	**5.8**	**6-26**
	Cases (n=8)	18.9*	5.4	12-26
	Controls (n=10)	12.8*	4.8	6-21
TST (n=19)		**456.6**	**66.0**	**303.0-563.0**
	Cases (n=9)	431.8	85.0	303.0-563.0
	Controls (n=10)	479.0	33.6	412.3-528.5
Sleep efficiency (n=19)		**95.7**	**6.4**	**70.7-99.3**
	Cases (n=9)	94.4	9.0	70.7-98.5
	Controls (n=10)	96.9	2.8	92.1-99.3

Sample characteristics presented separately for the total sample (n=19), and the cases (n=9) and controls (n=10). *denotes statistically significant differences between the cases and the controls at a statistical threshold of $p<0.05$; **denotes statistically significant differences at a statistical threshold of $p<0.001$ (one-way ANOVA). BMI = Body Mass Index; S-Testo = serum testosterone level (nmol/l); BDI-21 = 21-item Beck Depression Inventory; HDRS = Hamilton Depression Rating

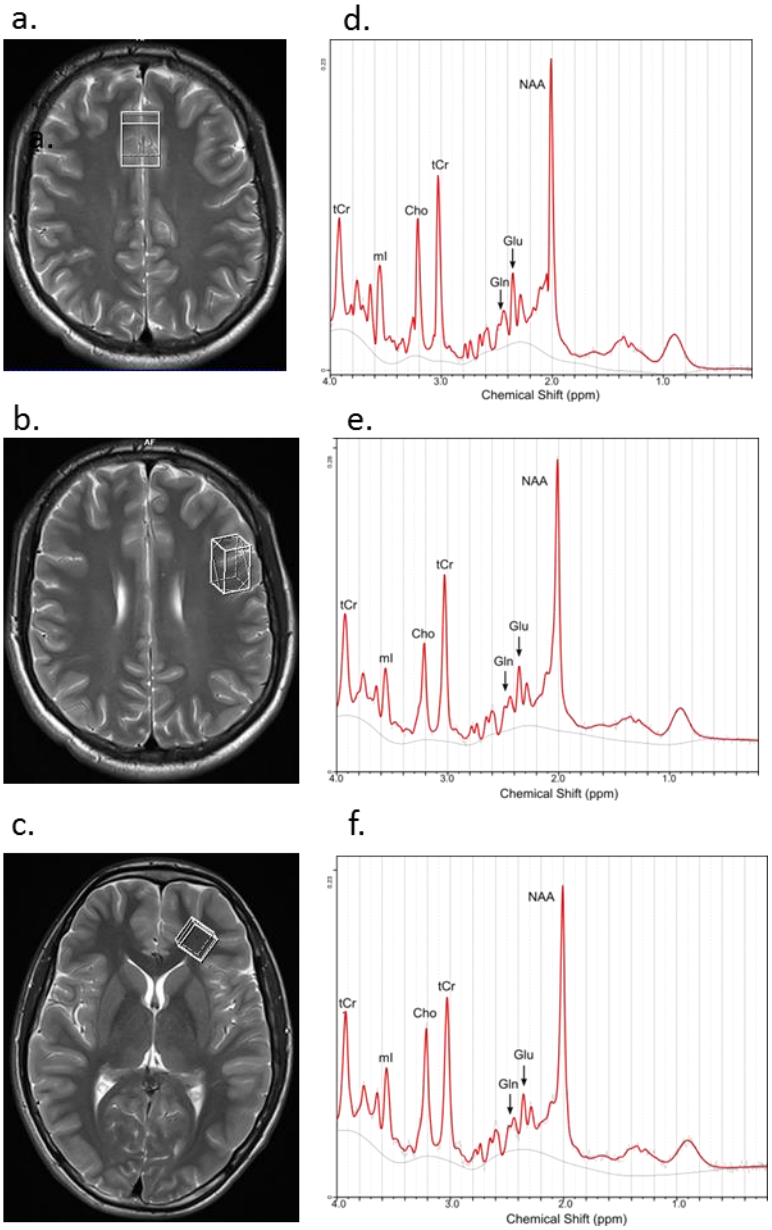
Scale; BAI = Beck Anxiety Inventory; GAF = Global Assessment of Functioning Scale; AIS = Athens Insomnia Scale; PDSS = Pediatric Daytime Sleepiness Scale, TST = total sleep time (min).

Table 2.

		BDI-21	HDRS	BAI	GAF	AIS	PDSS	TST	Sleep efficiency
mI (ACC)	**r**	-,573*	-,622**	-,552*	,690**	-,658**	-,576**[a]	,599**	,103
	p	,010	,004	,018	,001	,002	,015	,007	,676
	n	19	19	18	19	19	18	19	19
mI (DLPFC)	**r**	-0,561*	-,539*	-,261	,450	-,262	-,395[a]	,542*	,332
	p	,012	,026	,329	,070	,309	,130	,025	,193
	n	17	17	16	17	17	16	17	17

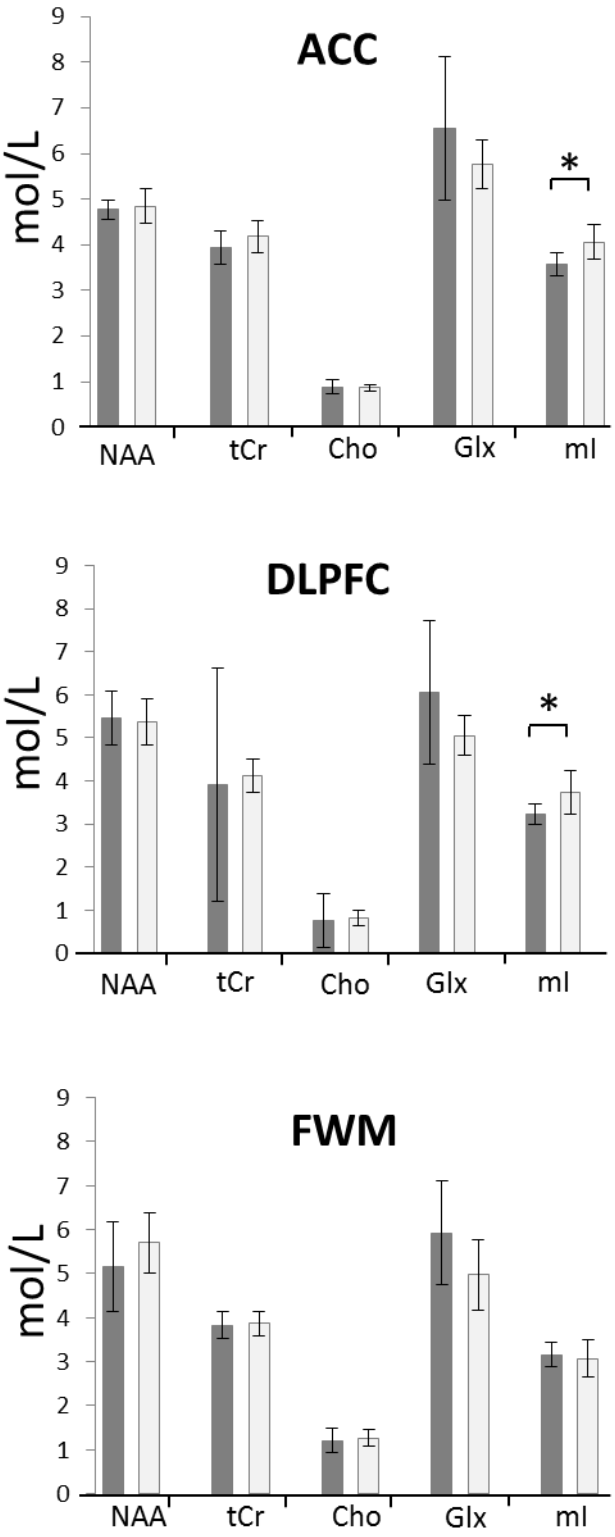
Correlations between myo-inositol (mI) cortical concentrations and clinical measures. * denotes correlations significant at the p<0.05 level, ** denotes correlations significant at the p<0.01 level. [a] denotes Pearson's correlations, all other correlations are Spearman's non-parametric correlations. mI = myo-inositol; ACC = anterior cingulate cortex; DLPFC = dorsolateral prefrontal cortex. BDI-21 = 21-item Beck Depression Inventory; HDRS = Hamilton Depression Rating Scale; BAI = Beck Anxiety Inventory; GAF = Global Assessment of Functioning Scale; AIS = Athens Insomnia Scale; PDSS = Pediatric Daytime Sleepiness Scale, TST = total sleep time (min).

Figure 1.



Location of the ^{1}H MRS single voxels in a) the anterior cingulate cortex (ACC), b) in the left dorsolateral prefrontal cortex (DLPFC), and c) frontal white matter (FWM), and the corresponding spectra from d) ACC, e) DLPFC , and f) FWM. tCr = total creatine; mI = myo-inositol; Cho = choline containing compounds; Gln = glutamine; Glu = glutamate; NAA = N-acetyl aspartate.

Figure 2.


ACC
mol/L
9
8
7
6
5
4
3
2
1
0
*
NAA
tCr
Cho
Glx
ml
DLPFC
mol/L
9
8
7
6
5
4
3
2
1
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tCr
Cho
Glx
ml
FWM
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9
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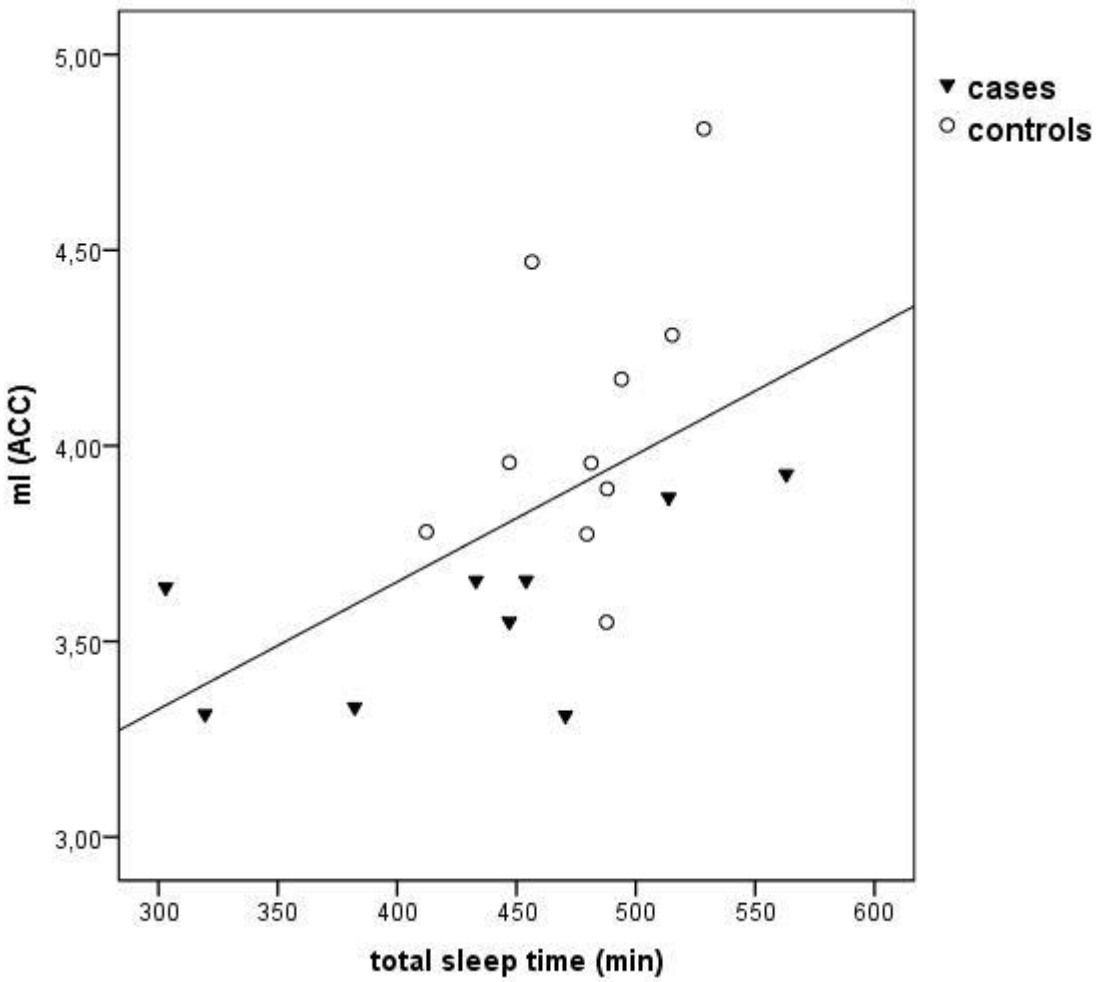
NAA
tCr
Cho
Glx
ml

Metabolite concentrations in a) the anterior cingulate cortex (ACC), b) the dorsolateral prefrontal cortex (DLPFC), and c) frontal white matter (FWM). Results are presented separately for the subgroups of depressed patients (; n=8 for ACC, n=6 for DLPFC, and n= 7 for FWM) and controls (; n=10 for all brain areas). Errors bars indicate ± SD. NAA= N-Acetyl aspartate; tCr = total creatine; Cho = choline-containing compounds; Glx = total glutamate-glutamine; mI = myo-inositol. *denotes statistically significant differences between the patients and the controls at a statistical threshold of $p<0.05$; One-Way ANOVA.

Figure 3.



Correlation between total sleep time and myo-inositol (mI) concentrations in the anterior cingulate cortex (ACC) in the total sample (n=19; cases ▼ and controls ◯). The solid line represents a linear regression line fitted to the data, R^2 0.30.