

Investigating The Influence of Methamphetamine on Brain Metabolism using ^1H -MRS

by

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Abbreviations

2D	Two-dimensional
3T	3 Tesla
ACC	Anterior cingulate cortex
ADHD	Attention deficit hyperactivity disorder
ANOVA	Analysis of variance
ATP	Adenosine triphosphate
BBB	Blood brain barrier
BNT	Boston Naming Test
BNT-SA-SF	Boston Naming Test – South African Short Form
BMI	Body mass index
CHESS	Chemical shift selective
Cho	Choline
CNS	Central nervous system
CP	Circularly polarised
Cr	Creatine
CSI	Chemical shift imaging
DTI	Diffusion tensor imaging
DLPFC	Dorsolateral prefrontal cortex
EPI	Echo planar imaging
FOV	Field of view
GABA	Gamma-aminobutyric acid
Gln	Glutamine
Glu	Glutamate
Glu+Gln/Glx	Glutamate + glutamine
GPC	Glycerophosphocholine
GPC+PCh	Glycerophosphocholine + phosphocholine
¹ H-MRS	Proton magnetic resonance spectroscopy
HREC	Human Research Ethics Committee
IDEAL	Infant Development, Environment, and Lifestyle
IIR	Innate immune response
Ins	<i>Myo</i> -inositol
KABC-II	Kaufman Assessment Battery for Children – Second Edition
MA	Methamphetamine

MPRAGE	Magnetisation-prepared rapid gradient echo
MRI	Magnetic resonance imaging
MRS	Magnetic resonance spectroscopy
NAA	<i>N</i> -acetyl-aspartate
NAAG	<i>N</i> -acetyl-aspartyl-glutamate
NAA+NAAG	<i>N</i> -acetyl-aspartate + <i>n</i> -acetyl-aspartyl-glutamate
NICU	Neonatal intensive care unit
PCh	Phosphocholine
PCr	Phosphocreatine
ppm	Parts per million
PRESS	Point resolved spectroscopy
SACENDU	South African Community Epidemiology Network on Drug Use
tCr	Total creatine
TR	Repetition time
TE	Echo time
vNav	Volume navigator
VOI	Voxel of interest

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Abstract

Introduction: Methamphetamine (MA) has been shown to have a detrimental relationship with neuronal integrity and viability, and has been associated with decreased executive function. The association of acute and short-term MA abstinence on brain metabolism, in adult MA abusers, is understudied. Negative relationships with brain metabolism, cognitive development and executive functioning in prenatally MA exposed children are reported, however these studies are limited. *The aim of this study was* to investigate the relationship between MA and brain metabolism in adults after acute and short-term abstinence. An additional aim was to investigate neurometabolite changes and relationship with general cognitive ability over time in prenatally MA exposed children.

Methods: Adult participants with a history of MA dependence ($n = 31$) and healthy-matched control participants ($n = 22$) were recruited and underwent 2D-chemical shift imaging ^1H -MRS (TR 2000ms, TE 30ms). The 2D-chemical shift imaging slice was positioned to include voxels from bilateral anterior cingulate and dorsolateral prefrontal cortices at two time points, i) acute MA abstinence (1.5 ± 0.6 weeks, $n=31$) and ii) short-term MA abstinence (5.1 ± 0.8 weeks, $n=22$). The change in metabolites between the MA abstinence time points were also investigated ($n = 19$). Relative metabolite concentrations of interest were *n*-acetyl-aspartate (NAA), *n*-acetyl-aspartate + *n*-acetyl-aspartyl-glutamate (NAA+NAAG), glutamate (Glu), glutamate + glutamine (Glu+Gln), *myo*-inositol (Ins), and glycerophosphocholine + phosphocholine (GPC+PCh). Additionally, 14 prenatally MA exposed children and 14 healthy matched control participants were recruited from a local hospital where records indicated MA use during pregnancy, underwent single-voxel ^1H -MRS (TR 2000ms, TE 30ms) at ages 6.4 ± 0.4 (MA exposed, $n=14$) and 6.5 ± 0.3 (controls, $n=14$) years (time point 1), and 8.1 ± 0.6 (MA exposed, $n=13$) and 8.1 ± 0.4 (controls, $n=11$) (time point 2) years and completed a battery of neurocognitive tasks assessing i) general cognitive ability and ii) visual-perceptual skills. The ^1H -MRS metabolite concentrations were then correlated with the neurocognitive task scores. Absolute metabolite concentrations of interest were creatine (Cr), phosphocreatine (PCr), Glu, GPC, Ins, NAA, GPC+PCh, NAA+NAAG, creatine + phosphocreatine (Cr+PCr), and Glu+Gln. The ^1H -MRS data were processed using LCModel and analysed with Statistica version 12.

Results: Adult MA abusers showed decreased NAA ($p < 0.05$) and NAA+NAAG ($p < 0.05$) in the left dorsolateral prefrontal cortex (DLPFC) at both time points. At the second time-point, decreased NAA+NAAG ($p < 0.05$) and increased Ins ($p < 0.05$) were also found in the right anterior cingulate cortex (ACC) of short-term abstinent MA abusers. Further, decreased NAA ($p < 0.05$) and NAA+NAAG ($p < 0.05$) was related to increased Ins ($p < 0.05$) in the right ACC. In prenatally exposed child participants, no metabolite differences were observed at the time of time point 1 and time point 2, respectively. The MA exposed group performed significantly poorer on the memory-related ($p < 0.05$) and abstract reasoning ($p < 0.05$) neurocognitive tasks at both time points. Over time, increased NAA ($p < 0.001$) were found in both groups, and decreased choline compounds (GPC - $p < 0.01$; GPC+PCh - $p < 0.05$) were observed in the prenatally exposed group. Additionally, the prenatally exposed group showed poorer performance in abstract reasoning and memory-related neurocognitive tasks over time compared with healthy controls.

Discussion: Decreased neuronal integrity and viability in the left DLPFC with acute and short term MA abstinence were observed in adults. With short term abstinence the right ACC also showed markers of neuroinflammation. The sequential impact of MA abstinence on brain metabolism requires further investigation. The child study illustrates that MA prenatally leads to poorer neurocognition and that over time, and with diagnosis, significant metabolite differences occur.

Conclusion: It is evident that MA abstinence has significant impact on neurometabolism, and the results found in this study contribute to understanding the impact of MA abstinence on the brain. The longitudinal impact of MA abstinence, however, need to be addressed in more detail. Additional research is required to fully elucidate the long-term associations between prenatal exposure to MA and changes in brain metabolism over time and into adolescence and adulthood.

Chapter 1

Introduction

Methamphetamine (MA), also known as “tik” (Parry et al., 2011), “speed”, “meth”, “chalk”, “crank”, “ice” or “glass” (Ernst et al., 2000) amongst other names, use has increased globally and has become a serious health concern (UNODC, 2012). MA, a synthetic derivative of amphetamine, is a white and odourless powder (Plüddemann et al., 2013) that has a relatively high lipid solubility due to the addition of a methyl group in the chemical structure, which allows the drug rapid transport across the blood-brain barrier (BBB) (Scott et al., 2007). MA can be taken orally, intranasally, intravenously or by smoking. It is a neurotoxic psychoactive stimulant that affects the central nervous system (CNS) and causes release of dopamine (Ernst et al., 2000), norepinephrine and epinephrine (Plüddemann et al., 2013) in the brain (Ernst et al., 2000; Plüddemann et al., 2013). The increase in dopamine, norepinephrine and epinephrine normally causes a sense of euphoria and energy, more commonly referred to as a “high”. Other cognitive and emotional associations with MA include feelings of increased physical and mental capacity, alertness, elevated self-esteem, an increase in libido and a surge in productivity (Cretzmeyer et al., 2003). Additional effects experienced are broad and include psychosis (including hallucinations), anxiety, violent behaviour, risky sexual behaviour, depression and suicide (Plüddemann et al., 2013).

MA abuse in Cape Town

A considerable increase in drug trafficking has been observed in South Africa since its re-entry into the global economy which followed after the first democratic election in 1994 (Plüddemann et al., 2008). South Africa’s geographic location, slack border control, weak criminal justice system and modern communication and banking systems as well as international trade links has made the country a desirable zone for the transshipment of drugs (Plüddemann et al., 2008). MA, however, only seemed to emerge in 2002 and was most commonly used in Cape Town (Plüddemann et al., 2013). Data was collected from specialist substance abuse treatment centres in Cape Town, which indicated an increase from 0.2% in 2002 to 19.3% in 2004 of patients who reported MA as their primary substance of abuse (Plüddemann et al., 2013). This number further increased to 46% in

the period between July and December 2014 (Dada et al., 2015). There is limited data available on MA-related presentations at government psychiatric services in Cape Town. These services usually serve the population which might not have access to specialist treatment centres, primarily because of affordability, availability and accessibility of these centres (Plüddemann et al., 2013). Plüddemann et al. (2013) found strong indications that the demand for psychiatric services related to MA use is much higher than what is currently provided. This is concerning, taking into account the constant increase in prevalence of MA use in the Cape Town area (Dada et al., 2015).

MA use among pregnant women is also increasing, as indicated by a recent study of a local mixed-race population within the Western Cape that indicated that in female participants in their twenties, 66% of non-pregnant and 92% of pregnant participants used MA (Jones et al., 2011). Cases where women are untreated for MA use and then fall pregnant holds significant risks for both the mother and the child. Women, in South Africa, who live in poor communities often do not seek, or have access to, medical care during pregnancy and are also not always informed about drug counselling and treatment. There is also a general lack of education regarding the impact of MA on prenatally MA exposed children. Then there is a fear of stigma from health care providers, related to drug-related pregnancies which adds to the risks for both the mother and child (Jones et al., 2011; Kwiatkowski, 2015). Prenatal drug exposure also holds significant risks for the developing child as well as complications during the pregnancy and birth, which includes, but not limited to, increased premature delivery, neonatal mortality and small gestational age (Brecht & Herbeck, 2014; Colby et al., 2012; Jones et al., 2011; Kwiatkowski, 2015). Considering the fact that MA is a sympathomimetic drug that stimulates the central nervous system, it passes readily through the placenta and blood brain barrier. This can have significant impact on the developing fetus, which could include decreased uteroplacental blood flow and fetal hypoxia (Golub et al., 2005; Won et al., 2001). Compromised behavioural patterns in neonates have also been observed, e.g. poor feeding, abnormal sleep patterns, under-arousal, reduced movement, growth restriction and hypertonia (LaGasse et al., 2011; Smith et al., 2003; Winslow et al., 2007). The impact of prenatal MA exposure on the fetus, and neonatal development is of increasing concern.

Neuropharmacology of MA

MA appears to primarily affect the dopaminergic system with the three main pathways being the nigrostriatal, mesolimbic and mesocortical pathways. The direct and indirect pathways which control the expression and direction of behaviour to predictive stimuli are found in the nigrostriatal pathways (Balleine et al., 2007; Nicola, 2007). The mesolimbic pathway is involved in reward processing (Koob & Bloom, 1988), effort related functions (Salamone et al., 2007), translation of emotions into actions (Mogenson et al., 1980) and direction of behaviour where stimuli and rewards are less predictable (Nicola, 2007). Finally, cognitive functions such as working memory are associated with the mesocortical pathway (Simon et al., 1980).

Acute MA use causes a release of dopamine into the nucleus accumbens and prefrontal cortex from the mesolimbic and mesocortical pathways (Fallon & Moore, 1978). This release of dopamine from the mesolimbic pathway is associated with the experience of euphoria (Drevets et al., 2001; Volkow et al., 1996). Synaptic concentrations of dopamine in the striatum in the nigrostriatal pathway is increased through vesicular monoamine transporter 2 and the dopamine transporter (Bustamante et al., 2002; Fowler et al., 2008; Haber & Knutson, 2010). MA acutely increases levels of glutamate in the striatum (Stephans & Yamamoto, 1994) and the prefrontal cortex (Stephans & Yamamoto, 1995) and glutamate levels can remain elevated for more than 28 hours, even after dopamine has returned to basal levels (Mark et al., 2007; Mark et al., 2004). This increase was related to an increase of vesicular glutamate transporter 1 expression, allowing the sequestration of glutamate in the cortex, which resulted in extended glutamate release into the striatum after MA administration (Mark et al., 2007). Over time, the glutamate increase could cause interneuronal damage, resulting in a dysregulation of thalamocortical signals, which might cause psychotic symptoms similar to that of schizophrenia (Hsieh et al., 2014).

Although cognitive performance can be increased with low doses of MA (Silber et al., 2006), high doses of MA can impair cognitive functioning (Muly et al., 1998). Acute use of MA can, therefore, increase glutaminergic signals to the cortex from the nigrostriatal as well as the mesolimbic pathways and increase dopaminergic signals from the mesocortical pathway (Hsieh et al., 2014).

Neurotoxic, neurocognitive and neurobiological impact of MA use in adults

MA-associated neurotoxicity has been related to psychotic symptoms, and impairments in neurocognitive performance (Barr et al., 2006; Cretzmeyer et al., 2003; Cruickshank & Dyer, 2009; Scott et al., 2007). Neurocognitive impairments appear to occur in executive functioning, learning, episodic memory, processing speed, motor skills, working memory, perceptual skills (Barr et al., 2006; Brooks et al., n.d.; Cruickshank & Dyer, 2009) and decision-making skills (Paulus et al., 2002), even with prolonged abstinence (> 1 year) (Chang et al., 2007). MA users were found to perform more poorly on tasks requiring selective attention and were more easily distracted (Chang et al., 2007).

Long-term use of MA, defined as using MA at a frequency of more than five times per week for a period of at least ten years, has shown to significantly decrease gray matter in the dorsolateral, orbitofrontal, prefrontal and superior temporal cortices (Nakama et al., 2011). At the time of the MRI scan, they had been abstinent for 18 days (Nakama et al., 2011).

Thompson et al. (2004) and Berman et al., (2008) also found gray matter loss, specifically in the anterior and posterior cingulate cortices. Berman et al. (2008) also reported high glucose metabolism in the posterior cingulate, low glucose metabolism in the anterior cingulate, as well as decreased hippocampal volumes. The decreased hippocampal volumes correlated with a neurocognitive word-recall test, with the conclusion that chronic MA use could be associated with a specific pattern of cerebral deterioration (Berman et al., 2008). This deterioration is often observed in neurodegenerative or psychotic disorders (Thompson et al., 2004) In both studies, the participants were active MA users at the time of the MR scan and had been using MA for at least 10 years. A similar study, with active MA users known with long-term use of MA also found reduced glucose in the thalamus and increased glucose metabolism in the parietal cortex (Brecht et al., 2004).

Neuronal damage to dopaminergic and serotonergic axons, as well as elevated cerebral temperature are caused by repeated exposure to MA (Cruickshank & Dyer, 2009; Scott et al., 2007). Hyperthermia in the brain is a result of damage to serotonergic neurons,

nerve terminal degeneration and reactive gliosis (Albers & Sonsalla, 1995) adding to the complexity of the neuropathology of MA (Albers & Sonsalla, 1995). Brain abnormalities have also been reported, these include inflammation, reduced neuronal density, reduced density of dopaminergic and serotonergic markers and can persist for years after MA use is stopped (Scott et al., 2007) (Cruickshank & Dyer, 2009).

Evidence of neuroinflammation, which is associated with an influx of neutrophils, lymphocytes, macrophages and fluid into an area of tissue injury, in MA abuse has been emerging. With the extensive injury MA causes, this reaction occurs within the brain through the activation of the innate immune system (Clark et al., 2013). Microglia become activated and initiate the innate immune response (IIR), which is the way the central nervous system responds to toxins (Clark et al., 2013), and is linked to the production of pro-inflammatory molecules including cytokines, chemokines and nitric oxide (Minagar et al., 2002). Microgliosis, through the innate immune response, seems to be increased throughout the brain in chronic MA addiction (Clark et al., 2013). Prolonged exposure to neuroinflammation could lead to cell death and subsequent further brain injury (Chang et al., 2007). MA users are also at risk of developing cognitive or degenerative disorders at an earlier age (Nakama et al., 2011).

The prevalence of MA-induced psychosis in MA dependent adults ranges between 10 and 60%, depending on the different studies conducted (Farrell & Marsden, 2002; Mahoney et al., 2008; Mcketin et al., 2006). Recreational use of MA was shown to increase the risk of developing psychotic symptoms two to threefold (Mcketin et al., 2010). MA-induced psychosis has been reported to persist for up to 6 months, as well as more than 6 months in some cases, as shown in studies conducted by Deng et al. (2012), Cretzmeyer et al. (2003) and Barr et al. (2006). Relapse of MA-induced psychosis symptoms has also been reported (Sato et al., 1992). However, the positive symptoms of MA-induced psychosis are difficult to distinguish from that of schizophrenia (Bramness et al., 2012; Connell, 1958; Janowsky & Risch, 1979; Medhus et al., 2013). As early as 1958, the similarity between MA-induced psychosis and schizophrenia were reported (Connell, 1958), including similar cognitive impairments. Deficits in working and verbal memory and other executive functions have been reported (Jacobs et al., 2008; Scott et al., 2007).

Where translation to animals are possible similar results have been found. (Castner & Goldman-Rakic, 1999; Nagai et al., 2007).

Various animal studies have been conducted to study the different models for MA-induced psychosis, such as the neurotoxicity model (Cadet & Krasnova, 2009; Davidson et al., 2001; Machiyama, 1992; Robinson & Becker, 1986), the behavioural sensitisation model (Castner & Goldman-Rakic, 1999; Featherstone et al., 2007) and the escalating dose-binge model (Segal & Kuczenski, 1997). In the neurotoxicity model MA is continuously administered. After 4-5 days, hallucinatory-like behaviour - 'wet dog' shakes, limb flicks, and excessive grooming and biting of the skin - was reported (Robinson & Becker, 1986). Brain damage, as a result of MA abuse, includes extensive neurotoxic damage within the nigrostriatal and mesolimbic dopaminergic pathways (Cadet & Krasnova, 2009; Davidson et al., 2001; Machiyama, 1992; Robinson & Becker, 1986). The behavioural sensitisation model uses lower doses of repeated MA exposure and has shown to model psychosis through increased locomotion, hallucinatory behaviours, deficits in pre-pulse inhibition, latent inhibition and other cognitive measures (Castner & Goldman-Rakic, 1999; Featherstone et al., 2007; Forrest et al., 2014; Kamei et al., 2006; Nagai et al., 2007). The escalating dose-binge model is built on the premise that a tolerance is developed to the sympathomimetic effects of the drug, which leads to an increase in dose and frequency to maintain the high levels of euphoria as produced by the drug (Segal & Kuczenski, 1997).

Clark et al. (2013) theorised that, during early abstinence, the innate immune response of the central nervous system could result in psychological and physiological stressors, resulting in sickness behaviour-like symptoms, which could possibly result in relapse. They further suggest that the use of anti-inflammatory medication during early abstinence could lower the effects of the excessive microglial activation, resulting in a decreased likelihood of relapse (McClay et al., 2013). Nordahl et al. (2003) suggest that the neurodegeneration caused by MA abuse is not permanent and that normalisation of the brain may take place over time. In contrast, Kim et al. (2006), report deficits persisting for longer than 6 months after withdrawal, although some improvements were observed with prolonged abstinence.

It is still relatively unknown whether the neurotoxic, neurobiological and neurocognitive damage can be reversed with prolonged abstinence (Jan et al., 2012; Nordahl et al., 2005; Salo et al., 2011). Investigations are typically done on the impact of MA on the brain of active MA users with only one study reporting results during abstinence of 18 days (Nakama et al., 2011). The impact of acute and short-term abstinence (2 – 6 weeks) from MA are largely understudied.

Neurotoxic, neurobiological and neurocognitive impact on children prenatally exposed to MA.

MA, which exerts effects on the fetal brain through crossing of the placenta and blood-brain barrier, can affect the developing brain in various ways (Won et al., 2001). Other MA related factors which may influence the developing brain include limited nutrition to the fetus because of placental insufficiency or altered maternal behaviour related to poor nutrition, decreased healthcare visits, increased exposure to violence and increased risk of mental illness and infections (Behnke et al., 2015; Kwiatkowski et al., 2014). These are all serious risk factors which could have detrimental impact on brain development (Abar et al., 2014; Behnke et al., 2015).

Prenatally MA-exposed neonates were reported to be shorter in height and had a smaller head circumference than non-exposed babies (Diaz et al., 2014; Shah et al., 2013). A poorer suckling reflex, decreased arousal, autonomic, physiological and central nervous system stress, poorer quality of movement, and a higher incidence of neonatal intensive care unit (NICU) admissions had also been reported (Diaz et al., 2014; Kiblawi et al., 2014; McDonnell-dowling & Kelly, 2015; Shah et al., 2013; Smith et al., 2003; Thompson et al., 2009). In addition, neonatal withdrawal from MA resulted in abnormal sleep patterns, poor feeding, tremors, hypertonia (Winslow et al., 2007) and, in some cases, complex partial seizures (Shah et al., 2013). Similarly, children exposed to MA prenatally were also reported to have increased emotional reactivity and mood disturbances (Diaz et al., 2014), increased aggressive behaviour (Abar et al., 2013; Smith et al., 2003) as well as lower cognitive functioning (Kirlic et al., 2013; Smith et al., 2003). Prenatal MA-exposure has been associated with a wide array of neurocognitive problems, specifically pertaining to executive functioning, working memory, verbal memory, visual-motor integration tasks, spatial memory and sustained attention (Abar et al., 2013; Chang et al.,

2004; Diaz et al., 2014; McDonnell-dowling & Kelly, 2015; Smith et al., 2011; Thompson et al., 2009; van Dyk et al., 2014). It is thus evident that prenatal exposure to MA poses a serious risk to brain development.

During the embryonic stage of fetal development, significant teratogenic relationships can occur with drug exposure (Behnke et al., 2015; Slamberová & Charousová, 2008). Other associations of MA on the fetal brain include abnormal growth and maturation as well as alterations in neurotransmitters, their receptors and brain organisation (Behnke et al., 2015). In neurotransmitter systems, MA increases the release and also blocks the reuptake of dopamine in striatal areas of the brain (Wouldes et al., 2004), which may directly alter developing neural circuitry resulting in ongoing deficits in neurodevelopment (Kwiatkowski et al., 2014; Wouldes et al., 2014).

Studies which included brain imaging of children exposed to MA prenatally have shown divergent development in neurons and glial cells as well as volumetric differences in subcortical brain regions (Chang et al., 2009; Chang et al., 2004; Cloak et al., 2009; Derauf et al., 2012). Glial cells, or microglia, detect pathological changes of external influences such as toxins or tissue damage in the brain and subsequently activate the innate immune response of the central nervous system. The innate immune response is associated with the production of pro-inflammatory molecules, including a response to neuroinflammation caused by toxins such as MA (Clark et al., 2013). Lee et al. (2009) conducted a study where isolated microglia and astrocytes of a 20-week old human fetal cerebral cortex were exposed to cocaine in vitro for 24 hours. Changes indicative of innate immune response activation were observed. Microglia and astrocytes are precursors of oligodendrocyte responses (Hampton et al., 2004). Oligodendrocytes play an important role in the myelination of the axonal tracts of the CNS (Simons & Trajkovic, 2006). The impact of prenatal exposure to MA on the innate immune response of the central nervous system is unknown. Cocaine and MA are both highly addictive psychostimulants, and produce similar effects on the central nervous system (Rawson et al., 2000). MA, however, exerts more severe effects and has a faster striatal uptake time (Fowler et al., 2008). It can therefore be hypothesised that relationships similar to the changes found by Lee et al. (2009) will be observed in children prenatally exposed to MA.

A study by Chang et al. (2004) included 13 prenatally MA exposed children and a control group of 15 children with no history of drug exposure. Six of the 13 MA exposed and one of the 15 controls were exposed to nicotine. The exposed group were exposed to MA prenatally for at least two trimesters. Both groups underwent structural MR scans as well as neurocognitive assessments. The exposed group showed smaller relative whole brain, putamen, globus pallidus and hippocampal volumes. Poorer performance on visual-motor integration tasks as well as lower sustained attention were reported for the exposed group compared to the control group. Poorer visual-motor integration could be attributed to smaller relative globus pallidus volumes, whereas poorer performance on attention-related tasks was related to decreased volumes in the hippocampus, putamen and globus pallidus.

Cloak et al. (2009) conducted a study with 29 MA exposed and 37 unexposed children, aged 3-4 years. The MA exposed children were exposed to MA for at least 2 trimesters. All the children underwent a structural MRI scan with regions of interest being the genu and splenium of the corpus callosum, bilateral frontal and parietal white matter, caudate, putamen, globus pallidus and thalamus. 12-axis diffusion tensor imaging (DTI) data were also obtained. The MA exposed group had lower diffusivity across all regions measured. They also showed a trend for higher fractional anisotropy in all the regions of interest. The MA exposed children showed lower diffusivity across all white matter regions, specifically in the right frontal, left and right parietal white matter, as well as a trend for higher fractional anisotropy in the left frontal white matter. The basal ganglia and thalamus showed no group differences (Cloak et al., 2009).

The Infant Development, Environment and Lifestyle (IDEAL) study that follows prenatally MA exposed children from birth is the largest United States government-funded prospective study of prenatally MA exposed children. A study conducted by Derauf et al. (2012) forms part of the IDEAL study. A total of 20 prenatally MA exposed children and 15 controls underwent structural MRI scans – examining cortical and subcortical brain volumes and cortical thickness. Additionally, tests on attention were conducted. It was reported that the exposed group had significantly reduced caudate nucleus volumes and cortical thickness increases in perisylvian and orbital-frontal cortices. Prenatal exposure to MA was positively related, whilst the caudate volume was

negatively related to the reaction time on the attention-related task. These findings suggest that MA exposed children may have attentional deficits caused by a reduction of caudate volume. MA exposure may also have distinct differential cortical impact on the developing central nervous system (Derauf et al., 2012).

A recent study by Roos et al. (2014) showed significantly increased left putamen volume in prenatally MA-exposed children. They also reported significantly reduced left hemisphere cortical thickness of the inferior parietal, parsopercularis and precuneus areas in PME children, which may indicate changes and probable dysfunction in striatal, parietal and temporal areas. These changes are functionally interrelated and are involved in attention and awareness, perception, motor function, memory and language function (Cavanna, 2006; Clower et al., 2001).

Various structural changes in the brain of prenatally MA-exposed children have been reported, however, the specific impact of neuroinflammation on the developing brain is still unknown. Additionally, it is evident that prenatal exposure to MA causes changes in neurodevelopment resulting in cognitive and behavioural deficits. Studies, to date, have been done on children younger than 6 years. There is a need for investigation the impact of prenatal MA exposure on the neurobiological and neurocognitive development of children of school-going age.

Proton magnetic resonance spectroscopy (^1H -MRS)

Proton magnetic resonance spectroscopy (^1H -MRS) is a non-invasive imaging technique and does not use ionising radiation. It is, subsequently, low risk for research on a variety of populations, including children. ^1H -MRS provides *in vivo* data on the concentration of neurometabolites, which are products of normal chemical metabolism and function, and are indicators of neurochemical activity, found in the body (Hellem et al., 2015). For the purpose of this study, the focus will be on ^1H -MRS and neurometabolites of interest in the human brain.

^1H -MRS has been gaining popularity in substance abuse studies, specifically to observe changes over time (Hellem et al., 2015). ^1H -MRS focuses on signals from hydrogen

protons that are present, in relatively high concentrations, in the brain and is typically presented as a collection of peaks or resonances within a spectrum. Each resonance is reported as parts per million (ppm) and identifies the location of a specific metabolite (Gujar et al., 2005). The most commonly observed resonances in ^1H -MRS are *n*-acetyl-aspartate (NAA), creatine (Cr), choline (Cho), *myo*-inositol (Ins), glutamate (Glu) and glutamine (Gln), and glutamate + glutamine (Glu+Gln) (Hellem et al., 2015).

N-acetyl-aspartate (NAA), a nervous system-specific metabolite, is synthesised from aspartate and acetyl-coenzyme A in neurons (Moffett et al., 2007). It is an amino acid which is found in the vertebrate brain, with one of the highest free amino acids and constitutes approximately 3-4% of the brain's osmolarity. *N*-acetyl-aspartate is primarily synthesised in neurons, and represents approximately 7% of neuron osmolarity that also has a high intracellular-extracellular gradient (Baslow, 2003). *N*-acetyl-aspartate is involved in myelin lipid turnover, and also plays a bioenergetic role in neuronal mitochondria. *N*-acetyl-aspartate is indirectly linked to adenosine triphosphate (ATP) metabolism, where the acetylation of aspartate facilitates its removal from neuronal mitochondria, resulting in the conversion of glutamate to alpha ketoglutarate which can enter the tricarboxylic acid cycle for energy production (Moffett et al., 2007). Subsequently, *N*-acetyl-aspartate is regarded as a MRS marker for neuronal health, viability and number. *N*-acetyl-aspartate is also a direct precursor for the synthesis of *n*-acetyl-aspartyl-glutamate (NAAG), the most concentrated neuropeptide in the human brain (Baslow, 2003; Moffett et al., 2007). *N*-acetyl-aspartate is related to neuronal and axonal integrity as well as mitochondrial bioenergetics (Gujar et al., 2005). Low concentrations of *n*-acetyl-aspartate have been related to neuronal loss and/or damage (Achtnichts et al., 2013). Abnormally high levels of *n*-acetyl-aspartate have been connected with progressive demyelinating cerebral atrophy, resulting in a disruption in neurotransmission and leads to neurological disturbances (Moffett et al., 2007). *N*-acetyl-aspartyl-glutamate is an important osmolyte in the brain (Baslow, 2000), and plays an important role in the modulation of neurotransmitter release (Moffett et al., 2007). Abnormally high levels of *n*-acetyl-aspartyl-glutamate, together with abnormally high levels of *n*-acetyl-aspartate results in a compromised communication system between neurons and glial cells. Continuous disruption of this communication system would result in progressive deterioration in neural function and subsequent failure of the CNS

(Baslow, 2000). *N*-acetyl-aspartyl-glutamate has also been reported to have neuroprotective properties, and requires further investigation (Neale et al., 2000).

Creatine (Cr) and phosphocreatine (PCr) serve as markers of energy metabolism (Eylers et al., 2015) as they contribute to a transient intracellular storage of metabolic energy through the phosphate-high energy bond exchange with adenosine triphosphate and is catalysed by creatine kinases (Joncquel-Chevalier Curt et al., 2015). Phosphocreatine is the phosphorylated form of creatine and is a form of energy storage in tissues, such as muscles and the brain, with high energetic needs, and is also directly related to brain functions (Joncquel-Chevalier Curt et al., 2015). Creatine also plays a modulatory role in neurotransmission (De Deyn & Macdonald, 1990). Creatine deficiency has been associated with hyperactivity and moderate cognitive deficits in animal as well as human studies (Hautman et al., 2014; Joncquel-Chevalier Curt et al., 2015). Creatine and phosphocreatine are sensitive to changes in brain metabolism and low creatine concentrations reflect mitochondrial dysfunction (Hellem et al., 2015; Sung et al., 2013). High creatine and phosphocreatine concentrations could have detrimental effects on the metabolic constancy of neurons and may produce instability in high-energy requiring processes, including neuroplasticity and glutamate turnover (Yuksel et al., 2015).

Choline (Cho) is a precursor of acetylcholine and phosphatidylcholine. The choline resonance includes choline, phosphocholine (PCh) and glycerophosphocholine (GPC). Very little brain choline is synthesised in the brain, and is largely obtained through dietary intake. Plasma choline is then transported across the blood brain barrier through diffusion (Babb et al., 2004). In the brain, choline is present only in small volumes as it is rapidly phosphorylated to phosphocholine, else it is not retained by the brain (Millington & Wurtman, 1982). Choline has been proposed to have neuroprotective and regenerative functions (Hurtado et al., 2011). The compounds of choline – glycerophosphocholine and phosphocholine – play an important role in the synthesis and degradation of cellular membranes and are sensitive to changes in membrane turnover (Gujar et al., 2005). A decrease in the availability of choline could result in cholinergic neurons being unable to maintain their essential functions (Babb et al., 2004) – cell-membrane signalling, lipid transport, the regulation of several metabolic pathways and is associated with neurological disorders (Zeisel & da Costa, 2009). High choline

synthesis in the brain, as a response to CNS injury or neurodegenerative/neuropsychiatric disorders, is consistent with neuronal damage (Nordahl et al., 2002; Pfefferbaum et al., 1999).

Myo-inositol (Ins) is one of the most abundant metabolites in the human brain. It is located mainly in glial cells (Haris et al., 2011) and is one of the major osmolytes in the central nervous system (Hellem et al., 2015; Robertson et al., 2001). Studies have shown that brain cells respond to extracellular hypotonicity or periods of osmotic stress (Haris et al., 2011) through increasing intracellular concentrations of *myo*-inositol (Hatashita et al., 1988). Several studies have also shown that brain osmolarity is increased by brain ischemia (Lee et al., 1994), hypernatremic states (Hatashita et al., 1988) and neuroinflammation (Clark et al., 2013). *Myo*-inositol is also involved in cell membrane and myelin sheath structures. Increased *myo*-inositol concentrations can also be the result of increased membrane turnover or damage to myelin sheath structures (Haris et al., 2011). *Myo*-inositol is considered to be a glial marker and represents glial proliferation, a central nervous system response to neural injury (Liu et al., 2000). Glial cells release gamma-amino butyric acid (GABA), the major inhibitory neurotransmitter in the brain, which modulates neuronal activity. Alterations of GABAergic function in the developing brain can result in neurodevelopmental disorders. In mature and injured brains, gamma-amino butyric acid from glia has anti-inflammatory actions through modulating microglial activity in the brain (Yoon & Lee, 2014). The functional and metabolic interplay between neurons and glial cells is crucial for sustained cerebral activity (Massucci et al., 2013). Glial cell health is therefore important for neurotransmission, as well as for the crucial role of glial cells in activating the innate immune response as a result of neuroinflammation in the central nervous system (Clark et al., 2013).

Glutamate (Glu) is an excitatory neurotransmitter and plays a critical role in brain function and brain metabolism (Hellem et al., 2015). Neurotransmitters are essential for the communication between neurons and are released from a presynaptic terminal into a synaptic cleft (Daikhin & Yudkoff, 2000). Neurotransmitters are bound to postsynaptic receptors which depolarises the neuron. This binding can cause metabolic changes within the brain. The level of glutamate in the synaptic cleft must be kept low to prevent

excessive excitation that can injure and kill susceptible neurons. Rapid replacement of a glutamate released from a presynaptic terminal is another requirement of effective neurotransmission (Huang et al., 1997). Glutamate is rapidly taken up into astrocytes, where it is converted to glutamine (Gln). Glutamine is released to neurons which then forms glutamate through mitochondrial glutaminase and is used for neurotransmission (Daikhin & Yudkoff, 2000). It is also a non-neuroactive intermediate in the recycling of glutamate and GABA (Soeiro-de-Souza et al., 2015). The astrocytic uptake of glutamate and release of glutamine, as well as the neuronal uptake of glutamine and release of glutamate is known as the glutamate-glutamine cycle (Massucci et al., 2013). Glutamate is also the metabolic precursor for GABA. Glutamine, which can only be synthesized by glia, is responsible for replacement of glutamate, and thus GABA, in GABAergic neurons. GABA synthesis is, therefore, limited by the availability of glutamate. (Petroff, 2002). All the glutamate is not channelled through the glutamate-glutamine cycle. Glutamate + glutamine (Glu+Gln or Glx) combined are closely linked in the glutamine-glutamate cycle of neurotransmission (Blüml et al., 2001; Sailasuta et al., 2010). An increase, or decrease, in glutamate + glutamine could indicate an increase, or decrease, in glutamate, glutamine or both (Soeiro-de-Souza et al., 2015). Excessive excitation of glutamate has been associated with neuronal injury and death (Daikhin & Yudkoff, 2000).

Proton magnetic resonance spectroscopy (^1H -MRS) in MA dependent adults

As mentioned previously, ^1H -MRS is a powerful non-invasive technique for obtaining *in vivo* concentrations of neurometabolites found in the brain (Hellem et al., 2015). Neurometabolites of interest in MA dependent adults are *n*-acetyl-aspartate, glutamate, creatine, *myo*-inositol and choline, specifically to determine the impact of abstinence on the brain.

Various ^1H -MRS studies report decreased *n*-acetyl-aspartate concentrations in the anterior cingulate cortex and frontal gray matter (Barr et al., 2006; Berman et al., 2008; Ernst et al., 2000; Hellem et al., 2015; Howells et al., 2014; Nordahl et al., 2002, 2003; Scott et al., 2007). Decreased *n*-acetyl-aspartate concentrations suggest decreased neuronal integrity and viability, which is indicative of drug-induced neuronal damage (Barr et al., 2006) or neuronal loss (Ende et al., 1997).

Ernst & Chang (2008) report a reduction in glutamate + glutamine in the frontal areas of the brain during early abstinence, which reached relatively normal concentrations after a 2 month abstinence period. Significant increases in glutamate in the frontal white matter of short-term (3-8 weeks) MA abstinent individuals were reported (Sailasuta et al., 2010). This increase in glutamate persisted into long-term abstinence (>20 weeks). They additionally reported a significant decrease in *n*-acetyl-aspartate concentration of short-term and long-term abstinent participants. The increase in glutamate and decrease in *n*-acetyl-aspartate is indicative of long-term neuronal damage in MA abstinent participants (Sailasuta et al., 2010).

Elevated choline metabolites, a marker of cellular membrane synthesis and turnover, in the anterior cingulate cortex (Barr et al., 2006; Ernst et al., 2000; Hellem et al., 2015; Nordahl et al., 2002, 2003; Scott et al., 2007) and frontal gray matter (Nordahl et al., 2003; Scott et al., 2007) were found in two ¹H-MRS studies. Increased levels of choline may be a compensatory response to MA-induced damage (Barr et al., 2006). A recent study by Howells et al., 2014 reports significantly decreased choline metabolites in the right dorsolateral prefrontal cortex which contradicts previous ¹H-MRS studies investigating neurometabolites in the anterior cingulate cortex and frontal gray matter of MA dependent adults (Ernst et al., 2000; Howells et al., 2014). Disruption of the cholinergic neurotransmitter system has been associated with dementia and age-related dysfunction of the central nervous system (Bartus et al., 1982). A disruption of the cholinergic neurotransmitter system, through a decrease of choline availability could have serious detrimental effects and result in premature ageing of the brain.

Four studies in MA dependence using ¹H-MRS report decreased *n*-acetyl-aspartate/creatine ratios, as well as higher choline/creatine ratios in the anterior cingulate cortex, which is suggestive of neuronal damage to the frontostriatal regions (Barr et al., 2006; Ernst et al., 2000; Nordahl et al., 2002, 2003). This could have a negative effect on neurotransmission and energy metabolism within the anterior cingulate cortex and dorsolateral prefrontal cortex, which could result in hyperactivity, moderate cognitive deficits (Hautman et al., 2014; Joncquel-Chevalier Curt et al., 2015) as well as a decline in the individual's executive functioning and cognitive control (Carter et al., 1998, 2000). Reduced activity in the frontostriatal circuit has also been associated with

inattention and hyperactivity related to attention-deficit hyperactivity disorder (ADHD) in adults and children (Cubillo et al., 2010) and abnormally high levels of *myo*-inositol (Ins) in frontal gray matter were also reported (Berman et al., 2008; Ernst et al., 2000; Nordahl et al., 2003; Scott et al., 2007). Increased levels of *myo*-inositol are indicative of increased glial cells, which forms part of the human body's innate immunity response (Clark et al., 2013; Sekine et al., 2008) and GABAergic function (Massucci et al., 2013; Yoon & Lee, 2014). Increased levels of glial cells, indicative of inflammation, are observed in chronic MA addiction and persists in early abstinence (± 5 weeks) from MA (Berman et al., 2008; Clark et al., 2013) and has also been associated with brain ischemia (Lee et al., 1994) and hypernatremic states within the brain (Hatashita et al., 1988). The increase in glial cells is reported to proportionately decline with continuous drug abstinence (± 2 years) (Clark et al., 2013; Sekine et al., 2008). The activation of the innate immune response occurs in the central nervous system and is a neuroinflammatory response to extensive injury caused by MA abuse (Clark et al., 2013). Prolonged neuroinflammation could lead to neuronal damage and death (Clark et al., 2013), and as the anterior cingulate cortex and dorsolateral prefrontal cortex, located in frontal gray matter, is involved in executive functioning and cognitive control (Carter et al., 1998, 2000) as well as impulsivity (Matsuo et al., 2009), could lead to cognitive impairment in the individual (Hautman et al., 2014; Joncquel-Chevalier Curt et al., 2015)

The impact of acute abstinence and whether the brain can completely recover from MA-induced damage and neurotoxicity is still largely understudied. A single study by Ernst et al., (2000) reports that neurotoxic effects from MA abuse can persist for as long as 4 years but most studies investigating the effect of abstinence from MA on the brain are performed on short-term (3-9 weeks) (Nordahl et al., 2005; Sailasuta et al., 2010) and long-term (20 weeks up to 3 years) (Nordahl et al., 2005; Sailasuta et al., 2010). The impact of abstinence from MA during acute abstinence (<2 weeks) into short-term abstinence (<6 weeks) and neuroinflammatory processes is still unknown, and will be addressed in this study. Additionally, long term recovery should also be investigated.

Proton magnetic resonance spectroscopy (¹H-MRS) in children exposed to MA prenatally

Limited research using ¹H-MRS has been done on children exposed to MA prenatally. Chang et al. (2009) found significant higher total creatine (tCr) and glutamate + glutamine have been reported in frontal white matter (Chang et al., 2009) and in the basal ganglia (Lester & Lagasse, 2010; Smith et al., 2001). Increased creatine is associated with detrimental effects on the metabolic steadiness of neurons which could result in instability in processes requiring a high level of energy supply such as glutamate turnover (Yuksel et al., 2015). Glutamate and glutamine are both neurotransmitters and are essential for effective communication between neurons. Disruption of the communication between neurons through increased excitation of glutamate has been connected with neuronal injury and death (Daikhin & Yudkoff, 2000). Abnormally high levels of *n*-acetyl-aspartate in frontal white matter was observed by Chang et al. (2009), which is associated with a disruption in neurotransmission and leads to neurological disturbances (Moffett et al., 2007).

The MA exposed children had a significantly lower *myo*-inositol/total creatine ratio in the frontal white matter (Chang et al., 2009). Additionally, the MA exposed children had significantly lower *myo*-inositol concentration and *myo*-inositol/total creatine ratio in the thalamus compared to the control group. *Myo*-inositol is considered to be a glial marker and is a response, by the central nervous system, to neural injury (Liu et al., 2000). Glial cells release gamma-amino butyric acid (GABA), which modulates neuronal activity. Alterations of GABAergic function in the developing brain can therefore result in neurodevelopmental disorders.

¹H-MRS studies conducted on children prenatally exposed to MA suggest aberrant neuronal and glial development, abnormal energy metabolism and higher neuronal density in the brain as a result of significantly higher total creatine and glutamate + glutamine concentrations in frontal white matter and basal ganglia, and *n*-acetyl-aspartate in frontal white matter, with, additionally, the decrease in *myo*-inositol concentrations and *myo*-inositol/total creatine ratios (Chang et al., 2009; Lester & Lagasse, 2010; Smith et al., 2001)

¹H-MRS studies have predominantly been done on children before school-going age. The impact of prenatal MA exposure on the neurobiological development of school-going children to determine whether regeneration and normalisation of neurometabolites within the brain is possible is still unknown.

Aims

The aim of this study was to investigate the relationship between MA and brain metabolism in adults after acute and short-term abstinence. An additional aim was to investigate neurometabolite changes and the association with general cognitive ability over time in prenatally MA exposed children.

It is still largely unknown whether the neurotoxic, neurobiological and neurocognitive damage can be reversed with prolonged abstinence. Investigations are typically done on the impact of MA on the brain of active MA users. The relationship between acute (<2 weeks) and short-term (<6 weeks) MA abstinence and brain metabolism, in adult MA abusers, is understudied. Whether the brain can completely recover from MA-induced damage and neurotoxicity is still understudied.

Negative relationships between brain metabolism, cognitive development and executive functioning in prenatally MA exposed children are reported, however these studies are limited. The impact of neuroinflammation on the developing brain is still unknown. Additionally, it is evident that prenatal exposure to MA causes changes in neurodevelopment resulting in cognitive and behavioural deficits. ¹H-MRS studies have predominantly been done on children before school-going age. The relationship between prenatal MA exposure and the neurobiological and neurocognitive development of school-going children to determine whether regeneration and normalisation of neurometabolites within the brain is possible is unknown, and will be addressed in this study.

Hypotheses

Hypothesis 1: Brain metabolism is expected to increase during acute to short-term abstinence in adults, when compared to healthy controls.

Hypothesis 2: Prenatally MA exposed children are expected to have decreased brain metabolism and neurocognition compared to neuro-typical developing children.

Chapter 2

The impact of abstinence from MA on brain metabolism in adult participants

ABSTRACT

Background: Methamphetamine (MA) use has increased globally and has become a serious health concern. ^1H -MRS studies on MA use have reported decreased *n*-acetyl-aspartate, indicating decreased neuronal integrity and viability. To the author's knowledge, there are no studies investigating the association of acute (<2 weeks) to short-term (<6 weeks) abstinence in MA abusers using ^1H -MRS techniques. This study aims to evaluate the relationship between MA use and neurometabolism to further understand the impact of MA and MA abstinence on cortical brain structures.

Methods: Adult participants with a history of MA dependence ($n = 31$) and healthy matched control participants ($n = 22$) were recruited and underwent 2D-chemical shift ^1H -MRS imaging (TR 2000ms, TE 30ms). The 2D-chemical shift imaging slice included voxels from bilateral anterior cingulate (ACC) and dorsolateral prefrontal cortices (DLPFC). Control participants were scanned once. The MA dependence group was scanned twice, i) after acute MA abstinence (1.5 ± 0.6 weeks, $n=31$) and ii) short-term MA abstinence (5.1 ± 0.8 weeks, $n=22$). The change in metabolites over time in MA abstinence were also investigated ($n = 19$). Relative metabolite concentrations, relative to Cr+PCr, of interest were *n*-acetyl-aspartate (NAA), *n*-acetyl-aspartate with *n*-acetyl-aspartyl-glutamate (NAA+NAAG), glutamate (Glu), glutamate with glutamine (Glu+Gln), *myo*-inositol (Ins), and glycerophosphocholine with phosphocholine (GPC+PCh).

Results: Decreased NAA and NAA+NAAG (left DLPFC) was observed in acute and short-term abstinence, compared to control participants. In addition, when compared to controls participants, short-term MA abstinence showed decreased NAA+NAAG and increased Ins in the right ACC. Further, when comparing the association of MA abstinence between time points acute and short-term abstinence, decreased NAA and NAA+NAAG was related to increased Ins in the right ACC. Several significant relationships with age and drug use history (age started using MA, length of MA use, and duration of abstinence) were also observed.

Conclusion: The results from this study shows that MA abstinence results in decreased neuronal integrity in cortical tissues in the left DLPFC and right ACC. Further, in short-term abstinence there was evidence of neuroinflammation within the right ACC. The present study shows damage to neuronal integrity in acute abstinence, persisting into short-term abstinence – and is accompanied by neuroinflammation. This is the first ¹H-MRS study to report the development of neuroinflammation with MA abstinence.

Introduction

Methamphetamine (MA) use has increased globally, has become a serious health concern (UNODC, 2012) and is a neurotoxic psychoactive stimulant that affects the central nervous system (Ernst et al., 2000; Plüddemann et al., 2013). The Medical Research Council, through the South African Community Epidemiology Network on Drug Use (SACENDU), reported an increase in Cape Town of MA as primary substance of abuse from 19.3% in 2004 (Plüddemann et al., 2013) to 46% in 2014 (Dada et al., 2015). This increase in prevalence, specifically in the Western Cape, in MA abuse is concerning and indicates the importance of understanding the impact MA exert on the brain in order to support the provision of support services.

¹H-MRS is a non-invasive magnetic resonance imaging technique which provides *in vivo* data on the concentration of neurometabolites found in the brain (Hellem et al., 2015) and has been gaining popularity in substance abuse studies to investigate the impact of MA abstinence on the brain of short-term (1-6 months) and long-term (1-5 years) (Balleine et al., 2007). MA abusers. To date, the acute impact of MA abstinence (<2 weeks) is unknown. Further, there is an absence of longitudinal assessment from acute to short-term abstinence (<6 weeks).

Previous ¹H-MRS studies on MA abstinence have reported decreased *n*-acetyl-aspartate (NAA) concentrations (Barr et al., 2006; Berman et al., 2008; Ernst et al., 2000; Hellem et al., 2015; Howells et al., 2014; Nordahl et al., 2002, 2003; Scott et al., 2007), a marker of neuronal integrity and viability, in several frontal gray matter brain regions, which is indicative of drug-induced neuronal damage (Barr et al., 2006) or neuronal loss (Ende et al., 1997). Ernst et al. (2000) additionally reported a trend for reduced NAA in frontal

white matter. Decreased (NAA) and glutamate (Glu) in the frontal white matter of short-term (3-9 weeks) MA abstinent individuals were reported by Sailasuta et al. (2010), supporting the neuronal / axonal injury of MA use.

Aside the decrease in neuronal integrity and viability in MA abstinence, studies have also reported significant increase in *myo*-inositol (Ins), indicative of increased activity or function of glial cells, i.e. increased activity of innate immune system, a central nervous system response to neural injury (Liu et al., 2000) in frontal gray matter (Berman et al., 2008; Ernst et al., 2000; Nordahl et al., 2003; Scott et al., 2007). This increase in *myo*-inositol is observed in chronic MA addiction and has been shown to persist in early abstinence from MA (Berman et al., 2008; Clark et al., 2013). Prolonged neuroinflammation is known to lead to neuronal damage and/or death (Clark et al., 2013).

Understanding the sequential impact of acute, and acute into short-term abstinence from MA is of great importance as no previous ¹H-MRS studies on the impact of acute abstinence or the transition from acute to short term abstinence. We fill these gaps in the current literature, as the results may be beneficial in developing potential interventions to support MA dependent individuals in their abstinence.

The aims of this study were to evaluate the impact of MA on neurometabolism, using ¹H-MRS, to further understand the impact of MA abstinence on cortical brain metabolism. We addressed the current gaps in the literature and assessed acute (<2 weeks), short-term (<6 weeks), and acute to short-term MA abstinence of adult participants residing in Cape Town.

Material and methods:

Participants

Adult male participants with a history of MA dependence (n = 31) and healthy matched control participants (n = 22) were recruited. MA dependent participants were admitted to a rehabilitation facility, ensuring that abstinence and duration of abstinence is accurate.). All participants (cases and controls) were scanned using a 3T Allegra Siemens head scanner. All MA participants were scanned at two time points i) acute MA abstinence (1.5±0.6 weeks, n=31) and ii) short-term MA abstinence (5.1±0.8 weeks, n=22)

whilst control participants were independently scanned at a single time (Figure 2.1). The impact of acute abstinence, compared to controls, was inspected at time point 1. At time point 2 the impact of short-term abstinence, compared to controls (data collected at time point 1) was investigated. The change in metabolites between the MA abstinence time points were also investigated (n = 19). (Figure 2.1)

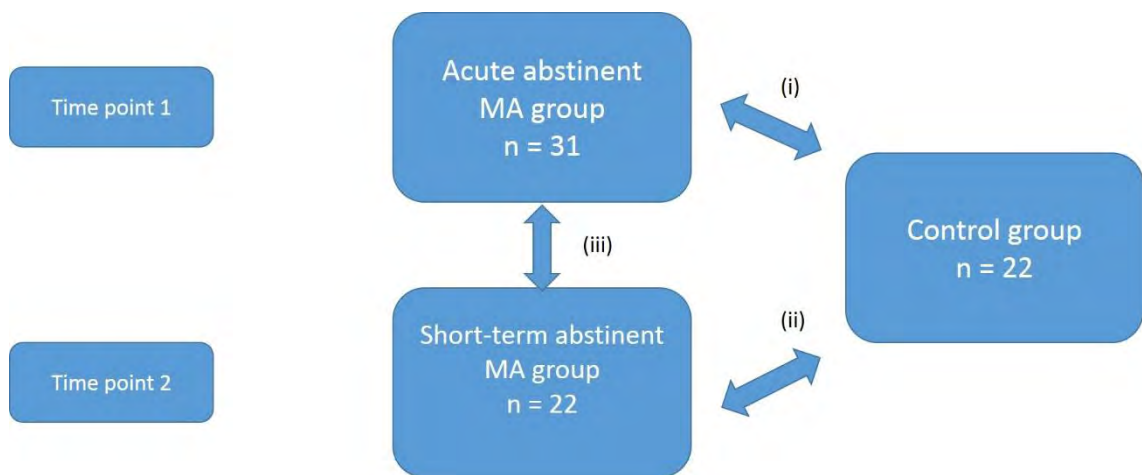


Figure 2.1 – ^1H -MRS scan data of participants in (i) acute abstinence from MA and control group were compared at time point 1. At time point 2, scan data from (ii) short-term MA abstinent participants were compared to the control group data. Further, the data of acute and short-term MA abstinent participants from both time points were compared (iii).

All participants (cases and controls) were required to complete an informed consent form as well as personal particulars, personal, familial medical history and drug use questionnaires. All drug use information (age started using MA, length of drug taking, drugs other than MA used) were obtained through self-report by MA participants. All information collected during this study were kept confidential and only used for scientific purposes. All documents were available in Afrikaans and English for easier understanding by the research participants. Scan data acquisition was between January 2013 and May 2014, and was approved by the Human Research Ethics Committee, Faculty of Health Sciences of the University of Cape Town – HREC Reference number: 554/2012 and was conducted in accordance with the Declaration of Helsinki (World Medical Association, 2008).

¹H-MRS imaging procedures

Participant scans were performed in a 3T Allegra Siemens head scanner using the standard CP single channel head coil. A high-resolution multi-echo MPRAGE (van der Kouwe, Benner, Salat, & Fischl, 2008) sequence (TR = 2530 ms, graded TE = 1.53, 3.21, 4.89, 6.57 ms, flip angle = 7°, FOV = 256 mm, slice thickness = 1.0 mm, 160 slices, scan time 10:49) was acquired. A 2D CSI ¹H-MRS slice was acquired (PRESS, TE = 30 ms, TR=2000 ms, Hamming filter, 2 averages, delta=-2.7 ppm delta frequency, weighted phase encoding, FOV = 160 × 200 mm, VOI = 90 × 100 mm, voxel size 10 × 8.0 mm, thickness 15 mm, automated CHES water suppression, scan time 10:52). The ¹H-MRS 2D slice was first positioned with standard reconstruction of the sagittal plane, finer positioning of the slice was achieved with the axial and coronal reconstructions. The slice position included bilateral voxels located in DLPFC and the ACC (Figure 2.2).

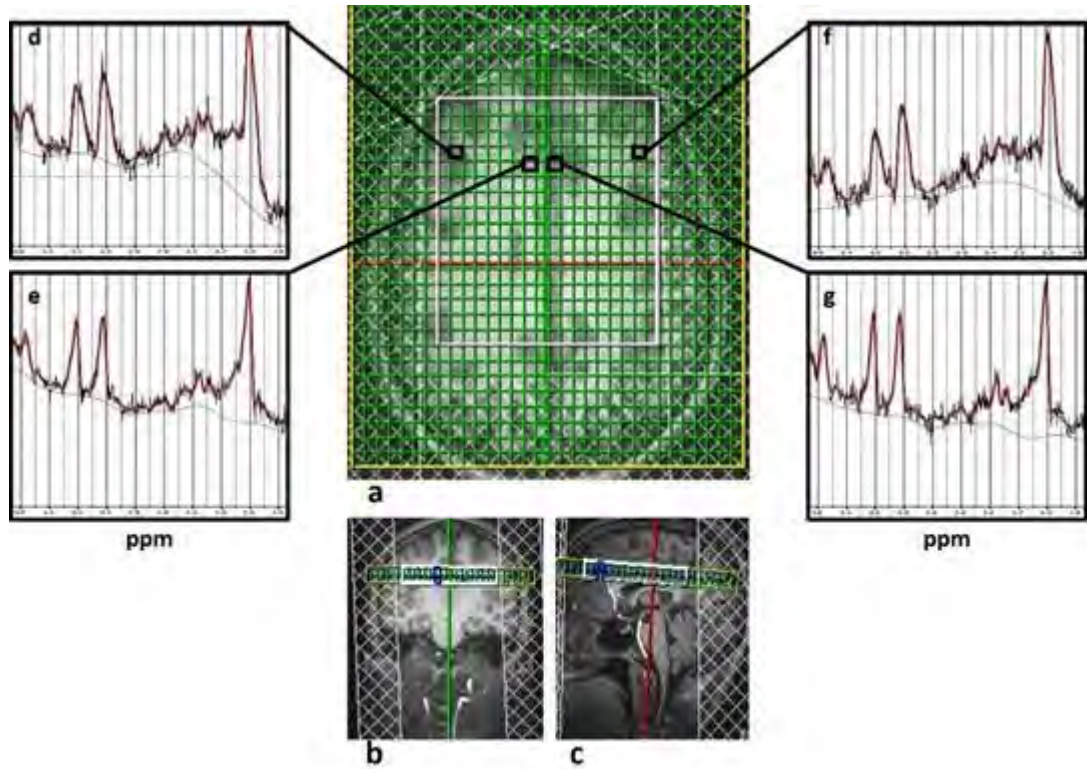


Figure 2.2 – Representative ¹H-MRS chemical shift imaging brain slice orientation on the 3D planes (a – axial, b – coronal, c – sagittal) and spectra of VOIs which included: (e & g) bilateral anterior cingulate cortices (ACC), and (d & f) bilateral dorsolateral prefrontal cortices (DLPFC).

¹H-MRS Data Analysis

Analysis of the CSI and ¹H-MRS spectra were performed in LCModel (Provencher, 1993), which fitted spectra in relation to basis spectra provided by Provencher (PRESS TE30). Default parameters within LCModel were used for the CSI processing, which applied Bayesian learning from the central voxel of interest (VOI) of the 2D-slice, including the VOI = 90 × 100 mm with voxel size 10 × 8.0 mm, this area included bilateral ACC and DLPFC. The relative concentrations of metabolites are reported in relation to creatine containing metabolites (Cr+PCr). Only metabolites with a Cramér-Rao of %SD < 20% for the brain regions of interest were included. Relative concentrations of *n*-acetyl-aspartate (NAA), *n*-acetyl-aspartate + *n*-acetyl-aspartyl-glutamate (NAA+NAAG), glutamate (Glu), glutamate + Glutamine (Glu+Gln), *myo*-inositol (Ins) and glycerophosphocholine + phosphocholine (GPC+PCh) are reported.

Statistical Analysis:

Statistical analysis were performed using the software package Statistica version 12 (Stasoft Incorporated, 2014). All raw data were tested for normality of distribution, using the Shapiro-Wilks test. Non-normal distributed data underwent Mann-Whitney U tests as appropriate, while the normally distributed data was analysed using parametric ANOVA.

At both time points the demographic data (age, age started using MA, length of drug use, and duration of abstinence) were non-normally distributed. At time point 1, all metabolite data were normally distributed. At time point 2, all metabolite data, except relative Glu in the right ACC and relative Glu+Gln in the right DLPFC, were normally distributed. Parametric ANOVA was applied for parametric data, and Mann-Whitney U tests were applied to non-parametric data.

To determine the changes in relative metabolite concentrations from acute (time point 1) to short-term MA abstinence (time point 2) dependent T-tests were applied.

To determine whether relationships were apparent between neurometabolites and drug use variables (age started using MA, length of drug use, and duration of abstinence), Spearman Rank Order correlations were applied to accommodate the distribution of drug use variable data. These correlations analyses were performed at each time point: acute (time point 1) and short-term MA abstinence (time point 2).

Data are reported as mean $\pm$ standard deviation. For group differences we report statistical test results, significance set at $p < 0.05$. For the correlations analyses we report the correlation co-efficient, significance set at $p < 0.05$. Refer to Appendix I for further detail.

Results

Experiment 2.1 –Acute abstinence

2.1.1 Age and drug use variables

Age and drug use is reported in Table 2.1.1. The only demographic information that was reliable to report - age - was found to not differ between groups.

Table 2.1.1 Age and drug use

	Healthy Controls n = 22		MA dependent n = 31	
	Mean	Stdev	Mean	Stdev
Age in years at time point 1	28.6	10.2	28.1	5.3
<i>Methamphetamine use</i>				
Age in years started using MA*	/		17.9	5.3
Length of MA use at time point 1*	/		10.4	3.7
Duration (weeks) of abstinence	/		1.5	0.6
<i>Other drugs</i>				
Nicotine use in the last year*	1 of 22		24 of 31	
Cannabis use in the last year*	2 of 22		10 of 31	
MDMA use in the last year*	/		2 of 31	
Cathinone use in the last year*	/		1 of 31	
Methaqualone use in the last year*	/		10 of 31	

*Self-reported by participants.

2.1.2 ^1H – MRS metabolite concentrations

Significant differences in relative metabolite concentrations were found for NAA metabolites in the left DLPFC: (1) NAA ($F_{(1, 48)} = 5.56$, $p < 0.05$); (2) NAA+NAAG ($F_{(1, 48)} = 6.32$, $p < 0.05$) (Figure 2.1.1). No other significant differences were found for left DLPFC. Further no significant differences were found in metabolite concentrations for right ACC, left ACC, or right DLPFC (Appendix I).

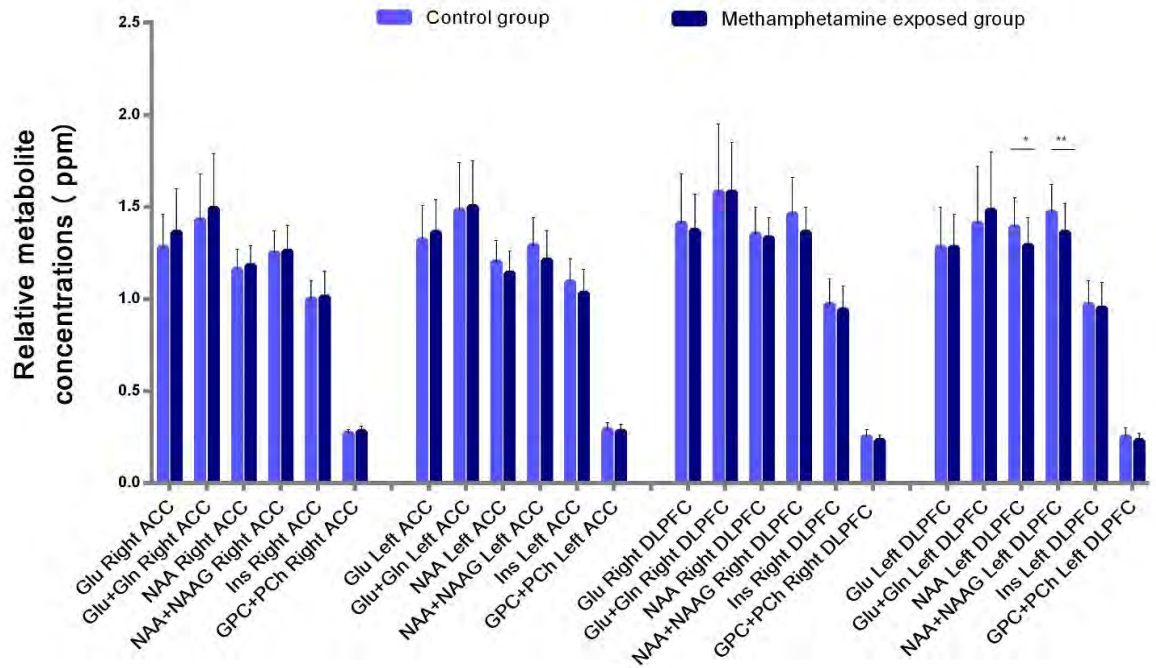


Figure 2.1.1 Relative ^1H -MRS CSI metabolite concentration in for control group and acute methamphetamine abstinence. The methamphetamine acute abstinence group had lower concentrations, in the left DLPFC, of **n*-acetyl-aspartate (NAA) ($p < 0.05$) and ***n*-acetyl-aspartate + *n*-acetyl-aspartyl-glutamate (NAA+NAAG) ($p < 0.05$) than the control group. Data are presented as mean $\pm$ stdev.

2.1.3 Age and drug use correlates with ^1H – MRS metabolite concentrations

Only relative NAA and NAA+NAAG were found to significantly correlate with age and drug use variables. Relative NAA in the right DLPFC correlated negatively with age (Spearman $R = -0.36$, $p < 0.05$) (Figure 2.1.2). Relative NAA+NAAG in the right DLPFC correlated negatively with: (a) age (Spearman $R = -0.47$, $p < 0.01$); (b) age started using MA (Spearman $R = -0.31$, $p < 0.05$); (c) length of MA use (Spearman $R = -0.37$, $p < 0.05$); and (d) duration of abstinence (Spearman $R = -0.33$, $p < 0.05$) (Figure 2.1.3). Relative NAA in the left DLPFC correlated negatively with (a) age (Spearman $R = -0.39$, $p < 0.01$); (b) age started using MA (Spearman $R = -0.32$, $p < 0.05$); (c) length of MA use (Spearman $R = -0.40$, $p < 0.01$); and (d) duration of abstinence (Spearman $R = -0.33$, $p < 0.05$) (Figure 2.1.4). Relative NAA+NAAG in the left DLPFC correlated negatively with: (a) age (Spearman $R = -$

0.29, $p < 0.05$); (b) age started using MA (Spearman $R = -0.32$, $p < 0.05$) ; (c) length of MA use (Spearman $R = -0.32$, $p < 0.05$); and (d) duration of abstinence (Spearman $R = -0.35$, $p < 0.05$) (Figure 2.1.5).

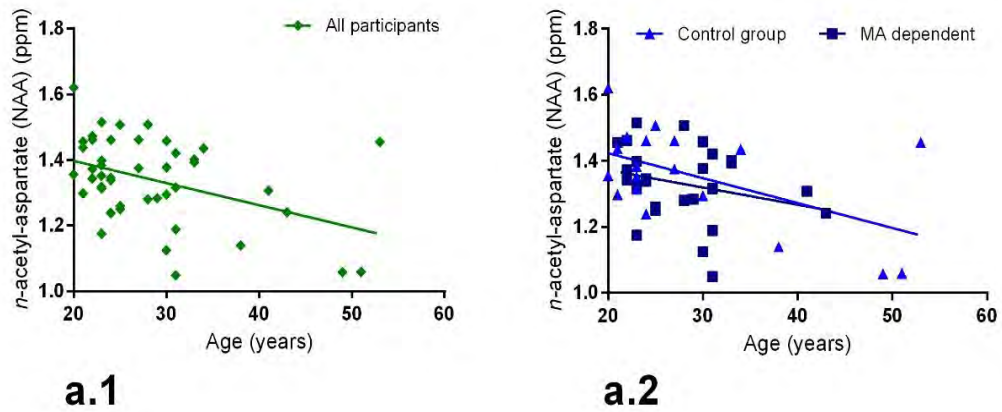


Figure 2.1.2 (a) Relative magnetic resonance spectroscopy metabolite concentration – n-acetyl-aspartate (NAA) – in the right DLPFC negatively correlated with age (Spearman $R = -0.36$, $p < 0.05$) at time point 1. (b) Additionally, the trend lines of the control and methamphetamine dependent groups are presented.

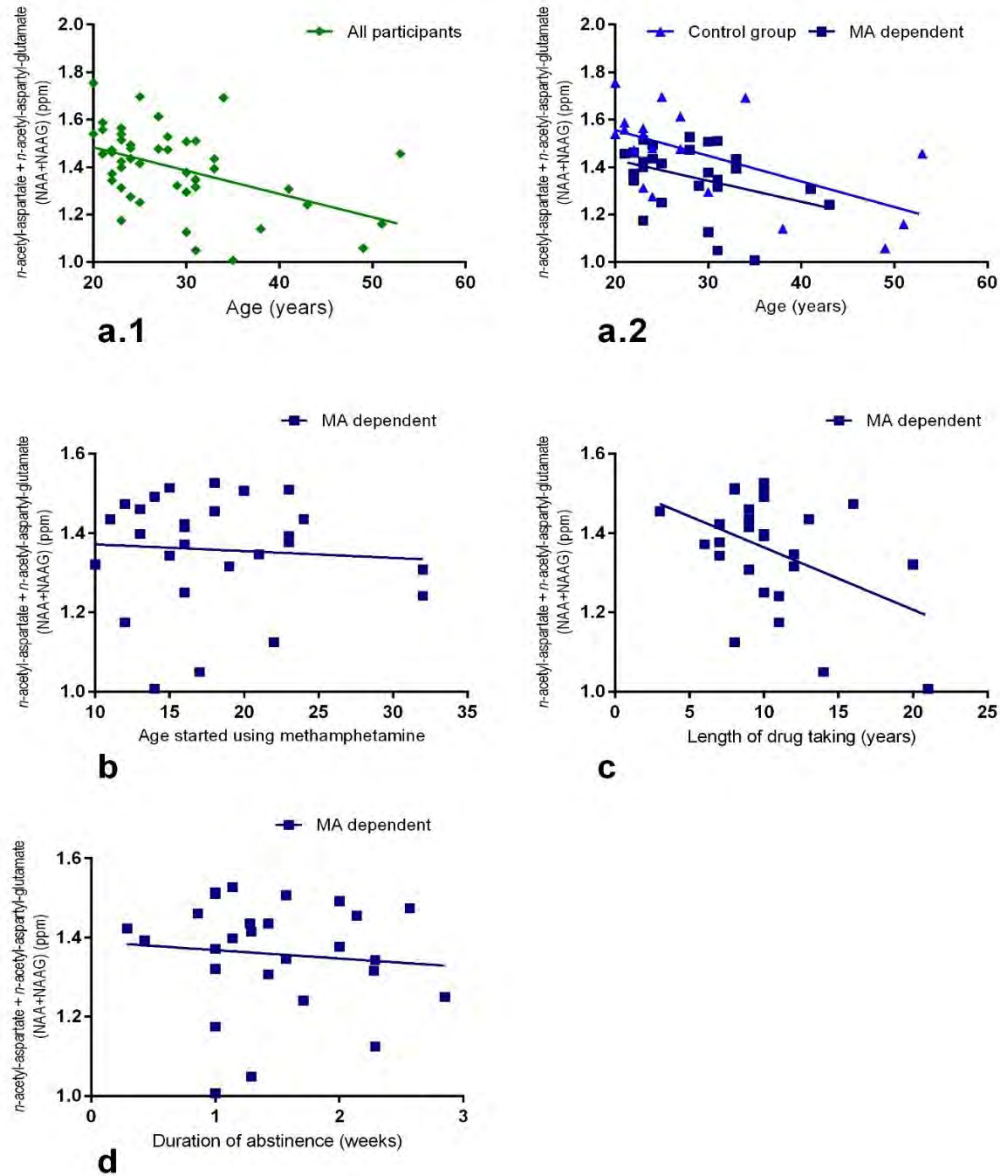


Figure 2.1.3 (a.1) Relative magnetic resonance spectroscopy metabolite concentration – *n*-acetyl-aspartate + *n*-acetyl-aspartyl-glutamate (NAA+NAAG) – in the right DLPFC negatively correlated with age (Spearman $R = -0.47, p < 0.01$) at time point 1. (a.2) Additionally, the trend lines of the control and methamphetamine dependent groups are presented. (b) Relative magnetic resonance spectroscopy metabolite concentration – *n*-acetyl-aspartate + *n*-acetyl-aspartyl-glutamate (NAA+NAAG) – in the right DLPFC negatively correlated with age started using MA (Spearman $R = -0.32, p < 0.05$) at time point 1 in the methamphetamine dependent group. (c) Relative magnetic resonance spectroscopy metabolite concentration – *n*-acetyl-aspartate + *n*-acetyl-aspartyl-glutamate (NAA+NAAG) – in the right DLPFC negatively correlated with age started using MA (Spearman $R = -0.32, p < 0.05$) at time point 1 in the methamphetamine dependent group. (d) Relative magnetic resonance spectroscopy metabolite concentration – *n*-acetyl-aspartate + *n*-acetyl-aspartyl-glutamate (NAA+NAAG) – in the right DLPFC negatively correlated with duration of abstinence (Spearman $R = -0.35, p < 0.05$) at time point 1 in the methamphetamine dependent group.

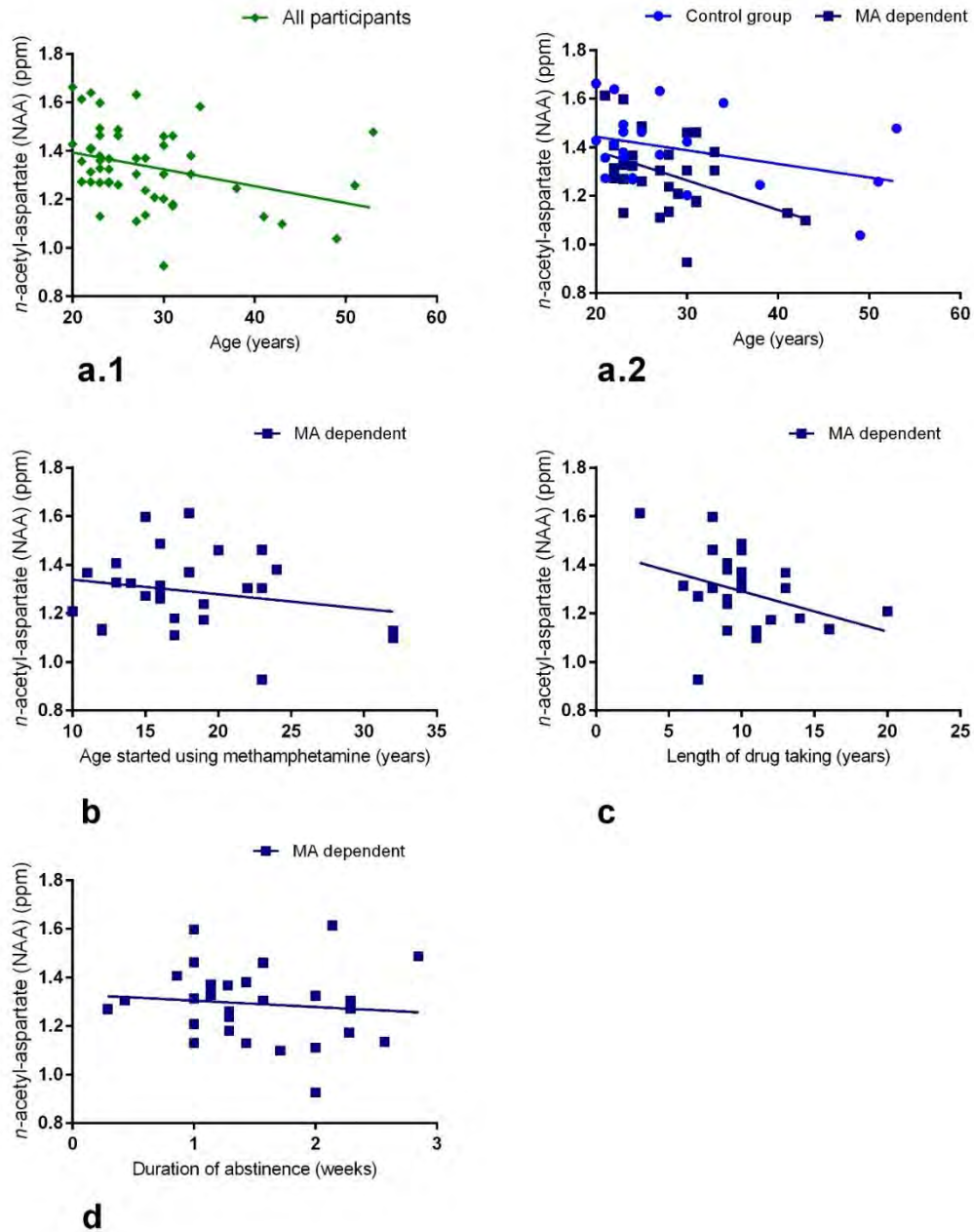


Figure 2.1.4 (a.1) Relative magnetic resonance spectroscopy metabolite concentration – n-acetyl-aspartate (NAA) – in the left DLPFC negatively correlated with age (Spearman $R = -0.39$, $p < 0.01$) at time point 1. (a.2) Additionally, the trend lines of the control and methamphetamine dependent groups are presented. (b) Relative magnetic resonance spectroscopy metabolite concentration – n-acetyl-aspartate (NAA) – in the left DLPFC negatively correlated with age started using methamphetamine (Spearman $R = -0.32$, $p < 0.05$) at time point 1 in the methamphetamine dependent group. (c) Relative magnetic resonance spectroscopy metabolite concentration – n-acetyl-aspartate (NAA) – in the left DLPFC negatively correlated with length of MA use (Spearman $R = -0.40$, $p < 0.01$) at time point 1 in the methamphetamine dependent group. (d) Relative magnetic resonance spectroscopy metabolite concentration – n-acetyl-aspartate (NAA) – in the left DLPFC negatively correlated with duration of abstinence (Spearman $R = -0.33$, $p < 0.05$) at time point 1 in the methamphetamine dependent group.

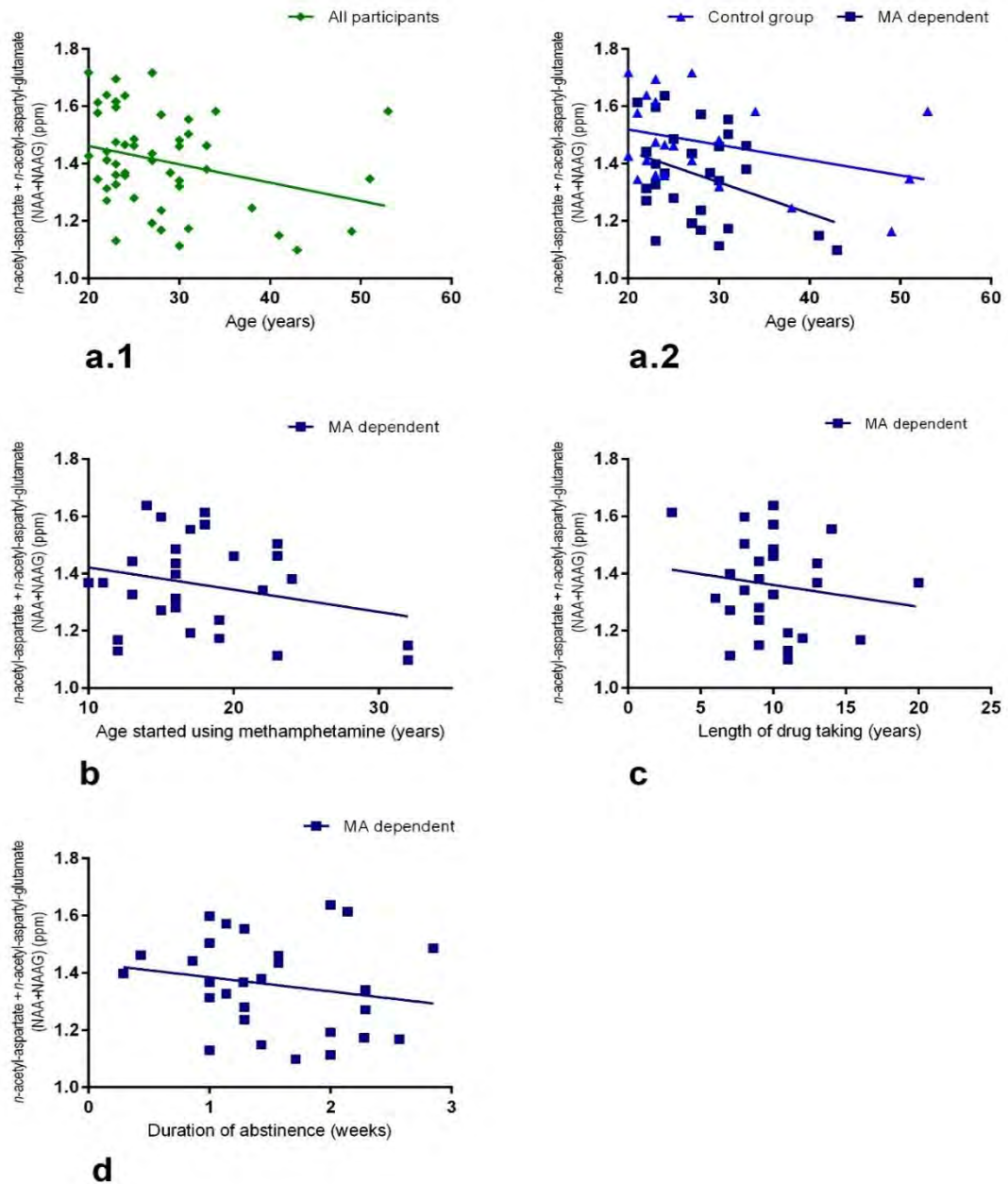


Figure 2.1.5 (a.1) Relative magnetic resonance spectroscopy metabolite concentration – *n*-acetyl-aspartate + *n*-acetyl-aspartyl-glutamate (NAA+NAAG) – in the left DLPFC negatively correlated with age (Spearman $R = -0.29$, $p < 0.05$) at time point 1. (a.2) Additionally, the trend lines of the control and methamphetamine dependent groups are presented. (b) Relative magnetic resonance spectroscopy metabolite concentration – *n*-acetyl-aspartate + *n*-acetyl-aspartyl-glutamate (NAA+NAAG) – in the left DLPFC negatively correlated with age started using methamphetamine (Spearman $R = -0.32$, $p < 0.05$) at time point 1 in the methamphetamine dependent group. (c) Relative magnetic resonance spectroscopy metabolite concentration – *n*-acetyl-aspartate + *n*-acetyl-aspartyl-glutamate (NAA+NAAG) – in the left DLPFC negatively correlated with length of MA use (Spearman $R = -0.32$, $p < 0.05$) at time point 1 in the methamphetamine dependent group. (d) Relative magnetic resonance spectroscopy metabolite concentration – *n*-acetyl-

aspartate + n-acetyl-aspartyl-glutamate (NAA+NAAG) – in the left DLPFC negatively correlated with duration of abstinence (Spearman R = -0.35, $p < 0.05$) at time point 1 in the methamphetamine dependent group.

Experiment 2.2 Short-term abstinence

2.2.1 Age and drug use variables

Age and drug use data are reported in Table 2.2.1. The only reliable demographic information that we were reliably able to report – age – was found to not differ between groups.

Table 2.2.1 Age and drug use

	Healthy Controls n = 22		MA dependent n = 22	
	Mean	Stdev	Mean	Stdev
Age in years at time point 2	28.6	10.2	27.6	5.1
<i>Methamphetamine use</i>				
Age in years started using MA*	/		17.1	5.0
Length of MA use at time point 2*	/		10.8	3.7
Duration (weeks) of abstinence	/		5.1	0.8
<i>Other drugs</i>				
Nicotine use in the last year*	1 of 22		19 of 22	
Cannabis use in the last year*	2 of 22		10 of 22	
MDMA use in the last year*	/		1 of 22	
Cathinone use in the last year*	/		1 of 22	
Methaqualone use in the last year*	/		9 of 22	

**Self-reported by participants.*

2.2.2 ^1H – MRS metabolite concentrations

Significant differences in relative metabolite concentrations were found for: (1) NAA+NAAG ($F_{(1, 39)} = 5.73$, $p < 0.05$) and (2) Ins ($F_{(1, 39)} = 4.90$, $p < 0.05$) in the right ACC; (3) NAA ($F_{(1, 38)} = 4.72$, $p < 0.05$) and (4) NAA+NAAG ($F_{(1, 38)} = 5.90$, $p < 0.05$) in the left DLPFC (Figure 2.1.2).

No significant differences were found for Glu, Glu+Gln, NAA, NAA+NAAG, Ins and GPC+PCh in the left ACC and right DLPFC. No further significant differences were found in the right ACC and left DLPFC. (Appendix II)

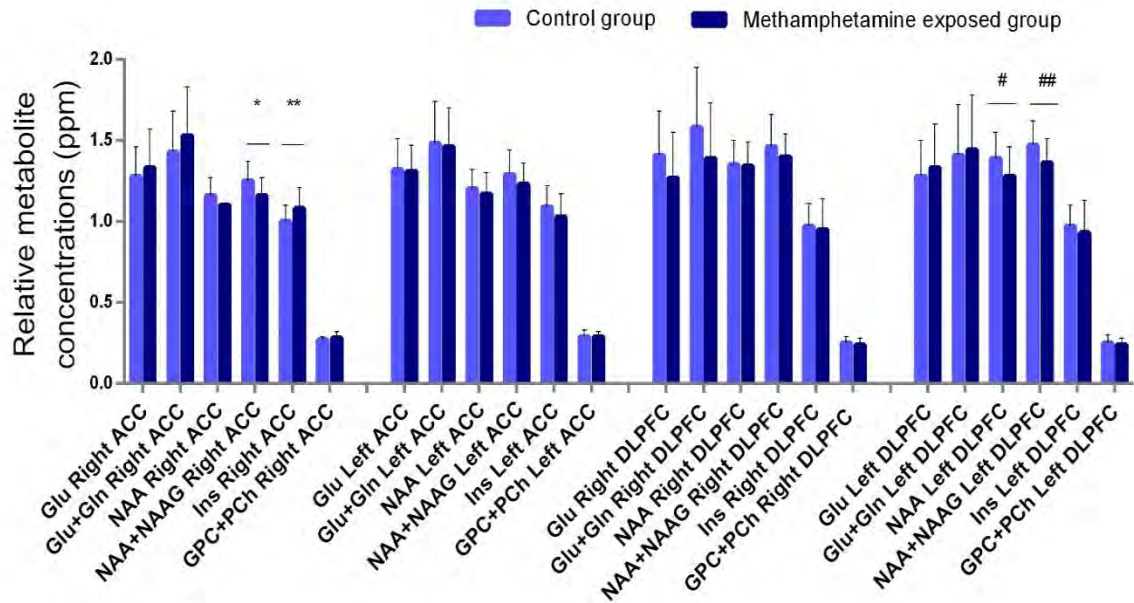


Figure 2.2.1 Relative ^1H -MRS CSI metabolite concentration in both groups. The methamphetamine acute abstinence group had lower concentrations in the right ACC, of $^*\text{n-acetyl-aspartate} + \text{n-acetyl-aspartyl-glutamate (NAA+NAAG)}$ ($p < 0.05$) and $^{**}\text{myo-inositol (Ins)}$ ($p < 0.05$) than the control group in the right ACC. In the left DLPFC, the methamphetamine exposed group had lower concentrations of $^*\text{n-acetyl-aspartate (NAA)}$ ($p < 0.05$) and $^{##}\text{n-acetyl-aspartate} + \text{n-acetyl-aspartyl-glutamate (NAA+NAAG)}$ ($p < 0.05$). Data are presented as mean $\pm$ stdev.

2.2.3 Demographics with ^1H – MRS metabolite concentrations

NAA+NAAG in the right ACC correlated negatively with (a) age (Spearman $R = -0.34$, $p < 0.05$); (b) length of MA use (Spearman $R = -0.31$, $p < 0.05$); and (c) duration of abstinence (Spearman $R = -0.31$, $p < 0.05$) (Figure 2.2.2). Ins in the right ACC correlated positively with duration of abstinence (Spearman $R = 0.43$, $p < 0.05$) (Figure 2.2.3). NAA in the right DLPFC correlated negatively with age (Spearman $R = -0.38$, $p < 0.05$) (Figure 2.2.4). NAA+NAAG in the right DLPFC correlated negatively with age (Spearman $R = -0.51$, $p < 0.001$) (Figure 2.2.5). NAA in the left DLPFC correlated negatively with (a) age (Spearman $R = -0.34$, $p < 0.05$) and (b) length of MA use (Spearman $R = -0.37$, $p < 0.05$) (Figure 2.2.6).

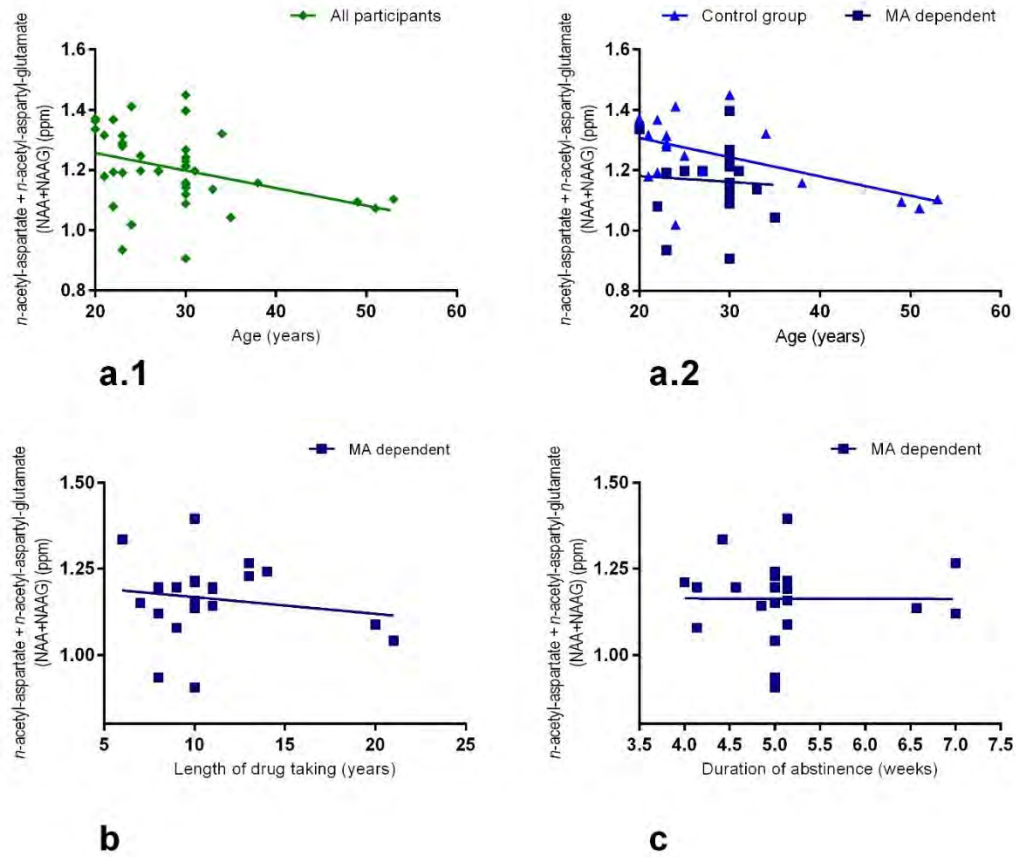


Figure 2.2.2 (a.1) Relative magnetic resonance spectroscopy metabolite concentration – *n*-acetyl-aspartate + *n*-acetyl-aspartyl-glutamate (NAA+NAAG) – in the right ACC negatively correlated with age (Spearman $R = -0.34$, $p < 0.05$) at time point 2. (a.2) Additionally, the trend lines of the control and methamphetamine dependent groups are presented. (b) Relative magnetic resonance spectroscopy metabolite concentration – *n*-acetyl-aspartate + *n*-acetyl-aspartyl-glutamate (NAA+NAAG) – in the right ACC negatively correlated with length of MA use (Spearman $R = -0.31$, $p < 0.05$) at time point 2 in the methamphetamine dependent group. (c) Relative magnetic resonance spectroscopy metabolite concentration – *n*-acetyl-aspartate + *n*-acetyl-aspartyl-glutamate (NAA+NAAG) – in the right ACC negatively correlated with duration of abstinence (Spearman $R = -0.31$, $p < 0.05$) at time point 2 in the methamphetamine dependent group.

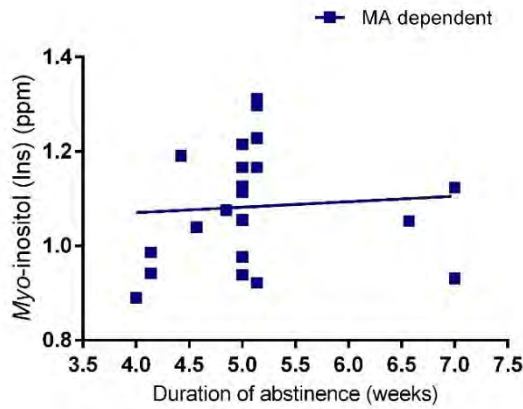


Figure 2.2.3 Relative magnetic resonance spectroscopy metabolite concentration – myo-inositol (Ins) – in the right ACC positively correlated with duration of abstinence (Spearman $R = 0.34$, $p < 0.05$) at time point 2 in the methamphetamine dependent group.

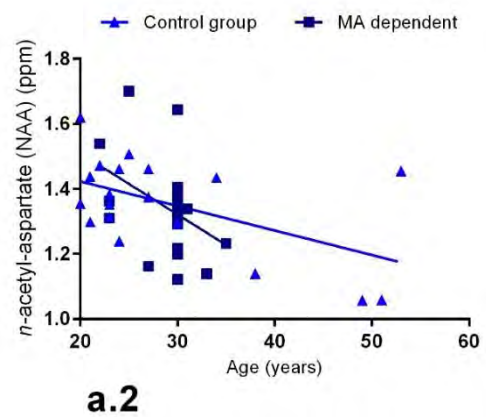
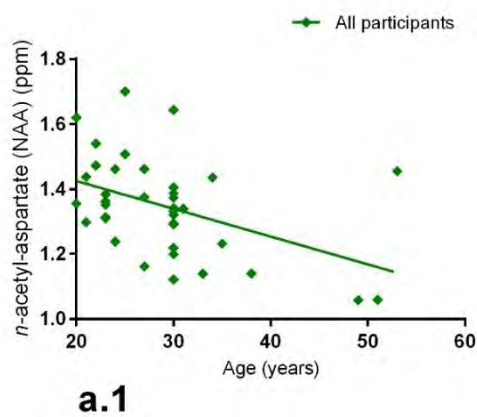


Figure 2.2.4 (a.1) Relative magnetic resonance spectroscopy metabolite concentration – n-acetyl-aspartate (NAA) – in the right DLPFC negatively correlated with age (Spearman $R = -0.38$, $p < 0.05$) at the time point 2. (a.2) Additionally, the trend lines of the control and methamphetamine dependent groups are presented.

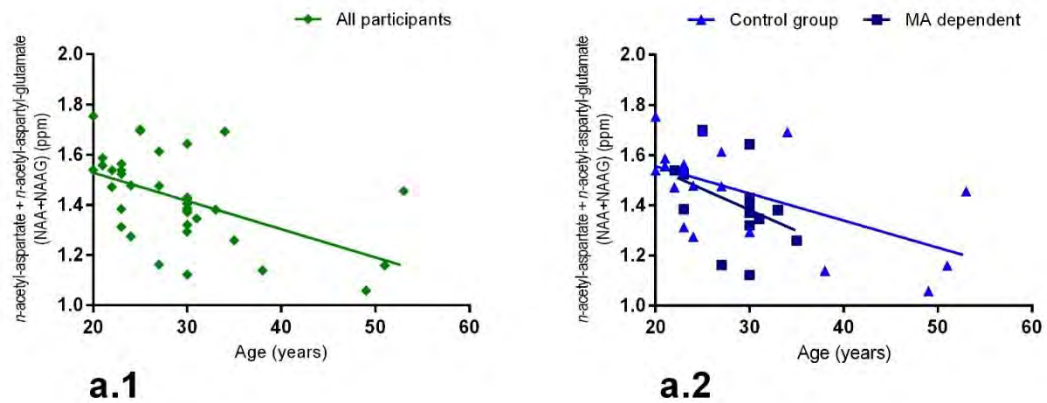


Figure 2.2.5 (a.1) Relative magnetic resonance spectroscopy metabolite concentration – *n*-acetyl-aspartate + *n*-acetyl-aspartyl-glutamate (NAA+NAAG) – in the right DLPFC negatively correlated with age (Spearman $R = -0.51$, $p < 0.001$) at time point 2. (a.2) Additionally, the trend lines of the control and methamphetamine dependent groups are presented.

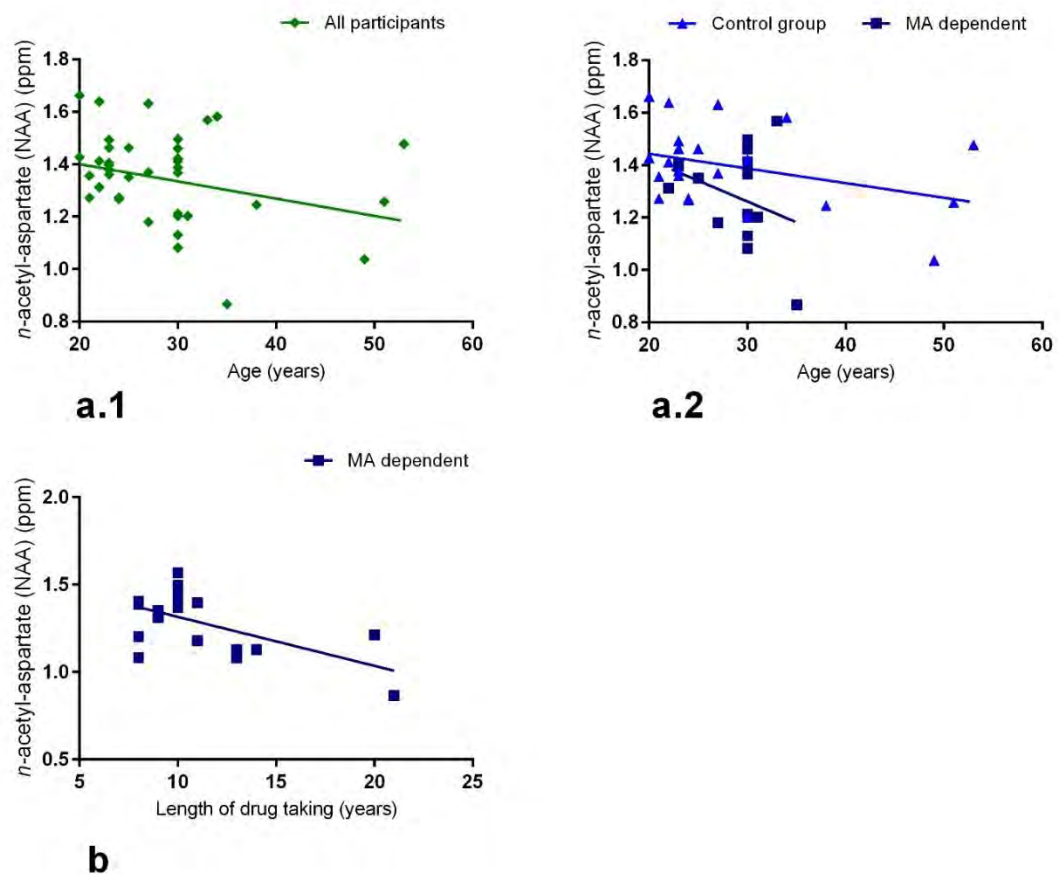


Figure 2.2.6 (a.1) Relative magnetic resonance spectroscopy metabolite concentration – *n*-acetyl-aspartate (NAA) – in the left DLPFC negatively correlated with age (Spearman $R = -0.34$, $p < 0.05$) at time point 2. (a.2) Additionally, the trend lines of the control and methamphetamine dependent groups are presented. (b) Relative magnetic resonance spectroscopy metabolite concentration – *n*-acetyl-aspartate (NAA) – in the left DLPFC negatively correlated with length of MA use (Spearman $R = -0.37$, $p < 0.05$) at time point 2 in the methamphetamine dependent group.

Experiment 2.3 –Acute to short-term abstinence

2.3.1 Age and drug use variables

Age and drug use data are reported in Table 2.3.1.

	Time point 1				Time point 2			
	n = 22							
	Mean	Stdev	Mean	Stdev	Mean	Stdev	Range	
Age in years			28.1	5.2			22.9-33.3	
<i>Methamphetamine use</i>								
Age in years started using MA*			17.1	5.0			12.1-22.1	
Length of MA use *			10.8	3.7			7.1-14.5	
Duration (weeks) of abstinence	1.5	0.6			5.1	0.8	0.9-5.9	
<i>Other drugs</i>								
Nicotine use in the last year*			19 of 22					
Cannabis use in the last year*			10 of 22					
MDMA use in the last year*			1 of 22					
Cathinone use in the last year*			1 of 22					
Methaqualone use in the last year*			9 of 22					

*Self-reported by participants.

2.3.2 ¹H – MRS metabolite concentrations

Significant differences in relative metabolite concentrations were found in the right ACC: (1) NAA ($T_{(1, 15)} = 2.39$, $p < 0.05$); (2) NAA+NAAG ($T_{(1, 16)} = 2.57$, $p < 0.05$); and (3) Ins ($T_{(1, 16)} = -2.41$, $p < 0.05$) (Figure 2.3.1).

No significant differences were found for Glu, Glu+Gln, NAA, NAA+NAAG, Ins and GPC+PCh in the left ACC, left DLPFC and right DLPFC; and Glu, Glu+Gln, and GPC+PCh in the right ACC. (Appendix I)

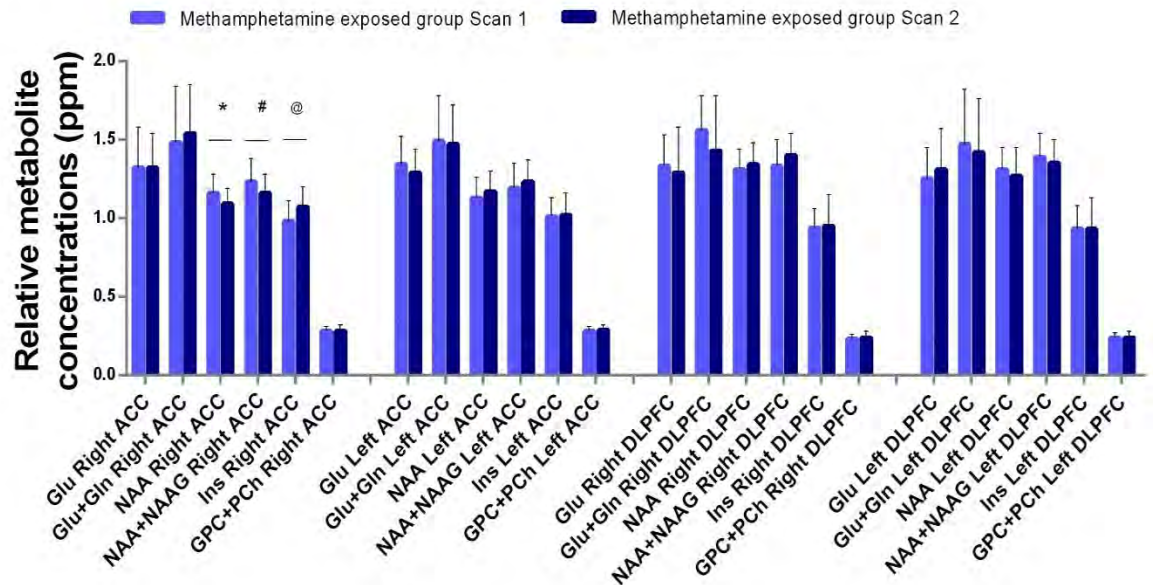


Figure 2.3.1 Relative ^1H -MRS CSI metabolite concentration in the methamphetamine exposed group showing the differences of acute to short-term abstinence. Lower concentrations in short-term abstinence were seen, when compared to acute abstinence concentrations: **n*-acetyl-aspartate (NAA)_($p < 0.05$), #*n*-acetyl-aspartate + *n*-acetyl-aspartyl glutamate (NAA+NAAG)_($p < 0.05$). Higher concentration of @*myo*-inositol (Ins)_($p < 0.05$) was seen in short-term abstinence. Data are presented as mean $\pm$ stdev.

Discussion

The main findings from this study are: (1) Decreased relative NAA+NAAG in the left DLPFC of the MA dependent group, when compared with the control group. (2) Decreased NAA+NAAG and increased Ins in the right ACC of the MA dependent group, compared to controls. (3) Decreased NAA and NAA+NAAG were related to increased Ins in the right ACC in acute to short-term MA abstinence. (4) NAA+NAAG bilaterally in the DLPFC and NAA in the left DLPFC were significantly correlated with age started using MA, length of MA use and duration of abstinence; NAA+NAAG in the right ACC significantly correlated with length of MA use and duration of abstinence; Ins in the right ACC was significantly correlated with duration of abstinence.

Acute abstinence from MA revealed decreased relative NAA+NAAG in the left DLPFC, indicating diminished neuronal integrity. Decreased NAA was not observed in the right DLPFC or ACC bilaterally. Low concentrations of NAA+NAAG have been related to neuronal and axonal integrity as well as mitochondrial bioenergetics (Gujar et al., 2005). To our knowledge, no studies investigating acute abstinence (<2 weeks) have been

reported in the literature. Howells et al. (2014) reported decreased relative NAA concentrations in the right ACC and right DLPFC, as well as decreased relative choline metabolites in the right DLPFC of MA users abstinent between 1 and 240 days. The results from acute abstinence are, in part, consistent with previous studies on short-term to long-term MA abstinence that have shown decreased relative NAA and relative NAA+NAAG in frontal gray matter and the ACC (Barr et al., 2006; Berman et al., 2008; Ernst et al., 2000; Hellem et al., 2015; Howells et al., 2014; Nordahl et al., 2002, 2003; Scott et al., 2007) and is indicative of drug-induced neuronal damage (Barr et al., 2006) or neuronal loss (Ende et al., 1997). The finding of the present study of decreased relative NAA and relative NAA+NAAG could indicate that acute abstinence initially affects the left DLPFC.

In *short-term abstinence*, decreased NAA+NAAG and increased Ins were found in the right ACC of short-term abstinent MA abusers. Increased Ins indicates an increased need for neuronal energy supply (Ernst et al., 2000) reflecting neuronal damage / death of glial cells through overstimulation or activity (Ernst et al., 2000). Decreased NAA+NAAG is a marker of neurodegeneration (Barr et al., 2006; Ende et al., 1997). Increased Ins indicates an increased need for neuronal energy supply (Ernst et al., 2000) and is indicative of neuro-inflammation (Clark et al., 2013; Sekine et al., 2008). Prolonged exposure to neuroinflammation leads to decreased Ins, reflecting neuronal degeneration (Huang et al., 2009). Previous ¹H-MRS studies which investigated the same brain areas found, additional to decreased NAA and increased Ins, increased Cho levels in frontal gray matter (Ernst et al., 2000; Nordahl et al., 2002; Nordahl et al., 2005; Sekine et al., 2002), and increased Glu in frontal gray matter (Bracken et al., 2011; Sailasuta et al., 2010). The present study showed decreased NAA and increased Ins only in the right ACC of short-term abstinent participants, consistent – in part – with previous studies, and could be attributed to previous studies investigating short-term (>3 weeks) and long-term (>20 weeks) abstinence, whereas the present study investigated abstinence only up to 6 weeks.

Examination of the *effects of time on acute to short-term abstinence*, showed decreased NAA and NAA+NAAG was related to increased Ins in the right ACC. This finding indicates that neuroinflammation and subsequent decreased integrity and viability of

neurons (Clark et al., 2013) persists from acute into short-term abstinence. Prolonged exposure to neuroinflammation is associated with neuronal damage and death (Clark et al., 2013). Structural MRI studies have reported significantly increased gray matter volumes in subcortical areas and parietal lobe between the first and fourth weeks of MA abstinence (Jernigan et al., 2005; London et al., 2014), supporting a physical reflection of inflammatory response in these brain tissue. This relationship between NAA, NAA+NAAG and Ins has not previously been reported and shows that neuroinflammation is initiated in short-term MA abstinence. It is important to note that prolonged exposure to neuroinflammation results in neuronal death (Linda Chang et al., 2007). The extent of damage caused by persistent neuroinflammation is unknown, and requires further investigation.

Significant relationships between drug use variables and neurometabolites were observed. Relative NAA+NAAG in the DLPFC bilaterally and NAA in the left DLPFC correlated negatively with age started using MA, length of MA use, and duration of abstinence. Additionally, NAA+NAAG in the right ACC correlated negatively with length of MA use and duration of abstinence. This is consistent with the results obtained from time point 1, as well as previous literature (Barr et al., 2006; Berman et al., 2008; Ernst et al., 2000; Hellem et al., 2015; Howells et al., 2014; Nordahl et al., 2002, 2003; Scott et al., 2007) and is indicative of drug-induced neuronal damage (Barr et al., 2006) or neuronal loss (Ende et al., 1997). Ins in the right ACC correlated positively with duration of abstinence, indicating an increase in glial cells, which forms part of the body's innate immune response to toxic stimuli. Increased levels of Ins and decreased NAA is indicative of neuroinflammation related to abstinence from MA (Berman et al., 2008; Clark et al., 2013). This correlates support our findings; our data indicate that there is a potential window of opportunity in which interventions that reduce neuroinflammatory processes from initiating; further study is required to investigate suitable pharmacological interventions.

Several *limitations* should be noted. Studies of substance abuse are almost invariably confounded by issues of selective disclosure and polysubstance use (Roos et al., 2014). This study relied on information obtained through self-report by participants, specifically pertaining to length of drug use, dosage, as well as other substances used.

Another limitation was the lack of drug dosage data. The study sample was small, which could be associated with statistical instability and poor reproducibility (Peterson, 2003). Multiple tissue types – both abundant and less abundant – are found within a voxel, which could complicate interpretation of metabolite levels. The purpose of this study was not to address the impact of partial voluming, however a representative image of our slice positioning is provided. Additionally, age is related to decreased NAA (Eylers et al., 2015). In the current study, the impact of MA use on this natural ageing process was not investigated and should be addressed in future studies. We do however report the significant correlations found in our results section. Finally, inclusion of GABA ^1H -MRS, using GABA editing, in future studies would provide greater insight neurometabolic processes that are seen in the standard ^1H -MRS metabolites, including that related to neuroinflammation. It has been suggested that MA leads to damage of cortical GABAergic interneurons (Hsieh et al., 2014). There is a close relationship between GABA, Ins, and glutamate, the inclusion of GABA would have provided greater insight the development of neuroinflammatory processes in MA abstinence.

Future studies

It is unknown whether the neuroinflammation that was observed exist in brain areas/structures other than the ACC will increase during abstinence or decrease over time. Additionally, the timeline in which the inflammation will subside, as well as whether it is related to further loss in neuronal integrity in additional brain regions requires further investigation. Previous studies (Berman et al., 2008; Ernst et al., 2000; Nordahl et al., 2003; Scott et al., 2007) report an increase in Ins in the right ACC, which has been shown to persist in early abstinence from MA (Berman et al., 2008; Clark et al., 2013), and to proportionately decline with continuous drug abstinence (Clark et al., 2013). This stresses the importance of investigating the longitudinal-long-term impact of abstinence from MA. The use of a questionnaire, such as the Kreek-McHugh-Schluger-Kellogg scale (KMSK scale) (Kellogg et al., 2003) to more accurately report drug dosage in drug addicts requires exploration. Furthermore, the development of a pharmacological intervention to curb the negative impact on brain metabolism during withdrawal needs to be investigated. Future studies should also aim to gain understanding of the cognitive and behavioural parameters caused by the damage during withdrawal. The results from this study warrants longitudinal research,

including larger participation groups, to determine whether recovery of the brain is possible.

In *conclusion*, the results from the present study suggest that with acute abstinence there is damage to neuronal integrity. With short-term abstinence this neuronal integrity is potentiated – and is accompanied by neuroinflammation. These data are the first ¹H-MRS data that show the development of neuroinflammation from acute to short-term MA abstinence.

Chapter 3

The impact of prenatal MA exposure on neurometabolism and neurocognitive development in child participants

ABSTRACT

Background: Methamphetamine (MA) use among pregnant women is increasing and holds significant risks for the developing child. ^1H -MRS studies on prenatal MA exposure suggest aberrant neuronal development and abnormal metabolism. This study aims to investigate neurometabolite changes and association with general cognitive ability over time in prenatally MA exposed children of school-going age.

Methods: Prenatally MA exposed children ($n=14$) and healthy-matched control ($n=14$) participants were recruited and underwent resting-state single-voxel ^1H -MRS (TR 2000ms, TE 30ms) with a voxel located in the anterior cingulate cortex (ACC) as well as a neurocognitive assessment battery at two time points: i) ages 6.4 ± 0.4 (MA exposed, $n=14$) and 6.5 ± 0.3 (controls, $n=14$) years and ii) 8.1 ± 0.6 (MA exposed, $n=13$) and 8.1 ± 0.4 (controls, $n=11$). The change in neurometabolites and neurocognitive assessment results over time were also investigated. Absolute metabolite concentrations of interest were creatine (Cr), phosphocreatine (PCr), creatine + phosphocreatine (Cr+PCr), glutamate (Glu), glutamate + glutamine (Glu+Gln), glycerophosphocholine (GPC), glycerophosphocholine + phosphocholine (GPC+PCh), *myo*-inositol (Ins), *n*-acetyl-aspartate (NAA), *n*-acetyl-aspartate + *n*-acetyl-aspartyl-glutamate (NAA+NAAG).

Results: The MA exposed group performed significantly poorer on neurocognitive tasks at both time points, when compared to the control group. Potential recovery was seen in short-term and verbal memory of MA exposed children. No metabolite differences were observed at either time point, however, over time increased NAA and decreased GPC and GPC+PCh were observed in the prenatally exposed group.

Conclusion: The results from this study support the current literature by showing that prenatal exposure to MA results in neurometabolite changes associated with neuronal maturation, and poorer neurocognition which persists into school-going age. However, evidence of improvement in neuronal maturation of the brain as well as improvement in short-term and verbal memory in prenatally MA exposed children was found, and indicates positive reorganisation of the neural network in the ACC.

Introduction

¹H-MRS research on children exposed to MA prenatally is limited. ¹H-MRS is a non-invasive imaging technique and is low risk for research including children. ¹H-MRS provides *in vivo* data on the concentration of neurometabolites, which are products of normal chemical metabolism and function, and are indicators of neurochemical activity, found in the body (Hellem et al., 2015). ¹H-MRS studies conducted on prenatally MA-exposed children younger than school-going age suggest aberrant neuronal and glial development, abnormal energy metabolism and higher neuronal density in the brain associated with significantly higher Creatine (Cr) and glutamate with glutamine (Glu+Gln) concentrations in frontal white matter and basal ganglia, and n-acetyl-aspartate (NAA) in frontal white matter with, additionally, a decrease in myo-Inositol (Ins) concentrations and Ins to Cr ratios (Chang et al., 2009; Lester & Lagasse, 2010; Smith et al., 2001).

Behavioural (Diaz et al., 2014) and mood disturbances (Abar et al., 2013; Smith et al., 2003), as well as lower cognitive functioning (Kirlic et al., 2013; Smith et al., 2003) in children exposed to MA prenatally have been reported. A wide range of neurocognitive problems have been reported, specifically pertaining to executive functioning, working memory, verbal memory, visual-motor integration tasks, spatial memory and sustained attention (Abar et al., 2013; Chang et al., 2004; Diaz et al., 2014; McDonnell-dowling & Kelly, 2015; Smith et al., 2011; Thompson et al., 2009; van Dyk et al., 2014). It is thus evident that prenatal exposure to MA poses a serious risk to brain development.

The aims of this study were to investigate the impact of prenatal MA exposure on neurometabolism and the neurocognitive development of children of school-going age at two time points – 6 years and 8 years old respectively, and to determine whether, over time, there is normalisation of neurometabolites and neurocognition.

Material and methods

This study followed a case-control longitudinal design

Participants

Fourteen prenatally MA exposed children and 14 healthy control participants were recruited from a local hospital where maternal medical records indicated MA use during pregnancy. Participants were matched for age, gender, race, and sociodemographic. All participants underwent resting-state single-voxel ^1H -MRS scans as well as a battery of neurocognitive assessment at two time points, i) Age 6.4 ± 0.4 years ($n=14$) and 6.5 ± 0.3 years ($n = 14$ _ for the MA exposed and control groups, respectively, and ii) Age 8.1 ± 0.6 years ($n=13$) and 8.1 ± 0.4 ($n=11$) years for the MA exposed and control groups, respectively. Additionally, the change in neurometabolites and neurocognitive assessment results were investigated over these time points (MA exposed, $n = 9$; Controls, $n = 7$). (Figure 3.1)

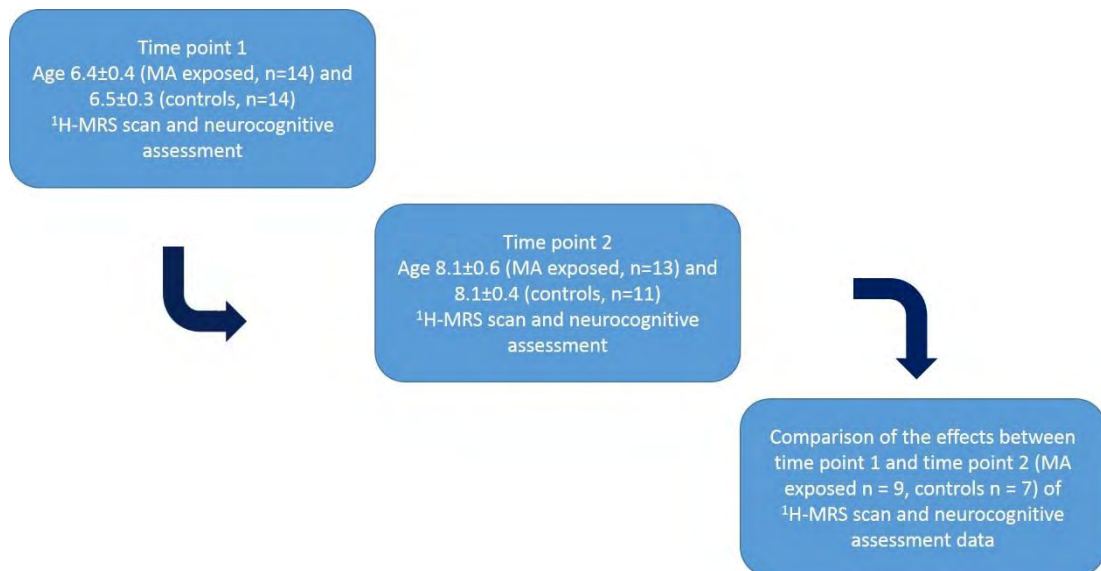


Figure 3.1 – ^1H -MRS scan data and neurocognitive assessment results of 6 year old MA exposed participants and control participants were compared at time point 1. At time point 2, scan data and neurocognitive assessment results of 8 year old MA exposed participants were compared to the control group. Further, the data from both time points were compared.

Parent(s) / legal guardian(s) of each participant were required to complete an informed consent form as well as a detailed demographic, socio-economic and medical history of the child, mother and family. All documents were available in Afrikaans and English for easier understanding by the research participants. All drug use related information were obtained through self-report by participants. Any history or presentation of pathology (e.g. bacterial meningitis, hypoglycaemia, serious head injury, premature birth, etc.) and substance abuse other than MA (e.g. nicotine, cannabis, cocaine, opiates and alcohol) resulted in exclusion from the study. All information collected during this study were

kept confidential and only used for scientific purposes. Data acquisition occurred between November 2012 and February 2015, and was approved by the Human Research Ethics Committee, Faculty of Health Sciences of the University of Cape Town – HREC Reference Number: 235/2009 and was conducted in accordance with the Declaration of Helsinki (World Medical Association, 2008).

¹H-MRS imaging procedures

Participant scans were performed in a 3T Allegra Siemens head scanner using the standard CP single channel head coil. For the placement of ACC voxels, a high-resolution, motion-navigated multi-echo MPRAGE (van der Kouwe et al., 2008) sequence (TR = 2530 ms, graded TE = 1.53, 3.21, 4.89, 6.57 ms, flip angle = 7°, matrix size of 224x224x144, FOV = 224 mm, voxel size of 1.3 x 1.0 x 1.0 mm) with an acquisition time of 5 minutes 20 seconds. Real-time motion and B0 corrected single voxel magnetic resonance spectroscopy (SVS) (Hess et al., 2011) of the ACC was acquired (PRESS, TE = 30 msec, TR = 1500 msec, 64 averages, delta = -2.6 ppm delta frequency, VOI 20 x 20 mm with a thickness of 15mm, scan time 2:16, with unsuppressed water MRS spectra for the same volume, two averages were acquired). The ACC voxel included bilateral grey matter (Figure 3.2).

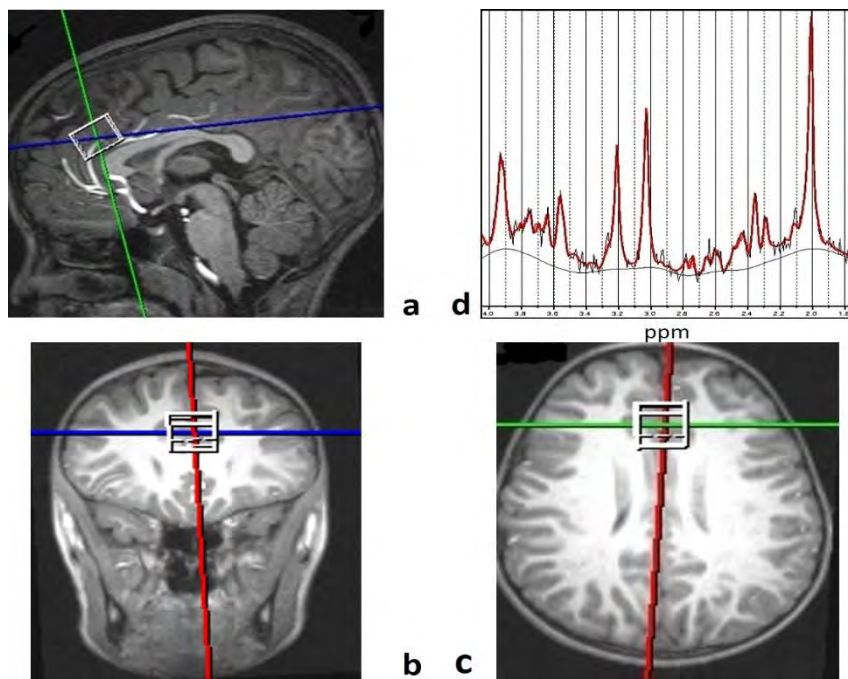


Figure 3.2 – Representative ^1H -MRS single voxel spectroscopy brain slice orientation on the 3D planes (a – sagittal, b – coronal, c – axial) and spectra of VOIs which included (d) bilateral anterior cingulate cortices (ACC).

^1H -MRS Data Analysis

Pre-processing of spectroscopy data to extract potential head movement artefact using software package developed by Hess, Dylan Tisdall, Andronesi, Meintjes, & Van Der Kouwe (2011) was applied. The ^1H -MRS spectra data were then processed in standard ^1H -MRS software LCModel (Provencher, 1993) which processed single-voxel spectroscopy spectra with their respective water reference file. Absolute metabolite concentrations were extracted and we report the following neurometabolites: Cr, PCr, Cr+PCr, Glu, Glu+Gln, GPC, GPC+PCh, Ins, NAA, NAA+NAAG (Hellem et al., 2015). We report absolute metabolite concentrations (mmol/l).

Neurocognitive assessment battery

A battery of neurocognitive assessments was also conducted with each participant. This battery included the Kaufman Assessment Battery for children – Second Edition (KABC-II) and the Boston Naming Test (South African Short Form) (BNT-SA-SF). The Kaufman Assessment Battery for children – Second Edition is divided into three levels, each for a different age group: i) children aged 3 years, ii) children aged 4-6 years, and iii) children aged 7-18 years, and measures overall processing and cognitive abilities. Factor-analytic studies, as described in the test manual, supports construct validity (Kaufman, 2004). The subtests of the KABC-II used in this study are: (1) *Block Counting* assesses simultaneous and visual processing specifically pertaining to spatial relationships, conceptualisation and visualisation. This subtest was administered only to 7+ year old participants. (2) *Pattern Reasoning* assesses induction and visualisation abilities through the manipulation of abstract designs and symbols. (3) *Atlantis* measures the ability to acquire new information through associative memory. (4) *Atlantis Delayed* is administered, without forewarning, 15-25 minutes after Atlantis, using the same stimuli, and assesses the ability to retrieve newly encoded information after a filled delay. Lastly, the (5) BNT-SA-SF was included, and is based on the original 60-item Boston Naming Test (BNT) (Kaplan & Goodglass, 1983, 2001). The BNT is a test of confrontation naming

ability and consists of 15 black and white drawings that are presented in order of increasing difficulty, ranging from everyday objects to less familiar objects.

Statistical Analysis

Statistical analysis were performed using the software package Statistica version 12 (Stasoft Incorporated, 2014). All raw data were tested for normality of distribution, using the Shapiro-Wilks test. Non-normal distributed data underwent Mann-Whitney U tests as appropriate, while the normally distributed data was analysed using ANOVA. Further, to address the relationship between the two time points, as well as on neurocognition, repeated measures ANOVA with Bonferroni post-hoc tests were performed to determine the impact of time on demographic data, neurocognitive assessment results, and brain metabolites. Spearman Rank Order correlation analysis was chosen due to the presentation of mixed data distribution. At time point 1 and time point 2 ¹H-MRS metabolite concentration with demographic (age, weight, height, body mass index) and neurocognitive assessment data (Block Counting raw score and scaled score, Pattern Reasoning raw score and scaled score, Atlantis raw score and scaled score, Atlantis Delayed raw score and scaled score) were determined.

Data are reported as mean $\pm$ standard deviation. For group differences statistical test results are reported, significance set at $p < 0.05$, which includes Bonferroni correction. For the correlations analyses the correlation co-efficient is reported, significance set at $p < 0.05$. Refer to Appendix II for further detail.

Results

Experiment 3.1

3.1.1 Demographic and MA drug use by mother during pregnancy

Demographic and drug use during pregnancy information is reported in Table 3.1.1. No significant demographic and non-MA drug variable differences were found at time point 1.

Table 3.1.1 Demographics and drug use

	Healthy Controls		Methamphetamine exposed <i>in utero</i>	
	n = 14		n = 14	
	7 females / 7 males		7 females / 7 males	
	Mean	Stdev	Mean	Stdev
Age in years at time point 1	6.5	0.3	6.4	0.4
Weight in kilograms at point 1	19.8	3.2	19.2	2.6
Height in metres at time point 1	1.1	0.1	1.1	0.1
Body mass index at time point 1	17.9	2.8	17.6	3.5
<i>Methamphetamine use</i>				
During first trimester	/		14 of 14*	
During second trimester	/		14 of 14*	
During third trimester	/		14 of 14*	
<i>Nicotine use</i>				
During first trimester	4 of 14		10 of 14	
During second trimester	4 of 14		10 of 14	
During third trimester	4 of 14		10 of 14	
<i>Alcohol use</i>				
During first trimester	1 of 14		2 of 14	
During second trimester	0 of 14		2 of 14	
During third trimester	0 of 14		2 of 14	

*Methamphetamine (MA) use 2-3 times per week_(n = 3); MA use 4-6 times per week_(n = 2); MA use daily_(n = 5); MA use frequency not available_(n = 4). MA use remained the same throughout the three trimesters.

Nicotine use - Control group: 2-3 times per week_(n = 4) throughout the three trimesters. MA exposed group: Never use nicotine_(n = 2); Nicotine use 2-3 times per week_(n = 6); Nicotine use 4-6 times per week_(n = 1); Nicotine use daily_(n = 2) throughout the three trimesters.

Alcohol use - Control group: Once per week or less_(n = 1) in the first trimester only. Methamphetamine exposed group: 4-6 times per week_(n = 1); Alcohol use daily_(n = 1) throughout the three trimesters.

3.1.2 Neurocognitive Tasks

The following significant neurocognitive task differences were found between the groups: The methamphetamine exposed group_(n = 14) scored significantly lower than the control group_(n = 14) on the following subtest on the KABC-II: (1) Pattern reasoning raw score ($z = 3.97$, $p < 0.001$, Figure 3.1.1), (2) Pattern reasoning scaled score ($F_{(1, 26)} = 26.66$, $p < 0.001$, Figure 3.1.2), (3) Atlantis raw score ($F_{(1, 26)} = 17.62$, $p < 0.001$, Figure 3.1.3), (4) Atlantis scaled score ($F_{(1, 26)} = 15.53$, $p < 0.001$, Figure 3.1.4), (5) Atlantis Delay raw score ($F_{(1, 26)} = 19.27$, $p < 0.001$, Figure 3.1.5), (6) Atlantis Delay scaled score ($F_{(1, 26)} = 14.44$, $p <$

0.001, Figure 3.1.6). The methamphetamine exposed group_(n = 14) also performed poorer than the control group_(n = 14) on the BNT-SASF ($F_{(1, 26)} = 11.68$, $p < 0.01$, Figure 3.1.7).

Block Counting was only administered to children aged 7 years (Control $n = 10$; MA exposed $n = 6$). No differences were observed for Block counting Raw Score or Block Counting Scaled Score. Refer to Appendix III for further detail.

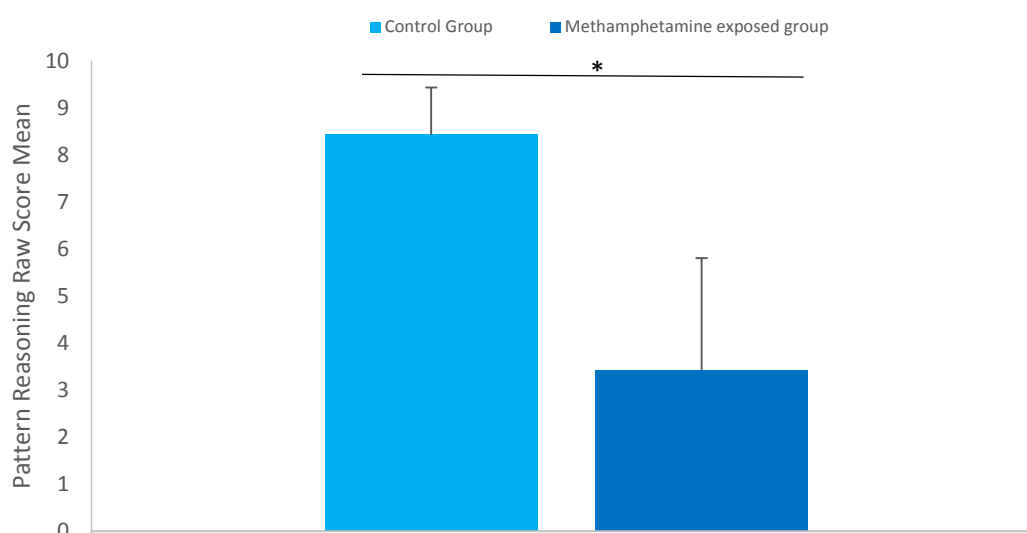


Figure 3.1.1 Pattern Reasoning Raw Score Mean between groups. The *methamphetamine exposed group_(n=14) performed significantly lower than the control group_(n=14), $p < 0.001$, data are presented as mean $\pm$ stdev.

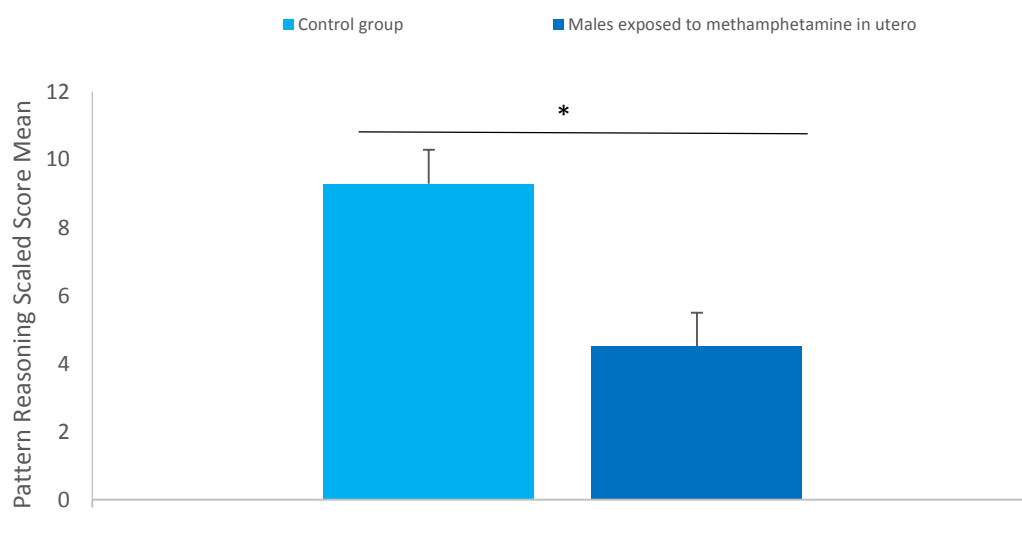


Figure 3.1.2 Pattern Reasoning Scaled Score Mean between groups. The *methamphetamine exposed group_(n=14) performed significantly lower than the control group_(n=14), $p < 0.001$, data are presented as mean $\pm$ stdev.

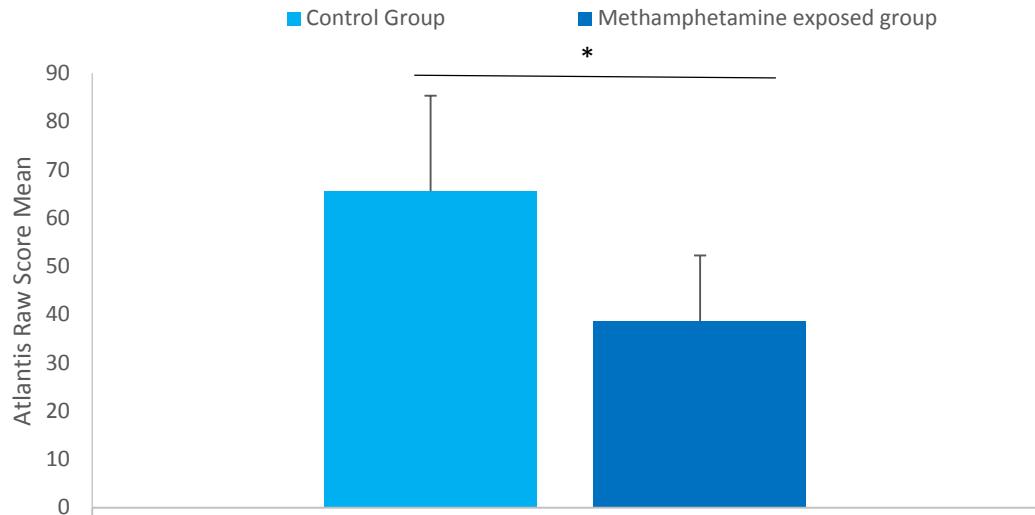


Figure 3.1.3 Atlantis Raw Score Mean between groups. The *methamphetamine exposed group ($n=14$) performed significantly lower than the control group ($n=14$), $p < 0.001$, data are presented as mean $\pm$ stdev.

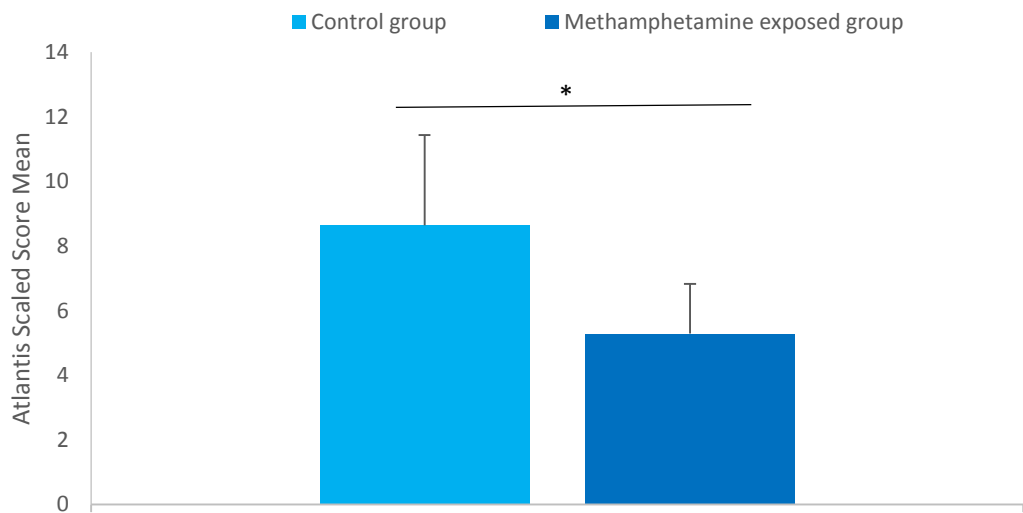


Figure 3.1.4 Atlantis Scaled Score Mean between groups. The *methamphetamine exposed group ($n=14$) performed significantly lower than the control group ($n=14$), $p < 0.001$, data are presented as mean $\pm$ stdev.

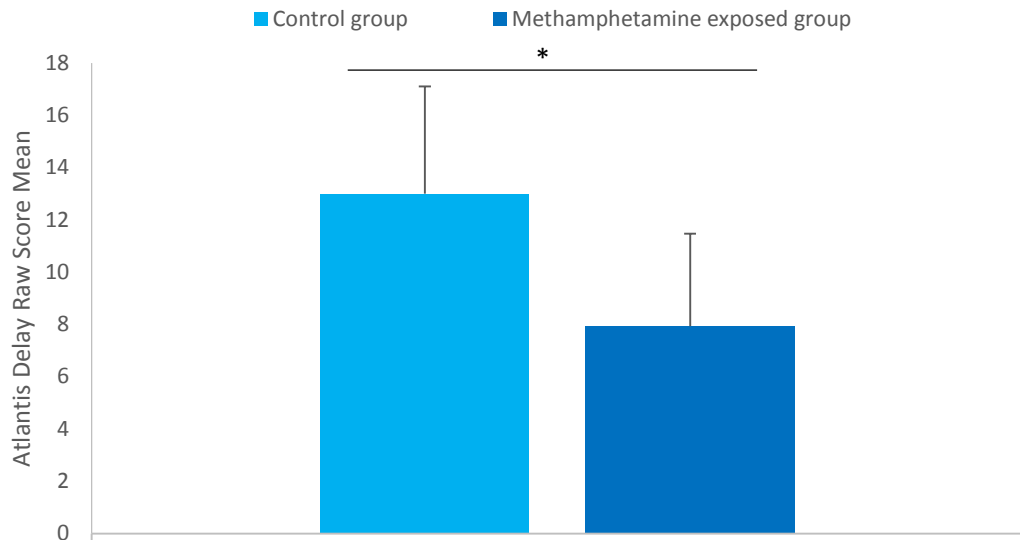


Figure 3.1.5 Atlantis Delayed Raw Score Mean between groups. The *methamphetamine exposed group_(n=14) performed significantly lower than the control group_(n=14). $p < 0.001$, data are presented as mean $\pm$ stdev.

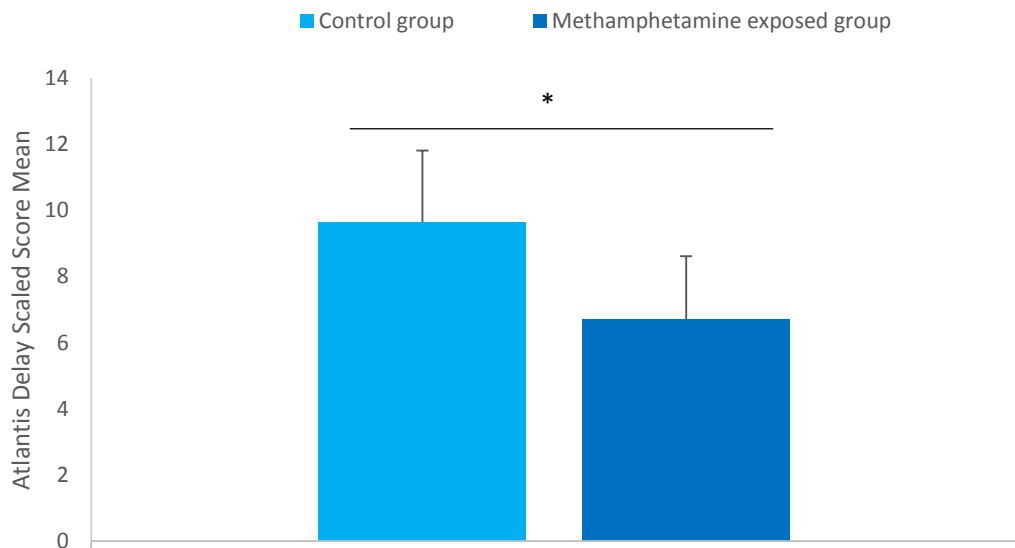


Figure 3.1.6 Atlantis Delayed Scaled Score Mean between groups. The *methamphetamine exposed group_(n=14) performed significantly lower than the control group_(n=14). $p < 0.001$, data are presented as mean $\pm$ stdev.

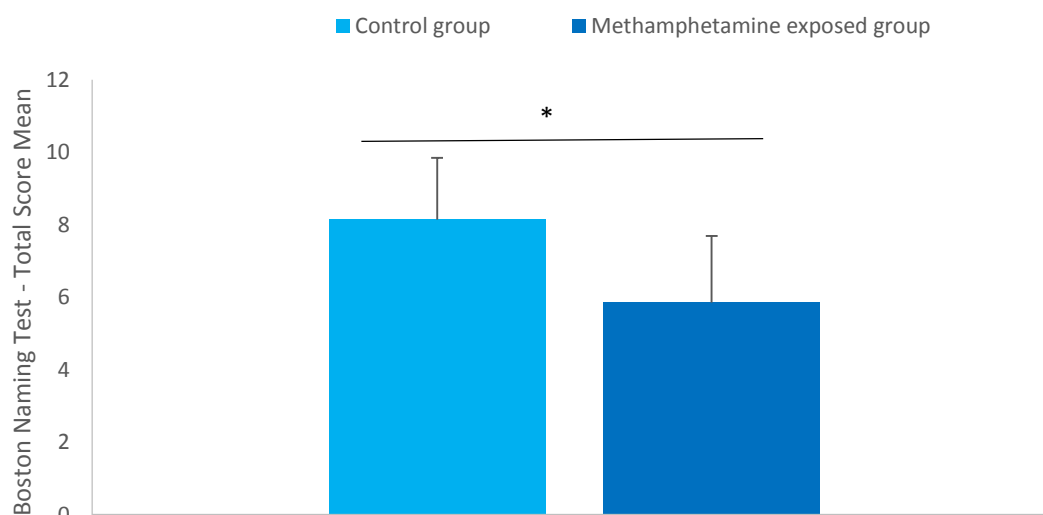


Figure 3.1.7 Boston Naming Test – Total Score Mean between groups. The *methamphetamine exposed group_(n=14) performed significantly lower than the control group_(n=14). $p < 0.01$, data are presented as mean $\pm$ stdev.

3.1.3 ^1H – MRS metabolite concentrations

No significant group differences were found between the two groups with respect to absolute ACC metabolite concentrations (Figure 3.1.8).

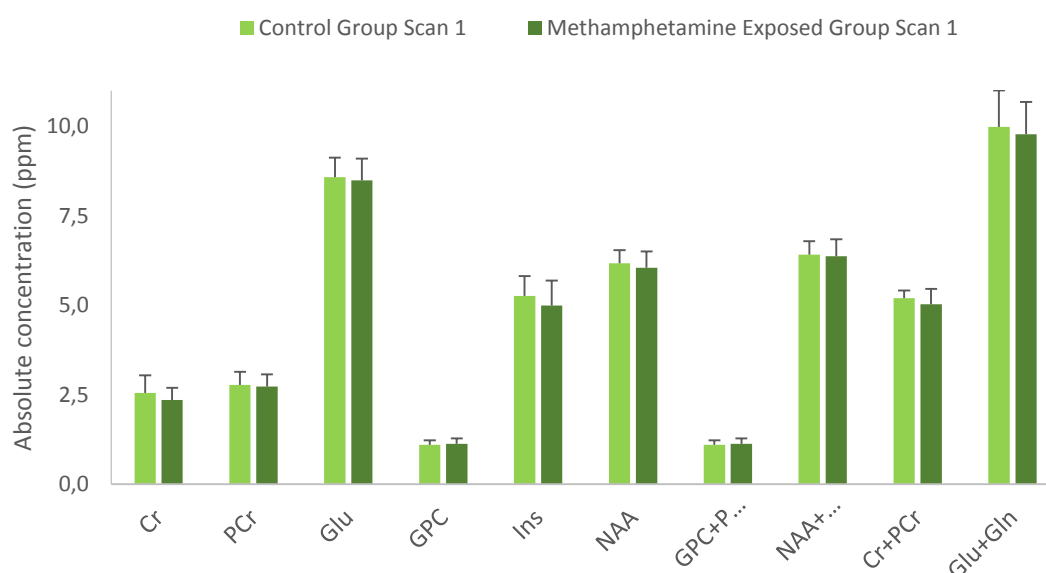


Figure 3.1.8 Absolute ^1H -magnetic resonance spectroscopy metabolite concentrations – creatine (Cr), phosphocreatine (PCr), glutamate (Glu), glycerophosphocholine (GPC), myo-inositol (Ins), n-acetyl-aspartate (NAA), glycerophosphocholine + phosphocholine (GPC+PCh), n-acetyl-aspartate + n-acetyl-aspartyl-glutamate (NAA+NAAG), creatine + phosphocreatine (Cr+PCr) and glutamate + glutamine (Glu+Gln) in the ACC. No significant differences between groups were found.

3.1.4 Demographics with ^1H – MRS metabolite concentrations

3.1.4.1 Age

Both groups' age were positively correlated with absolute ^1H -MRS metabolites in the ACC: (a) GPC (Spearman $R = 0.52$, $p < 0.01$), (b) GPC+PCh (Spearman $R = 0.52$, $p < 0.01$), (c) NAA (Spearman $R = 0.52$, $p < 0.01$), (d) NAA+NAAG (Spearman $R = 0.42$, $p < 0.05$), Figure 3.1.9.

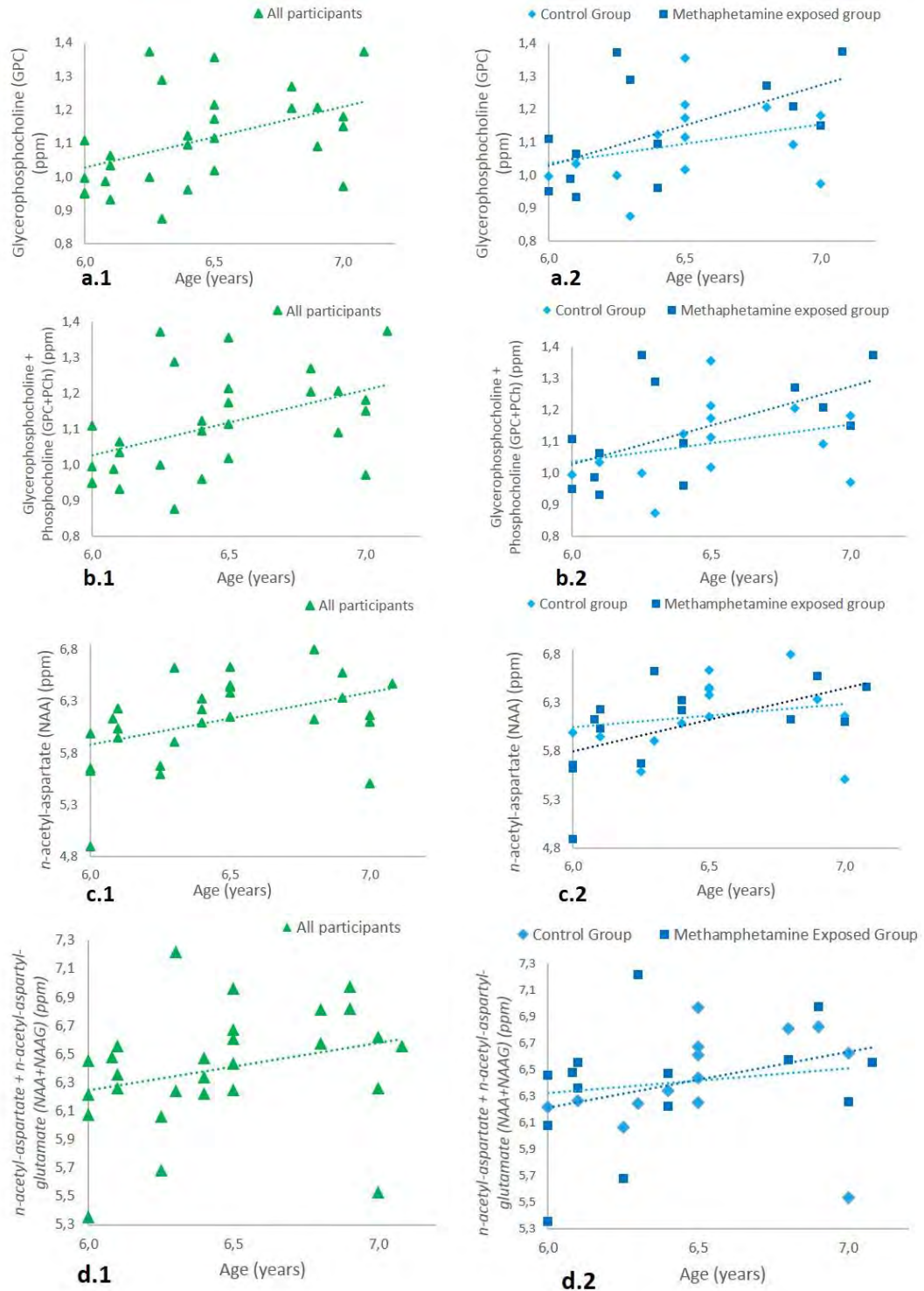


Figure 3.1.9 (a.1) Absolute magnetic resonance spectroscopy metabolite concentration – glycerophosphocholine (GPC) – in the ACC positively correlated with age (Spearman $R = 0.52$, $p < 0.005$) at time

point 1. (a.2) Additionally, the trend lines of the control and methamphetamine exposed groups are presented. (b.1) Absolute magnetic resonance spectroscopy metabolite concentration – glycerophosphocholine + phosphocholine (GPC+PCh) – in the ACC positively correlated with age (Spearman $R = 0.52$, $p < 0.01$) at time point 1. (b.2) Additionally, the trend lines of the control and methamphetamine exposed groups are presented. (c.1) Absolute magnetic resonance spectroscopy metabolite concentration – *n*-acetyl-aspartate (NAA) – in the ACC positively correlated with age (Spearman $R = 0.52$, $p < 0.01$) at time point 1. (c.2) Additionally, the trend lines of the control and methamphetamine exposed groups are presented. (d.1) Absolute magnetic resonance spectroscopy metabolite concentration – *n*-acetyl-aspartate + *n*-acetyl-aspartyl-glutamate (NAA+NAAG) – in the ACC positively correlated with age (Spearman $R = 0.42$, $p < 0.05$) at time point 1. (d.2) Additionally, the trend lines of the control and methamphetamine exposed groups are presented.

3.1.5 Weight with ^1H -MRS metabolites

Both groups' weight, at time point 1, were significantly correlated with absolute choline ^1H -MRS metabolites in the ACC: (a) GPC (Spearman $R = 0.54$, $p < 0.01$), and (b) GPC+PCh (Spearman $R = 0.54$, $p < 0.01$), Figure 3.1.10.

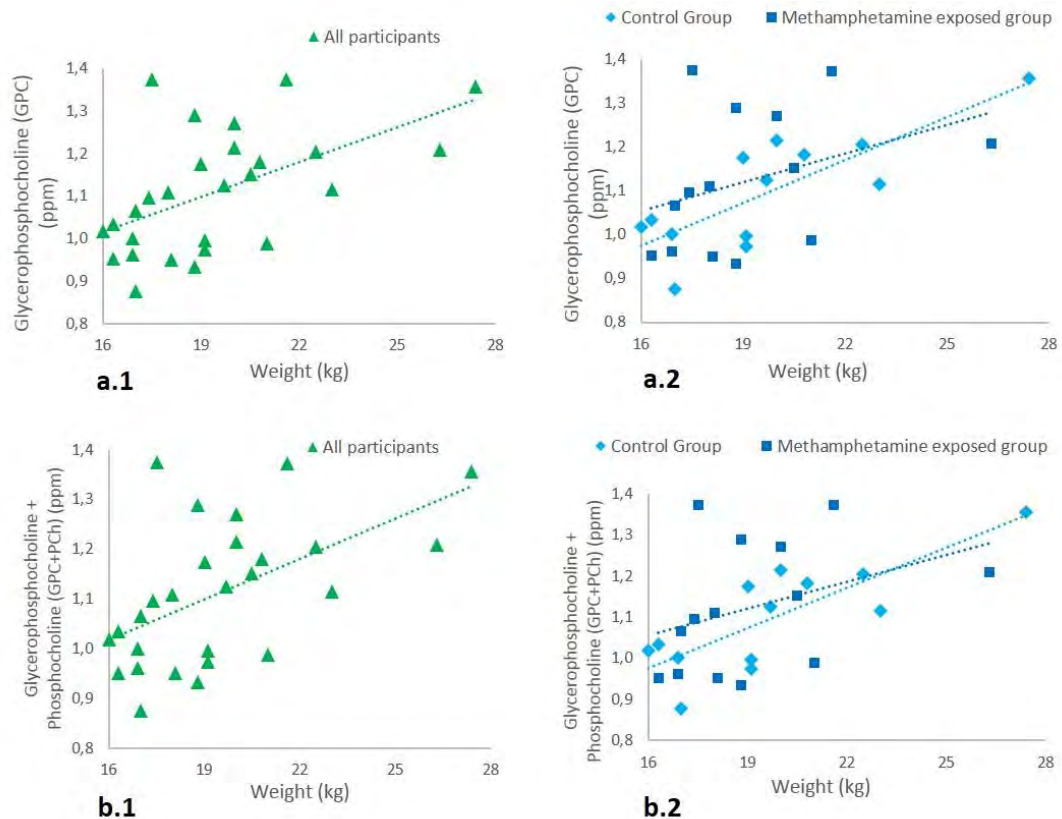


Figure 3.1.10 (a.1) Absolute magnetic resonance spectroscopy metabolite concentration – glycerophosphocholine (GPC) – in the ACC positively correlated with weight (Spearman $R = 0.54$, $p < 0.01$) at time point 1. (a.2) Additionally, the trend lines of the control and methamphetamine exposed groups are presented. (b.1) Absolute magnetic resonance spectroscopy metabolite concentration – glycerophosphocholine + phosphocholine (GPC+PCh) – in the ACC positively correlated with weight (Spearman $R = 0.54$, $p < 0.01$) at time point 1. (b.2) Additionally, the trend lines of the control and methamphetamine exposed groups are presented.

3.1.6 Neurocognitive tasks with ¹H – MRS metabolite concentrations

No significant relationships between neurocognitive task results and ¹H-MRS metabolite concentrations were observed at time point 1 (Appendix III).

Experiment 3.2

3.2.1 Demographic and MA drug use by mother during pregnancy

Demographic and drug use during pregnancy information is reported in Table 3.2.1. No significant demographic and non-MA drug variable differences were found at time point 2.

Table 3.2.1 Demographics and drug use

	Healthy Controls		Methamphetamine exposed in utero	
	n = 11		n = 13	
	8 females / 3 males		5 females / 8 males	
	Mean	Stdev	Mean	Stdev
Age in years at time point 2	8.1	0.4	8.1	0.6
Weight in kilograms at time point 2	23.1	2.5	22.2	3.4
Height in metres at time point 2	1.3	0.1	1.2	0.0
Body mass index at time point 2	14.7	1.3	14.9	2.1
<i>Methamphetamine use</i>				
During first trimester	/		13 of 13*	
During second trimester	/		13 of 13*	
During third trimester	/		13 of 13*	
<i>Nicotine use</i>				
During first trimester	11 of 11		11 of 13	
During second trimester	11 of 11		11 of 13	
During third trimester	11 of 11		11 of 13	
<i>Alcohol use</i>				
During first trimester	1 of 11		4 of 13	
During second trimester	1 of 11		4 of 13	
During third trimester	1 of 11		4 of 13	

*Methamphetamine (MA) use 2-3 times per week_(n = 3); MA use 4-6 times per week in the first trimester_(n = 2); MA use 4-6 times per week in the second and third trimesters_(n = 3); MA use daily during the second and third trimesters_(n = 2); MA use daily during the first trimester_(n = 3); MA use frequency not available_(n = 6).

Nicotine use - Control group: 2-3 times per week_(n = 6); 4-6 times per week_(n = 1); nicotine used daily_(n = 4) throughout the three trimesters; nicotine use frequency not available_(n = 2). MA exposed group: Nicotine use 2-3 times per week_(n = 6); Nicotine use 4-6 times per week_(n = 1); Nicotine use daily_(n = 2), throughout the three trimesters.

Alcohol use - Control group: Once per week or less_(n = 1) throughout the three trimesters. Methamphetamine exposed group: 2-3 times per week_(n = 2); 4-6 times per week_(n = 1); Alcohol use daily_(n = 1) throughout the three trimesters. Alcohol use frequency not available_(n = 2).

3.2.2 Neurocognitive task performance

The following significant neurocognitive task differences were found between the groups: methamphetamine exposed group_(n = 14) scored significantly lower than the control group_(n = 14) on the following subtests of the Kaufman Assessment Battery for Children (KABC-II , Second Edition) : Block Counting Raw Score ($F_{(1, 22)} = 4.47$, $p < 0.05$, Figure 3.2.1), and Block Counting Scaled Score ($F_{(1, 22)} = 5.07$, $p < 0.05$), Figure 3.2.2). No differences were found for Pattern Reasoning Raw Score, Pattern Reasoning Scaled Score, Atlantis Raw Score, Atlantis Scaled Score, Atlantis Delayed Raw Score, Atlantis Delayed Scaled Score or Boston Naming Test – SASF. Refer to Appendix III for further detail.

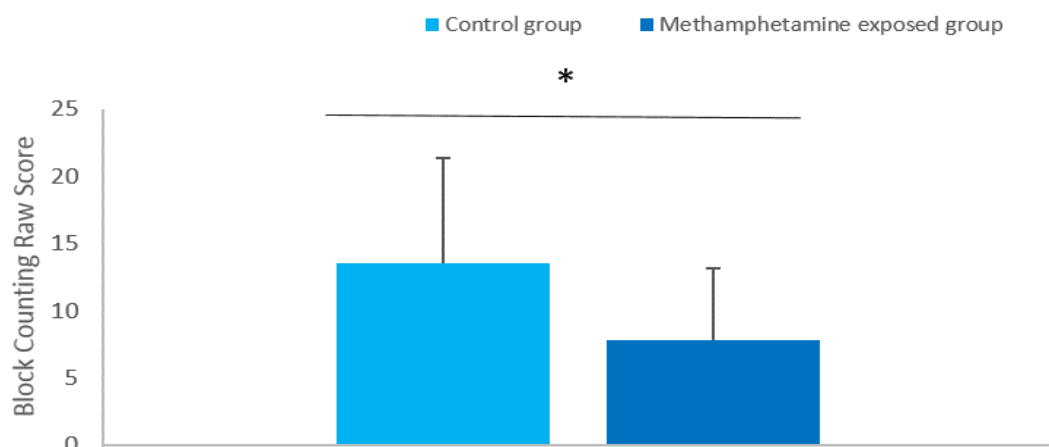


*Figure 3.2.1 Block Counting Raw Score Mean between groups. The *methamphetamine exposed group_(n=13) performed significantly lower than the control group_(n=11), $p < 0.05$, data are presented as mean $\pm$ stdev.*

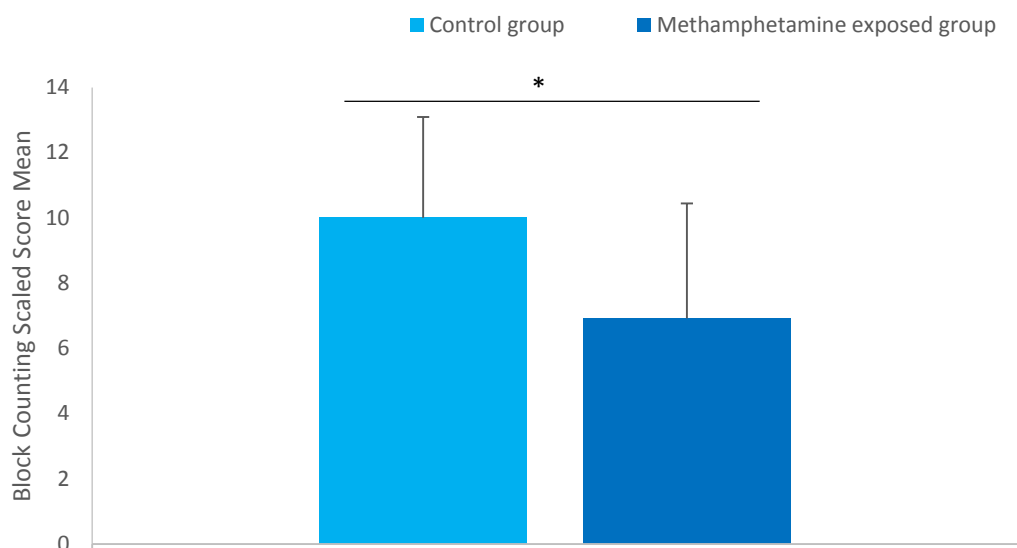


Figure 3.2.2 Block Counting Scaled Score Mean between groups. The *methamphetamine exposed group_(n=13) performed significantly lower than the control group_(n=11). $p < 0.05$, data are presented as mean $\pm$ stdev.

3.2.3 ^1H – MRS metabolite concentrations

No significant group differences were found between the two groups with respect to absolute ACC metabolite concentrations (Figure 3.2.3).

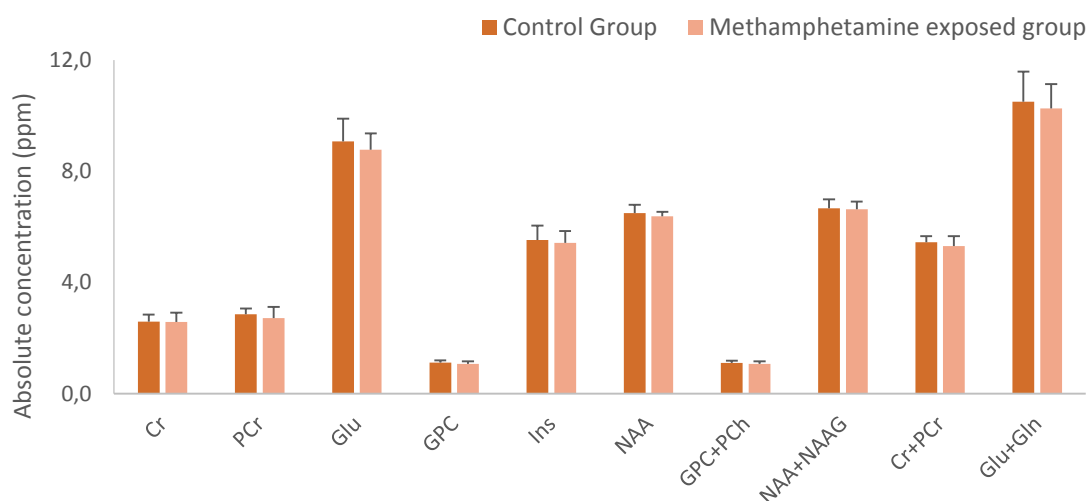


Figure 3.2.3 Absolute ^1H -magnetic resonance spectroscopy metabolite concentrations – creatine (Cr), phosphocreatine (PCr), glutamate (Glu), glycerophosphocholine (GPC), myo-inositol (Ins), n-acetyl-aspartate (NAA), glycerophosphocholine + phosphocholine (GPC+PCh), n-acetyl-aspartate + n-acetyl-aspartyl-glutamate (NAA+NAAG), creatine + phosphocreatine (Cr+PCr) and glutamate + glutamine (Glu+Gln) in the ACC. No significant differences between groups were found, data are presented as mean $\pm$ stdev.

3.2.4 Demographics with ^1H – MRS metabolite concentrations

3.2.4.1 Body mass index (BMI)

Both groups' BMI were positively correlated with Ins in the ACC, Figure 3.2.4.

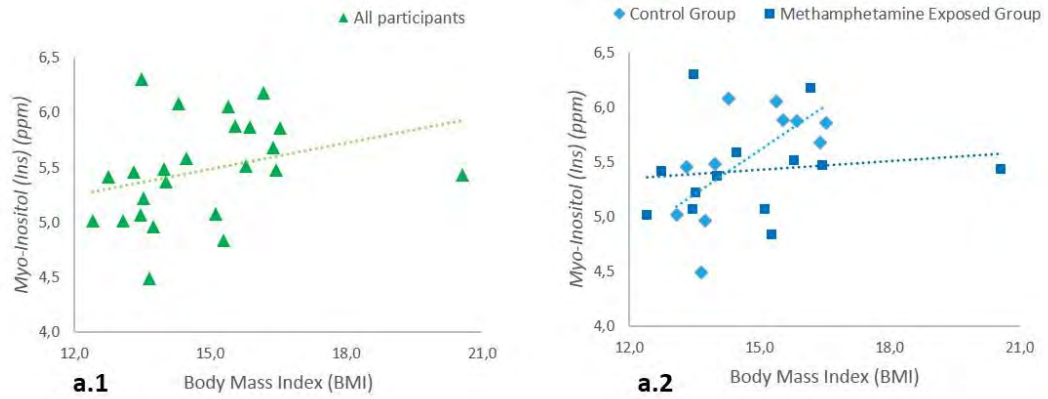


Figure 3.2.4 (a) Absolute magnetic resonance spectroscopy metabolite concentration – myo-inositol (ins) – in the ACC positively correlated with body mass index (Spearman $R = 0.46$, $p < 0.05$) at time point 2. (b) Additionally, the trend lines of the control and methamphetamine exposed groups are presented.

3.2.5 Neurocognitive task performance with ^1H – MRS metabolite concentrations

Significant relationships were found between the groups with respect to absolute metabolite concentrations and the neurocognitive tasks: (a) Atlantis scaled score with NAA+NAAG (Spearman $R = 0.47$, $p < 0.05$), (b) Atlantis Delayed scaled score with GPC (Spearman $R = -0.55$, $p < 0.05$), (c) Atlantis Delayed scaled score with GPC+PCh (Spearman $R = -0.50$, $p < 0.05$), (d) Boston Naming Test – SASF with NAA (Spearman $R = 0.46$, $p < 0.05$), (e) BNT-SA-SF with NAA+NAAG (Spearman $R = 0.41$, $p < 0.05$), Figure 3.2.5.

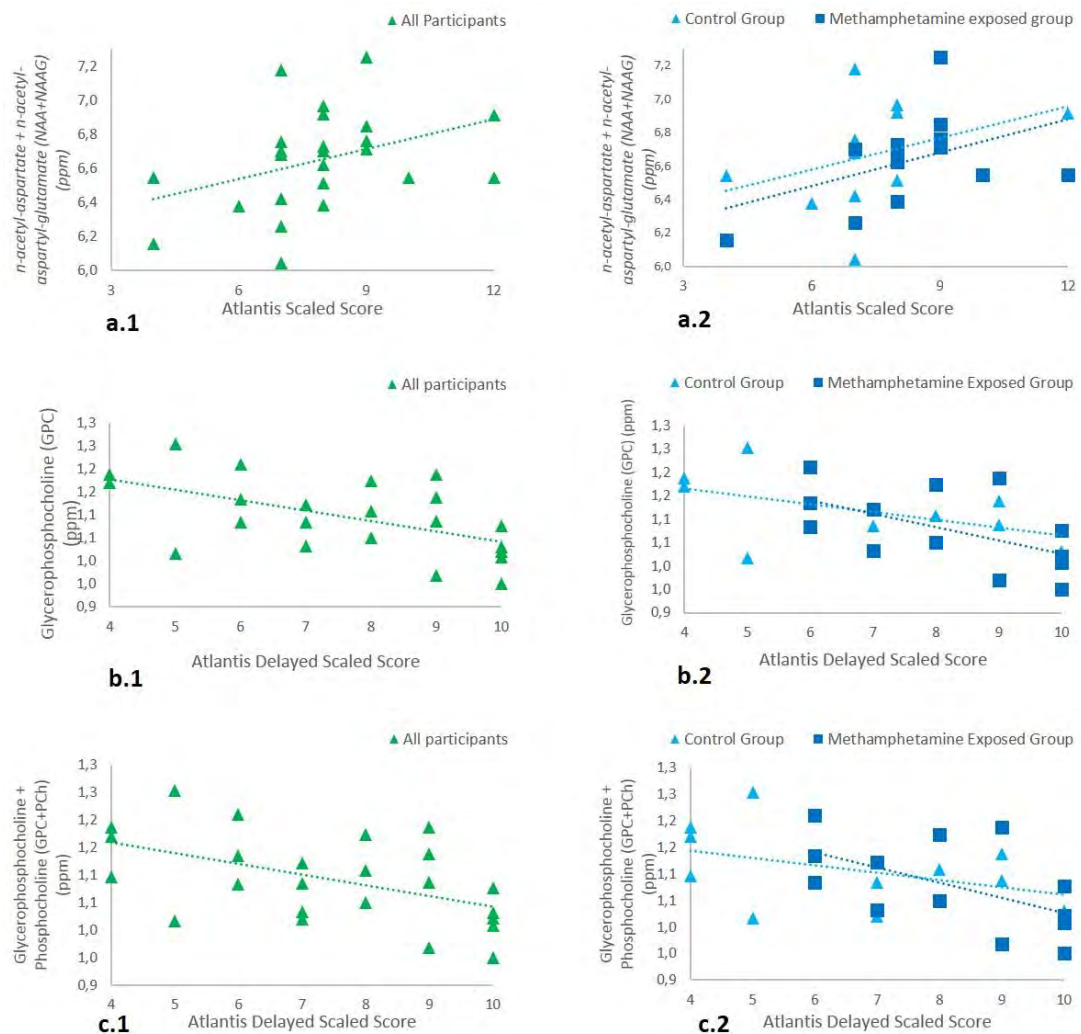


Figure 3.2.5 (a.1) N-acetyl-aspartate + n-acetyl-aspartyl-glutamate (NAA+NAAG) correlated positively with Atlantis scaled score (Spearman $R = 0.47$, $p < 0.05$). (a.2) Additionally, the trend lines of the control and methamphetamine exposed groups are presented. (b.1) Glycerophosphocholine (GPC) correlated negatively with Atlantis Delayed scaled score (Spearman $R = -0.55$, $p < 0.05$). (b.2) Additionally, the trend lines of the control and methamphetamine exposed groups are presented. (c.1) Glycerophosphocholine + phosphocholine (GPC+PCh) correlated negatively with Atlantis Delayed scaled score (Spearman $R = -0.50$, $p < 0.05$). (c.2) Additionally, the trend lines of the control and methamphetamine exposed groups are presented. (d.1) N-acetyl-aspartate (NAA) correlated positively with Boston Naming Test – SASF total score (Spearman $R = 0.46$, $p < 0.05$). (d.2) Additionally, the trend lines of the control and methamphetamine exposed groups are presented. (e.1) N-acetyl-aspartate + n-acetyl-aspartyl-glutamate (NAA+NAAG) correlated positively with Boston Naming Test – SASF total score (Spearman $R = 0.41$, $p < 0.05$). (e.2) Additionally, the trend lines of the control and methamphetamine exposed groups are presented.

Experiment 3.3

3.3.1 Demographic and MA drug use by mother during pregnancy

Several demographics recorded did change over time, 2 years older: age, weight, height and BMI, as expected (Table 3.3.1).

Table 3.3.1 Demographics and drug use

	Healthy Controls				Methamphetamine exposed <i>in utero</i>			
	n = 7				n = 9			
	5 females / 2 males				5 females / 4 males			
	Scan 1		Scan 2		Scan 1		Scan 2	
	Mean	Stdev	Mean	Stdev	Mean	Stdev	Mean	Stdev
Age in years	6.4	0.3	8.1	0.4	6.5	0.4	8.0	0.5
Weight in kilograms	18.6	2.4	22.6	3.0	19.6	2.9	23.0	3.5
Height in metres	1.1	0.1	1.2	0.1	1.1	0.1	1.2	0.0
BMI at time of scan 1	16.7	2.8	14.5	1.3	17.7	3.9	15.5	2.2
<i>Methamphetamine use</i>								
During first trimester	/				14 of 14*			
During second trimester	/				14 of 14*			
During third trimester	/				14 of 14*			
<i>Nicotine use</i>								
During first trimester	4 of 14				10 of 14			
During second trimester	4 of 14				10 of 14			
During third trimester	4 of 14				10 of 14			
<i>Alcohol use</i>								
During first trimester	1 of 14				2 of 14			
During second trimester	0 of 14				2 of 14			
During third trimester	0 of 14				2 of 14			

*Methamphetamine (MA) use 2-3 times per week_(n = 3); MA use 4-6 times per week_(n = 2); MA use daily_(n = 5); MA use frequency not available_(n = 4). MA use remained the same throughout the three trimesters.

Nicotine use - Control group: 2-3 times per week_(n = 4) throughout the three trimesters. MA exposed group: Never use nicotine_(n = 2); Nicotine use 2-3 times per week_(n = 6); Nicotine use 4-6 times per week_(n = 1); Nicotine use daily_(n = 2) throughout the three trimesters.

3.3.2 Neurocognitive task performance

Several significant differences were found with increasing age, 2 years age increase, on the KABC-II and the BNT-SA-SF – total score: (1) Pattern Reasoning raw score significantly differed over time ($F_{(1,14)} = 31.86, p < 0.001$) (Figure 3.3.1), age increased Pattern Reasoning raw scores ($p < 0.001$), Pattern Reasoning raw score further significantly differed by time when main diagnosis was considered ($F_{(1,14)} = 17.68, p < 0.001$), specifically methamphetamine exposed children at time point 1 had significantly lower scores than the control group and age of both groups ($p < 0.05$) (Figure 3.3.2). (2) Atlantis raw score ($F_{(1, 14)} = 11.89, p < 0.05$). Post-hoc analyses showed that the methamphetamine exposed group scored lower than the control group at time point 1, and higher than the control group at time point 2. Both groups scored higher at time point 2 ($p < 0.05$) (Figure 3.3.3) (3) Boston Naming Test – total score ($F_{(1, 14)} = 5.54, p < 0.05$). On closer inspection, post-hoc analysis showed that the methamphetamine exposed group scored lower than the control group at time point 1, and higher than the control group at time point 2. Both groups scored higher at time point 2 ($p < 0.05$) (Figure 3.3.4).

Over time, and with consideration to main diagnosis, the following significant results were observed: Pattern Reasoning raw score ($F_{(1, 14)} = 5.54, p < 0.05$). Specifically, the methamphetamine exposed group, at time point 1, scored lower than the control group at time point 1 ($p < 0.05$) and at time point 2 ($p < 0.05$). The methamphetamine exposed group did, however, score higher at time point 2 when compared to time point 1 ($p < 0.001$) (Figure 3.3.1). (2) Pattern Reasoning scaled score ($F_{(1, 14)} = 12.78, p < 0.05$). Post-hoc analysis showed that the methamphetamine exposed group scored significantly lower than the control group, at time point 1 ($p < 0.05$) (Figure 3.3.2). (3) Atlantis Delayed raw score ($F_{(1, 14)} = 5.31, p < 0.05$). The control group scored significantly lower at time point 2 when compared to time point 1. The post-hoc analysis did not yield a significant result (Figure 3.3.3) (4) Atlantis Delayed scaled score ($F_{(1, 14)} = 7.13, p < 0.05$). Through post-hoc analysis, it was found that the control group scored significantly lower at time point 2 when compared to time point 1 (Figure 3.3.4). Refer to Appendix III for further information.

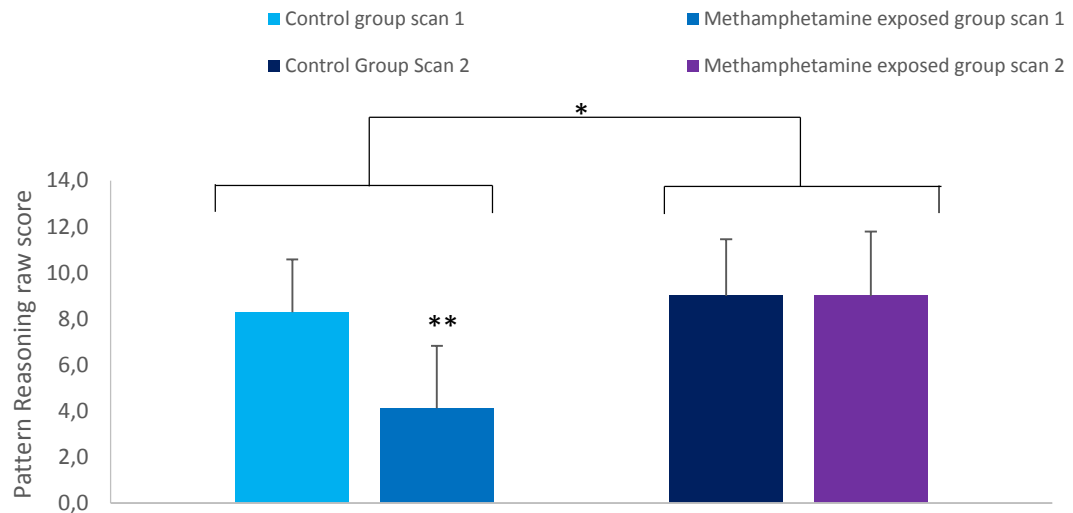


Figure 3.3.1 Pattern Reasoning raw scores time point 1 and time point 2 for both groups. *Scores increased with age ($p < 0.001$) and **children exposed to methamphetamine in utero's score at time point 1 was lower than time point 2 and was found to be lower than controls at time point 1 and time point 2 ($p < 0.001$). Data are presented as mean $\pm$ stdev.

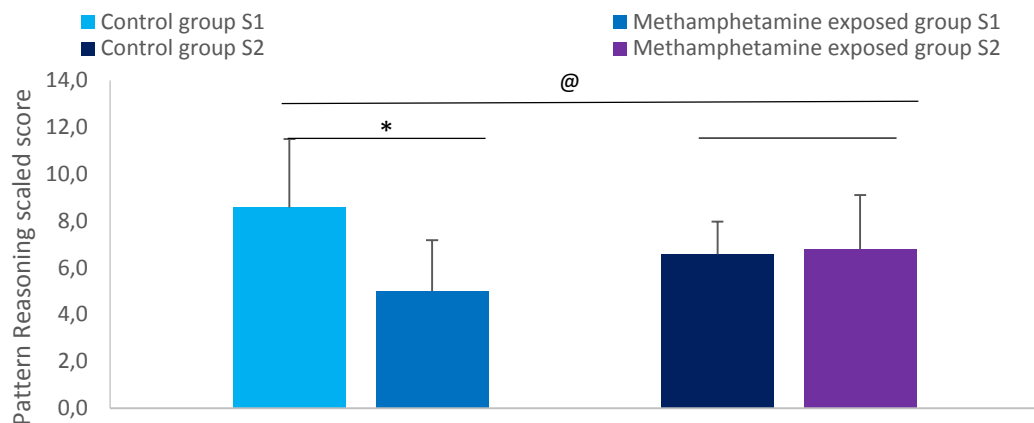


Figure 3.3.2 Pattern Reasoning scaled score difference, @over time and with diagnosis, was found: *control group time point 1 and methamphetamine exposed group time point 1, $p < 0.05$. Data are presented as mean $\pm$ stdev.

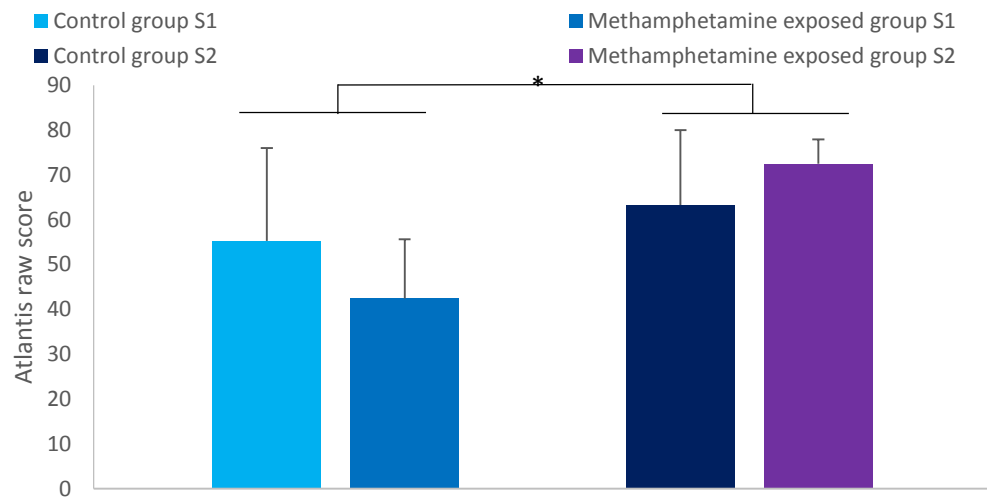


Figure 3.3.3 Atlantis raw score difference *over time. At time point 1, the methamphetamine exposed group scored lower than the control group, and higher than the control group at the time of time point 2. Both groups scored higher at the time of time point 2. $p < 0.05$, Data are presented as mean $\pm$ stdev.

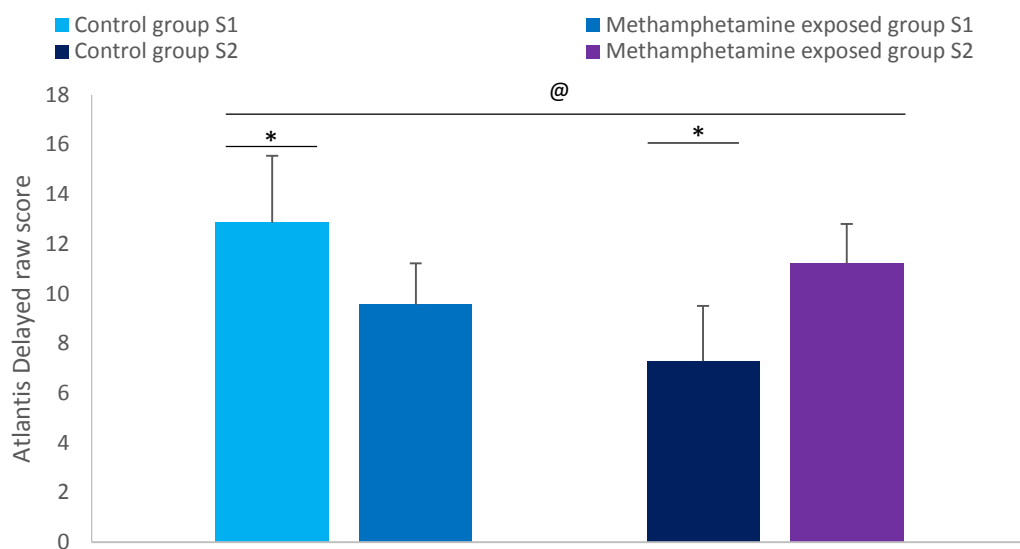


Figure 3.3.4 Atlantis Delayed raw score differences, @over time and with diagnosis, were found: *control group time point 1 and time point 2, $p < 0.05$. Data are presented as mean $\pm$ stdev.

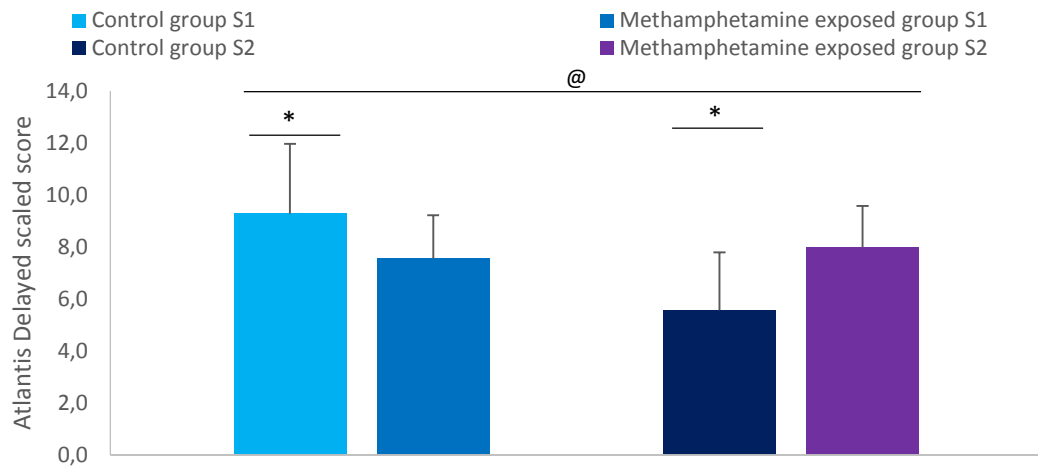


Figure 3.3.5 Atlantis Delayed scaled score differences, @over time and with diagnosis, were found: *control group time point 1 and time point 2, $p < 0.05$. Data are presented as mean $\pm$ stdev.

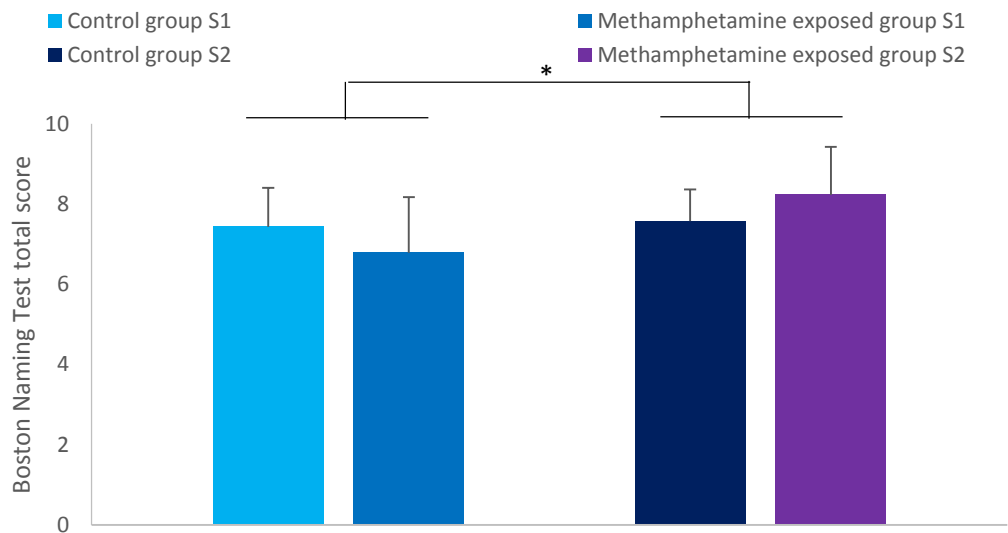


Figure 3.3.6 Boston Naming Test total score *over time. The methamphetamine exposed group scored lower than the control group at the time of time point 1, and higher than the control group at the time of time point 2. Both groups scored higher at the time of time point 2, $p < 0.05$. Data are presented as mean $\pm$ stdev.

3.3.3 ^1H – MRS metabolite concentrations

^1H -MRS metabolite concentration differences with age and diagnosis

Over time, and with consideration to main diagnosis, the following significant absolute choline metabolite concentration differences were found: (1) GPC ($F_{(1, 12)} = 15.32$, $p < 0.01$), post-hoc analysis did not yield further results. (2) GPC+PCh ($F_{(1, 14)} = 10.90$, $p < 0.05$), where children exposed to methamphetamine in utero at time point 1 showed decreased GPC+PCh compared with the control children at time point 1 ($p < 0.05$). NAA increased with age ($F_{(1, 14)} = 16.59$, $p < 0.001$), no other metabolite differences were found (Figure 3.3.7).

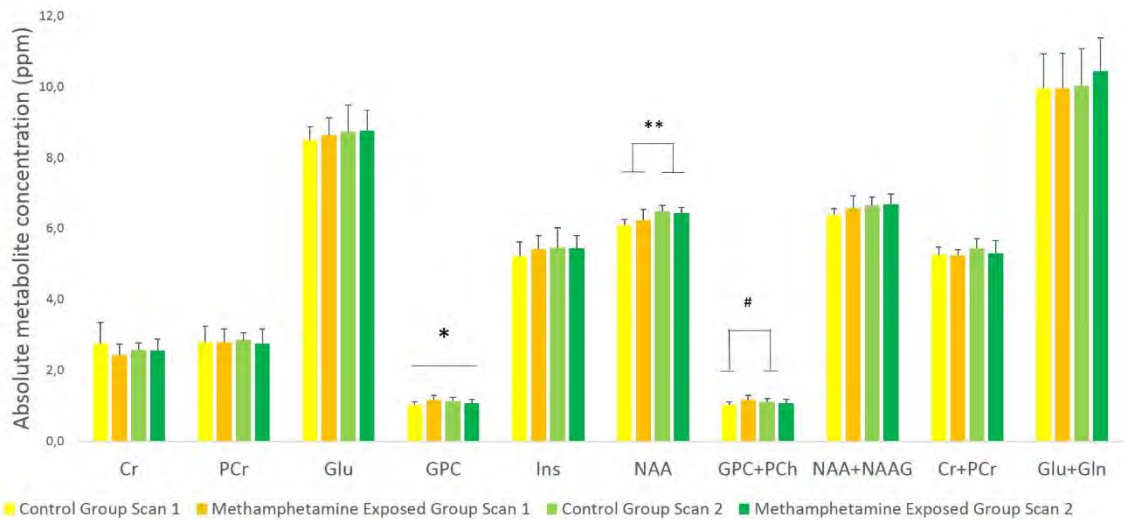


Figure 3.3.7 Absolute ^1H -magnetic resonance spectroscopy metabolite concentration differences, were found for *glycerophosphocholine (GPC) ($p < 0.01$), **n-acetyl-aspartate (NAA) increased in both groups over time, $p < 0.01$ and #glycerophosphocholine + phosphocholine (GPC+PCh) changed over time with diagnosis ($p < 0.05$) were found in the methamphetamine exposed group when compared to the control group. Data are presented as mean $\pm$ stdev.

Discussion

The main findings of this study are: (1) The MA exposed group showed delays in simultaneous and visual processing, abstract reasoning, associative memory, short-term memory and working memory when compared to controls, at time point 1. (2) Significant relationships were observed between neurocognitive results and neurometabolites, suggestive of improvement in selective attention, working memory, controlled information processing, short-term memory and verbal memory in MA exposed children. (3) Over time, decreased GPC and GPC+PCh and increased NAA was observed in MA exposed children, compared to controls, which supports evidence of recovery or a latent neuronal maturation of the brain.

Time point 1 – age 6 years old

No significant demographic or neurometabolite differences were observed between the two groups at the age of 6 years. However, for the neurocognitive assessment, MA exposed group performed significantly poorer than the control group on Pattern Reasoning, Atlantis, Atlantis Delayed and the BNT-SA-SF, indicating deficits in simultaneous and visual processing, abstract reasoning, associative memory, short-term memory and working memory in MA exposed children. These observed deficits could be attributed to a delay in maturation or damage related to MA exposure.

Demographic data showed significant relationships with neurometabolites in the ACC. Age in both groups were positively correlated with GPC, GPC+PCh, NAA and NAA+NAAG concentrations. Additionally, weight in both groups positively correlated with GPC and GPC+PCh. In normal postconceptional ageing, an increase in NAA is associated with a decrease in total visible choline – including GPC and PCh (Blüml et al., 1999). The increase in GPC and GPC+PCh indicates increased membrane turnover and could indicate either increased structural integrity and signalling of cell membranes (Blüml et al., 2012) or demyelination / neuronal degeneration (Kato et al., 1998). NAA and NAA+NAAG have been shown to increase between 3 months and 2 years of age, remain unchanged between the ages of 2 and 5, where after an increase is observed which plateau's in adolescence (Blüml et al., 2012). The increase could indicate a delay in maturation and that synaptic pruning is still being effected (Costa et al., 2002; Pouwels et al., 1999) and could affect the communication system between neurons and glial cells (Baslow, 2000).

Time point 2 – age 8 years old

No significant demographic or neurometabolite differences were observed between the two groups at 8 years of age. For the cognitive tasks performed the MA exposed group performed significantly poorer on Block Counting, indicating a continued delay in simultaneous and visual processing associated with prenatal MA exposure. Both groups' BMI correlated positively with Ins concentration in the ACC. Ins has been reported, in neuro-typical development, to decrease from birth to reach a plateau around the age of 5 years of age. There is limited information available which could explain the observed increase in Ins, in relation to increased BMI. However, possible explanations

for the observed increase in Ins could be the result of increased membrane turnover or damage to myelin sheath structures (Haris et al., 2011) or a central nervous system response to neural injury (Liu et al., 2000). Significant relationships, in both groups, were observed between neurocognitive results and neurometabolites of the ACC, specifically the Atlantis and BNT-SA-SF. The Atlantis, which measures the ability to acquire new information through associative memory, scores positively correlated with NAA+NAAG, whereas NAA+NAAG is an important osmolyte (Baslow, 2000) and is important for the modulation of neurotransmitter release (Moffett et al., 2007). The relationship between Atlantis scores and NAA+NAAG concentration could indicate an improvement in selective attention, working memory and controlled information processing in the ACC (Carter et al., 1998). The Atlantis Delayed score correlated negatively with GPC and GPC+PCh concentrations. Atlantis Delayed measures short-term memory through the ability to retrieve newly encoded information after a filled delay, and GPC and GPC+PCh play an important role in synthesis and degradation of cellular membranes. Blüml et al. (2012) reports choline metabolites to reach a plateau around 5 years of age. Therefore, this relationship could again indicate healthy maturation and, additionally, improvement in memory-related functions of the ACC (Carter et al., 1998). BNT-SA-SF correlated positively with NAA and NAA+NAAG. BNT-SA-SF measures confrontation naming ability related to verbal memory, and NAA and NAA+NAAG concentration are associated with neuronal integrity and viability. Therefore, this relationship could be indicative of an improvement in verbal memory – a function in part regulated by the ACC (Carter et al., 1998).

Differences between the two time points

Over time, the MA exposed group showed decreased GPC and GPC+PCh and increased NAA concentrations when compared to controls. In neuro-typical metabolic brain maturation, choline metabolite concentrations have been reported to decrease after birth and reach a low plateau at approximately 5 years of age, whereas NAA has been shown to increase between the age of 5-12 years (Blüml et al., 2012). GPC and GPC+PCh are choline-containing metabolites and are an essential nutrient involved in arousal, cognition, learning, memory and motor function (Brandon, 2004). Increased NAA is associated with increased neuronal integrity and viability. NAA is also a catalyst in the production of neuronal membranes and myelin (Gujar et al., 2005). Decreased GPC and

GPC+PCh together with increased NAA supports evidence of recovery or improvement in neuronal maturation of the brain.

Several significant differences on neurocognitive assessment results were observed with increasing age: The MA exposed group obtained significantly lower scores on Pattern Reasoning than the control group at both time points, and could suggest delays or difficulties with abstract reasoning in MA exposed children. On the Atlantis subtest, the MA exposed group scored lower than the control group at time point 1 but higher than the control group at time point 2. This score increase at time point 2 could be indicative of recovery in short-term memory processes in MA exposed children. A similar result was seen on the BNT-SA-SF where the MA exposed group scored lower than the control group at time point 1 and higher at time point 2, again a possible indication of recovery in confrontation naming ability/verbal memory. This is an interesting finding that requires further exploration. The control group scored significantly lower at time point 2, when compared to time point 1, on Atlantis Delayed – a measure of recalling newly encoded information after a filled delay / short-term memory.

Several *limitations* should be noted. There are no South African norms for the KABC-II. It remains, however, one of the less culturally loaded tests of cognitive functioning that is available (Greenop et al., 2012). Studies of substance abuse are almost invariably confounded by issues of selective disclosure and polysubstance use (Roos et al., 2014). This study relied on information obtained through self-report by parent(s) / caregiver(s), specifically pertaining to medical history, and drug use related information – including the use of other substances and could potentially introduce a recall-bias. The impact of nicotine exposure requires further investigation and should be included in future studies. The study sample was small, which could be associated with statistical instability and poor reproducibility (Peterson, 2003). Finally, multiple tissue types – both abundant and less abundant - are found within a voxel, which could complicate interpretation of metabolite levels, the analyses of the present study did not address the impact of partial voluming, however a representative image of the voxel positioning is provided (Figure 3.2).

Future research

It is unknown whether the neurocognitive deficits observed in the current study will persist into adolescence, or whether a reorganisation, through neuroplastic change of network activity within the ACC (Murphy & Corbett, 2009), will be able to overcome these deficits. The possible recovery of short-term memory and verbal memory in MA exposed children warrants further investigation and stresses the importance of investigating the long-term impact of prenatal MA exposure on neurocognition. The development of a questionnaire to more accurately report drug dosage in drug addicts, specifically during pregnancy, requires exploration. The results from this study warrants further longitudinal research studies, including larger cohorts, to determine whether full recovery of the neurometabolites and improvement in neurocognitive functioning is possible.

In *conclusion*, the results from this study indicate that prenatal MA-exposure results in poorer neurocognition and significant metabolite changes occur at the measured time points. However, this is the first ¹H-MRS study to show evidence of recovery or improvement in neuronal maturation of the brain, as well as improvement in short-term and verbal memory in children exposed to MA in utero.

Chapter 4

Summary and Conclusion

MA has been associated with drug-induced neuronal damage (Barr et al., 2006) and neuronal loss (Ende et al., 1997) in the ACC and frontal gray matter of adult abusers. Whether the brain can completely recover from the damage and neurotoxicity caused by MA abuse is still unknown. The present study investigated the impact of acute and short-term abstinence on neurometabolism as well as the impact over time of acute to short-term abstinence. Limited ^1H -MRS research has been done on children prenatally exposed to MA and has been limited to children before school-going age. Previous studies report aberrant neuronal and glial development, abnormal energy metabolism and higher neuronal density in the brain (Chang et al., 2009; Lester & Lagasse, 2010; Smith et al., 2001). The present study investigated the relationship between prenatal MA exposure and neurometabolism and neurocognitive development of school-going aged children to determine whether regeneration and normalisation, over time, of neurometabolites is possible.

To refresh, the impact of acute and short-term abstinence are: (1) Decreased relative NAA+NAAG, reflecting compromised neuronal and axonal integrity (Gujar et al., 2005) in the left DLPFC of the MA dependent group, when compared with the control group. This change was not observed in the right DLPFC or ACC bilaterally and suggest that the left DLPFC is susceptible to acute abstinence else was already damaged during MA use. (2) Decreased NAA+NAAG, reflecting neurodegeneration (Barr et al., 2006; Ende et al., 1997), and increased Ins, indicative of neuroinflammation (Clark et al., 2013; Sekine et al., 2008), was observed only in the right ACC of the MA dependent group, compared to controls. This finding is, in part, consistent with previous studies investigating short-term and long-term abstinence from MA. (3) Decreased NAA and NAA+NAAG were related to increased Ins in the right ACC in acute to short-term MA abstinence, indicating that neuroinflammation and subsequent decreased integrity and viability of neurons (Clark et al., 2013) persist from acute into short-term abstinence. (4) NAA+NAAG bilaterally in the DLPFC and NAA in the left DLPFC were significantly correlated with age started using MA, length of MA use and duration of abstinence. NAA+NAAG in the right ACC significantly correlated with length of MA use and duration of abstinence. The observed decrease of NAA and NAA+NAAG shows drug-induced neuronal

damage (Barr et al., 2006) or neuronal loss (Ende et al., 1997). Ins in the right ACC was significantly correlated with duration of abstinence, supporting neuroinflammation related to abstinence from MA (Berman et al., 2008; Clark et al., 2013).

Previous studies investigating the impact of abstinence from MA were predominantly done on short-term (3-9 weeks) (Nordahl et al., 2005; Sailasuta et al., 2010) and long-term (20 weeks up to 3 years) (Nordahl et al., 2005; Sailasuta et al., 2010). No previous ¹H-MRS studies investigating the impact of acute (<2 weeks) to short-term (<6 weeks) abstinence in MA abusers have been found, and was addressed in the present study.

Considering the relationship between prenatal exposure and neurometabolism and neurocognition of school-going children the main findings of this study are: (1) The MA exposed group showed delays in simultaneous and visual processing, abstract reasoning, associative memory, short-term memory and working memory when compared to controls. This is consistent with GPC and GPC+PCh that was significantly correlated with age and suggests enhanced neuronal membrane turnover (Nordahl et al., 2002; Pfefferbaum et al., 1999) in MA exposed children, which suggests a delay in neuronal maturation. (2) Significant relationships were observed between neurocognitive results and neurometabolites - increased NAA and NAA+NAAG and decreased GPC and GPC+PCh, suggestive of improvement in selective attention, working memory, controlled information processing, short-term memory and verbal memory in MA exposed children (Baslow, 2000; Moffett et al., 2007). (3) Over time, decreased GPC and GPC+PCh and increased NAA was observed in MA exposed children, compared to controls, which supports evidence of recovery or improvement in neuronal maturation of the brain (Blüml et al., 2012; Brandon, 2004).

Previous ¹H-MRS studies on prenatally MA exposed children have primarily been done on children before school-going age. The present study investigated the impact of prenatal MA exposure on neurometabolism and neurocognitive development of children of school-going age (6-8 years of age).

The results from this study accentuate the importance of understanding the impact of MA on both the developing brain and the mature brain. In abstinent adults,

neurodegeneration was shown to worsen over time and was related to neuroinflammation (Clark et al., 2013; Ernst et al., 2000; Sekine et al., 2008) that persisted into short-term abstinence which suggests progressive neuronal damage during acute to short-term abstinence. In prenatally exposed children, however, evidence of improvement in short-term and verbal memory was seen through significant relationships with NAA, NAA+NAAG, GPC and GPC+PCh in scores on Atlantis – a measurement of the ability to acquire new information through associative memory, Atlantis Delayed – a measure of short-term memory through the ability to retrieve newly encoded information after a filled delay, and BNT-SA-SF – a measure of confrontation naming ability related to verbal memory. Over time, decreased GPC and GPC+PCh and increased NAA and NAA+NAAG was seen in MA exposed children, as is seen in neurotypical metabolic brain maturation (Blüml et al., 2012), and indicates recovery/improvement in neuronal maturation.

It is unknown whether the neuroinflammation that was observed in abstinent adult participants will increase during longer abstinence, decrease over time, what the timeline is in which the inflammation will subside, as well as whether it is related to further loss in neuronal integrity. Previous studies (Berman et al., 2008; Ernst et al., 2000; Nordahl et al., 2003; Scott et al., 2007) report an increase in Ins indicative of neuroinflammation (Clark et al., 2013; Sekine et al., 2008), which has been shown to persist in early abstinence (± 5 weeks) from MA (Berman et al., 2008; Clark et al., 2013), and to proportionately decline with continuous drug abstinence (± 2 years) (Clark et al., 2013; Sekine et al., 2008). The neuroinflammation and the accompanying decreased integrity and viability of neurons (Clark et al., 2013) observed in abstinent adult participants, additionally supports the development of a pharmacological intervention development to reduce the damaging impact on brain metabolism during withdrawal as prolonged exposure to neuroinflammation results in neuronal death (Chang et al., 2007). This stresses the importance of investigating the long-term impact of abstinence from MA. Understanding the cognitive and behavioural deficits caused by damage to neurometabolism during withdrawal.

It is necessary to re-emphasize core limitations that need to be addressed in future studies. In both the adult and child studies, larger participation groups are required to provide for statistical stability and improved reproducibility (Peterson, 2003). Since both

investigations relied on self-reported medical history and drug-related information, a potential bias may be introduced. Development of a questionnaire to accurately report medical history and, specifically drug-related information is of great importance in future MA addiction studies. Second, there are no South African norms for the KABC-II., which formed part of the neurocognitive assessment battery used in the prenatally exposed child investigation. It remains, however, one of the less culturally loaded tests of cognitive functioning that is available (Greenop et al., 2012). The development of a neurocognitive test based on South African populations with South African norms will be beneficial for future studies.

Conclusion

With the significant and continuously growing prevalence of MA abuse that has been seen, specifically in the Western Cape where this study was conducted, the results of this study provides a valuable contribution to existing literature. This is, to our knowledge, the first ¹H-MRS study investigating the impact of acute abstinence from MA in adults as well as the impact of prenatal MA exposure on children of school-going age. The results from this study – in both adults and children – lead to the identification of a need for additional and future research that could benefit the all MA users substantially through the development of treatment / assessment methods. The results from this study could also be utilised in educational programs for schools and rehabilitation centres to educate the community on the dangers of MA – with the aim of lowering the incidence of MA addiction and related complications affecting individuals, families, and communities. This study is the first to show the development of neuroinflammation from acute to short-term abstinence from MA in adults, as well as evidence of recovery/improvement in neuronal maturation in the brain, accompanied by improvement in short-term and verbal memory in prenatally MA exposed children.

Bibliography

- Abar, B., Lagasse, L. L., Newman, E., Smith, L. M., Huestis, M., Neal, C., ... Lester, B. M. (2013). Examining the Relationships Between Prenatal Methamphetamine Exposure, Early Adversity, and Child Neurobehavioral Disinhibition. *Psychology of Addictive Behaviors*, 27(3), 1-21.
- Abar, B., LaGasse, L. L., Wouldes, T., Derauf, C., Newman, E., Shah, R., ... Lester, B. M. (2014). Cross-national Comparison of Prenatal Methamphetamine Exposure on Infant and Early Child Physical Growth : A Natural Experiment. *Prevention Science*, 15, 767-776.
- Achtnichts, L., Gonen, O., Rigotti, D. J., Babb, J. S., Naegelin, Y., Penner, I.-K., ... Gass, A. (2013). Global N-acetylaspartate concentration in benign and non-benign multiple sclerosis patients of long disease duration. *European Journal of Radiology*, 82(12), e848-52.
- Albers, D. S., & Sonsalla, P. K. (1995). Methamphetamine-induced hyperthermia and dopaminergic neurotoxicity in mice: pharmacological profile of protective and nonprotective agents. *The Journal of Pharmacology and Experimental Therapeutics*, 275(3), 1104-1114.
- Babb, S. M., Ke, Y., Lange, N., Kaufman, M. J., Renshaw, P. F., & Cohen, B. M. (2004). Oral choline increases choline metabolites in human brain. *Psychiatry Research: Neuroimaging*, 130(1), 1-9.
- Balleine, B. W., Delgado, M. R., & Hikosaka, O. (2007). The Role of the Dorsal Striatum in Reward and Decision-Making. *Journal of Neuroscience*, 27(31), 8161-8165.
- Barr, A. M., Panenka, W. J., MacEwan, G. W., Thornton, A. E., Lang, D. J., Honer, W. G., & Lecomte, T. (2006). The need for speed: An update on methamphetamine addiction. *Journal of Psychiatry and Neuroscience*, 31(5), 301-313.
- Bartus, R. T., Dean, R. L., Beer, B., & Lippa, a S. (1982). The cholinergic hypothesis of geriatric memory dysfunction. *Science (New York, N.Y.)*, 217(4558), 408-414.
- Baslow, M. H. (2000). Functions of N-acetyl-L-aspartate and N-acetyl-L-aspartylglutamate in the vertebrate brain: Role in glial cell-specific signaling. *Journal of Neurochemistry*, 75(2), 453-459.
- Baslow, M. H. (2003). N-acetylaspartate in the vertebrate brain: Metabolism and function. *Neurochemical Research*, 28(6), 941-953.
- Behnke, M., Smith, V. C., & On, C. (2015). Prenatal Substance Abuse : Short- and Long-term Effects on the Exposed Fetus. *Pediatrics*, 131(3), 1009-1024.

- Berman, S., Neill, J. O., Fears, S., Bartzokis, G., & London, E. D. (2008). Abuse of Amphetamines and Structural Abnormalities in Brain. *Annals of the New York Academy of Sciences*, 1141, 195–220.
- Blüml, S., Moreno-Torres, a, & Ross, B. D. (2001). [1-13C]glucose MRS in chronic hepatic encephalopathy in man. *Magnetic Resonance in Medicine : Official Journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine*, 45(6), 981–93.
- Blüml, S., Seymour, K. J., & Ross, B. D. (1999). Developmental changes in choline- and ethanolamine-containing compounds measured with proton-decoupled 31P MRS in in vivo human brain. *Magnetic Resonance in Medicine*, 42(4), 643–654.
- Bluml, S., Wisnowski, J. L., Nelson, M. D., Paquette, L., Gilles, F. H., Kinney, H. C., & Panigrahy, a. (2012). Metabolic Maturation of the Human Brain From Birth Through Adolescence: Insights Fom In Vivo Magnetic Resonance Spectroscopy. *Cereb. Cortex*, (December), 2944–2955.
- Bracken, B. K., Jensen, J. E., Prescott, A. P., Cohen, B. M., Renshaw, P. F., & Ongur, D. (2011). Brain metabolite concentrations across cortical regions in healthy adults. *Brain Research*, 1369, 89–94.
- Bramness, J. G., Gundersen, Ø. H., Guterstam, J., Rognli, E. B., Konstenius, M., Løberg, E., ... Franck, J. (2012). Amphetamine-induced psychosis - a separate diagnostic entity or primary psychosis triggered in the vulnerable ? *BMC Psychiatry*, 12(221), 1–7.
- Brandon, E. P. (2004). Choline Transporter 1 Maintains Cholinergic Function in Choline Acetyltransferase Haploinsufficiency. *Journal of Neuroscience*, 24(24), 5459–5466.
- Brecht, M. L., & Herbeck, D. M. (2014). Pregnancy and fetal loss reported by methamphetamine-using women. *Substance Abuse: Research and Treatment*, 8, 25–33.
- Brecht, M.-L., O'Brien, A., von Mayrhauser, C., & Anglin, M. D. (2004). Methamphetamine use behaviors and gender differences. *Addictive Behaviors*, 29(1), 89–106.
- Brooks, S., Burch, K., Simon, M., Nilsson, E., Schioth, H., Cocolas, E., ... Stein, D. J. (n.d.). Working memory training improves impulse-control in methamphetamine dependence. *In Review*.
- Bustamante, D., You, Z.-B., Castel, M.-N., Johansson, S., Goiny, M., Terenius, L., ... Herrera-Marschitz, M. (2002). Effect of single and repeated methamphetamine treatment on neurotransmitter release in substantia nigra and neostriatum of the

- rat. *Journal of Neurochemistry*, 83(3), 645–54.
- Cadet, J. L., & Krasnova, I. N. (2009). Molecular Bases of Methamphetamine- Induced Neurodegeneration. *International Review of Neurobiology*, 88(January), 101–119.
- Carter, C. S., Braver, T. S., Barch, D. M., Botvinick, M. M., Noll, D., & Cohen, J. D. (1998). Anterior cingulate cortex, error detection, and the online monitoring of performance. *Science*, 280(5364), 747–9.
- Carter, C. S., Macdonald, a M., Botvinick, M., Ross, L. L., Stenger, V. a, Noll, D., & Cohen, J. D. (2000). Parsing executive processes: strategic vs. evaluative functions of the anterior cingulate cortex. *Proceedings of the National Academy of Sciences of the United States of America*, 97(4), 1944–1948.
- Castner, S. A., & Goldman-Rakic, P. S. (1999). Long-Lasting Psychotomimetic Consequences of Repeated Low-Dose Amphetamine Exposure in Rhesus Monkeys. *Neuropsychopharmacology*, 20(1), 10–28.
- Cavanna, A. E. (2006). The precuneus: a review of its functional anatomy and behavioural correlates. *Brain*, 129(3), 564–583.
- Chang, L., Alicata, D., Ernst, T., & Volkow, N. (2007). Structural and metabolic brain changes in the striatum associated with methamphetamine abuse. *Addiction*, 102(SUPPL. 1), 16–32.
- Chang, L., Cloak, C., Jiang, C. S., Farnham, S., Tokeshi, B., Buchthal, S., ... Ernst, T. (2009). Altered neurometabolites and motor integration in children exposed to methamphetamine in utero. *NeuroImage*, 48(2), 391–397.
- Chang, L., Smith, L. M., LoPresti, C., Yonekura, M. L., Kuo, J., Walot, I., & Ernst, T. (2004). Smaller subcortical volumes and cognitive deficits in children with prenatal methamphetamine exposure. *Psychiatry Research - Neuroimaging*, 132(2), 95–106.
- Clark, K. H., Wiley, C. a., & Bradberry, C. W. (2013). Psychostimulant Abuse and Neuroinflammation: Emerging Evidence of Their Interconnection. *Neurotoxicity Research*, 23(2), 174–188.
- Cloak, C. C., Ernst, T., Fujii, L., Hedemark, B., & Chang, L. (2009). Lower diffusion in white matter of children with prenatal methamphetamine exposure. *Neurology*, 72(24), 2068–2075.
- Clower, D. M., West, R. A., Lynch, J. C., & Strick, P. L. (2001). The inferior parietal lobule is the target of output from the superior colliculus, hippocampus, and cerebellum. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, 21(16), 6283–6291.

- Colby, J. B., Smith, L., Connor, M. J. O., Bookheimer, S. Y., Horn, J. D. Van, & Sowell, E. R. (2012). White matter microstructural alterations in children with prenatal methamphetamine / polydrug exposure. *Psychiatry Research: Neuroimaging*, 204(2-3), 140-148.
- Connell, P. H. (1958). *Amphetamine Psychosis*.
- Costa, M. O. R., Lacerda, M. T. C., Garcia Otaduy, M. C., Cerri, G. G., & da Costa Leite, C. (2002). Proton magnetic resonance spectroscopy: Normal findings in the cerebellar hemisphere in childhood. *Pediatric Radiology*, 32(11), 787-792.
- Cretzmeyer, M., Sarrazin, M. V., Huber, D. L., Block, R. I., & Hall, J. A. (2003). Treatment of methamphetamine abuse: research findings and clinical directions. *Journal of Substance Abuse Treatment*, 24(3), 267-277.
- Cruickshank, C. C., & Dyer, K. R. (2009). A review of the clinical pharmacology of methamphetamine. *Addiction*, 104(7), 1085-1099.
- Cubillo, A., Halari, R., Ecker, C., Giampietro, V., Taylor, E., & Rubia, K. (2010). Reduced activation and inter-regional functional connectivity of fronto-striatal networks in adults with childhood Attention-Deficit Hyperactivity Disorder (ADHD) and persisting symptoms during tasks of motor inhibition and cognitive switching. *J Psychiatr Res*, 44(10), 629-639.
- Dada, Siphokazi, B., Harker, N., Williams, Y., Erasmus, J., Parry, C., Bhana, A., ... Elizabeth, P. (2015). *SOUTH AFRICAN COMMUNITY EPIDEMIOLOGY NETWORK ON DRUG USE (SACENDU)*.
- Daikhin, Y., & Yudkoff, M. (2000). Compartmentation of brain glutamate metabolism in neurons and glia. *The Journal of Nutrition*, 130(4S Suppl), 1026S-31S.
- Davidson, C., Gow, A. J., Lee, T. H., & Ellinwood, E. H. (2001). Methamphetamine neurotoxicity : necrotic and apoptotic mechanisms and relevance to human abuse and treatment. *Brain Research Reviews*, 36, 1-22.
- De Deyn, P. P., & Macdonald, R. L. (1990). Guanidino compounds that are increased in cerebrospinal fluid and brain of uremic patients inhibit GABA and glycine responses on mouse neurons in cell culture. *Ann.Neurol.*, 28(5), 627-633.
- Deng, X., Huang, Z., Li, X., Li, Y., Wang, Y., Wu, D., ... Yang, X. (2012). Long-term follow-up of patients treated for psychotic symptoms that persist after stopping illicit drug use. *Shanghai Archives of Psychiatry*, 24(5), 271-278.
- Derauf, C., Lester, B. M., Neyzi, N., Kekatpure, M., Gracia, L., Davis, J., ... Kosofsky, B. (2012). Subcortical and Cortical Structural Central Nervous System Changes and

- Attention Processing Deficits in Preschool-Aged Children with Prenatal Methamphetamine and Tobacco Exposure. *Developmental Neuroscience*, 34(4), 327–341.
- Diaz, S. D., Smith, L. M., Lagasse, L. L., Derauf, C., Newman, E., Shah, R., ... Lester, B. M. (2014). Effects of prenatal methamphetamine exposure on behavioral and cognitive findings at 7.5 years of age. *Journal of Pediatrics*, 164(6), 1333–1338.
- Drevets, W. C., Gautier, C., Price, J. C., Kupfer, D. J., Kinahan, P. E., Grace, a. a., ... Mathis, C. a. (2001). Amphetamine-induced dopamine release in human ventral striatum correlates with euphoria. *Biological Psychiatry*, 49(2), 81–96.
- Ende, G. R., Laxer, K. D., Knowlton, R. C., Matson, G. B., Schuff, N., Fein, G., & Weiner, M. W. (1997). Temporal lobe epilepsy: bilateral hippocampal metabolite changes revealed at proton MR spectroscopic imaging. *Radiology*, 202(3), 809–817.
- Ernst, T., Chang, L., Leonido-Yee, M., & Speck, O. (2000). Evidence for long-term neurotoxicity associated with methamphetamine abuse: A ¹H MRS study. *Neurology*, 54(6), 1344–1349.
- Eylers, V. V., Maudsley, A. A., Bronzlik, P., Dellani, P. R., Lanfermann, H., & Ding, X.-Q. (2015). Detection of Normal Aging Effects on Human Brain Metabolite Concentrations and Microstructure with Whole-Brain MR Spectroscopic Imaging and Quantitative MR Imaging. *AJNR. American Journal of Neuroradiology*, November, ajnr.A4557–.
- Fallon, J. H., & Moore, R. Y. (1978). Catecholamine innervation of the basal forebrain. IV. Topography of the dopamine projection to the basal forebrain and neostriatum. *The Journal of Comparative Neurology*, 180(3), 545–580.
- Farrell, M., & Marsden, J. (2002). Methamphetamine : drug use and psychoses becomes a major public health issue in the Asia Pacific region. *Addiction*, 97, 771–772.
- Featherstone, R. E., Kapur, S., & Fletcher, P. J. (2007). The amphetamine-induced sensitized state as a model of schizophrenia. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, 31, 1556–1571.
- Forrest, A. D., Coto, C. A., & Siegel, S. J. (2014). Animal models of psychosis: current state and future directions. *Curr. Behav. Neurosci. Rep*, 1, 100–116.
- Fowler, J. S., Volkow, N. D., Logan, J., Alexoff, D., Telang, F., Wang, G., ... Apelskog, K. (2008). Fast uptake and long-lasting binding of methamphetamine in the human brain: comparison with cocaine. *NeuroImage*, 43(4), 756–763.
- Golub, M., Costa, L., Crofton, K., Frank, D., Fried, P., Gladen, B., ... Vore, M. (2005). NTP-

- CERHR Expert Panel Report on the Reproductive and Developmental Toxicity Of Amphetamine and Methamphetamine. *Birth Defects Research. Part B*, 74, 471–584.
- Greenop, K., Fry, J., & de Sousa, D. (2012). The Kaufman Assessment Battery in South Africa. In S. L. & K. Cockcroft (Ed.), *Psychological assessment in South Africa: research and applications* (pp. 86–103). South Africa: Little White Bakkie.
- Gujar, S. K., Maheshwari, S., Björkman-Burtscher, I., & Sundgren, P. C. (2005). Magnetic resonance spectroscopy. *Journal of NeuroOphthalmology*, 25(3), 217–226.
- Haber, S. N., & Knutson, B. (2010). The Reward Circuit: Linking Primate Anatomy and Human Imaging. *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology*, 35(1), 4–26.
- Hampton, D. W., Rhodes, K. E., Zhao, C., Franklin, R. J. M., & Fawcett, J. W. (2004). THE RESPONSES OF OLIGODENDROCYTE PRECURSOR CELLS , ASTROCYTES AND MICROGLIA TO A CORTICAL STAB INJURY , IN THE BRAIN. *Neuroscience*, 127(4), 813–820.
- Haris, M., Cai, K., Singh, A., Hariharan, H., & Reddy, R. (2011). In vivo Mapping of brain myo-inositol. *NeuroImage*, 54(3), 2079–2085.
- Hatashita, S., Hoff, J. T., & Salamat, S. M. (1988). Ischemic brain edema and the osmotic gradient between blood and brain. *Journal of Cerebral Blood Flow and Metabolism: Official Journal of the International Society of Cerebral Blood Flow and Metabolism*, 8(4), 552–9.
- Hautman, E. R., Kokenge, A. N., Udobi, K. C., Williams, M. T., Vorhees, C. V., & Skelton, M. R. (2014). Female mice heterozygous for creatine transporter deficiency show moderate cognitive deficits. *Journal of Inherited Metabolic Disease*, 37(1), 63–68.
- Hellem, T., Shi, X., Latendresse, G., & Renshaw, P. F. (2015). The Utility of Magnetic Resonance Spectroscopy for Understanding Substance Use Disorders: A Systematic Review of the Literature. *Journal of the American Psychiatric Nurses Association*, 21(4), 244–275.
- Hess, A. T., Dylan Tisdall, M., Andronesi, O. C., Meintjes, E. M., & Van Der Kouwe, A. J. W. (2011). Real-time motion and B0 corrected single voxel spectroscopy using volumetric navigators. *Magnetic Resonance in Medicine*, 66(2), 314–323.
- Howells, F. M., Uhlmann, A., Temmingh, H., Sinclair, H., Meintjes, E., Wilson, D., & Stein, D. J. (2014). 1H-magnetic resonance spectroscopy (1H-MRS) in methamphetamine dependence and methamphetamine induced psychosis. *Schizophrenia Research*, 153, 122–128.

- Hsieh, J. H., Stein, D. J., & Howells, F. M. (2014). The neurobiology of methamphetamine induced psychosis. *Frontiers in Human Neuroscience*, 8(July), 537.
- Huang, R., Sochocka, E., & Hertz, L. (1997). Cell Culture Studies of the Role of Elevated Extracellular Glutamate and K⁺ in Neuronal Cell Death During and After Anoxia / Ischemia. *Neuroscience and Biobehavioural Reviews*, 21(2), 129–134.
- Huang, Y. N., Wu, C. H., Lin, T. C., & Wang, J. Y. (2009). Methamphetamine induces heme oxygenase-1 expression in cortical neurons and glia to prevent its toxicity. *Toxicology and Applied Pharmacology*, 240(3), 315–326.
- Hurtado, O., Lizasoain, I., & Moro, M. Á. (2011). Neuroprotection and recovery: recent data at the bench on citicoline. *Stroke; a Journal of Cerebral Circulation*, 42(1 Suppl), S33–5.
- Jacobs, E., Fujii, D., Schiffman, J., & Bello, I. (2008). An Exploratory Analysis of Neurocognition in Methamphetamine- induced Psychotic Disorder and Paranoid Schizophrenia. *Cognitive and Behavioral Neurology*, 21(2), 98–103.
- Jan, R. K., Kydd, R. R., & Russell, B. R. (2012). Functional and Structural Changes Associated with Methamphetamine Abuse. *Brain Sciences*, 2, 434–482.
- Janowsky, D. S., & Risch, C. (1979). Amphetamine psychosis and psychotic symptoms. *Psychopharmacology*, 65(1), 73–77.
- Jernigan, T. L., Gamst, A. C., Archibald, S. L., Fennema-Notestine, C., Mindt, M. R., Marcotte, T. L., ... Grant, I. (2005). Effects of methamphetamine dependence and HIV infection on cerebral morphology. *American Journal of Psychiatry*, 162(8), 1461–1472.
- Joncquel-Chevalier Curt, M., Voicu, P.-M., Fontaine, M., Dessein, A.-F., Porchet, N., Mention-Mulliez, K., ... Vamecq, J. (2015). Creatine biosynthesis and transport in health and disease. *Biochimie*, 119, 146–165.
- Jones, H. E., Browne, F. a, Myers, B. J., Carney, T., Ellerson, R. M., Kline, T. L., ... Wechsberg, W. M. (2011). Pregnant and nonpregnant women in Cape Town, South Africa: drug use, sexual behavior, and the need for comprehensive services. *International Journal of Pediatrics*, 1–8.
- Kamei, H., Nagai, T., Nakano, H., Togan, Y., Takayanagi, M., Takahashi, K., ... Yamada, K. (2006). Repeated Methamphetamine Treatment Impaired Recognition Memory through a Failure of Novelty-Induced ERK1/2 Activation in the Prefrontal Cortex of Mice. *Biological Psychiatry*, 59, 75–84.
- Kaplan, Goodglass, & W. (1983). *Boston Naming Test*. Philadelphia: Lea & Febiger.

- Kaplan, Goodglass, & W. (2001). *Boston Naming Test*. Philadelphia: Lippincott, Williams & Wilkins.
- Kato, T., Inubushi, T., & Kato, N. (1998). Magnetic resonance spectroscopy in affective disorders. *Journal of Neuropsychiatry and Clinical Neurosciences*, 10(2), 133–147.
- Kaufman, A. S. (2004). *Kaufman Assessment Battery for Children-II (KABC-II)*. Circle Pines, MN: American Guidance Service.
- Kellogg, S. H., Mchugh, P. F., Bell, K., Schluger, J. H., Schluger, P., Ste, K., ... Kreek, M. J. (2003). The Kreek-McHugh-Schluger-Kellogg scale: a new , rapid method for quantifying substance abuse and its possible applications. *Drug and Alcohol Dependence*, 69(2), 137–150.
- Kiblawi, Z. N., Smith, L. M., Diaz, S. D., LaGasse, L. L., Derauf, C., Newman, E., ... Lester, B. (2014). Prenatal methamphetamine exposure and neonatal and infant neurobehavioral outcome: results from the IDEAL study. *Substance Abuse*, 35(1), 68–73.
- Kim, S. J., Lyoo, I. K., Hwang, J., Chung, A., Hoon Sung, Y., Kim, J., ... Renshaw, P. F. (2006). Prefrontal grey-matter changes in short-term and long-term abstinent methamphetamine abusers. *The International Journal of Neuropsychopharmacology*, 9(2), 221–228.
- Kirlic, N., Newman, E., Lagasse, L. L., Derauf, C., Shah, R., Smith, L. M., ... Lester, B. M. (2013). Cortisol reactivity in two-year-old children prenatally exposed to methamphetamine. *Journal of Studies on Alcohol and Drugs*, 74(3), 447–51.
- Koob, G. F., & Bloom, F. E. (1988). Cellular and molecular mechanisms of drug dependence. *Science (New York, N.Y.)*, 242(4879), 715–723.
- Kwiatkowski, M. A. (2015). *Effects of Methamphetamine on Prenatally Exposed Children in Cape Town: Cognition and intrinsic functional brain connectivity*.
- Kwiatkowski, M. A., Roos, A., Stein, D. J., Thomas, K. G. F., & Donald, K. (2014). Effects of prenatal methamphetamine exposure: A review of cognitive and neuroimaging studies. *Metabolic Brain Disease*, 29(2), 245–254.
- LaGasse, L. L., Woudes, T., Newman, E., Smith, L. M., Shah, R. Z., Derauf, C., ... Lester, B. M. (2011). Prenatal methamphetamine exposure and neonatal neurobehavioral outcome in the USA and New Zealand. *Neurotoxicology and Teratology*, 33(1), 166–75.
- Lee, C., Lehrmann, E., Hayashi, T., Amable, R., Tsai, S., Chen, J., ... Freed, W. J. (2009). Gene Expression Profiling Reveals Distinct Cocaine-Responsive Genes in Human

- Fetal CNS Cell Types. *Journal of Addiction Medicine*, 3(4), 218–226.
- Lee, J. ., Arcinue, E., & Ross, B. . (1994). Brief report: Organic osmolytes in the brain of an infant with hypernatremia. *New England Journal of Medicine*, 331, 439–499.
- Lester, B. M., & Lagasse, L. L. (2010). Children of Addicted Women. *Journal of Addictive Diseases*, 29(2), 259–276.
- Liu, L., Rudin, M., & Kozlova, E. N. (2000). Glial cell proliferation in the spinal cord after dorsal rhizotomy or sciatic nerve transection in the adult rat. *Experimental Brain Research. Experimentelle Hirnforschung. Expérimentation Cérébrale*, 131(1), 64–73.
- London, E. D., Kohno, M., Morales, A. M., & Ballard, M. E. (2014). Chronic methamphetamine abuse and corticostriatal deficits revealed by neuroimaging. *Brain Research*, 1–12.
- Machiyama, Y. (1992). Chronic Methamphetamine Intoxication Model of Schizophrenia in Animals. *Schizophrenia Bulletin*, 18(1), 107–113.
- Mahoney, James, J. I., Kalechstein, A. D., De La Garza, R. I., & Newton, T. F. (2008). Presence and Persistence of Psychotic Symptoms in Cocaine- versus Methamphetamine-dependent Participants. *American Journal of Addiction*, 17(2), 83–98.
- Mark, K. A., Quinton, M. S., Russek, S. J., & Yamamoto, B. K. (2007). Dynamic changes in vesicular glutamate transporter 1 function and expression related to methamphetamine-induced glutamate release. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, 27(25), 6823–6831.
- Mark, K. A., Soghomonian, J. J., & Yamamoto, B. K. (2004). High-Dose Methamphetamine Acutely Activates the Striatonigral Pathway to Increase Striatal Glutamate and Mediate Long-Term Dopamine Toxicity. *Journal of Neuroscience*, 24(50), 11449–11456.
- Massucci, F. A., DiNuzzo, M., Giove, F., Maraviglia, B., Castillo, I. P., Marinari, E., & De Martino, A. (2013). Energy metabolism and glutamate-glutamine cycle in the brain: a stoichiometric modeling perspective. *BMC Systems Biology*, 7(1), 103.
- Matsuo, K., Nicoletti, M., Nemoto, K., Hatch, J. P., Peluso, M. a M., Nery, F. G., & Soares, J. C. (2009). A voxel-based morphometry study of frontal gray matter correlates of impulsivity. *Human Brain Mapping*, 30(May 2008), 1188–1195.
- McClay, J. L., Adkins, D. E., Vunck, S. a., Batman, A. M., Vann, R. E., Clark, S. L., ... van den Oord, E. J. C. G. (2013). Large-scale neurochemical metabolomics analysis identifies multiple compounds associated with methamphetamine exposure.

Metabolomics, 9(2), 392–402.

- Mcdonnell-dowling, K., & Kelly, J. P. (2015). Sources of variation in the design of preclinical studies assessing the effects of amphetamine-type stimulants in pregnancy and lactation. *Behavioural Brain Research*, 279, 87–99.
- Mcketin, R., Hickey, K., Devlin, K., & Lawrence, K. (2010). The risk of psychotic symptoms associated with recreational methamphetamine use. *Drug and Alcohol Review*, 29(July), 358–363.
- Mcketin, R., McLaren, J., Lubman, D. I., & Hides, L. (2006). The prevalence of psychotic symptoms among methamphetamine users. *Addiction*, 101, 1473–1478.
- Medhus, S., Mordal, J., Holm, B., Mørland, J., & Bramness, J. G. (2013). A comparison of symptoms and drug use between patients with methamphetamine associated psychoses and patients diagnosed with schizophrenia in two acute psychiatric wards. *Psychiatry Research*, 206(1), 17–21.
- Millington, W. R., & Wurtman, R. J. (1982). Choline administration elevates brain phosphorylcholine concentrations. *Journal of Neurochemistry*, 38(6), 1748–52.
- Minagar, A., Shapshak, P., Fujimura, R., Ownby, R., Heyes, M., & Eisdorfer, C. (2002). The role of macrophage/microglia and astrocytes in the pathogenesis of three neurologic disorders: HIV-associated dementia, Alzheimer disease, and multiple sclerosis. *Journal of the Neurological Sciences*, 202(1-2), 13–23.
- Moffett, J. R., Ross, B., Arun, P., Madhavarao, C. N., & Namboodiri, M. A. . (2007). N-acetylaspartate in the CNS: from neurodiagnostics to neurobiology. *Progress in Neurobiology*, 81(2), 89–131.
- Mogenson, G., Jones, D., & Yim, C. (1980). From Motivation to Action - Functional Interface Between the Limbic System and the Motor System. *Progress in Neurobiology*, 14(2-3), 69–97.
- Muly, E. C., Szigeti, K., & Goldman-Rakic, P. S. (1998). D1 receptor in interneurons of macaque prefrontal cortex: distribution and subcellular localization. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, 18(24), 10553–10565.
- Murphy, T. H., & Corbett, D. (2009). Plasticity during stroke recovery: from synapse to behaviour. *Nature Reviews. Neuroscience*, 10(12), 861–872.
- Nagai, T., Takuma, K., Dohniwa, M., Ibi, D., Mizoguchi, H., Kamei, H., ... Yamada, K. (2007). Repeated methamphetamine treatment impairs spatial working memory in rats : reversal by clozapine but not haloperidol. *Psychopharmacology*, 194, 21–32.
- Nakama, H., Chang, L., Fein, G., Shimotsu, R., Jiang, C. S., & Ernst, T. (2011).

- Methamphetamine users show greater than normal age-related cortical gray matter loss. *Addiction*, 106(8), 1474–1483.
- Neale, J. H., Bzdega, T., & Wroblewska, B. (2000). N-Acetylaspartylglutamate: The Most Abundant Peptide Neurotransmitter in the Mammalian Central Nervous System. *Journal of Neurochemistry*, 75(2), 443–452.
- Nicola, S. M. (2007). The nucleus accumbens as part of a basal ganglia action selection circuit. *Psychopharmacology*, 191(3), 521–50.
- Nordahl, T. E., Salo, R., & Leamon, M. (2003). Neuropsychological effects of chronic methamphetamine use on neurotransmitters and cognition: a review. *The Journal of Neuropsychiatry and Clinical Neurosciences*, 15(3), 317–325.
- Nordahl, T. E., Salo, R., Possin, K., Gibson, D. R., Flynn, N., Leamon, M., ... Sullivan, E. V. (2002). Low N-acetyl-aspartate and high choline in the anterior cingulum of recently abstinent methamphetamine-dependent subjects: A preliminary proton MRS study. *Psychiatry Research - Neuroimaging*, 116(1-2), 43–52.
- Nordahl TE, Salo R, Natsuaki Y, Galloway GP, Waters C, Moore CD, Kile S, B. M. (2005). Methamphetamine Users in Sustained Abstinence. *Archives of General Psychiatry*, 62, 444–452.
- Parry, C. D. H., Plüddemann, A., Myers, B., Wechsberg, W. M., & Flisher, a J. (2011). Methamphetamine use and sexual risk behaviour in Cape Town, South Africa: a review of data from 8 studies conducted between 2004 and 2007. *African Journal of Psychiatry*, 14(5), 372–376.
- Paulus, M. P., Hozack, N. E., Zauscher, B. E., Frank, L., Brown, G. G., Braff, D. L., & Schuckit, M. a. (2002). Behavioral and functional neuroimaging evidence for prefrontal dysfunction in methamphetamine-dependent subjects. *Neuropsychopharmacology*, 26(1), 53–63.
- Peterson, B. S. (2003). Conceptual, methodological, and statistical challenges in brain imaging studies of developmentally based psychopathologies. *Development and Psychopathology*, 15, 811–832.
- Petroff, O. A. C. (2002). GABA and Glutamate in the Human Brain. *The Neuroscientist*, 8(6), 562–573.
- Pfefferbaum, A., Adalsteinsson, E., Spielman, D., Sullivan, E. V., & Lim, K. O. (1999). In vivo spectroscopic quantification of the N-acetyl moiety, creatine, and choline from large volumes of brain gray and white matter: Effects of normal aging. *Magnetic Resonance in Medicine*, 284, 276–284.

- Plüddemann, A., Dada, S., Parry, C., Kader, R., Parker, J., Temmingh, H., ... Lewis, I. (2013). Monitoring the prevalence of methamphetamine-related presentations at psychiatric hospitals in Cape Town, South Africa. *African Journal of Psychiatry*, 16(1), 45–49.
- Plüddemann, A., Myers, B. J., & Parry, C. D. H. (2008). Surge in treatment admissions related to methamphetamine use in Cape Town, South Africa: implications for public health. *Drug and Alcohol Review*, 27(2), 185–189.
- 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. *Pediatric Research*, 46, 474–485.
- Provencher, S. W. (1993). Estimation of metabolite concentrations from localized in vivo proton NMR spectra. *Magnetic Resonance in Medicine*, 30(6), 672–679.
- Rawson, R., Huber, A., Brethen, P., Obert, J., Gulati, V., Shoptaw, S., & Ling, W. (2000). Methamphetamine and cocaine users: differences in characteristics and treatment retention. *Journal of Psychoactive Drugs*, 32(2), 233–238.
- Robertson, N. J., Lewis, R. H., Cowan, F. M., Allsop, J. M., Counsell, S. J., Edwards, a D., & Cox, I. J. (2001). Early increases in brain myo-inositol measured by proton magnetic resonance spectroscopy in term infants with neonatal encephalopathy. *Pediatric Research*, 50(6), 692–700.
- Robinson, T. E., & Becker, J. B. (1986). Enduring Changes in Brain and Behavior Produced by Chronic Amphetamine Administration : A Review and Evaluation of Animal Models of Amphetamine Psychosis. *Brain Research Reviews*, 11, 157–198.
- Roos, A., Jones, G., Howells, F. M., Stein, D. J., & Donald, K. a. (2014). Structural brain changes in prenatal methamphetamine-exposed children. *Metabolic Brain Disease*, 29(2), 341–349.
- Sailasuta, N., Abulseoud, O., Hernandez, M., Haghani, P., & Ross, B. D. (2010). Metabolic abnormalities in abstinent methamphetamine dependent subjects. *Substance Abuse: Research and Treatment*, 4(1), 9–20.
- Salamone, J. D., Correa, M., Farrar, a., & Mingote, S. M. (2007). Effort-related functions of nucleus accumbens dopamine and associated forebrain circuits. *Psychopharmacology*, 191(3), 461–482.
- Salo, R., Buonocore, M. H., Leamon, M., Natsuaki, Y., Waters, C., Moore, C. D., ... Nordahl, T. E. (2011). Extended findings of brain metabolite normalization in MA-

- dependent subjects across sustained abstinence: A proton MRS study. *Drug and Alcohol Dependence*, 113(2-3), 133-138.
- Sato, M., Numachi, Y., & Hanamura, T. (1992). Relapse of Paranoid Psychotic State in Methamphetamine Model of Schizophrenia. *Schizophrenia Bulletin*, 18(1), 115-122.
- Scott, J. C., Woods, S. P., Matt, G. E., Meyer, R. A., Heaton, R. K., Atkinson, J. H., & Grant, I. (2007). Neurocognitive Effects of Methamphetamine: A Critical Review and Meta-analysis. *Neuropsychology Review*, 17(3), 275-297.
- Segal, D. S., & Kuczenski, R. (1997). An Escalating Dose “ Binge ” Model of Amphetamine Psychosis: Behavioral and Neurochemical Characteristics. *The Journal of Neuroscience*, 17(7), 2551-2566.
- Sekine, Y., Minabe, Y., Kawai, M., Suzuki, K., Iyo, M., Isoda, H., ... Ashby, C. R. (2002). Metabolite alterations in basal ganglia associated with methamphetamine-related psychiatric symptoms. A proton MRS study. *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology*, 27(3), 453-61.
- Sekine, Y., Ouchi, Y., Sugihara, G., Takei, N., Yoshikawa, E., Nakamura, K., ... Cadet, J. L. (2008). Methamphetamine causes microglial activation in the brains of human abusers. *The Journal of Neuroscience*, 28(22), 5756-5761.
- Shah, R., Diaz, S. D., Arria, A., LaGasse, L. L., Derauf, C., Newman, E., ... Lester, B. M. (2013). Prenatal Methamphetamine Exposure and Short-Term Maternal and Infant Medical Outcomes. *American Journal of Perinatology*, 29(5), 391-400.
- Silber, B. Y., Croft, R. J., Papafotiou, K., & Stough, C. (2006). The acute effects of d-amphetamine and methamphetamine on attention and psychomotor performance. *Psychopharmacology*, 187(2), 154-169.
- Simon, H., Scatton, B., & Moal, M. L. (1980). Dopaminergic A10 neurones are involved in cognitive functions. *Nature*, 286(5769), 150-151.
- Simons, M., & Trajkovic, K. (2006). Neuron-glia communication in the control of oligodendrocyte function and myelin biogenesis. *Journal of Cell Science*, 119, 4381-4389.
- Slamberová, R., & Charousová, P. (2008). Methamphetamine--a drug of pregnant female drug addicts. *Ceskoslovenska Fysiologie / Ustredni Ustav Biologicky*, 57(1), 15-23.
- Smith, L. M., Chang, L., Yonekura, M. L., Grob, C., Osborn, D., & Ernst, T. (2001). Brain proton magnetic resonance spectroscopy in children exposed to methamphetamine in utero. *Neurology*, 57(2), 255-260.
- Smith, L. M., LaGasse, L. L., Derauf, C., Newman, E., Shah, R., Haning, W., ... Lester, B.

- M. (2011). Motor and cognitive outcomes through three years of age in children exposed to prenatal methamphetamine. *Neurotoxicology and Teratology*, 33(1), 176–184.
- Smith, L., Yonekura, M. L., Wallace, T., Berman, N., Kuo, J., & Berkowitz, C. (2003). Effects of prenatal methamphetamine exposure on fetal growth and drug withdrawal symptoms in infants born at term. *Journal of Developmental and Behavioral Pediatrics : JDBP*, 24(1), 17–23.
- Soeiro-de-Souza, M. G., Henning, A., Machado-Vieira, R., Moreno, R. A., Pastorello, B. F., da Costa Leite, C., ... Otaduy, M. C. G. (2015). Anterior cingulate Glutamate–Glutamine cycle metabolites are altered in euthymic bipolar I disorder. *European Neuropsychopharmacology*, 25(12), 2221–2229.
- Stephans, S. E., & Yamamoto, B. K. (1994). Methamphetamine-induced neurotoxicity: roles for glutamate and dopamine efflux. *Synapse (New York, N.Y.)*, 17(3), 203–9.
- Stephans, S. E., & Yamamoto, B. Y. (1995). Effect of repeated methamphetamine administrations on dopamine and glutamate efflux in rat prefrontal cortex. *Brain Research*, 700(1-2), 99–106.
- Sung, Y. H., Carey, P. D., Stein, D. J., Ferrett, H. L., Spottiswoode, B. S., Renshaw, P. F., & Yurgelun-Todd, D. a. (2013). Decreased frontal N-acetylaspartate levels in adolescents concurrently using both methamphetamine and marijuana. *Behavioural Brain Research*, 246, 154–161.
- Thompson, B. L., Levitt, P., & Stanwood, G. D. (2009). Prenatal exposure to drugs: effects on brain development and implications for policy and education. *Nature Reviews Neuroscience*, 10(4), 303–312.
- Thompson, P. M., Hayashi, K. M., Simon, S. L., Geaga, J. a, Hong, M. S., Sui, Y., ... London, E. D. (2004). Structural abnormalities in the brains of human subjects who use methamphetamine. *The Journal of Neuroscience*, 24(26), 6028–6036.
- UNODC. (2012). *World Drug Report 2012. New Directions for Youth Development* (Vol. 2012).
- van der Kouwe, A. J. W., Benner, T., Salat, D. H., & Fischl, B. (2008). Brain morphometry with multiecho MPRAGE. *NeuroImage*, 40(2), 559–69.
- van Dyk, J., Ramanjam, V., Church, P., Koren, G., & Donald, K. (2014). Maternal methamphetamine use in pregnancy and long-term neurodevelopmental and behavioral deficits in children. *Journal of Population Therapeutics and Clinical Pharmacology*, 21(2), 185–196.

- Volkow, N. D., Wang, G. J., Fowler, J. S., Gatley, S. J., Ding, Y. S., Logan, J., ... Lieberman, J. (1996). Relationship between psychostimulant-induced "high" and dopamine transporter occupancy. *Proceedings of the National Academy of Sciences of the United States of America*, 93(19), 10388–10392.
- Winslow, B. T., Voorhees, K. I., & Pehl, K. a. (2007). Methamphetamine abuse. *American Family Physician*, 76(8), 1169–1174.
- Won, L., Bubula, N., McCoy, H., & Heller, A. (2001). Methamphetamine concentrations in fetal and maternal brain following prenatal exposure. *Neurotoxicology and Teratology*, 23(4), 349–54.
- World Medical Association. World Medical Association Declaration of Helsinki - Ethical principles for medical research involving human subjects. adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the 59th WMA General Assembly, Seoul, October 2008 (2008).
- Wouldes, T. A., LaGasse, L. L., Huestis, M. A., DellaGrotta, S., Dansereau, L. M., & Lester, B. M. (2014). Prenatal methamphetamine exposure and neurodevelopmental outcomes in children from 1 to 3 years. *Neurotoxicology and Teratology*, 42, 77–84.
- Wouldes, T., LaGasse, L., Sheridan, J., & Lester, B. (2004). Maternal methamphetamine use during pregnancy and child outcome: what do we know? *Nzmj*, 117(1206), 1–10.
- Yoon, B.-E., & Lee, C. J. (2014). GABA as a rising gliotransmitter. *Frontiers in Neural Circuits*, 8(December), 141.
- Yuksel, C., Du, F., Ravichandran, C., Goldbach, J. R., Thida, T., Lin, P., ... Cohen, B. M. (2015). Abnormal high-energy phosphate molecule metabolism during regional brain activation in patients with bipolar disorder. *Molecular Psychiatry*, 20(9), 1079–1084.
- Zeisel, S. H., & da Costa, K.-A. (2009). Choline: an essential nutrient for public health. *Nutrition Reviews*, 67(11), 615–23.

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Appendix I

[illegible]

Meth	Mixed-race	25	16	9		1.29	No matrix		Meth only		1.719	2.057	1.252	1.331	1.053	0.254	1.492	1.654	1.473	1.501	1.176	0.309	1.282	1.598	1.259	1.415	0.794	0.257	1.29	1.654	1.26	1.28	0.84	0.204	
Meth	Mixed-race	30	22	8		2.29	Matrix		Yes	Ecstasy, Speed, Kat, Cocaine												1.213	1.442	1.125	1.125	0.919	0.238	1.178	1.381	1.304	1.34	0.95	0.244		
Meth	Mixed-race	23	13	10	3	1.14	No matrix	Yes	Meth only		1.573	1.735	1.131	1.169	1.148	0.265	1.32	1.492	1.228	1.336	0.96	0.296	1.368	1.368	1.398	1.398	1.002	0.231	1.24	1.42	1.327	1.327	0.853	0.218	
Meth	Mixed-race	31	17	14	1	1.29	No matrix	Yes	Yes	Cocaine, Mandrax, Dagga	1.422	1.47	1.254	1.412	1.068	0.327	1.458	1.634	1.274	1.432	1.126	0.321	1.045	1.3	1.049	1.049	0.779	0.234	1.168	1.599	1.18	1.554	0.907	0.237	
Meth	Mixed-race	22	15	7	3	2.29	No matrix	Yes	Meth only		1.526	1.526	1.169	1.196	0.91	0.291	1.456	1.456	1.134	1.134	1.119	0.261	1.249	1.249	1.343	1.343	0.657	0.219	1.144	1.144	1.271	1.271	0.865	0.198	
Meth	Mixed-race	28	19	9	4	1.29	No matrix	Yes	Meth only		1.905	1.93	1.156	1.273	1.314	0.27	1.467	1.661	1.145	1.227	0.742	0.224							1.188	1.188	1.237	1.237	1.137	0.144	
Meth	Mixed-race	43	32	11	0.5	1.71	Matrix	Yes	Meth only		0.921	0.921	1.14	1.14	0.901	0.227	1.314	1.314	1.153	1.17	1.02	0.25	1.38	1.38	1.241	1.241	1.166	0.262	1.123	1.123	1.098	1.123	0.246		
Meth	Mixed-race	22	16	6		1			Meth only		1.306	1.674	1.253	1.253	0.946	0.249	1.551	1.564	1.279	1.279	1.095	0.251	1.371	1.371	1.372	1.372	0.791	0.243	1.472	1.847	1.313	1.313	1.108	0.136	
Meth	Mixed-race	28	19	10		2	No matrix	No	Meth only		1.573	1.573	1.454	1.531	0.976	0.296																			
Meth	Mixed-race	29	10	20	0.5	1	Matrix	Yes	Meth only		1.238	1.238	1.076	1.076	1.231	0.311	1.359	1.445	0.929	0.94	1.094	0.292	1.295	1.295	1.283	1.321	1.106	0.299	1.357	1.357	1.208	1.368	1.018		
Meth	Mixed-race	30	23	7	0.5	2	Matrix	Yes	Meth only		1.187	1.253	1.203	1.393	0.908	0.321	1.371	1.652	1.095	1.385	0.957	0.286	1.695	2.137	1.377	1.377	0.681	0.179	1.316	1.67	0.926	1.113	0.835	0.202	
Meth	Mixed-race	24	14	10	2	2		Yes	Yes	Mandrax	0.965	0.965	1.063	1.063	1.092	0.305	1.049	1.049	1.061	1.191	1.212	0.313	1.536	1.752	1.346	1.492	1.034	0.247	1.274	1.898	1.324	1.637	0.914	0.304	
Meth	Mixed-race	27	16	13		1.57	No matrix	Yes	Meth only								1.388	1.492	1.15	1.369	0.958	0.277							1.332	1.332	1.304	1.435	0.995	0.269	
Meth	Mixed-race	25	16	10		2.85	No matrix	Yes	Yes	Mandrax	0.991	1.092	1.091	1.091	0.806	0.255	1.033	1.201	1.049	1.049	0.806	0.233	1.35	1.736	1.25	1.25	0.996	0.203	0.944	1.05	1.486	1.486	1.18	0.271	
Meth	Mixed-race	21	18	3		2.14	No matrix	Yes	Meth only		1.232	1.24	1.318	1.365	1.28	0.318	1.358	1.646	0.92	0.92	1.221	0.266	1.75	2.028	1.455	1.455	1.126	0.208	1.466	1.466	1.613	1.613	1.141	0.206	
Meth	Mixed-race	31	19	12	0.5	2.28	No matrix	Yes	Yes	Ecstasy	1.386	1.386	1.246	1.516	1.002	0.259	1.332	1.332	1.3	1.544	1.099	0.291	1.436	1.436	1.316	1.316	1.041	0.247			1.173	1.173	1.126	0.213	
Meth	Mixed-race	31	21	12		1.57	Matrix	No	Meth only		1.329	1.517	1.131	1.217	0.964	0.253	1.422	1.422	1.08	1.093	0.964	0.25	1.198	1.198	1.189	1.346	0.924	0.183							
Meth	Mixed-race	24	11	13	1	1.28	No matrix	Yes	Yes	Rocks	1.379	1.525	1.339	1.339	0.93	0.31	1.495	1.686	1.044	1.059	0.987	0.252	1.132	1.447	1.338	1.435	0.886	0.228	1.681	2.2	1.367	1.367	0.887	0.211	
Meth	Mixed-race	33	24	9	1	1.43	No matrix	Yes	Yes	Mandrax	1.336	1.394	1.363	1.577	1.213	0.36	0.97	1.208	1.173	1.195	1.043	0.312	1.181	1.603	1.401	1.435	0.99	0.239	1.269	1.269	1.38	1.38	0.98	0.242	
Meth	Mixed-race	41	32	9		1.43	No matrix	Yes	Meth only		1.301	1.353	1.175	1.175	0.97	0.29	1.188	1.483	1.271	1.385	1.04	0.365	1.281	1.281	1.307	1.307	1.015	0.309	1.357	1.849	1.129	1.149	0.904	0.209	
Meth	Mixed-race	35	14	21	0.125	1	Matrix	Yes	Yes	Dagga, Mandrax	0.835	1.111	1.086	1.158	0.749	0.268							1.003	1.603		1.007	0.736	0.179							
Meth	Black	31	23	8	2	1	No matrix	Yes	Yes	Dagga, Mandrax	1.349	1.385	1.332	1.462	1.027	0.319	1.106	1.293	1.16	1.303	1.033	0.292	1.578	2.052	1.421	1.51	0.84	0.205	1.246	1.246	1.461	1.503	0.81	0.315	
Meth	Mixed-race	23	15	8		1	No matrix	Yes	Meth only		1.611	1.653	0.997	1.129	0.975	0.248	1.594	1.755	0.945	1.013	0.984	0.241	1.769	1.769	1.514	1.514	1.037	0.222	1.569	1.649	1.597	1.597	1.146	0.199	
Meth	Mixed-race	33	23	10	2	0.43	No matrix	Yes	Yes	Dagga, Mandrax	1.507	1.662	1.041	1.17	0.776	0.252	1.464	1.464	1.183	1.243	0.93	0.282	1.469	1.603	1.393	1.393	1.024	0.218	1.088	1.305	1.304	1.462	0.711	0.229	
Meth	Mixed-race	22	13	9	0.5	0.86	Matrix	Yes	Yes	Dagga, Mandrax	1.399	1.932	1.118	1.255	0.919	0.269	1.505	1.955	1.063	1.063	0.816	0.261	1.289	1.357	1.461	1.461	0.893	0.19	1.259	1.239	1.406	1.442	0.73	0.241	
Meth	Mixed-race	23	12	11		1	No matrix	Yes	Yes	Dagga, Mandrax	1.458	1.681	1.115	1.115	0.996	0.259	1.137	1.137	1.031	1.031	0.887	0.261	1.265	1.805	1.175	1.175	0.929	0.271	0.837	0.837	1.13	1.13	1.109	0.24	
Meth	Mixed-race	27	17	11	0.25	2	Matrix	Yes	Yes	Dagga	1.182	1.182	1.149	1.346	1.026	0.275	1.204	1.204	1.099	1.133	1.142	0.296								1.319	1.664	1.11	1.192	0.718	0.22

Left ACC – All groups

Variable	All Groups Descriptive Statistics (Acute abstinence (1).sta)				
	Valid N	Mean	Minimum	Maximum	Std.Dev.
Glu - Scan 1 Left ACC	50	1,339080	0,943000	1,640000	0,181732
Glu+Gln - Scan 1 Left ACC	50	1,494900	1,049000	2,081000	0,254897
NAA - Scan 1 Left ACC	50	1,167840	0,920000	1,473000	0,125561
NAA+NAAG - Scan 1 Left ACC	50	1,242260	0,920000	1,544000	0,161668
Ins - Scan 1 Left ACC	50	1,056160	0,742000	1,340000	0,131414
GPC+PCh - Scan 1 Left ACC	50	0,284660	0,219000	0,379000	0,035512

Right DLPFC – All groups

Variable	All Groups Descriptive Statistics (Acute abstinence (1).sta)				
	Valid N	Mean	Minimum	Maximum	Std.Dev.
Glu - Scan 1 Right DLPFC	46	1,384674	0,990000	1,992000	0,230509
Glu+Gln - Scan 1 Right DLPFC	46	1,577239	0,990000	2,137000	0,312401
NAA - Scan 1 Right DLPFC	45	1,339778	1,049000	1,620000	0,129239
NAA+NAAG - Scan 1 Right DLPFC	46	1,398435	1,007000	1,754000	0,171416
Ins - Scan 1 Right DLPFC	46	0,953413	0,657000	1,186000	0,134832
GPC+PCh - Scan 1 Right DLPFC	46	0,236413	0,158000	0,351000	0,037357

Left DLPFC – All groups

Variable	All Groups Descriptive Statistics (Acute abstinence (1).sta)				
	Valid N	Mean	Minimum	Maximum	Std.Dev.
Glu - Scan 1 Left DLPFC	47	1,278043	0,837000	1,681000	0,195250
Glu+Gln - Scan 1 Left DLPFC	47	1,448787	0,837000	2,200000	0,314742
NAA - Scan 1 Left DLPFC	50	1,336600	0,926000	1,662000	0,162020
NAA+NAAG - Scan 1 Left DLPFC	50	1,409280	1,098000	1,718000	0,166589
Ins - Scan 1 Left DLPFC	50	0,962080	0,711000	1,252000	0,136174
GPC+PCh - Scan 1 Left DLPFC	49	0,235816	0,136000	0,339000	0,045114

Age and drug use variables – Control group

Variable	Group=Control Descriptive Statistics (Acute abstinence (1).sta)				
	Valid N	Mean	Minimum	Maximum	Std.Dev.
Age	22	28,63636	20,00000	53,00000	10,16786
Age started taking MA	22	0,00000	0,00000	0,00000	0,00000
Length of drug taking	22	0,00000	0,00000	0,00000	0,00000
Duration of abstinence Scan 1	22	0,00000	0,00000	0,00000	0,00000

Right ACC – Control group

Variable	Group=Control Descriptive Statistics (Acute abstinence (1).sta)				
	Valid N	Mean	Minimum	Maximum	Std.Dev.
Glu - Scan 1 Right ACC	19	1,281105	0,951000	1,760000	0,184587
Glu+Gln - Scan 1 Right ACC	19	1,434211	0,951000	1,881000	0,253591
NAA - Scan 1 Right ACC	20	1,160200	0,908000	1,367000	0,108246
NAA+NAAAG - Scan 1 Right ACC	20	1,251350	1,019000	1,449000	0,120028
Ins - Scan 1 Right ACC	20	1,004850	0,867000	1,202000	0,097896
GPC+PCh - Scan 1 Right ACC	20	0,273800	0,232000	0,324000	0,021768

Left ACC – Control group

Variable	Group=Control Descriptive Statistics (Acute abstinence (1).sta)				
	Valid N	Mean	Minimum	Maximum	Std.Dev.
Glu - Scan 1 Left ACC	22	1,318091	0,943000	1,630000	0,185521
Glu+Gln - Scan 1 Left ACC	22	1,484682	1,078000	1,952000	0,263169
NAA - Scan 1 Left ACC	22	1,201591	1,032000	1,457000	0,121414
NAA+NAAAG - Scan 1 Left ACC	22	1,288955	1,032000	1,511000	0,150370
Ins - Scan 1 Left ACC	22	1,089136	0,809000	1,340000	0,125834
GPC+PCh - Scan 1 Left ACC	22	0,288318	0,219000	0,355000	0,035376

Right DLPFC – Control group

Variable	Group=Control Descriptive Statistics (Acute abstinence (1).sta)				
	Valid N	Mean	Minimum	Maximum	Std.Dev.
Glu - Scan 1 Right DLPFC	19	1,406737	0,990000	1,992000	0,268036
Glu+Gln - Scan 1 Right DLPFC	19	1,576737	0,990000	2,087000	0,371416
NAA - Scan 1 Right DLPFC	19	1,353368	1,058000	1,620000	0,148752
NAA+NAAAG - Scan 1 Right DLPFC	19	1,455842	1,058000	1,754000	0,197982
Ins - Scan 1 Right DLPFC	19	0,969526	0,775000	1,186000	0,137196
GPC+PCh - Scan 1 Right DLPFC	19	0,245526	0,158000	0,351000	0,041163

Left DLPFC – Control group

Variable	Group=Control Descriptive Statistics (Acute abstinence (1).sta)				
	Valid N	Mean	Minimum	Maximum	Std.Dev.
Glu - Scan 1 Left DLPFC	20	1,280850	0,843000	1,622000	0,219948
Glu+Gln - Scan 1 Left DLPFC	20	1,406800	0,843000	1,865000	0,309021
NAA - Scan 1 Left DLPFC	22	1,394909	1,037000	1,662000	0,155185
NAA+NAAAG - Scan 1 Left DLPFC	22	1,472727	1,163000	1,718000	0,152959
Ins - Scan 1 Left DLPFC	22	0,973045	0,769000	1,252000	0,131635
GPC+PCh - Scan 1 Left DLPFC	22	0,247727	0,180000	0,339000	0,049395

Age and drug use variables – MA group

Variable	Group=Meth Descriptive Statistics (Acute abstinence (1).sta)				
	Valid N	Mean	Minimum	Maximum	Std.Dev.
Age	31	28,09677	21,00000	43,00000	5,325128
Age started taking MA	31	17,93548	10,00000	32,00000	5,297392
Length of drug taking	31	10,41935	3,00000	21,00000	3,676721
Duration of abstinence Scan 1	31	1,50677	0,29000	2,85000	0,612625

Right ACC - MA group

Variable	Group=Meth Descriptive Statistics (Acute abstinence (1).sta)				
	Valid N	Mean	Minimum	Maximum	Std.Dev.
Glu - Scan 1 Right ACC	29	1,359586	0,835000	1,905000	0,238887
Glu+Gln - Scan 1 Right ACC	29	1,494931	0,921000	2,057000	0,302326
NAA - Scan 1 Right ACC	29	1,182379	0,997000	1,454000	0,107058
NAA+NAAAG - Scan 1 Right ACC	29	1,257655	1,063000	1,577000	0,143740
Ins - Scan 1 Right ACC	29	1,005897	0,749000	1,314000	0,137354
GPC+PCh - Scan 1 Right ACC	29	0,282379	0,227000	0,360000	0,033408

Left ACC - MA group

Variable	Group=Meth Descriptive Statistics (Acute abstinence (1).sta)				
	Valid N	Mean	Minimum	Maximum	Std.Dev.
Glu - Scan 1 Left ACC	28	1,355571	0,970000	1,640000	0,180351
Glu+Gln - Scan 1 Left ACC	28	1,502929	1,049000	2,081000	0,252772
NAA - Scan 1 Left ACC	28	1,141321	0,920000	1,473000	0,124454
NAA+NAAAG - Scan 1 Left ACC	28	1,205571	0,920000	1,544000	0,163322
Ins - Scan 1 Left ACC	28	1,030250	0,742000	1,334000	0,132074
GPC+PCh - Scan 1 Left ACC	28	0,281786	0,224000	0,379000	0,035997

Right DLPFC - MA group

Variable	Group=Meth Descriptive Statistics (Acute abstinence (1).sta)				
	Valid N	Mean	Minimum	Maximum	Std.Dev.
Glu - Scan 1 Right DLPFC	27	1,369148	1,003000	1,769000	0,204010
Glu+Gln - Scan 1 Right DLPFC	27	1,577593	1,198000	2,137000	0,270942
NAA - Scan 1 Right DLPFC	26	1,329846	1,049000	1,514000	0,114989
NAA+NAAAG - Scan 1 Right DLPFC	27	1,358037	1,007000	1,527000	0,140059
Ins - Scan 1 Right DLPFC	27	0,942074	0,657000	1,166000	0,134575
GPC+PCh - Scan 1 Right DLPFC	27	0,230000	0,179000	0,309000	0,033749

Left DLPFC - MA group

Variable	Group=Meth Descriptive Statistics (Acute abstinence (1).sta)					
	Valid N	Mean	Minimum	Maximum	Std.Dev.	
Glu - Scan 1 Left DLPFC	27	1,275963	0,837000	1,681000	0,179122	
Glu+Gln - Scan 1 Left DLPFC	27	1,479889	0,837000	2,200000	0,321122	
NAA - Scan 1 Left DLPFC	28	1,290786	0,926000	1,613000	0,154797	
NAA+NAAAG - Scan 1 Left DLPFC	28	1,359429	1,098000	1,637000	0,162203	
Ins - Scan 1 Left DLPFC	28	0,953464	0,711000	1,180000	0,141424	
GPC+PCh - Scan 1 Left DLPFC	27	0,226111	0,136000	0,315000	0,039610	

Frequency tables

Age and drug use variables

Age

Category	Frequency table: Age (Acute abstinence (1).sta) Shapiro-Wilk W=.82338, p=.00000					
	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
15,00000<x<=20,00000	2	2	3,77358	3,7736	3,77358	3,7736
20,00000<x<=25,00000	23	25	43,39623	47,1698	43,39623	47,1698
25,00000<x<=30,00000	14	39	26,41509	73,5849	26,41509	73,5849
30,00000<x<=35,00000	8	47	15,09434	88,6792	15,09434	88,6792
35,00000<x<=40,00000	1	48	1,88679	90,5660	1,88679	90,5660
40,00000<x<=45,00000	2	50	3,77358	94,3396	3,77358	94,3396
45,00000<x<=50,00000	1	51	1,88679	96,2264	1,88679	96,2264
50,00000<x<=55,00000	2	53	3,77358	100,0000	3,77358	100,0000
Missing	0	53	0,00000		0,00000	100,0000

Age started taking MA

Frequency table: Age started taking MA (Acute abstinence (1).sta) Shapiro-Wilk W=,84567, p=,00001						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
-5,00000<x<=0,000000	22	22	41,50943	41,5094	41,50943	41,5094
0,000000<x<=5,000000	0	22	0,00000	41,5094	0,00000	41,5094
5,000000<x<=10,00000	1	23	1,88679	43,3962	1,88679	43,3962
10,00000<x<=15,00000	9	32	16,98113	60,3774	16,98113	60,3774
15,00000<x<=20,00000	13	45	24,52830	84,9057	24,52830	84,9057
20,00000<x<=25,00000	6	51	11,32075	96,2264	11,32075	96,2264
25,00000<x<=30,00000	0	51	0,00000	96,2264	0,00000	96,2264
30,00000<x<=35,00000	2	53	3,77358	100,0000	3,77358	100,0000
Missing	0	53	0,00000		0,00000	100,0000

Length of using MA

Frequency table: Length of drug taking (Acute abstinence (1).sta) Shapiro-Wilk W=,84781, p=,00001						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
-5,00000<x<=0,000000	22	22	41,50943	41,5094	41,50943	41,5094
0,000000<x<=5,000000	1	23	1,88679	43,3962	1,88679	43,3962
5,000000<x<=10,00000	19	42	35,84906	79,2453	35,84906	79,2453
10,00000<x<=15,00000	8	50	15,09434	94,3396	15,09434	94,3396
15,00000<x<=20,00000	2	52	3,77358	98,1132	3,77358	98,1132
20,00000<x<=25,00000	1	53	1,88679	100,0000	1,88679	100,0000
Missing	0	53	0,00000		0,00000	100,0000

Duration of abstinence

Frequency table: Duration of abstinence Scan 1 (Acute abstinence (1).sta) Shapiro-Wilk W=,85343, p=,00001						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
-,500000<x<=0,000000	22	22	41,50943	41,5094	41,50943	41,5094
0,000000<x<=,500000	2	24	3,77358	45,2830	3,77358	45,2830
,50000000<x<=1,000000	7	31	13,20755	58,4906	13,20755	58,4906
1,000000<x<=1,500000	8	39	15,09434	73,5849	15,09434	73,5849
1,500000<x<=2,000000	8	47	15,09434	88,6792	15,09434	88,6792
2,000000<x<=2,500000	4	51	7,54717	96,2264	7,54717	96,2264
2,500000<x<=3,000000	2	53	3,77358	100,0000	3,77358	100,0000
Missing	0	53	0,00000		0,00000	100,0000

Metabolites per brain area

Glu - right ACC

Frequency table: Glu - Scan 1 Right ACC (Acute abstinence (1).sta) Shapiro-Wilk W=,98690, p=,86407						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
,6000000<x<=,8000000	0	0	0,00000	0,0000	0,00000	0,0000
,8000000<x<=1,000000	5	5	10,41667	10,4167	9,43396	9,4340
1,000000<x<=1,200000	7	12	14,58333	25,0000	13,20755	22,6415
1,200000<x<=1,400000	21	33	43,75000	68,7500	39,62264	62,2642
1,400000<x<=1,600000	10	43	20,83333	89,5833	18,86792	81,1321
1,600000<x<=1,800000	4	47	8,33333	97,9167	7,54717	88,6792
1,800000<x<=2,000000	1	48	2,08333	100,0000	1,88679	90,5660
Missing	5	53	10,41667		9,43396	100,0000

Glu+Gln - right ACC

Frequency table: Glu+Gln - Scan 1 Right ACC (Acute abstinence (1).sta) Shapiro-Wilk W=,98448, p=,76957						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
,8000000<x<=1,000000	3	3	6,25000	6,2500	5,66038	5,6604
1,000000<x<=1,200000	5	8	10,41667	16,6667	9,43396	15,0943
1,200000<x<=1,400000	12	20	25,00000	41,6667	22,64151	37,7358
1,400000<x<=1,600000	12	32	25,00000	66,6667	22,64151	60,3774
1,600000<x<=1,800000	9	41	18,75000	85,4167	16,98113	77,3585
1,800000<x<=2,000000	5	46	10,41667	95,8333	9,43396	86,7925
2,000000<x<=2,200000	2	48	4,16667	100,0000	3,77358	90,5660
Missing	5	53	10,41667		9,43396	100,0000

NAA - right ACC

Frequency table: NAA - Scan 1 Right ACC (Acute abstinence (1).sta) Shapiro-Wilk W=,98151, p=,62977						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
,8000000<x<=,9000000	0	0	0,00000	0,0000	0,00000	0,0000
,9000000<x<=1,000000	2	2	4,08163	4,0816	3,77358	3,7736
1,000000<x<=1,100000	9	11	18,36735	22,4490	16,98113	20,7547
1,100000<x<=1,200000	20	31	40,81633	63,2653	37,73585	58,4906
1,200000<x<=1,300000	11	42	22,44898	85,7143	20,75472	79,2453
1,300000<x<=1,400000	6	48	12,24490	97,9592	11,32075	90,5660
1,400000<x<=1,500000	1	49	2,04082	100,0000	1,88679	92,4528
Missing	4	53	8,16327		7,54717	100,0000

NAA+NAAG – right ACC

Frequency table: NAA+NAAG - Scan 1 Right ACC (Acute abstinence (1).sta) Shapiro-Wilk W=,97060, p=,25569						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
,9000000<x<=1,000000	0	0	0,00000	0,0000	0,00000	0,0000
1,000000<x<=1,100000	6	6	12,24490	12,2449	11,32075	11,3208
1,100000<x<=1,200000	16	22	32,65306	44,8980	30,18868	41,5094
1,200000<x<=1,300000	9	31	18,36735	63,2653	16,98113	58,4906
1,300000<x<=1,400000	11	42	22,44898	85,7143	20,75472	79,2453
1,400000<x<=1,500000	4	46	8,16327	93,8776	7,54717	86,7925
1,500000<x<=1,600000	3	49	6,12245	100,0000	5,66038	92,4528
Missing	4	53	8,16327		7,54717	100,0000

Ins – right ACC

Frequency table: Ins - Scan 1 Right ACC (Acute abstinence (1).sta) Shapiro-Wilk W=,96823, p=,20567						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
,6000000<x<=,7000000	0	0	0,00000	0,0000	0,00000	0,0000
,7000000<x<=,8000000	2	2	4,08163	4,0816	3,77358	3,7736
,8000000<x<=,9000000	4	6	8,16327	12,2449	7,54717	11,3208
,9000000<x<=1,000000	21	27	42,85714	55,1020	39,62264	50,9434
1,000000<x<=1,100000	13	40	26,53061	81,6327	24,52830	75,4717
1,100000<x<=1,200000	4	44	8,16327	89,7959	7,54717	83,0189
1,200000<x<=1,300000	4	48	8,16327	97,9592	7,54717	90,5660
1,300000<x<=1,400000	1	49	2,04082	100,0000	1,88679	92,4528
Missing	4	53	8,16327		7,54717	100,0000

GPC+PCh - right acc

Frequency table: GPC+PCh - Scan 1 Right ACC (Acute abstinence (1).sta) Shapiro-Wilk W=,95826, p=,08033						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
,2000000<x<=,2200000	0	0	0,00000	0,0000	0,00000	0,0000
,2200000<x<=,2400000	2	2	4,08163	4,0816	3,77358	3,7736
,2400000<x<=,2600000	13	15	26,53061	30,6122	24,52830	28,3019
,2600000<x<=,2800000	15	30	30,61224	61,2245	28,30189	56,6038
,2800000<x<=,3000000	8	38	16,32653	77,5510	15,09434	71,6981
,3000000<x<=,3200000	6	44	12,24490	89,7959	11,32075	83,0189
,3200000<x<=,3400000	3	47	6,12245	95,9184	5,66038	88,6792
,3400000<x<=,3600000	2	49	4,08163	100,0000	3,77358	92,4528
Missing	4	53	8,16327		7,54717	100,0000

Glu - left ACC

Frequency table: Glu - Scan 1 Left ACC (Acute abstinence (1).sta) Shapiro-Wilk W=,96082, p=,09621						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
,8000000<x<=,9000000	0	0	0,00000	0,0000	0,00000	0,0000
,9000000<x<=1,000000	2	2	4,00000	4,0000	3,77358	3,7736
1,000000<x<=1,100000	5	7	10,00000	14,0000	9,43396	13,2075
1,100000<x<=1,200000	5	12	10,00000	24,0000	9,43396	22,6415
1,200000<x<=1,300000	4	16	8,00000	32,0000	7,54717	30,1887
1,300000<x<=1,400000	14	30	28,00000	60,0000	26,41509	56,6038
1,400000<x<=1,500000	9	39	18,00000	78,0000	16,98113	73,5849
1,500000<x<=1,600000	9	48	18,00000	96,0000	16,98113	90,5660
1,600000<x<=1,700000	2	50	4,00000	100,0000	3,77358	94,3396
Missing	3	53	6,00000		5,66038	100,0000

Glu+Gln - left ACC

Frequency table: Glu+Gln - Scan 1 Left ACC (Acute abstinence (1).sta) Shapiro-Wilk W = ,97764, p = ,45736						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
,8000000<x<=1,000000	0	0	0,00000	0,0000	0,00000	0,0000
1,000000<x<=1,200000	6	6	12,00000	12,0000	11,32075	11,3208
1,200000<x<=1,400000	12	18	24,00000	36,0000	22,64151	33,9623
1,400000<x<=1,600000	13	31	26,00000	62,0000	24,52830	58,4906
1,600000<x<=1,800000	14	45	28,00000	90,0000	26,41509	84,9057
1,800000<x<=2,000000	4	49	8,00000	98,0000	7,54717	92,4528
2,000000<x<=2,200000	1	50	2,00000	100,0000	1,88679	94,3396
Missing	3	53	6,00000		5,66038	100,0000

NAA - left ACC

Frequency table: NAA - Scan 1 Left ACC (Acute abstinence (1).sta) Shapiro-Wilk W = ,96388, p = ,12921						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
,8000000<x<=,9000000	0	0	0,00000	0,0000	0,00000	0,0000
,9000000<x<=1,000000	3	3	6,00000	6,0000	5,66038	5,6604
1,000000<x<=1,100000	13	16	26,00000	32,0000	24,52830	30,1887
1,100000<x<=1,200000	18	34	36,00000	68,0000	33,96226	64,1509
1,200000<x<=1,300000	12	46	24,00000	92,0000	22,64151	86,7925
1,300000<x<=1,400000	0	46	0,00000	92,0000	0,00000	86,7925
1,400000<x<=1,500000	4	50	8,00000	100,0000	7,54717	94,3396
Missing	3	53	6,00000		5,66038	100,0000

NAA+NAAG – left ACC

Frequency table: NAA+NAAG - Scan 1 Left ACC (Acute abstinence (1).sta) Shapiro-Wilk W=.97128, p=.26077						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
,8000000<x<=,9000000	0	0	0,00000	0,0000	0,00000	0,0000
,9000000<x<=1,000000	2	2	4,00000	4,0000	3,77358	3,7736
1,000000<x<=1,100000	9	11	18,00000	22,0000	16,98113	20,7547
1,100000<x<=1,200000	11	22	22,00000	44,0000	20,75472	41,5094
1,200000<x<=1,300000	9	31	18,00000	62,0000	16,98113	58,4906
1,300000<x<=1,400000	9	40	18,00000	80,0000	16,98113	75,4717
1,400000<x<=1,500000	7	47	14,00000	94,0000	13,20755	88,6792
1,500000<x<=1,600000	3	50	6,00000	100,0000	5,66038	94,3396
Missing	3	53	6,00000		5,66038	100,0000

Ins – left ACC

Frequency table: Ins - Scan 1 Left ACC (Acute abstinence (1).sta) Shapiro-Wilk W=.98151, p=.61726						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
,6000000<x<=,7000000	0	0	0,00000	0,0000	0,00000	0,0000
,7000000<x<=,8000000	1	1	2,00000	2,0000	1,88679	1,8868
,8000000<x<=,9000000	4	5	8,00000	10,0000	7,54717	9,4340
,9000000<x<=1,000000	14	19	28,00000	38,0000	26,41509	35,8491
1,000000<x<=1,100000	10	29	20,00000	58,0000	18,86792	54,7170
1,100000<x<=1,200000	13	42	26,00000	84,0000	24,52830	79,2453
1,200000<x<=1,300000	6	48	12,00000	96,0000	11,32075	90,5660
1,300000<x<=1,400000	2	50	4,00000	100,0000	3,77358	94,3396
Missing	3	53	6,00000		5,66038	100,0000

GPC+PCh - left ACC

Frequency table: GPC+PCh - Scan 1 Left ACC (Acute abstinence (1).sta) Shapiro-Wilk W = ,96890, p = ,20864						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
,2000000<x<=,2200000	1	1	2,00000	2,0000	1,88679	1,8868
,2200000<x<=,2400000	3	4	6,00000	8,0000	5,66038	7,5472
,2400000<x<=,2600000	11	15	22,00000	30,0000	20,75472	28,3019
,2600000<x<=,2800000	7	22	14,00000	44,0000	13,20755	41,5094
,2800000<x<=,3000000	12	34	24,00000	68,0000	22,64151	64,1509
,3000000<x<=,3200000	10	44	20,00000	88,0000	18,86792	83,0189
,3200000<x<=,3400000	3	47	6,00000	94,0000	5,66038	88,6792
,3400000<x<=,3600000	1	48	2,00000	96,0000	1,88679	90,5660
,3600000<x<=,3800000	2	50	4,00000	100,0000	3,77358	94,3396
Missing	3	53	6,00000		5,66038	100,0000

Glu - right DLPFC

Frequency table: Glu - Scan 1 Right DLPFC (Acute abstinence (1).sta) Shapiro-Wilk W = ,97737, p = ,50280						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
,8000000<x<=1,000000	1	1	2,17391	2,1739	1,88679	1,8868
1,000000<x<=1,200000	9	10	19,56522	21,7391	16,98113	18,8679
1,200000<x<=1,400000	16	26	34,78261	56,5217	30,18868	49,0566
1,400000<x<=1,600000	12	38	26,08696	82,6087	22,64151	71,6981
1,600000<x<=1,800000	7	45	15,21739	97,8261	13,20755	84,9057
1,800000<x<=2,000000	1	46	2,17391	100,0000	1,88679	86,7925
Missing	7	53	15,21739		13,20755	100,0000

Glu+Gln - right DLPFC

Frequency table: Glu+Gln - Scan 1 Right DLPFC (Acute abstinence (1).sta) Shapiro-Wilk W =,96162, p=,13259						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
,800000<x<=1,000000	1	1	2,17391	2,1739	1,88679	1,8868
1,000000<x<=1,200000	4	5	8,69565	10,8696	7,54717	9,4340
1,200000<x<=1,400000	11	16	23,91304	34,7826	20,75472	30,1887
1,400000<x<=1,600000	8	24	17,39130	52,1739	15,09434	45,2830
1,600000<x<=1,800000	8	32	17,39130	69,5652	15,09434	60,3774
1,800000<x<=2,000000	9	41	19,56522	89,1304	16,98113	77,3585
2,000000<x<=2,200000	5	46	10,86957	100,0000	9,43396	86,7925
Missing	7	53	15,21739		13,20755	100,0000

NAA - right DLPFC

Frequency table: NAA - Scan 1 Right DLPFC (Acute abstinence (1).sta) Shapiro-Wilk W =,96410, p=,17486						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
,9000000<x<=1,000000	0	0	0,00000	0,0000	0,00000	0,0000
1,000000<x<=1,100000	3	3	6,66667	6,6667	5,66038	5,6604
1,100000<x<=1,200000	4	7	8,88889	15,5556	7,54717	13,2075
1,200000<x<=1,300000	8	15	17,77778	33,3333	15,09434	28,3019
1,300000<x<=1,400000	15	30	33,33333	66,6667	28,30189	56,6038
1,400000<x<=1,500000	11	41	24,44444	91,1111	20,75472	77,3585
1,500000<x<=1,600000	3	44	6,66667	97,7778	5,66038	83,0189
1,600000<x<=1,700000	1	45	2,22222	100,0000	1,88679	84,9057
Missing	8	53	17,77778		15,09434	100,0000

NAA+NAAG – right DLPFC

Frequency table: NAA+NAAG - Scan 1 Right DLPFC (Acute abstinence (1).sta) Shapiro-Wilk W=,97597, p=,45195						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
,9000000<x<=1,000000	0	0	0,00000	0,0000	0,00000	0,0000
1,000000<x<=1,100000	3	3	6,52174	6,5217	5,66038	5,6604
1,100000<x<=1,200000	4	7	8,69565	15,2174	7,54717	13,2075
1,200000<x<=1,300000	4	11	8,69565	23,9130	7,54717	20,7547
1,300000<x<=1,400000	10	21	21,73913	45,6522	18,86792	39,6226
1,400000<x<=1,500000	12	33	26,08696	71,7391	22,64151	62,2642
1,500000<x<=1,600000	9	42	19,56522	91,3043	16,98113	79,2453
1,600000<x<=1,700000	3	45	6,52174	97,8261	5,66038	84,9057
1,700000<x<=1,800000	1	46	2,17391	100,0000	1,88679	86,7925
Missing	7	53	15,21739		13,20755	100,0000

Ins – right DLPFC

Frequency table: Ins - Scan 1 Right DLPFC (Acute abstinence (1).sta) Shapiro-Wilk W=,97518, p=,42486						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
,6000000<x<=,7000000	2	2	4,34783	4,3478	3,77358	3,7736
,7000000<x<=,8000000	6	8	13,04348	17,3913	11,32075	15,0943
,8000000<x<=,9000000	7	15	15,21739	32,6087	13,20755	28,3019
,9000000<x<=1,000000	13	28	28,26087	60,8696	24,52830	52,8302
1,000000<x<=1,100000	9	37	19,56522	80,4348	16,98113	69,8113
1,100000<x<=1,200000	9	46	19,56522	100,0000	16,98113	86,7925
Missing	7	53	15,21739		13,20755	100,0000

GPC+PCh - right DLPFC

Frequency table: GPC+PCh - Scan 1 Right DLPFC (Acute abstinence (1).sta) Shapiro-Wilk W =,97660, p=,47428						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
,1000000<x<=,1500000	0	0	0,00000	0,0000	0,00000	0,0000
,1500000<x<=,2000000	7	7	15,21739	15,2174	13,20755	13,2075
,2000000<x<=,2500000	26	33	56,52174	71,7391	49,05660	62,2642
,2500000<x<=,3000000	11	44	23,91304	95,6522	20,75472	83,0189
,3000000<x<=,3500000	1	45	2,17391	97,8261	1,88679	84,9057
,3500000<x<=,4000000	1	46	2,17391	100,0000	1,88679	86,7925
Missing	7	53	15,21739		13,20755	100,0000

Glu - left DLPFC

Frequency table: Glu - Scan 1 Left DLPFC (Acute abstinence (1).sta) Shapiro-Wilk W =,97479, p=,39792						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
,6000000<x<=,8000000	0	0	0,00000	0,0000	0,00000	0,0000
,8000000<x<=,1,000000	5	5	10,63830	10,6383	9,43396	9,4340
1,000000<x<=,1,200000	10	15	21,27660	31,9149	18,86792	28,3019
1,200000<x<=,1,400000	19	34	40,42553	72,3404	35,84906	64,1509
1,400000<x<=,1,600000	11	45	23,40426	95,7447	20,75472	84,9057
1,600000<x<=,1,800000	2	47	4,25532	100,0000	3,77358	88,6792
Missing	6	53	12,76596		11,32075	100,0000

Glu+Gln - left DLPC

Frequency table: Glu+Gln - Scan 1 Left DLPC (Acute abstinence (1).sta) Shapiro-Wilk W =,98035, p=,60680						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
,600000<x<=,800000	0	0	0,00000	0,0000	0,00000	0,0000
,800000<x<=1,000000	4	4	8,51064	8,5106	7,54717	7,5472
1,000000<x<=1,200000	6	10	12,76596	21,2766	11,32075	18,8679
1,200000<x<=1,400000	13	23	27,65957	48,9362	24,52830	43,3962
1,400000<x<=1,600000	7	30	14,89362	63,8298	13,20755	56,6038
1,600000<x<=1,800000	9	39	19,14894	82,9787	16,98113	73,5849
1,800000<x<=2,000000	7	46	14,89362	97,8723	13,20755	86,7925
2,000000<x<=2,200000	1	47	2,12766	100,0000	1,88679	88,6792
Missing	6	53	12,76596		11,32075	100,0000

NAA - left DLPC

Frequency table: NAA - Scan 1 Left DLPC (Acute abstinence (1).sta) Shapiro-Wilk W =,98561, p=,79748						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
,800000<x<=,900000	0	0	0,00000	0,0000	0,00000	0,0000
,900000<x<=1,000000	1	1	2,00000	2,0000	1,88679	1,8868
1,000000<x<=1,100000	2	3	4,00000	6,0000	3,77358	5,6604
1,100000<x<=1,200000	6	9	12,00000	18,0000	11,32075	16,9811
1,200000<x<=1,300000	11	20	22,00000	40,0000	20,75472	37,7358
1,300000<x<=1,400000	13	33	26,00000	66,0000	24,52830	62,2642
1,400000<x<=1,500000	11	44	22,00000	88,0000	20,75472	83,0189
1,500000<x<=1,600000	2	46	4,00000	92,0000	3,77358	86,7925
1,600000<x<=1,700000	4	50	8,00000	100,0000	7,54717	94,3396
Missing	3	53	6,00000		5,66038	100,0000

NAA+NAAG – left DLPPFC

Frequency table: NAA+NAAG - Scan 1 Left DLPPFC (Acute abstinence (1).sta) Shapiro-Wilk W =,97386, p=,32977						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
1,000000<x<=1,100000	1	1	2,00000	2,00000	1,88679	1,8868
1,100000<x<=1,200000	7	8	14,00000	16,00000	13,20755	15,0943
1,200000<x<=1,300000	4	12	8,00000	24,00000	7,54717	22,6415
1,300000<x<=1,400000	12	24	24,00000	48,00000	22,64151	45,2830
1,400000<x<=1,500000	12	36	24,00000	72,00000	22,64151	67,9245
1,500000<x<=1,600000	7	43	14,00000	86,00000	13,20755	81,1321
1,600000<x<=1,700000	5	48	10,00000	96,00000	9,43396	90,5660
1,700000<x<=1,800000	2	50	4,00000	100,00000	3,77358	94,3396
Missing	3	53	6,00000		5,66038	100,0000

Ins – left DLPPFC

Frequency table: Ins - Scan 1 Left DLPPFC (Acute abstinence (1).sta) Shapiro-Wilk W =,97254, p=,29276						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
,6000000<x<=,7000000	0	0	0,00000	0,00000	0,00000	0,0000
,7000000<x<=,8000000	5	5	10,00000	10,00000	9,43396	9,4340
,8000000<x<=,9000000	12	17	24,00000	34,00000	22,64151	32,0755
,9000000<x<=1,000000	14	31	28,00000	62,00000	26,41509	58,4906
1,000000<x<=1,100000	7	38	14,00000	76,00000	13,20755	71,6981
1,100000<x<=1,200000	11	49	22,00000	98,00000	20,75472	92,4528
1,200000<x<=1,300000	1	50	2,00000	100,00000	1,88679	94,3396
Missing	3	53	6,00000		5,66038	100,0000

GPC+PCh - left DL PFC

Frequency table: GPC+PCh - Scan 1 Left DL PFC (Acute abstinence (1).sta) Shapiro-Wilk W = ,97044, p = ,25217						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
,1000000<x<=,1500000	2	2	4,08163	4,0816	3,77358	3,7736
,1500000<x<=,2000000	7	9	14,28571	18,3673	13,20755	16,9811
,2000000<x<=,2500000	27	36	55,10204	73,4694	50,94340	67,9245
,2500000<x<=,3000000	7	43	14,28571	87,7551	13,20755	81,1321
,3000000<x<=,3500000	6	49	12,24490	100,0000	11,32075	92,4528
Missing	4	53	8,16327		7,54717	100,0000

Mann-Whitney U test - Age and drug use variables

Mann-Whitney U Test (w/ continuity correction) (Acute abstinence (1).sta) By variable Group Marked tests are significant at p <,05000									
variable	Rank Sum Control	Rank Sum Meth	U	Z	p-value	Z adjusted	p-value	Valid N Control	Valid N Meth
Age	529,0000	902,000	276,0000	-1,16429	0,244307	-1,16840	0,242648	22	31
Age started taking MA	253,0000	1178,000	0,0000	-6,14637	0,000000	-6,38314	0,000000	22	31
Length of drug taking	253,0000	1178,000	0,0000	-6,14637	0,000000	-6,39079	0,000000	22	31
Duration of abstinence Scan 1	253,0000	1178,000	0,0000	-6,14637	0,000000	-6,38606	0,000000	22	31
									2*1sided exact p
									0,246651
									0,000000
									0,000000
									0,000000

ANOVA – right ACC

Univariate Results for Each DV (Acute abstinence (1).sta) Sigma-restricted parameterization Effective hypothesis decomposition																									
Effect	De	Glu -	Glu -	Glu -	Glu -	Glu+Gln	Glu+Gln	Glu+Gln	NAA -	NAA -	NAA -	NAA+NA	NAA+NA	NAA+NA	NAA+NA	Ins -	Ins -	Ins -	Ins -	GPC+PC	GPC+PC	GPC+PC	GPC+PC	GPC+PC	
	gr.	Scan 1	Scan 1	Scan 1	Scan 1	- Scan 1	- Scan 1	- Scan 1	Right	Right	Right	AG - Scan	AG - Scan	AG - Scan	AG - Scan	Scan 1	Scan 1	Scan 1	Scan 1	h - Scan 1	h - Scan 1	h - Scan 1	h - Scan 1	h - Scan 1	
	of	Right	Right	Right	Right	Right	Right	Right	ACC	ACC	ACC	1 Right	1 Right	1 Right	1 Right	Right	Right	Right	Right	Right	Right	Right	Right	Right	
	Fr	ACC	ACC	ACC	ACC	ACC	ACC	ACC	ACC	ACC	ACC	ACC	ACC	ACC	ACC	ACC	ACC	ACC	ACC	ACC	ACC	ACC	ACC	ACC	
	ee	SS	MS	F	p	SS	F	p	SS	MS	F	p	SS	MS	F	p	SS	MS	F	p	SS	MS	F	p	
do	Int																								
m	1	80,04712	80,04712	1665,248	0,000000	98,48976	98,48976	1218,937	0,000000	63,03417	63,03417	5336,651	0,000000	72,54891	72,54891	3959,395	0,000000	45,93367	45,93367	3156,371	0,000000	3,549435	3,549435	4056,604	0,000000
er																									
ce																									
pt																									
Gr	1	0,07070	0,07070	1,471	0,231401	0,04232	0,04232	0,524	0,472887	0,00527	0,00527	0,446	0,507387	0,00002	0,00002	0,001	0,973402	0,00150	0,00150	0,103	0,749801	0,000868	0,000868	0,992	0,324491
ou																									
p																									
Er	46	2,21118	0,04807			3,71679	0,08080			0,54333	0,01181			0,84287	0,01832		0,66942	0,01455				0,040249	0,000875		
ro																									
r																									
tal	47	2,28189				3,75911				0,54860				0,84289			0,67092					0,041117			

ANOVA – left ACC

Univariate Results for Each DV (Acute abstinence (1).sta) Sigma-restricted parameterization Effective hypothesis decomposition																								
De	Glu -	Glu -	Glu -	Glu -	Glu -	Glu+Gln	Glu+Gln	Glu+Gln	NAA -	NAA -	NAA -	NAA+NA	NAA+NA	NAA+NA	NAA+NA	NAA+NA	Ins -	Ins -	Ins -	GPC+PC	GPC+PC	GPC+PC	GPC+PC	
gr.	Scan 1	Scan 1	Scan 1	Scan 1	Scan 1	- Scan 1	- Scan 1	- Scan 1	Scan 1	Scan 1	Scan 1	AG - Scan	AG - Scan	AG - Scan	AG - Scan	AG - Scan	Scan 1	Scan 1	Scan 1	h - Scan 1	h - Scan 1	h - Scan 1	h - Scan 1	
of	Left	Left	Left	Left	Left	Left	Left	Left	Left	Left	Left	1 Left	1 Left	1 Left	1 Left	1 Left	Left	Left	Left	Left	Left	Left	Left	
Fr	ACC	ACC	ACC	ACC	ACC	ACC	ACC	ACC	ACC	ACC	ACC	ACC	ACC	ACC	ACC	ACC	ACC	ACC	ACC	ACC	ACC	ACC	ACC	
ee	SS	MS	F	p	SS	MS	F	p	SS	MS	F	p	SS	MS	F	p	SS	MS	F	p	SS	MS	p	
do	1	88,06915	88,06915	2640,443	0,000000	109,9661	109,9661	1660,096	0,000000	67,62741	67,62741	4460,375	0,000000	76,66317	76,66317	3079,275	0,000000	55,33896	55,33896	3305,900	4,004227	4,004227	3137,111	0,000000
m	Int																							
erc	1	0,01731	0,01731	0,519	0,474809	0,0041	0,0041	0,062	0,804543	0,04475	0,04475	2,952	0,092239	0,08566	0,08566	3,441	0,069762	0,04272	0,04272	2,552	0,000526	0,000526	0,412	0,524067
ep	Gr	1	0,01731	0,01731	0,519	0,474809	0,0041	0,062	0,804543	0,04475	0,04475	2,952	0,092239	0,08566	0,08566	3,441	0,069762	0,04272	0,04272	2,552	0,000526	0,000526	0,412	0,524067
t	Gr	1	0,01731	0,01731	0,519	0,474809	0,0041	0,062	0,804543	0,04475	0,04475	2,952	0,092239	0,08566	0,08566	3,441	0,069762	0,04272	0,04272	2,552	0,000526	0,000526	0,412	0,524067
	Gr	1	0,01731	0,01731	0,519	0,474809	0,0041	0,062	0,804543	0,04475	0,04475	2,952	0,092239	0,08566	0,08566	3,441	0,069762	0,04272	0,04272	2,552	0,000526	0,000526	0,412	0,524067
	Gr	1	0,01731	0,01731	0,519	0,474809	0,0041	0,062	0,804543	0,04475	0,04475	2,952	0,092239	0,08566	0,08566	3,441	0,069762	0,04272	0,04272	2,552	0,000526	0,000526	0,412	0,524067
	Gr	1	0,01731	0,01731	0,519	0,474809	0,0041	0,062	0,804543	0,04475	0,04475	2,952	0,092239	0,08566	0,08566	3,441	0,069762	0,04272	0,04272	2,552	0,000526	0,000526	0,412	0,524067
	Gr	1	0,01731	0,01731	0,519	0,474809	0,0041	0,062	0,804543	0,04475	0,04475	2,952	0,092239	0,08566	0,08566	3,441	0,069762	0,04272	0,04272	2,552	0,000526	0,000526	0,412	0,524067
	Gr	1	0,01731	0,01731	0,519	0,474809	0,0041	0,062	0,804543	0,04475	0,04475	2,952	0,092239	0,08566	0,08566	3,441	0,069762	0,04272	0,04272	2,552	0,000526	0,000526	0,412	0,524067
	Gr	1	0,01731	0,01731	0,519	0,474809	0,0041	0,062	0,804543	0,04475	0,04475	2,952	0,092239	0,08566	0,08566	3,441	0,069762	0,04272	0,04272	2,552	0,000526	0,000526	0,412	0,524067
	Gr	1	0,01731	0,01731	0,519	0,474809	0,0041	0,062	0,804543	0,04475	0,04475	2,952	0,092239	0,08566	0,08566	3,441	0,069762	0,04272	0,04272	2,552	0,000526	0,000526	0,412	0,524067
	Gr	1	0,01731	0,01731	0,519	0,474809	0,0041	0,062	0,804543	0,04475	0,04475	2,952	0,092239	0,08566	0,08566	3,441	0,069762	0,04272	0,04272	2,552	0,000526	0,000526	0,412	0,524067
	Gr	1	0,01731	0,01731	0,519	0,474809	0,0041	0,062	0,804543	0,04475	0,04475	2,952	0,092239	0,08566	0,08566	3,441	0,069762	0,04272	0,04272	2,552	0,000526	0,000526	0,412	0,524067
	Gr	1	0,01731	0,01731	0,519	0,474809	0,0041	0,062	0,804543	0,04475	0,04475	2,952	0,092239	0,08566	0,08566	3,441	0,069762	0,04272	0,04272	2,552	0,000526	0,000526	0,412	0,524067
	Gr	1	0,01731	0,01731	0,519	0,474809	0,0041	0,062	0,804543	0,04475	0,04475	2,952	0,092239	0,08566	0,08566	3,441	0,069762	0,04272	0,04272	2,552	0,000526	0,000526	0,412	0,524067
	Gr	1	0,01731	0,01731	0,519	0,474809	0,0041	0,062	0,804543	0,04475	0,04475	2,952	0,092239	0,08566	0,08566	3,441	0,069762	0,04272	0,04272	2,552	0,000526	0,000526	0,412	0,524067
	Gr	1	0,01731	0,01731	0,519	0,474809	0,0041	0,062	0,804543	0,04475	0,04475	2,952	0,092239	0,08566	0,08566	3,441	0,069762	0,04272	0,04272	2,552	0,000526	0,000526	0,412	0,524067
	Gr	1	0,01731	0,01731	0,519	0,474809	0,0041	0,062	0,804543	0,04475	0,04475	2,952	0,092239	0,08566	0,08566	3,441	0,069762	0,04272	0,04272	2,552	0,000526	0,000526	0,412	0,524067
	Gr	1	0,01731	0,01731	0,519	0,474809	0,0041	0,062	0,804543	0,04475	0,04475	2,952	0,092239	0,08566	0,08566	3,441	0,069762	0,04272	0,04272	2,552	0,000526	0,000526	0,412	0,524067
	Gr	1	0,01731	0,01731	0,519	0,474809	0,0041	0,062	0,804543	0,04475	0,04475	2,952	0,092239	0,08566	0,08566	3,441	0,069762	0,04272	0,04272	2,552	0,000526	0,000526	0,412	0,524067
	Gr	1	0,01731	0,01731	0,519	0,474809	0,0041	0,062	0,804543	0,04475	0,04475	2,952	0,092239	0,08566	0,08566	3,441	0,069762	0,04272	0,04272	2,552	0,000526	0,000526	0,412	0,524067
	Gr	1	0,01731	0,01731	0,519	0,474809	0,0041	0,062	0,804543	0,04475	0,04475	2,952	0,092239	0,08566	0,08566	3,441	0,069762	0,04272	0,04272	2,552	0,000526	0,000526	0,412	0,524067
	Gr	1	0,01731	0,01731	0,519	0,474809	0,0041	0,062	0,804543	0,04475	0,04475	2,952	0,092239	0,08566	0,08566	3,441	0,069762	0,04272	0,04272	2,552	0,000526	0,000526	0,412	0,524067
	Gr	1	0,01731	0,01731	0,519	0,474809	0,0041	0,062	0,804543	0,04475	0,04475	2,952	0,092239	0,08566	0,08566	3,441	0,069762	0,04272	0,04272	2,552	0,000526	0,000526	0,412	0,524067
	Gr	1	0,01731	0,01731	0,519	0,474809	0,0041	0,062	0,804543	0,04475	0,04475	2,952	0,092239	0,08566	0,08566	3,441	0,069762	0,04272	0,04272	2,552	0,000526	0,000526	0,412	0,524067
	Gr	1	0,01731	0,01731	0,519	0,474809	0,0041	0,062	0,804543	0,04475	0,04475	2,952	0,092239	0,08566	0,08566	3,441	0,069762	0,04272	0,04272	2,552	0,000526	0,000526	0,412	0,524067
	Gr	1	0,01731	0,01731	0,519	0,474809	0,0041	0,062	0,804543	0,04475	0,04475	2,952	0,092239	0,08566	0,08566	3,441	0,069762	0,04272	0,04272	2,552	0,000526	0,000526	0,412	0,524067
	Gr	1	0,01731	0,01731	0,519	0,474809	0,0041	0,062	0,804543	0,04475	0,04475	2,952	0,092239	0,08566	0,08566	3,441	0,069762	0,04272	0,04272	2,552	0,000526	0,000526	0,412	0,524067
	Gr	1	0,01731	0,01731	0,519	0,474809	0,0041	0,062	0,804543	0,04475	0,04475	2,952	0,092239	0,08566	0,08566	3,441	0,069762	0,04272	0,04272	2,552	0,000526	0,000526	0,412	0,524067
	Gr	1	0,01731	0,01731	0,519	0,474809	0,0041	0,062	0,804543	0,04475	0,04475	2,952	0,092239	0,08566	0,08566	3,441	0,069762	0,04272	0,04272	2,552	0,000526	0,000526	0,412	0,524067
	Gr	1	0,01731	0,01731	0,519	0,474809	0,0041	0,062	0,804543	0,04475	0,04475	2,952	0,092239	0,08566	0,08566	3,441	0,069762	0,04272	0,04272	2,552	0,000526	0,000526	0,412	0,524067
	Gr	1	0,01731	0,01731	0,519	0,474809	0,0041	0,062	0,804543	0,04475	0,04475	2,952	0,092239	0,08566	0,08566	3,441	0,069762	0,04272	0,04272	2,552	0,000526	0,000526	0,412	0,524067
	Gr	1	0,01731	0,01731	0,519	0,474809	0,0041	0,062	0,804543	0,04475	0,04475	2,952	0,092239	0,08566	0,08566	3,441	0,069762	0,04272	0,04272	2,552	0,000526	0,000526	0,412	0,524067
	Gr	1	0,01731	0,01731	0,519	0,474809	0,0041	0,062	0,804543	0,04475	0,04475	2,952	0,092239	0,08566	0,08566	3,441	0,069762	0,04272	0,04272	2,552	0,000526	0,000526	0,412	0,524067
	Gr	1	0,01731	0,01731	0,519	0,474809	0,0041	0,062	0,804543	0,04475	0,04475	2,952	0,092239	0,08566	0,08566	3,441	0,069762	0,04272	0,04272	2,552	0,000526	0,000526	0,412	0,524067
	Gr	1	0,01731	0,01731	0,519	0,474809	0,0041	0,062	0,804543	0,04475	0,04475	2,952	0,092239	0,08566	0,08566	3,441	0,069762	0,04272	0,04272	2,552	0,000526	0,000526	0,412	0,524067
	Gr	1	0,01731	0,01731	0,519	0,474809	0,0041	0,062	0,804543	0,04475	0,04475	2,952	0,092239	0,08566	0,08566	3,441	0,069762	0,04272	0,04272	2,552	0,000526	0,000526	0,412	0,524067
	Gr	1	0,01731	0,01731	0,519	0,474809	0,0041	0,062	0,804543	0,04475	0,04475	2,952	0,092239	0,08566	0,08566	3,441	0,069762	0,04272	0,04272	2,552	0,000526	0,000526	0,412	0,524067
	Gr	1	0,01731	0,01731	0,519	0,474809	0,0041	0,062	0,804543	0,04475	0,04475	2,952	0,092239	0,08566	0,08566	3,441	0,069762	0,04272	0,04272	2,552	0,000526	0,000526	0,412	0,524067
	Gr	1	0,01731	0,01731	0,519	0,474809	0,0041	0,062	0,804543	0,04475	0,04475	2,952	0,092239	0,08566	0,08566	3,441	0,069762	0,04272	0,04272	2,552	0,000526	0,000526	0,412	0,524067
	Gr	1	0,01731	0,01731	0,519	0,474809	0,0041	0,062	0,804543	0,04475	0,04475	2,952	0,092239	0,08566	0,08566	3,441	0,069762	0,04272	0,04272	2,552	0,000526	0,00052		

ANOVA – right DLPFC

Univariate Results for Each DV (Acute abstinence (1),sta) Sigma-restricted parameterization Effective hypothesis decomposition																									
Deg of Freedom	Glu - Scan 1 Right DLPFC SS	Glu - Scan 1 Right DLPFC MS	Glu - Scan 1 Right DLPFC F	Glu - Scan 1 Right DLPFC p	Glu+Gln - Scan 1 Right DLPFC p	NAA - Scan 1 Right DLPFC MS	NAA - Scan 1 Right DLPFC F	NAA - Scan 1 Right DLPFC p	NAA+NA AG - Scan 1 Right DLPFC SS	NAA+NA AG - Scan 1 Right DLPFC MS	NAA+NA AG - Scan 1 Right DLPFC F	NAA+NA AG - Scan 1 Right DLPFC p	Ins - Scan 1 Right DLPFC MS	Ins - Scan 1 Right DLPFC F	Ins - Scan 1 Right DLPFC p	GPC+PC h - Scan 1 Right DLPFC SS	GPC+PC h - Scan 1 Right DLPFC MS	GPC+PC h - Scan 1 Right DLPFC F	GPC+PC h - Scan 1 Right DLPFC p						
Intercept	1	85,45014	85,45014	1643,216	0,000000	109,1590	109,1590	1068,951	0,000000	79,03605	79,03605	4662,895	0,000000	87,75724	87,75724	3469,594	0,000000	40,44851	40,44851	2271,846	0,000000	2,502875	2,502875	1874,594	0,000000
Group	1	0,00607	0,00607	0,117	0,734368	0,0000	0,0000	0,000	1,000000	0,000	0,00607	0,00607	0,358	0,552567	0,07802	3,085	0,086156	0,00419	0,00419	0,235	0,630237	0,002020	0,002020	1,513	0,225386
Error	43	2,23608	0,05200			0,1021	4,3911			0,72885	0,01695			1,08761	0,02529		0,76558	0,01780				0,057412	0,001335		
Total	44	2,24214					4,3911			0,73492				1,16563				0,76977				0,059432			

ANOVA – left DLPFC

Univariate Results for Each DV (Acute abstinence (1),sta) Sigma-restricted parameterization Effective hypothesis decomposition																								
Effect	Group	Glu - Scan 1 Left DLPFC SS	Glu - Scan 1 Left DLPFC MS	Glu - Scan 1 Left DLPFC F	Glu+Gln - Scan 1 Left DLPFC p	NAA - Scan 1 Left DLPFC MS	NAA - Scan 1 Left DLPFC F	NAA - Scan 1 Left DLPFC p	NAA+NA AG - Scan 1 Left DLPFC SS	NAA+NA AG - Scan 1 Left DLPFC MS	NAA+NA AG - Scan 1 Left DLPFC F	NAA+NA AG - Scan 1 Left DLPFC p	Ins - Scan 1 Left DLPFC SS	Ins - Scan 1 Left DLPFC MS	Ins - Scan 1 Left DLPFC F	Ins - Scan 1 Left DLPFC p	GPC+PC h - Scan 1 Left DLPFC SS	GPC+PC h - Scan 1 Left DLPFC MS	GPC+PC h - Scan 1 Left DLPFC F	GPC+PC h - Scan 1 Left DLPFC p				
Intercept	1	73,71977	73,71977	1857,193	0,000000	928,2382	94,50755	94,50755	82,35377	82,35377	3846,251	0,000000	91,57290	91,57290	3870,349	0,000000	41,16585	41,16585	2325,405	0,000000	2,475028	2,475028	1339,427	0,000000
Group	1	0,00072	0,00072	0,018	0,893173	0,6723	0,06845	0,06845	0,11784	0,11784	5,504	0,023547	0,14596	0,14596	6,169	0,016881	0,00434	0,00434	0,245	0,622792	0,002438	0,002438	1,319	0,256942
Error	44	1,74654	0,03969				0,10181	4,47981	0,94210	0,02141			1,04104	0,02366			0,77892	0,01770			0,081304	0,001848		
Total	45	1,74727						4,54826	1,05994				1,18701				0,78326				0,083742			

Summary - Relative metabolite concentrations – Acute abstinence

	Healthy Controls n = 22		MA dependent n = 31	
	Mean	Stdev	Mean	Stdev
<i>Anterior cingulate cortex</i>				
Right hemisphere				
Glutamate (Glu)	1.28	0.2	1.36	0.2
Glutamate + Glutamine (Glu+Gln)	1.43	0.3	1.49	0.3
N-acetyl-aspartate (NAA)	1.16	0.1	1.18	0.1
N-acetyl-aspartyl + N-acetyl-aspartyl-glutamate (NAA+NAAG)	1.25	0.1	1.26	0.1
Myo-inositol (Ins)	1.00	0.1	1.01	0.1
Glycerophosphocholine + phosphocholine (GPC+PCh)	0.27	0.0	0.28	0.0
Left hemisphere				
Glutamate (Glu)	1.32	0.2	1.36	0.2
Glutamate + Glutamine (Glu+Gln)	1.48	0.3	1.50	0.3
N-acetyl-aspartate (NAA)	1.20	0.1	1.14	0.1
N-acetyl-aspartyl + N-acetyl-aspartyl-glutamate (NAA+NAAG)	1.29	0.2	1.21	0.2
Myo-inositol (Ins)	1.09	0.1	1.03	0.1
Glycerophosphocholine + phosphocholine (GPC+PCh)	0.29	0.0	0.28	0.0
<i>Dorsolateral prefrontal cortex</i>				
Right hemisphere				
Glutamate (Glu)	1.41	0.3	1.37	0.2
Glutamate + Glutamine (Glu+Gln)	1.58	0.4	1.58	0.3
N-acetyl-aspartate (NAA)	1.35	0.1	1.33	0.1
N-acetyl-aspartyl + N-acetyl-aspartyl-glutamate (NAA+NAAG)	1.46	0.2	1.36	0.1
Myo-inositol (Ins)	0.97	0.1	0.94	0.1
Glycerophosphocholine + phosphocholine (GPC+PCh)	0.25	0.0	0.23	0.0
Left hemisphere				
Glutamate (Glu)	1.29	0.2	1.28	0.2
Glutamate + Glutamine (Glu+Gln)	1.41	0.3	1.48	0.3
N-acetyl-aspartate (NAA) *	1.39	0.2	1.29	0.2
N-acetyl-aspartyl + N-acetyl-aspartyl-glutamate (NAA+NAAG) **	1.47	0.2	1.36	0.2
Myo-inositol (Ins)	0.97	0.1	0.95	0.1
Glycerophosphocholine + phosphocholine (GPC+PCh)	0.25	0.0	0.23	0.0

Significant group differences in brain metabolites using ^1H -MRS CSI. The methamphetamine acute abstinence group had lower concentrations, in the left DLPFC, of *n-acetyl-aspartate (NAA)_(p < 0.05) and **n-acetyl-aspartate + n-acetyl-aspartyl-glutamate (NAA+NAAG)_(p < 0.05) than the control group.

Spearman Rank Order correlations

Spearman Rank Order Correlations (Acute abstinence (1).sta) MID pairwise deleted Marked correlations are significant at p < .05000					
Pair of Variables	Valid N	Spearman R	t(N-2)	p-value	
Age & Glu - Scan 1 Right ACC	48	-0,125301	-0,85658	0,396116	
Age & Glu+Gln - Scan 1 Right ACC	48	-0,118972	-0,81268	0,420588	
Age & NAA - Scan 1 Right ACC	49	-0,109868	-0,75781	0,452349	
Age & NAA+NAAAG - Scan 1 Right ACC	49	-0,192887	-1,34768	0,184223	
Age & Ins - Scan 1 Right ACC	49	0,045173	0,31001	0,757925	
Age & GPC+PCh - Scan 1 Right ACC	49	0,160559	1,11521	0,270431	
Age & Glu - Scan 1 Left ACC	50	-0,193851	-1,36901	0,177370	
Age & Glu+Gln - Scan 1 Left ACC	50	-0,107301	-0,74772	0,458276	
Age & NAA - Scan 1 Left ACC	50	0,004507	0,03123	0,975218	
Age & NAA+NAAAG - Scan 1 Left ACC	50	-0,018704	-0,12961	0,897419	
Age & Ins - Scan 1 Left ACC	50	0,093563	0,65108	0,518100	
Age & GPC+PCh - Scan 1 Left ACC	50	0,126248	0,88173	0,382317	
Age & Glu - Scan 1 Right DLPFC	46	-0,100093	-0,66730	0,508068	
Age & Glu+Gln - Scan 1 Right DLPFC	46	-0,048643	-0,32305	0,748191	
Age & NAA - Scan 1 Right DLPFC	45	-0,359025	-2,52246	0,015435	
Age & NAA+NAAAG - Scan 1 Right DLPFC	46	-0,468674	-3,51928	0,001019	
Age & Ins - Scan 1 Right DLPFC	46	0,239977	1,63974	0,108191	
Age & GPC+PCh - Scan 1 Right DLPFC	46	-0,079878	-0,53155	0,597713	
Age & Glu - Scan 1 Left DLPFC	47	-0,050405	-0,33856	0,736515	
Age & Glu+Gln - Scan 1 Left DLPFC	47	0,068636	0,46151	0,646655	
Age & NAA - Scan 1 Left DLPFC	50	-0,388827	-2,92396	0,005261	
Age & NAA+NAAAG - Scan 1 Left DLPFC	50	-0,294384	-2,13412	0,037969	
Age & Ins - Scan 1 Left DLPFC	50	-0,030564	-0,21185	0,833119	
Age & GPC+PCh - Scan 1 Left DLPFC	49	0,120588	0,83279	0,409176	
Age started taking MA & Glu - Scan 1 Right ACC	48	0,156950	1,07784	0,286723	
Age started taking MA & Glu+Gln - Scan 1 Right ACC	48	0,029162	0,19787	0,844019	
Age started taking MA & NAA - Scan 1 Right ACC	49	0,168655	1,17304	0,246689	
Age started taking MA & NAA+NAAAG - Scan 1 Right ACC	49	0,120311	0,83084	0,410264	
Age started taking MA & Ins - Scan 1 Right ACC	49	-0,016975	-0,11639	0,907837	
Age started taking MA & GPC+PCh - Scan 1 Right ACC	49	0,085575	0,58883	0,558795	

Age started taking MA & Glu - Scan 1 Left ACC	50	0,043360	0,30069	0,764950
Age started taking MA & Glu+Gln - Scan 1 Left ACC	50	-0,028463	-0,19728	0,844444
Age started taking MA & NAA - Scan 1 Left ACC	50	-0,061675	-0,42811	0,670484
Age started taking MA & NAA+NAAG - Scan 1 Left ACC	50	-0,077127	-0,53595	0,594468
Age started taking MA & Ins - Scan 1 Left ACC	50	-0,212102	-1,50370	0,139210
Age started taking MA & GPC+PCh - Scan 1 Left ACC	50	-0,080774	-0,56145	0,577101
Age started taking MA & Glu - Scan 1 Right DLPFC	46	-0,028483	-0,18901	0,850952
Age started taking MA & Glu+Gln - Scan 1 Right DLPFC	46	0,032935	0,21858	0,827986
Age started taking MA & NAA - Scan 1 Right DLPFC	45	-0,100232	-0,66059	0,512396
Age started taking MA & NAA+NAAG - Scan 1 Right DLPFC	46	-0,308364	-2,15024	0,037072
Age started taking MA & Ins - Scan 1 Right DLPFC	46	-0,038404	-0,25493	0,799963
Age started taking MA & GPC+PCh - Scan 1 Right DLPFC	46	-0,212460	-1,44223	0,156320
Age started taking MA & Glu - Scan 1 Left DLPFC	47	-0,067767	-0,45564	0,650841
Age started taking MA & Glu+Gln - Scan 1 Left DLPFC	47	0,066437	0,44666	0,657261
Age started taking MA & NAA - Scan 1 Left DLPFC	50	-0,317711	-2,32145	0,024554
Age started taking MA & NAA+NAAG - Scan 1 Left DLPFC	50	-0,321984	-2,35626	0,022591
Age started taking MA & Ins - Scan 1 Left DLPFC	50	-0,052580	-0,36479	0,716873
Age started taking MA & GPC+PCh - Scan 1 Left DLPFC	49	-0,099409	-0,68491	0,496767
Length of drug taking & Glu - Scan 1 Right ACC	48	0,105427	0,71905	0,475747
Length of drug taking & Glu+Gln - Scan 1 Right ACC	48	-0,015281	-0,10365	0,917896
Length of drug taking & NAA - Scan 1 Right ACC	49	-0,067146	-0,46137	0,646661
Length of drug taking & NAA+NAAG - Scan 1 Right ACC	49	-0,110474	-0,76204	0,449846
Length of drug taking & Ins - Scan 1 Right ACC	49	-0,038007	-0,26075	0,795425
Length of drug taking & GPC+PCh - Scan 1 Right ACC	49	0,070513	0,48462	0,630195
Length of drug taking & Glu - Scan 1 Left ACC	50	0,105281	0,73349	0,466829
Length of drug taking & Glu+Gln - Scan 1 Left ACC	50	-0,010661	-0,07387	0,941422
Length of drug taking & NAA - Scan 1 Left ACC	50	-0,256332	-1,83731	0,072359
Length of drug taking & NAA+NAAG - Scan 1 Left ACC	50	-0,253069	-1,81231	0,076196
Length of drug taking & Ins - Scan 1 Left ACC	50	-0,212247	-1,50478	0,138934
Length of drug taking & GPC+PCh - Scan 1 Left ACC	50	-0,090382	-0,62876	0,532487
Length of drug taking & Glu - Scan 1 Right DLPFC	46	-0,170169	-1,14548	0,258203
Length of drug taking & Glu+Gln - Scan 1 Right DLPFC	46	-0,059986	-0,39862	0,692102
Length of drug taking & NAA - Scan 1 Right DLPFC	45	-0,258008	-1,75116	0,087049

Length of drug taking & NAA+NAAAG - Scan 1 Right DLPFC	46	-0,373319	-2,66930	0,010606
Length of drug taking & Ins - Scan 1 Right DLPFC	46	-0,014194	-0,09416	0,925408
Length of drug taking & GPC+PCh - Scan 1 Right DLPFC	46	-0,182774	-1,23316	0,224065
Length of drug taking & Glu - Scan 1 Left DLPFC	47	-0,012122	-0,08132	0,935545
Length of drug taking & Glu+Gln - Scan 1 Left DLPFC	47	0,107102	0,72262	0,473652
Length of drug taking & NAA - Scan 1 Left DLPFC	50	-0,403826	-3,05824	0,003635
Length of drug taking & NAA+NAAAG - Scan 1 Left DLPFC	50	-0,320915	-2,34753	0,023069
Length of drug taking & Ins - Scan 1 Left DLPFC	50	-0,080669	-0,56072	0,577599
Length of drug taking & GPC+PCh - Scan 1 Left DLPFC	49	-0,078206	-0,53780	0,593254
Duration of abstinence Scan 1 & Glu - Scan 1 Right ACC	48	0,058401	0,39677	0,693372
Duration of abstinence Scan 1 & Glu+Gln - Scan 1 Right ACC	48	-0,087498	-0,59573	0,554279
Duration of abstinence Scan 1 & NAA - Scan 1 Right ACC	49	0,100559	0,69291	0,491777
Duration of abstinence Scan 1 & NAA+NAAAG - Scan 1 Right ACC	49	0,029981	0,20563	0,837967
Duration of abstinence Scan 1 & Ins - Scan 1 Right ACC	49	-0,019951	-0,13681	0,891767
Duration of abstinence Scan 1 & GPC+PCh - Scan 1 Right ACC	49	0,164263	1,14164	0,259388
Duration of abstinence Scan 1 & Glu - Scan 1 Left ACC	50	0,033239	0,23041	0,818752
Duration of abstinence Scan 1 & Glu+Gln - Scan 1 Left ACC	50	-0,026505	-0,18370	0,855023
Duration of abstinence Scan 1 & NAA - Scan 1 Left ACC	50	-0,265011	-1,90413	0,062897
Duration of abstinence Scan 1 & NAA+NAAAG - Scan 1 Left ACC	50	-0,230244	-1,63922	0,107706
Duration of abstinence Scan 1 & Ins - Scan 1 Left ACC	50	-0,116800	-0,81479	0,419217
Duration of abstinence Scan 1 & GPC+PCh - Scan 1 Left ACC	50	-0,124664	-0,87049	0,388366
Duration of abstinence Scan 1 & Glu - Scan 1 Right DLPFC	46	-0,020016	-0,13280	0,894958
Duration of abstinence Scan 1 & Glu+Gln - Scan 1 Right DLPFC	46	0,033758	0,22406	0,823751
Duration of abstinence Scan 1 & NAA - Scan 1 Right DLPFC	45	-0,222082	-1,49358	0,142586
Duration of abstinence Scan 1 & NAA+NAAAG - Scan 1 Right DLPFC	46	-0,329076	-2,31159	0,025544
Duration of abstinence Scan 1 & Ins - Scan 1 Right DLPFC	46	-0,025461	-0,16894	0,866617
Duration of abstinence Scan 1 & GPC+PCh - Scan 1 Right DLPFC	46	-0,255501	-1,75299	0,086569
Duration of abstinence Scan 1 & Glu - Scan 1 Left DLPFC	47	0,001145	0,00768	0,993908
Duration of abstinence Scan 1 & Glu+Gln - Scan 1 Left DLPFC	47	0,129992	0,87947	0,383817
Duration of abstinence Scan 1 & NAA - Scan 1 Left DLPFC	50	-0,333850	-2,45376	0,017818

Duration of abstinence Scan 1 & NAA+NAAAG - Scan 1 Left DLPFC	50	-0,352290	-2,60793	0,012105
Duration of abstinence Scan 1 & Ins - Scan 1 Left DLPFC	50	-0,027408	-0,18996	0,850139
Duration of abstinence Scan 1 & GPC+PCh - Scan 1 Left DLPFC	49	-0,154175	-1,06976	0,290191

Short-term abstinence
Full dataset

Group	Gender	Race	Age	Age started taking MA	Length of drug taking	Average dose	Duration of abstinence Scan 2	Level of education	Smoking History	Other Drug History	Other Drugs Info	Glu - Scan 1 Right ACC	Glu+Glu n - Scan 1 Left ACC	NAA - Scan 1 Right ACC	NAA+N - Scan 1 Left ACC	Ins - Scan 1 Right ACC	GPC+P Ch - Scan 1 Right ACC	Glu - Scan 1 Left ACC	Glu+Glu n - Scan 1 Left ACC	NAA - Scan 1 Left ACC	NAA+N - Scan 1 Left ACC	Ins - Scan 1 Left ACC	GPC+P Ch - Scan 1 Left ACC	Glu - Scan 1 Right DLPFC	Glu+Glu n - Scan 1 Right DLPFC	NAA - Scan 1 Right DLPFC	NAA+N - Scan 1 Right DLPFC	Ins - Scan 1 Right DLPFC	GPC+P Ch - Scan 1 Right DLPFC	Glu - Scan 1 Left DLPFC	Glu+Glu n - Scan 1 Left DLPFC	NAA - Scan 1 Left DLPFC	NAA+N - Scan 1 Left DLPFC	Ins - Scan 1 Left DLPFC	GPC+P Ch - Scan 1 Left DLPFC	GPC+P Ch - Scan 1 Left DLPFC				
Control	Male	Mixed-race	30	0	0	0	0	Undergrad	No	No		1,362	1,809	1,348	1,449	0,921	0,277	1,312	1,269	1,189	1,189	1,008	0,274	1,456	1,889	1,294	1,294	0,837	0,24	1,236	1,594	1,202	1,32	0,808	0,239					
Control	Male	White	23	0	0	0	0	Undergrad	No	No		1,76	1,881	1,204	1,287	1,089	0,272	1,57	1,805	1,295	1,295	0,957	0,275	0,99	0,99	1,313	1,313	0,857	0,234	1,222	1,222	1,36	1,36	0,824	0,227					
Control	Male	White	27	0	0	0	0	Undergrad	No	No		1,349	1,545	1,065	1,196	0,991	0,262	1,212	1,373	1,3	1,451	1,143	0,311	1,081	1,092	1,375	1,476	0,966	0,235	1,534	1,814	1,631	1,717	1,084	0,217					
Control	Male	White	23	0	0	0	0	Undergrad	No	No		1,502	1,648	1,174	1,279	0,949	0,299	1,63	1,952	1,457	1,457	1,117	0,355							1,482	1,836	1,493	1,616	1,051	0,26					
Control	Male	Black	22	0	0	0	0	Undergrad	No	No		1,352	1,697	1,367	1,367	0,936	0,268	1,55	1,55	1,119	1,208	1,164	0,26									1,639	1,639	1,252	0,285					
Control	Male	Black	34	0	0	0	0	No matrix	No	No		1,402	1,671	1,208	1,32	1,129	0,324	1,348	1,512	1,183	1,35	1,34	0,314	1,992	1,992	1,435	1,692	1,144	0,248	1,622	1,622	1,582	1,582	1,044	0,207					
Control	Male	White	25	0	0	0	0	Honours	No	No		1,09	1,428	1,247	1,247	0,867	0,284	1,373	1,44	1,117	1,169	1,166	0,312	1,536	1,536	1,507	1,695	0,937	0,264	1,217	1,604	1,462	1,462	0,918	0,241					
Control	Male	White	21	0	0	0	0	Undergrad	No	No		1,457	1,639	1,036	1,179	0,882	0,247	1,16	1,278	1,156	1,324	0,951	0,236	1,673	2,087	1,437	1,557	0,801	0,158	1,176	1,393	1,272	1,345	0,769	0,185					
Control	Male	White	27	0	0	0	0	Undergrad	No	No								1,513	1,513	1,257	1,474	1,107	0,296	1,105	1,345	1,461	1,613	1,114	0,219	1,588	1,865	1,369	1,411	1,03	0,198					
Control	Male	Black	24	0	0	0	0	Honours	No	No		1,355	1,355	1,239	1,411	0,938	0,248	1,508	1,76	1,1	1,19	1,01	0,219	1,414	1,414	1,461	1,478	0,904	0,186	0,913	0,913	1,273	1,358	0,936	0,18					
Control	Male	White	23	0	0	0	0	Undergrad	No	No		1,216	1,216	1,17	1,313	0,942	0,262	1,441	1,765	1,129	1,344	0,982	0,25	1,028	1,028	1,352	1,539	0,775	0,252	0,843	0,843	1,379	1,475	0,822	0,301					
Control	Male	White	22	0	0	0	0	Undergrad	No	Yes	Occasional	0,951	0,951	1,115	1,193	1,012	0,276	1,073	1,236	1,103	1,143	1,08	0,3	1,19	1,19	1,472	1,472	0,817	0,277	1,253	1,253	1,412	1,412	1,01	0,205					
Control	Male	White	23	0	0	0	0	Undergrad	No	No		1,105	1,216	1,2	1,289	0,955	0,232	1,398	1,398	1,444	1,511	1,22	0,308	1,44	1,678	1,384	1,564	0,973	0,249	1,182	1,182	1,463	1,695	0,843	0,294					
Control	Male	Black	24	0	0	0	0	Undergrad	Yes	No		1,341	1,518	1,019	1,019	1,007	0,274	1,321	1,794	1,032	1,032	1,106	0,251	1,386	1,827	1,238	1,275	0,938	0,239	1,165	1,165	1,267	1,466	0,979	0,208					
Control	Male	White	30	0	0	0	0	PhD	No	No								1,344	1,607	1,413	1,476	1,225	0,333							1,254	1,606	1,422	1,482	0,87	0,274					
Control	Male	White	53	0	0	0	0	Honours	No	No		1,196	1,476	1,103	1,103	1,168	0,253	1,303	1,569	1,067	1,106	1,105	0,243	1,75	2,028	1,455	1,126	0,208	1,281	1,281	1,477	1,583	0,933	0,182						
Control	Male	Black	20	0	0	0	0	Undergrad	No	No		1,105	1,105	1,2	1,371	0,989	0,288	1,183	1,183	1,254	1,431	0,904	0,313	1,549	1,989	1,355	1,539	0,792	0,276	1,552	1,552	1,427	1,427	0,914	0,245					
Control	Male	Black	38	0	0	0	0	PhD	No	No				1,146	1,157	1,202	0,276	1,236	1,681	1,106	1,106	1,147	0,305	1,234	1,234	1,14	1,14	0,96	0,226	1,429	1,429	1,245	1,245	1,164	0,28					

Control	Male	Black	49	0	0	0	0	0	1,084	1,134	1,095	1,095	0,892	0,283	0,943	1,079	1,076	1,088	0,809	0,255	1,489	1,814	1,058	1,058	1,026	0,296			1,037	1,163	0,876	0,339
Control	Male	Mixed-race	51	0	0	0	0	0	1,229	1,293	0,908	1,073	1,133	0,287	1,078	1,078	1,171	1,209	1,226	0,311	1,235	1,235	1,059	1,16	1,186	0,24	0,944	0,944	1,258	1,347	1,138	0,315
Control	Male	Mixed-race	21	0	0	0	0	0	1,263	1,263	1,228	1,316	1,069	0,307	1,052	1,085	1,237	1,346	0,992	0,298	1,475	1,861	1,298	1,587	1,11	0,267	1,431	1,725	1,356	1,577	1,157	0,231
Control	Male	Mixed-race	20	0	0	0	0	0	1,222	1,405	1,132	1,363	1,026	0,257	1,45	1,736	1,23	1,458	1,202	0,324	1,705	1,729	1,62	1,754	1,158	0,351	1,293	1,293	1,662	1,718	0,985	0,337
Meth	Male	Mixed-race	25	16		9			1,38	1,646	1,173	1,197	1,039	0,317	1,312	1,616	1,229	1,358	1,087	0,305	1,68	1,68	1,7	1,7	0,958	0,233	1,701	1,701	1,35	1,35	1,318	0,214
Meth	Male	Mixed-race	30	22	8																											
Meth	Male	Mixed-race	23	13	10	3	5		1,989	1,989	0,906	0,906	1,215	0,274	1,657	1,852	1,201	1,27	1,183	0,348	0,842	0,842	1,405	1,405	0,963	0,322	1,326	1,326	1,496	1,517	0,627	0,302
Meth	Male	Mixed-race	31	17	14	1	5		1,175	1,175	1,242	1,242	1,166	0,298	1,097	1,097	1,368	1,368	0,922	0,305	1,299	1,229	1,408	1,408	0,919	0,258	0,99	0,99	1,13	1,412	0,773	0,24
Meth	Male	Mixed-race	26	18	8	7	7		1,149	1,216	0,954	1,12	1,123	0,306	1,354	1,354	1,087	1,087	1,11	0,28	0,972	0,972	1,291	1,379	0,887	0,3	1,725	1,725	1,388	1,388	1,019	0,308
Meth	Male	Mixed-race	43	32	11	0,5	4,85		1,177	1,177	1,076	1,142	1,076	0,238	1,444	1,617	1,221	1,221	1,033	0,297												
Meth	Male	Mixed-race	28	19	10		5,14		1,157	1,157		1,396	1,166	0,32	1,121	1,121	1,13	1,137	1,116	0,312	1,139	1,768	1,643	1,643	1,07	0,296						
Meth	Male	Mixed-race	29	10	20	0,5	5,14		1,187	1,567	0,957	1,088	0,922	0,283	1,221	1,301	0,911	0,977	0,84	0,276	1,737	1,737	1,386	1,386	1,099	0,198	1,245	1,245	1,212	1,366	0,988	0,274
Meth	Male	Mixed-race	24	14	10	2	5,14		1,372	1,574	1,102	1,158	1,228	0,348	1,397	1,75	1,087	1,198	1,211	0,323	1,26	1,627	1,199	1,37	1,073	0,21	0,915	0,915	1,367	1,4	1,087	0,263
Meth	Male	Mixed-race	27	16	13		5		1,411	1,547	1,136	1,229	0,977	0,215	1,291	1,869	1,216	1,335	0,855	0,277	0,94	1,079	1,218	1,372	0,685	0,194	1,417	1,417	1,08	1,352	0,744	0,186
Meth	Male	Mixed-race	25	16	10		5,14		1,587	1,989	1,209	1,215	1,312	0,324							1,528	1,765	1,342	1,424	1,327	0,292	1,476	1,689	1,412	1,506	1,309	0,248
Meth	Male	Mixed-race	28	21	7	3	5		1,831	1,831	1,151	1,151	1,126	0,248	1,592	1,66	1,145	1,136	1,093	0,234	1,123	1,338	1,331	1,43	0,91	0,222						
Meth	Male	Mixed-race	24	11	13	1	7		1,411	1,789	1,219	1,267	0,931	0,314	1,5	1,5	1,308	1,465	1,199	0,324	1,011	1,166	1,373	1,428	0,59	0,294	0,976	1,185	1,13	1,13	0,71	0,242
Meth	Male	Mixed-race	35	14	21	0,125	5		1,326	1,869	0,993	1,042	0,938	0,279	1,228	1,415	1,034	1,056	0,993	0,273	1,258	1,31	1,232	1,259	0,991	0,197	1,227	1,551	0,866	1,049	0,851	0,183
Meth	Male	Black	31	23	8	2	5		1,035	1,035	1,173	1,197	1,114	0,302	1,284	1,44	1,261	1,291	1,022	0,334	1,674	1,966	1,339	1,345	0,921	0,238	1,517	1,658	1,202	1,202	1,038	0,267
Meth	Male	Mixed-race	23	15	8		5		1,047		0,927	0,935	1,055	0,214	1,312	1,444	1,104	1,161	1,053	0,261	1,601	1,771	1,31	1,384	1,242	0,203	1,378	1,378	1,405	1,469	0,841	0,256
Meth	Male	Mixed-race	33	23	10	2	6,57		1,268	1,379	1,062	1,136	1,053	0,262	1,045	1,045	1,395	1,395	1,243	0,29			1,139	1,381	1,098	0,215			1,568	1,568		0,32
Meth	Male	Mixed-race	22	13	9	0,5	4,14		1,151	1,467	1,019	1,079	0,942	0,271	1,243	1,459	1,011	1,011	0,813	0,254			1,539	1,539		0,284	1,5	2,08	1,312	1,312	1,126	0,19

Meth	Male	Mixed-race	23	12	11		5,14	No matric	Yes	Yes	Dagga, Mandrax	1,267	1,267	1,191	1,191	1,297	0,273	1,255	1,255	1,302	1,332	1,038	0,272	1,227	1,227		1,227	1,362	1,524	0,971	0,24	1,228	1,228	1,396	1,396	0,751	0,257
Meth	Male	Mixed-race	27	17	11	0,25	4,14	Matric	Yes	Yes	Dagga	1,384	1,899	1,101	1,197	0,986	0,254	1,376	1,687	1,053	1,216	0,865	0,232					1,162	1,162	0,726	0,214			1,18	1,391	0,93	0,208
Meth	Male	Mixed-race	30	20	10	0,75	4	No matric	Yes	Yes	Dagga	1,441	1,679	1,12	1,211	0,89	0,3	1,196	1,514	1,132	1,195	0,834	0,304	1,16	1,16	1,32	1,32	0,734	0,256	1,733	1,912	1,46	1,509	0,843	0,25		
Meth	Male	Mixed-race	20	14	6	0,5	4,42	No matric	Yes	Yes	Dagga, Mandrax	1,281	1,281	1,331	1,336	1,191	0,249	1,26	1,26	1,298	1,303	1,097	0,249														

Short-term abstinence
Descriptive statistics
Age and drug use variables – all groups

Variable		All Groups Descriptive Statistics (Short term abstinence.sta)																																			
		Valid N				Mean				Minimum				Maximum				Std.Dev.																			
Age		44				28,11364				20,00000				53,00000				7,977340																			
Age started taking MA		44				8,54545				0,00000				32,00000				9,327266																			
Length of drug taking		44				5,38636				0,00000				21,00000				6,031761																			
Duration of abstinence Scan 2		44				2,55432				0,00000				7,00000				2,643140																			

Right ACC - all groups

All Groups Descriptive Statistics (Short term abstinence.sta)						
Variable	Valid N	Mean	Minimum	Maximum	Std.Dev.	
Glu - Scan 1 Right ACC	40	1,309175	0,951000	1,989000	0,212753	
Glu+Gln - Scan 1 Right ACC	39	1,481615	0,951000	1,989000	0,281036	
NAA - Scan 1 Right ACC	40	1,131150	0,906000	1,367000	0,114182	
NAA+NAAg - Scan 1 Right ACC	41	1,206390	0,906000	1,449000	0,124105	
Ins - Scan 1 Right ACC	41	1,044976	0,867000	1,312000	0,118637	
GPC+PCh - Scan 1 Right ACC	41	0,277195	0,214000	0,348000	0,029801	

Left ACC - all groups

Variable	All Groups Descriptive Statistics (Short term abstinence.sta)				
	Valid N	Mean	Minimum	Maximum	Std.Dev.
Glu - Scan 1 Left ACC	42	1,313881	0,943000	1,657000	0,169752
Glu+Gln - Scan 1 Left ACC	42	1,474262	1,045000	1,952000	0,249365
NAA - Scan 1 Left ACC	42	1,188762	0,911000	1,457000	0,123289
NAA+NAAG - Scan 1 Left ACC	42	1,258786	0,977000	1,511000	0,144317
Ins - Scan 1 Left ACC	42	1,061143	0,809000	1,340000	0,132285
GPC+PCh - Scan 1 Left ACC	42	0,287929	0,219000	0,355000	0,033598

Right DLPFC - all groups

Variable	All Groups Descriptive Statistics (Short term abstinence.sta)				
	Valid N	Mean	Minimum	Maximum	Std.Dev.
Glu - Scan 1 Right DLPFC	36	1,340028	0,842000	1,992000	0,279921
Glu+Gln - Scan 1 Right DLPFC	36	1,490472	0,842000	2,087000	0,364392
NAA - Scan 1 Right DLPFC	39	1,347051	1,058000	1,700000	0,148954
NAA+NAAG - Scan 1 Right DLPFC	39	1,426718	1,058000	1,754000	0,169304
Ins - Scan 1 Right DLPFC	38	0,958605	0,590000	1,327000	0,161272
GPC+PCh - Scan 1 Right DLPFC	39	0,245000	0,158000	0,351000	0,040273

Left DLPFC - all groups

Variable	All Groups Descriptive Statistics (Short term abstinence.sta)				
	Valid N	Mean	Minimum	Maximum	Std.Dev.
Glu - Scan 1 Right DLPFC	36	1,340028	0,842000	1,992000	0,279921
Glu+Gln - Scan 1 Right DLPFC	36	1,490472	0,842000	2,087000	0,364392
NAA - Scan 1 Right DLPFC	39	1,347051	1,058000	1,700000	0,148954
NAA+NAAG - Scan 1 Right DLPFC	39	1,426718	1,058000	1,754000	0,169304
Ins - Scan 1 Right DLPFC	38	0,958605	0,590000	1,327000	0,161272
GPC+PCh - Scan 1 Right DLPFC	39	0,245000	0,158000	0,351000	0,040273

Age and drug use variables – control group

Variable	Group=Control Descriptive Statistics (Short term abstinence.sta)				
	Valid N	Mean	Minimum	Maximum	Std.Dev.
Age	22	28,63636	20,00000	53,00000	10,16786
Age started taking MA	22	0,00000	0,00000	0,00000	0,00000
Length of drug taking	22	0,00000	0,00000	0,00000	0,00000
Duration of abstinence Scan 2	22	0,00000	0,00000	0,00000	0,00000

Right ACC – control group

Variable	Group=Control Descriptive Statistics (Short term abstinence.sta)				
	Valid N	Mean	Minimum	Maximum	Std.Dev.
Glu - Scan 1 Right ACC	19	1,281105	0,951000	1,760000	0,184587
Glu+Gln - Scan 1 Right ACC	19	1,434211	0,951000	1,881000	0,253591
NAA - Scan 1 Right ACC	20	1,160200	0,908000	1,367000	0,108246
NAA+NAAG - Scan 1 Right ACC	20	1,251350	1,019000	1,449000	0,120028
Ins - Scan 1 Right ACC	20	1,004850	0,867000	1,202000	0,097896
GPC+PCh - Scan 1 Right ACC	20	0,273800	0,232000	0,324000	0,021768

Left ACC – control group

Variable	Group=Control Descriptive Statistics (Short term abstinence.sta)				
	Valid N	Mean	Minimum	Maximum	Std.Dev.
Glu - Scan 1 Left ACC	22	1,318091	0,943000	1,630000	0,185521
Glu+Gln - Scan 1 Left ACC	22	1,484682	1,078000	1,952000	0,263169
NAA - Scan 1 Left ACC	22	1,201591	1,032000	1,457000	0,121414
NAA+NAAG - Scan 1 Left ACC	22	1,288955	1,032000	1,511000	0,150370
Ins - Scan 1 Left ACC	22	1,089136	0,809000	1,340000	0,125834
GPC+PCh - Scan 1 Left ACC	22	0,288318	0,219000	0,355000	0,035376

Right DLPFC – control group

Variable	Group=Control Descriptive Statistics (Short term abstinence.sta)				
	Valid N	Mean	Minimum	Maximum	Std.Dev.
Glu - Scan 1 Right DLPFC	19	1,406737	0,990000	1,992000	0,268036
Glu+Gln - Scan 1 Right DLPFC	19	1,576737	0,990000	2,087000	0,371416
NAA - Scan 1 Right DLPFC	19	1,353368	1,058000	1,620000	0,148752
NAA+NAAG - Scan 1 Right DLPFC	19	1,455842	1,058000	1,754000	0,197982
Ins - Scan 1 Right DLPFC	19	0,969526	0,775000	1,186000	0,137196
GPC+PCh - Scan 1 Right DLPFC	19	0,245526	0,158000	0,351000	0,041163

Left DLPFC – control group

Variable	Group=Control Descriptive Statistics (Short term abstinence.sta)				
	Valid N	Mean	Minimum	Maximum	Std.Dev.
Glu - Scan 1 Left DLPFC	20	1,280850	0,843000	1,622000	0,219948
Glu+Gln - Scan 1 Left DLPFC	20	1,406800	0,843000	1,865000	0,309021
NAA - Scan 1 Left DLPFC	22	1,394909	1,037000	1,662000	0,155185
NAA+NAAG - Scan 1 Left DLPFC	22	1,472727	1,163000	1,718000	0,152959
Ins - Scan 1 Left DLPFC	22	0,973045	0,769000	1,252000	0,131635
GPC+PCh - Scan 1 Left DLPFC	22	0,247727	0,180000	0,339000	0,049395

Age and drug use variables – MA group

Variable	Group=Meth Descriptive Statistics (Short term abstinence.sta)				
	Valid N	Mean	Minimum	Maximum	Std.Dev.
Age	22	27,59091	20,00000	43,00000	5,133078
Age started taking MA	22	17,09091	10,00000	32,00000	5,013402
Length of drug taking	22	10,77273	6,00000	21,00000	3,702404
Duration of abstinence Scan 2	22	5,10864	4,00000	7,00000	0,796608

Right ACC - MA group

Variable	Group=Meth Descriptive Statistics (Short term abstinence.sta)				
	Valid N	Mean	Minimum	Maximum	Std.Dev.
Glu - Scan 1 Right ACC	21	1,334571	1,035000	1,989000	0,237010
Glu+Gln - Scan 1 Right ACC	20	1,526650	1,035000	1,989000	0,304396
NAA - Scan 1 Right ACC	20	1,102100	0,906000	1,331000	0,115184
NAA+NAAG - Scan 1 Right ACC	21	1,163571	0,906000	1,396000	0,114767
Ins - Scan 1 Right ACC	21	1,083190	0,890000	1,312000	0,126101
GPC+PCh - Scan 1 Right ACC	21	0,280429	0,214000	0,348000	0,036105

Left ACC - MA group

Variable	Group=Meth Descriptive Statistics (Short term abstinence.sta)				
	Valid N	Mean	Minimum	Maximum	Std.Dev.
Glu - Scan 1 Left ACC	20	1,309250	1,045000	1,657000	0,155234
Glu+Gln - Scan 1 Left ACC	20	1,462800	1,045000	1,869000	0,239523
NAA - Scan 1 Left ACC	20	1,174650	0,911000	1,395000	0,126915
NAA+NAAG - Scan 1 Left ACC	20	1,225600	0,977000	1,465000	0,133187
Ins - Scan 1 Left ACC	20	1,030350	0,813000	1,243000	0,135482
GPC+PCh - Scan 1 Left ACC	20	0,287500	0,232000	0,348000	0,032440

Right DLPFC - MA group

Variable	Group=Meth Descriptive Statistics (Short term abstinence.sta)				
	Valid N	Mean	Minimum	Maximum	Std.Dev.
Glu - Scan 1 Right DLPFC	17	1,265471	0,842000	1,737000	0,281760
Glu+Gln - Scan 1 Right DLPFC	17	1,394059	0,842000	1,966000	0,341398
NAA - Scan 1 Right DLPFC	20	1,341050	1,122000	1,700000	0,152756
NAA+NAAG - Scan 1 Right DLPFC	20	1,399050	1,122000	1,700000	0,136160
Ins - Scan 1 Right DLPFC	19	0,947684	0,590000	1,327000	0,185438
GPC+PCh - Scan 1 Right DLPFC	20	0,244500	0,194000	0,322000	0,040473

Left DLPFC - MA_group

Variable	Group=Meth Descriptive Statistics (Short term abstinence.sta)				
	Valid N	Mean	Minimum	Maximum	Std.Dev.
Glu - Scan 1 Left DLPFC	16	1,334188	0,915000	1,733000	0,271516
Glu+Gln - Scan 1 Left DLPFC	16	1,437063	0,915000	2,080000	0,341246
NAA - Scan 1 Left DLPFC	18	1,279778	0,866000	1,568000	0,179864
NAA+NAAG - Scan 1 Left DLPFC	18	1,355500	1,049000	1,568000	0,150424
Ins - Scan 1 Left DLPFC	17	0,931529	0,627000	1,318000	0,199341
GPC+PCh - Scan 1 Left DLPFC	18	0,243167	0,169000	0,320000	0,044206

Frequency tables - age and drug use variables

Frequency table: Age (Short term abstinence.sta) Shapiro-Wilk W=,79789, p=,00000						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
15,00000<x<=20,00000	3	3	6,81818	6,8182	6,81818	6,8182
20,00000<x<=25,00000	19	22	43,18182	50,0000	43,18182	50,0000
25,00000<x<=30,00000	12	34	27,27273	77,2727	27,27273	77,2727
30,00000<x<=35,00000	5	39	11,36364	88,6364	11,36364	88,6364
35,00000<x<=40,00000	1	40	2,27273	90,9091	2,27273	90,9091
40,00000<x<=45,00000	1	41	2,27273	93,1818	2,27273	93,1818
45,00000<x<=50,00000	1	42	2,27273	95,4545	2,27273	95,4545
50,00000<x<=55,00000	2	44	4,54545	100,0000	4,54545	100,0000
Missing	0	44	0,00000		0,00000	100,0000

Age started using MA

Frequency table: Age started taking MA (Short term abstinence.sta) Shapiro-Wilk W=,80611, p=,00000						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
-5,00000<x<=0,000000	22	22	50,00000	50,0000	50,00000	50,0000
0,000000<x<=5,000000	0	22	0,00000	50,0000	0,00000	50,0000
5,000000<x<=10,00000	1	23	2,27273	52,2727	2,27273	52,2727
10,00000<x<=15,00000	8	31	18,18182	70,4545	18,18182	70,4545
15,00000<x<=20,00000	8	39	18,18182	88,6364	18,18182	88,6364
20,00000<x<=25,00000	4	43	9,09091	97,7273	9,09091	97,7273
25,00000<x<=30,00000	0	43	0,00000	97,7273	0,00000	97,7273
30,00000<x<=35,00000	1	44	2,27273	100,0000	2,27273	100,0000
Missing	0	44	0,00000		0,00000	100,0000

Length of MA use

Frequency table: Length of drug taking (Short term abstinence.sta) Shapiro-Wilk W=,80200, p=,00000						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
-5,00000<x<=0,000000	22	22	50,00000	50,0000	50,00000	50,0000
0,000000<x<=5,000000	0	22	0,00000	50,0000	0,00000	50,0000
5,000000<x<=10,00000	14	36	31,81818	81,8182	31,81818	81,8182
10,00000<x<=15,00000	6	42	13,63636	95,4545	13,63636	95,4545
15,00000<x<=20,00000	1	43	2,27273	97,7273	2,27273	97,7273
20,00000<x<=25,00000	1	44	2,27273	100,0000	2,27273	100,0000
Missing	0	44	0,00000		0,00000	100,0000

Duration of abstinence

Frequency table: Duration of abstinence Scan 2 (Short term abstinence.sta) Shapiro-Wilk W=,74276, p=,00000						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
-1,00000<x<=0,000000	22	22	50,00000	50,0000	50,00000	50,0000
0,000000<x<=1,000000	0	22	0,00000	50,0000	0,00000	50,0000
1,000000<x<=2,000000	0	22	0,00000	50,0000	0,00000	50,0000
2,000000<x<=3,000000	0	22	0,00000	50,0000	0,00000	50,0000
3,000000<x<=4,000000	1	23	2,27273	52,2727	2,27273	52,2727
4,000000<x<=5,000000	13	36	29,54545	81,8182	29,54545	81,8182
5,000000<x<=6,000000	5	41	11,36364	93,1818	11,36364	93,1818
6,000000<x<=7,000000	3	44	6,81818	100,0000	6,81818	100,0000
Missing	0	44	0,00000		0,00000	100,0000

Metabolites per brain area

Glu - right ACC

Frequency table: Glu - Scan 1 Right ACC (Short term abstinence.sta) Shapiro-Wilk W=,91299, p=,00467						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
,8000000<x<=1,000000	1	1	2,50000	2,5000	2,27273	2,2727
1,000000<x<=1,200000	13	14	32,50000	35,0000	29,54545	31,8182
1,200000<x<=1,400000	16	30	40,00000	75,0000	36,36364	68,1818
1,400000<x<=1,600000	7	37	17,50000	92,5000	15,90909	84,0909
1,600000<x<=1,800000	1	38	2,50000	95,0000	2,27273	86,3636
1,800000<x<=2,000000	2	40	5,00000	100,0000	4,54545	90,9091
Missing	4	44	10,00000		9,09091	100,0000

Glu+Gln - right ACC

Frequency table: Glu+Gln - Scan 1 Right ACC (Short term abstinence.sta) Shapiro-Wilk W=,96807, p=,32693						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
,8000000<x<=1,000000	1	1	2,56410	2,5641	2,27273	2,2727
1,000000<x<=1,200000	6	7	15,38462	17,9487	13,63636	15,9091
1,200000<x<=1,400000	9	16	23,07692	41,0256	20,45455	36,3636
1,400000<x<=1,600000	9	25	23,07692	64,1026	20,45455	56,8182
1,600000<x<=1,800000	7	32	17,94872	82,0513	15,90909	72,7273
1,800000<x<=2,000000	7	39	17,94872	100,0000	15,90909	88,6364
Missing	5	44	12,82051		11,36364	100,0000

NAA - right ACC

Frequency table: NAA - Scan 1 Right ACC (Short term abstinence.sta) Shapiro-Wilk W=,97324, p=,45307						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
,8000000<x<=,9000000	0	0	0,00000	0,0000	0,00000	0,0000
,9000000<x<=1,000000	6	6	15,00000	15,0000	13,63636	13,6364
1,000000<x<=1,100000	7	13	17,50000	32,5000	15,90909	29,5455
1,100000<x<=1,200000	16	29	40,00000	72,5000	36,36364	65,9091
1,200000<x<=1,300000	8	37	20,00000	92,5000	18,18182	84,0909
1,300000<x<=1,400000	3	40	7,50000	100,0000	6,81818	90,9091
Missing	4	44	10,00000		9,09091	100,0000

NAA+NAAG - right ACC

Frequency table: NAA+NAAG - Scan 1 Right ACC (Short term abstinence.sta) Shapiro-Wilk W=,98590, p=,88323						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
,8000000<x<=,9000000	0	0	0,00000	0,0000	0,00000	0,0000
,9000000<x<=1,000000	2	2	4,87805	4,8780	4,54545	4,5455
1,000000<x<=1,100000	6	8	14,63415	19,5122	13,63636	18,1818
1,100000<x<=1,200000	14	22	34,14634	53,6585	31,81818	50,0000
1,200000<x<=1,300000	9	31	21,95122	75,6098	20,45455	70,4545
1,300000<x<=1,400000	8	39	19,51220	95,1220	18,18182	88,6364
1,400000<x<=1,500000	2	41	4,87805	100,0000	4,54545	93,1818
Missing	3	44	7,31707		6,81818	100,0000

Ins - right ACC

Frequency table: Ins - Scan 1 Right ACC (Short term abstinence.sta) Shapiro-Wilk W=,94999, p=,06992						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
,8000000<x<=,9000000	4	4	9,75610	9,7561	9,09091	9,0909
,9000000<x<=1,000000	14	18	34,14634	43,9024	31,81818	40,9091
1,000000<x<=1,100000	9	27	21,95122	65,8537	20,45455	61,3636
1,100000<x<=1,200000	9	36	21,95122	87,8049	20,45455	81,8182
1,200000<x<=1,300000	4	40	9,75610	97,5610	9,09091	90,9091
1,300000<x<=1,400000	1	41	2,43902	100,0000	2,27273	93,1818
Missing	3	44	7,31707		6,81818	100,0000

GPC+PCh - right ACC

Frequency table: GPC+PCh - Scan 1 Right ACC (Short term abstinence.sta) Shapiro-Wilk W= ,98794, p= ,93585						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
,2000000<x<=,2200000	2	2	4,87805	4,8780	4,54545	4,5455
,2200000<x<=,2400000	2	4	4,87805	9,7561	4,54545	9,0909
,2400000<x<=,2600000	7	11	17,07317	26,8293	15,90909	25,0000
,2600000<x<=,2800000	13	24	31,70732	58,5366	29,54545	54,5455
,2800000<x<=,3000000	8	32	19,51220	78,0488	18,18182	72,7273
,3000000<x<=,3200000	6	38	14,63415	92,6829	13,63636	86,3636
,3200000<x<=,3400000	2	40	4,87805	97,5610	4,54545	90,9091
,3400000<x<=,3600000	1	41	2,43902	100,0000	2,27273	93,1818
Missing	3	44	7,31707		6,81818	100,0000

Glu - left ACC

Frequency table: Glu - Scan 1 Left ACC (Short term abstinence.sta) Shapiro-Wilk W= ,98774, p= ,92642						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
,8000000<x<=,9000000	0	0	0,00000	0,0000	0,00000	0,0000
,9000000<x<=1,000000	1	1	2,38095	2,3810	2,27273	2,2727
1,000000<x<=1,100000	5	6	11,90476	14,2857	11,36364	13,6364
1,100000<x<=1,200000	4	10	9,52381	23,8095	9,09091	22,7273
1,200000<x<=1,300000	9	19	21,42857	45,2381	20,45455	43,1818
1,300000<x<=1,400000	12	31	28,57143	73,8095	27,27273	70,4545
1,400000<x<=1,500000	4	35	9,52381	83,3333	9,09091	79,5455
1,500000<x<=1,600000	5	40	11,90476	95,2381	11,36364	90,9091
1,600000<x<=1,700000	2	42	4,76190	100,0000	4,54545	95,4545
Missing	2	44	4,76190		4,54545	100,0000

Glu+Gln - left ACC

Frequency table: Glu+Gln - Scan 1 Left ACC (Short term abstinence.sta) Shapiro-Wilk W=,96756, p=,27281						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
,800000<x<=1,000000	0	0	0,00000	0,0000	0,00000	0,0000
1,000000<x<=1,200000	7	7	16,66667	16,6667	15,90909	15,9091
1,200000<x<=1,400000	9	16	21,42857	38,0952	20,45455	36,3636
1,400000<x<=1,600000	11	27	26,19048	64,2857	25,00000	61,3636
1,600000<x<=1,800000	11	38	26,19048	90,4762	25,00000	86,3636
1,800000<x<=2,000000	4	42	9,52381	100,0000	9,09091	95,4545
Missing	2	44	4,76190		4,54545	100,0000

NAA - left ACC

Frequency table: NAA - Scan 1 Left ACC (Short term abstinence.sta) Shapiro-Wilk W=,97607, p=,51500						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
,8000000<x<=,90000000	0	0	0,00000	0,0000	0,00000	0,0000
,90000000<x<=1,0000000	1	1	2,38095	2,3810	2,27273	2,2727
1,000000<x<=1,100000	9	10	21,42857	23,8095	20,45455	22,7273
1,100000<x<=1,200000	13	23	30,95238	54,7619	29,54545	52,2727
1,200000<x<=1,300000	12	35	28,57143	83,3333	27,27273	79,5455
1,300000<x<=1,400000	4	39	9,52381	92,8571	9,09091	88,6364
1,400000<x<=1,500000	3	42	7,14286	100,0000	6,81818	95,4545
Missing	2	44	4,76190		4,54545	100,0000

NAA+NAAG - left ACC

Frequency table: NAA+NAAG - Scan 1 Left ACC (Short term abstinence.sta) Shapiro-Wilk W=,96578, p=,23667						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
,9000000<x<=1,000000	1	1	2,38095	2,3810	2,27273	2,2727
1,000000<x<=1,100000	5	6	11,90476	14,2857	11,36364	13,6364
1,100000<x<=1,200000	11	17	26,19048	40,4762	25,00000	38,6364
1,200000<x<=1,300000	7	24	16,66667	57,1429	15,90909	54,5455
1,300000<x<=1,400000	10	34	23,80952	80,9524	22,72727	77,2727
1,400000<x<=1,500000	7	41	16,66667	97,6190	15,90909	93,1818
1,500000<x<=1,600000	1	42	2,38095	100,0000	2,27273	95,4545
Missing	2	44	4,76190		4,54545	100,0000

Ins - left ACC

Frequency table: Ins - Scan 1 Left ACC (Short term abstinence.sta) Shapiro-Wilk W=,96737, p=,26879						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
,7000000<x<=,8000000	0	0	0,00000	0,0000	0,00000	0,0000
,8000000<x<=,9000000	6	6	14,28571	14,2857	13,63636	13,6364
,9000000<x<=1,000000	7	13	16,66667	30,9524	15,90909	29,5455
1,000000<x<=1,100000	10	23	23,80952	54,7619	22,72727	52,2727
1,100000<x<=1,200000	12	35	28,57143	83,3333	27,27273	79,5455
1,200000<x<=1,300000	6	41	14,28571	97,6190	13,63636	93,1818
1,300000<x<=1,400000	1	42	2,38095	100,0000	2,27273	95,4545
Missing	2	44	4,76190		4,54545	100,0000

GPC+PCh - left ACC

Frequency table: GPC+PCh - Scan 1 Left ACC (Short term abstinence.sta) Shapiro-Wilk W=,97261, p=,40237						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
,200000<x<=,2200000	1	1	2,38095	2,3810	2,27273	2,2727
,2200000<x<=,2400000	3	4	7,14286	9,5238	6,81818	9,0909
,2400000<x<=,2600000	7	11	16,66667	26,1905	15,90909	25,0000
,2600000<x<=,2800000	8	19	19,04762	45,2381	18,18182	43,1818
,2800000<x<=,3000000	5	24	11,90476	57,1429	11,36364	54,5455
,3000000<x<=,3200000	11	35	26,19048	83,3333	25,00000	79,5455
,3200000<x<=,3400000	5	40	11,90476	95,2381	11,36364	90,9091
,3400000<x<=,3600000	2	42	4,76190	100,0000	4,54545	95,4545
Missing	2	44	4,76190		4,54545	100,0000

Glu - right DLPFC

Frequency table: Glu - Scan 1 Right DLPFC (Short term abstinence.sta) Shapiro-Wilk W=,97068, p=,44449						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
,6000000<x<=,8000000	0	0	0,00000	0,0000	0,00000	0,0000
,8000000<x<=1,000000	4	4	11,11111	11,1111	9,09091	9,0909
1,000000<x<=1,200000	9	13	25,00000	36,1111	20,45455	29,5455
1,200000<x<=1,400000	7	20	19,44444	55,5556	15,90909	45,4545
1,400000<x<=1,600000	8	28	22,22222	77,7778	18,18182	63,6364
1,600000<x<=1,800000	7	35	19,44444	97,2222	15,90909	79,5455
1,800000<x<=2,000000	1	36	2,77778	100,0000	2,27273	81,8182
Missing	8	44	22,22222		18,18182	100,0000

Glu+Gln - right DLPFC

Frequency table: Glu+Gln - Scan 1 Right DLPFC (Short term abstinence.sta) Shapiro-Wilk W=,93319, p=,03130						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
,600000<x<=1,800000	0	0	0,00000	0,0000	0,00000	0,0000
,800000<x<=1,000000	3	3	8,33333	8,3333	6,81818	6,8182
1,000000<x<=1,200000	7	10	19,44444	27,7778	15,90909	22,7273
1,200000<x<=1,400000	7	17	19,44444	47,2222	15,90909	38,6364
1,400000<x<=1,600000	2	19	5,55556	52,7778	4,54545	43,1818
1,600000<x<=1,800000	8	27	22,22222	75,0000	18,18182	61,3636
1,800000<x<=2,000000	7	34	19,44444	94,4444	15,90909	77,2727
2,000000<x<=2,200000	2	36	5,55556	100,0000	4,54545	81,8182
Missing	8	44	22,22222		18,18182	100,0000

NAA - right DLPFC

Frequency table: NAA - Scan 1 Right DLPFC (Short term abstinence.sta) Shapiro-Wilk W=,97954, p=,68682						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
,9000000<x<=1,000000	0	0	0,00000	0,0000	0,00000	0,0000
1,000000<x<=1,100000	2	2	5,12821	5,1282	4,54545	4,5455
1,100000<x<=1,200000	5	7	12,82051	17,9487	11,36364	15,9091
1,200000<x<=1,300000	6	13	15,38462	33,3333	13,63636	29,5455
1,300000<x<=1,400000	13	26	33,33333	66,6667	29,54545	59,0909
1,400000<x<=1,500000	8	34	20,51282	87,1795	18,18182	77,2727
1,500000<x<=1,600000	2	36	5,12821	92,3077	4,54545	81,8182
1,600000<x<=1,700000	3	39	7,69231	100,0000	6,81818	88,6364
Missing	5	44	12,82051		11,36364	100,0000

NAA+NAAG - right DLPFC

Frequency table: NAA+NAAG - Scan 1 Right DLPFC (Short term abstinence.sta) Shapiro-Wilk W=,98047, p=,72047						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
,900000<x<=1,000000	0	0	0,00000	0,0000	0,00000	0,0000
1,000000<x<=1,100000	1	1	2,56410	2,5641	2,27273	2,2727
1,100000<x<=1,200000	4	5	10,25641	12,8205	9,09091	11,3636
1,200000<x<=1,300000	3	8	7,69231	20,5128	6,81818	18,1818
1,300000<x<=1,400000	9	17	23,07692	43,5897	20,45455	38,6364
1,400000<x<=1,500000	9	26	23,07692	66,6667	20,45455	59,0909
1,500000<x<=1,600000	7	33	17,94872	84,6154	15,90909	75,0000
1,600000<x<=1,700000	5	38	12,82051	97,4359	11,36364	86,3636
1,700000<x<=1,800000	1	39	2,56410	100,0000	2,27273	88,6364
Missing	5	44	12,82051		11,36364	100,0000

Ins - right DLPFC

Frequency table: Ins - Scan 1 Right DLPFC (Short term abstinence.sta) Shapiro-Wilk W=,99225, p=,99485						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
,5000000<x<=,60000000	1	1	2,63158	2,6316	2,27273	2,2727
,60000000<x<=,70000000	1	2	2,63158	5,2632	2,27273	4,5455
,70000000<x<=,80000000	4	6	10,52632	15,7895	9,09091	13,6364
,80000000<x<=,90000000	6	12	15,78947	31,5789	13,63636	27,2727
,90000000<x<=1,000000	13	25	34,21053	65,7895	29,54545	56,8182
1,00000000<x<=1,100000	5	30	13,15789	78,9474	11,36364	68,1818
1,10000000<x<=1,200000	6	36	15,78947	94,7368	13,63636	81,8182
1,20000000<x<=1,300000	1	37	2,63158	97,3684	2,27273	84,0909
1,30000000<x<=1,400000	1	38	2,63158	100,0000	2,27273	86,3636
Missing	6	44	15,78947		13,63636	100,0000

GPC+PCh - right DLPFC

Frequency table: GPC+PCh - Scan 1 Right DLPFC (Short term abstinence.sta) Shapiro-Wilk W=,98294, p=,80768						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
,1000000<x<=,1500000	0	0	0,00000	0,0000	0,00000	0,0000
,1500000<x<=,2000000	5	5	12,82051	12,8205	11,36364	11,3636
,2000000<x<=,2500000	19	24	48,71795	61,5385	43,18182	54,5455
,2500000<x<=,3000000	13	37	33,33333	94,8718	29,54545	84,0909
,3000000<x<=,3500000	1	38	2,56410	97,4359	2,27273	86,3636
,3500000<x<=,4000000	1	39	2,56410	100,0000	2,27273	88,6364
Missing	5	44	12,82051		11,36364	100,0000

Glu - left DLPFC

Frequency table: Glu - Scan 1 Left DLPFC (Short term abstinence.sta) Shapiro-Wilk W=,96510, p=,30705						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
,6000000<x<=,8000000	0	0	0,00000	0,0000	0,00000	0,0000
,8000000<x<=,1,000000	7	7	19,44444	19,4444	15,90909	15,9091
1,000000<x<=1,200000	3	10	8,33333	27,7778	6,81818	22,7273
1,200000<x<=1,400000	12	22	33,33333	61,1111	27,27273	50,0000
1,400000<x<=1,600000	10	32	27,77778	88,8889	22,72727	72,7273
1,600000<x<=1,800000	4	36	11,11111	100,0000	9,09091	81,8182
Missing	8	44	22,22222		18,18182	100,0000

Glu+Gln - left DLPFC

Frequency table: Glu+Gln - Scan 1 Left DLPFC (Short term abstinence.sta) Shapiro-Wilk W=,97282, p=,50747						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
,600000<x<=,8000000	0	0	0,00000	0,0000	0,00000	0,0000
,800000<x<=1,000000	6	6	16,66667	16,6667	13,63636	13,6364
1,000000<x<=1,200000	3	9	8,33333	25,0000	6,81818	20,4545
1,200000<x<=1,400000	9	18	25,00000	50,0000	20,45455	40,9091
1,400000<x<=1,600000	5	23	13,88889	63,8889	11,36364	52,2727
1,600000<x<=1,800000	8	31	22,22222	86,1111	18,18182	70,4545
1,800000<x<=2,000000	4	35	11,11111	97,2222	9,09091	79,5455
2,000000<x<=2,200000	1	36	2,77778	100,0000	2,27273	81,8182
Missing	8	44	22,22222		18,18182	100,0000

NAA - left DLPFC

Frequency table: NAA - Scan 1 Left DLPFC (Short term abstinence.sta) Shapiro-Wilk W=,97807, p=,61809						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
,700000<x<=,8000000	0	0	0,00000	0,0000	0,00000	0,0000
,800000<x<=,9000000	1	1	2,50000	2,5000	2,27273	2,2727
,900000<x<=1,000000	0	1	0,00000	2,5000	0,00000	2,2727
1,000000<x<=1,100000	3	4	7,50000	10,0000	6,81818	9,0909
1,100000<x<=1,200000	3	7	7,50000	17,5000	6,81818	15,9091
1,200000<x<=1,300000	8	15	20,00000	37,5000	18,18182	34,0909
1,300000<x<=1,400000	9	24	22,50000	60,0000	20,45455	54,5455
1,400000<x<=1,500000	11	35	27,50000	87,5000	25,00000	79,5455
1,500000<x<=1,600000	2	37	5,00000	92,5000	4,54545	84,0909
1,600000<x<=1,700000	3	40	7,50000	100,0000	6,81818	90,9091
Missing	4	44	10,00000		9,09091	100,0000

NAA+NAAG – left DLPFC

Frequency table: NAA+NAAG - Scan 1 Left DLPFC (Short term abstinence.sta) Shapiro-Wilk W=,97148, p=,40030						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
,9000000<x<=1,000000	0	0	0,00000	0,0000	0,00000	0,0000
1,000000<x<=1,100000	2	2	5,00000	5,0000	4,54545	4,5455
1,100000<x<=1,200000	2	4	5,00000	10,0000	4,54545	9,0909
1,200000<x<=1,300000	2	6	5,00000	15,0000	4,54545	13,6364
1,300000<x<=1,400000	13	19	32,50000	47,5000	29,54545	43,1818
1,400000<x<=1,500000	9	28	22,50000	70,0000	20,45455	63,6364
1,500000<x<=1,600000	7	35	17,50000	87,5000	15,90909	79,5455
1,600000<x<=1,700000	3	38	7,50000	95,0000	6,81818	86,3636
1,700000<x<=1,800000	2	40	5,00000	100,0000	4,54545	90,9091
Missing	4	44	10,00000		9,09091	100,0000

Ins – left DLPFC

Frequency table: Ins - Scan 1 Left DLPFC (Short term abstinence.sta) Shapiro-Wilk W=,97936, p=,68020						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
,5000000<x<=,6000000	0	0	0,00000	0,0000	0,00000	0,0000
,6000000<x<=,7000000	1	1	2,56410	2,5641	2,27273	2,2727
,7000000<x<=,8000000	5	6	12,82051	15,3846	11,36364	13,6364
,8000000<x<=,9000000	10	16	25,64103	41,0256	22,72727	36,3636
,9000000<x<=1,000000	8	24	20,51282	61,5385	18,18182	54,5455
1,000000<x<=1,100000	8	32	20,51282	82,0513	18,18182	72,7273
1,100000<x<=1,200000	4	36	10,25641	92,3077	9,09091	81,8182
1,200000<x<=1,300000	1	37	2,56410	94,8718	2,27273	84,0909
1,300000<x<=1,400000	2	39	5,12821	100,0000	4,54545	88,6364
Missing	5	44	12,82051		11,36364	100,0000

GPC+PCh - left DLPFC

Frequency table: GPC+PCh - Scan 1 Left DLPFC (Short term abstinence.sta) Shapiro-Wilk W=,96602, p=,26732						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
,1500000<x<=,2000000	8	8	20,00000	20,0000	18,18182	18,1818
,2000000<x<=,2500000	15	23	37,50000	57,5000	34,09091	52,2727
,2500000<x<=,3000000	10	33	25,00000	82,5000	22,72727	75,0000
,3000000<x<=,3500000	7	40	17,50000	100,0000	15,90909	90,9091
Missing	4	44	10,00000		9,09091	100,0000

Mann-Whitney U test - Age and drug use variables

variable	Mann-Whitney U Test (w/ continuity correction) (Short term abstinence.sta) By variable Group Marked tests are significant at p <,050000									
	Rank Sum Control	Rank Sum Meth	U	Z	p-value	Z adjusted	p-value	Valid N Control	Valid N Meth	2*1sided exact p
Age	454,0000	536,0000	201,0000	-0,95064	0,341787	-0,95404	0,340063	22	22	0,345324
Length of drug taking	253,0000	737,0000	0,0000	-5,66864	0,000000	-6,07184	0,000000	22	22	0,000000
Age started taking MA	253,0000	737,0000	0,0000	-5,66864	0,000000	-6,06204	0,000000	22	22	0,000000
Duration of abstinence Scan 2	253,0000	737,0000	0,0000	-5,66864	0,000000	-6,08539	0,000000	22	22	0,000000

Mann-Whitney U test - Glu right ACC

Mann-Whitney U Test (w/ continuity correction) (Short term abstinence.sta) By variable Group Marked tests are significant at p <,05000										
variable	Rank Sum Control	Rank Sum Meth	U	Z	p-value	Z adjusted	p-value	Valid N Control	Valid N Meth	2*1sided exact p
Glu - Scan 1 Right ACC	368,0000	452,0000	178,0000	-0,568763	0,569517	-0,568817	0,569481	19	21	0,573472

ANOVA – right ACC

Univariate Results for Each DV (Short term abstinence.sta) Sigma-restricted parameterization Effective hypothesis decomposition

Effect	De gr. of Freedom	Glu+Gln - Scan 1 Right ACC SS	Glu+Gln - Scan 1 Right ACC MS	Glu+Gln - Scan 1 Right ACC F	Glu+Gln - Scan 1 Right ACC p	NAA - Scan 1 Right ACC SS	NAA - Scan 1 Right ACC MS	NAA - Scan 1 Right ACC F	NAA - Scan 1 Right ACC p	NAA+NAAG - Scan 1 Right ACC MS	NAA+NAAG - Scan 1 Right ACC F	NAA+NAAG - Scan 1 Right ACC p	Ins - Scan 1 Right ACC SS	Ins - Scan 1 Right ACC MS	Ins - Scan 1 Right ACC F	Ins - Scan 1 Right ACC p	GPC+PCh - Scan 1 Right ACC SS	GPC+PCh - Scan 1 Right ACC MS	GPC+PCh - Scan 1 Right ACC F	GPC+PCh - Scan 1 Right ACC p
Intercept	1	84,38168	84,38168	1094,999	0,000000	49,05021	49,05021	55,62128	0,000000	55,62128	4750,386	0,000000	40,89514	40,89514	8261,487	0,000000	2,931790	2,931790	3632,870	0,000000
Group	1	0,11894	0,11894	1,544	0,222129	0,02340	0,02340	0,02340	1,905	0,08207	7,009	0,011956	0,07000	0,07000	5,583	0,023658	0,000632	0,000632	0,783	0,381970
Error	36	2,77419	0,07706			0,44222	0,01228	0,42152	0,01171				0,45140	0,01254			0,029053	0,000807		
Total	37	2,89314				0,46562		0,50359					0,52140				0,029685			

ANOVA – left ACC

Univariate Results for Each DV (Short term abstinence.sta) Sigma-restricted parameterization Effective hypothesis decomposition

Effect	Deg. of Freedom	Glu - Scan 1 Left ACC MS	Glu - Scan 1 Left ACC F	Glu - Scan 1 Left ACC p	Glu+Gln - Scan 1 Left ACC SS	Glu+Gln - Scan 1 Left ACC MS	Glu+Gln - Scan 1 Left ACC F	Glu+Gln - Scan 1 Left ACC p	NAA - Scan 1 Left ACC MS	NAA - Scan 1 Left ACC F	NAA - Scan 1 Left ACC p	NAA+NAAG - Scan 1 Left ACC MS	NAA+NAAG - Scan 1 Left ACC F	NAA+NAAG - Scan 1 Left ACC p	Ins - Scan 1 Left ACC SS	Ins - Scan 1 Left ACC MS	Ins - Scan 1 Left ACC F	Ins - Scan 1 Left ACC p	GPC+PCh - Scan 1 Left ACC SS	GPC+PCh - Scan 1 Left ACC MS	GPC+PCh - Scan 1 Left ACC F	GPC+PCh - Scan 1 Left ACC p
Intercept	1	72,3163	72,3163	2450,09	0,000000	91,01347	91,01347	59,1540	59,1540	3843,61	0,000000	66,24079	66,24079	3263,617	47,0613	47,0613	2763,15	0,000000	3,473555	3,473555	3002,482	0,000000
Group	1	0,00082	0,00082	0,028	0,86855	0,00502	0,00502	0,00760	0,00760	0,494	0,48619	0,04205	0,04205	2,072	0,157832	0,03620	0,03620	2,126	0,000007	0,000007	0,006	0,938329
Error	40	1,18063	0,02952		2,54448	0,06361	0,06361	0,01539	0,01539	0,81187	0,02030				0,68127	0,01703			0,046276	0,001157		
Total	41	1,18145			2,54949			0,62321		0,85392					0,71748				0,046283			

ANOVA – left DLPFC

Univariate Results for Each DV (Short term abstinence.sta) Sigma-restricted parameterization Effective hypothesis decomposition																									
Deg. of Freedom	Glu - Scan 1 Left DLPFC C SS	Glu - Scan 1 Left DLPFC C MS	Glu - Scan 1 Left DLPFC C F	Glu - Scan 1 Left DLPFC C p	Glu+Glu - Scan 1 Left DLPFC C SS	Glu+Glu - Scan 1 Left DLPFC C MS	Glu+Glu - Scan 1 Left DLPFC C F	Glu+Glu - Scan 1 Left DLPFC C p	NAA - Scan 1 Left DLPFC C SS	NAA - Scan 1 Left DLPFC C MS	NAA - Scan 1 Left DLPFC C F	NAA - Scan 1 Left DLPFC C p	NAA+NA AG - Scan 1 Left DLPFC SS	NAA+NA AG - Scan 1 Left DLPFC MS	NAA+NA AG - Scan 1 Left DLPFC F	NAA+NA AG - Scan 1 Left DLPFC p	Ins - Scan 1 Left DLPFC C SS	Ins - Scan 1 Left DLPFC C MS	Ins - Scan 1 Left DLPFC C F	Ins - Scan 1 Left DLPFC C p	GPC+P Ch - Scan 1 Left DLPFC SS	GPC+P Ch - Scan 1 Left DLPFC MS	GPC+P Ch - Scan 1 Left DLPFC F	GPC+P Ch - Scan 1 Left DLPFC p	
Intercept	60,78597	60,78597	1020,617	0,000000	71,889370	63,30156	2787,442	0,000000	70,68299	70,68299	3427,661	0,000000	31,93960	31,93960	1192,327	0,000000	0,000000	0,000000	0,000000	0,000000	2,063924	2,063924	1052,673	0,000000	
Group	1	0,02529	0,02529	0,425	0,519035							0,012940	0,17397	0,17397	8,437	0,006421	0,00929	0,00929	0,347	0,559863	0,000005	0,000005	0,002	0,960686	
Error	34	2,02498	0,05956						0,77212	0,02271			0,70113	0,02062				0,91078	0,02679			0,066662	0,001961		
Total	35	2,05027							0,92842				0,87510					0,92007				0,066667			

Summary - Relative metabolite concentrations – Short-term abstinence

	Healthy Controls n = 22		MA dependent n = 22	
	Mean	Stdev	Mean	Stdev
<i>Anterior cingulate cortex</i>				
Right hemisphere				
Glutamate (Glu)	1.28	0.2	1.33	0.2
Glutamate + Glutamine (Glu+Gln)	1.43	0.3	1.53	0.3
N-acetyl-aspartate (NAA)	1.16	0.1	1.10	0.1
N-acetyl-aspartyl + N-acetyl-aspartyl-glutamate (NAA+NAAG) *	1.25	0.1	1.16	0.1
Myo-inositol (Ins) **	1.00	0.1	1.08	0.1
Glycerophosphocholine + phosphocholine (GPC+PCh)	0.27	0.0	0.28	0.0
Left hemisphere				
Glutamate (Glu)	1.32	0.2	1.31	0.2
Glutamate + Glutamine (Glu+Gln)	1.48	0.3	1.46	0.2
N-acetyl-aspartate (NAA)	1.20	0.1	1.17	0.1
N-acetyl-aspartyl + N-acetyl-aspartyl-glutamate (NAA+NAAG)	1.29	0.2	1.23	0.1
Myo-inositol (Ins)	1.09	0.1	1.03	0.1
Glycerophosphocholine + phosphocholine (GPC+PCh)	0.29	0.0	0.29	0.0
<i>Dorsolateral prefrontal cortex</i>				
Right hemisphere				
Glutamate (Glu)	1.41	0.3	1.27	0.3
Glutamate + Glutamine (Glu+Gln)	1.58	0.4	1.39	0.3
N-acetyl-aspartate (NAA)	1.35	0.1	1.34	0.2
N-acetyl-aspartyl + N-acetyl-aspartyl-glutamate (NAA+NAAG)	1.46	0.2	1.40	0.1
Myo-inositol (Ins)	0.97	0.1	0.95	0.2
Glycerophosphocholine + phosphocholine (GPC+PCh)	0.25	0.0	0.24	0.0
Left hemisphere				
Glutamate (Glu)	1.28	0.2	1.33	0.3
Glutamate + Glutamine (Glu+Gln)	1.41	0.3	1.44	0.3
N-acetyl-aspartate (NAA) #	1.39	0.2	1.28	0.2
N-acetyl-aspartyl + N-acetyl-aspartyl-glutamate (NAA+NAAG) ##	1.47	0.2	1.36	0.2
Myo-inositol (Ins)	0.97	0.1	0.93	0.2
Glycerophosphocholine + phosphocholine (GPC+PCh)	0.25	0.0	0.24	0.0

Significant group differences in brain metabolites using 1H-MRS CSI. The methamphetamine acute abstinence group had lower concentrations in the right ACC, of *n-acetyl-aspartate + n-acetyl-aspartyl-glutamate (NAA+NAAG)($p < 0.05$) and **myo-inositol (Ins)($p < 0.05$) than the control group in the right ACC. In the left DLPFC, the methamphetamine exposed group had lower concentrations of #n-acetyl-aspartate (NAA)($p < 0.05$) and ##n-acetyl-aspartate + n-acetyl-aspartyl-glutamate (NAA+NAAG)($p < 0.05$).

Spearman Rank Order correlations

Spearman Rank Order Correlations (Short term abstinence.sta) MD pairwise deleted Marked correlations are significant at p <,05000						
Pair of Variables	Valid N	Spearman R	t(N-2)	p-value		
Age & Glu - Scan 1 Right ACC	40	-0,039987	-0,24669	0,806473		
Age & Glu+Gln - Scan 1 Right ACC	39	0,030625	0,18637	0,853172		
Age & NAA - Scan 1 Right ACC	40	-0,233706	-1,48169	0,146668		
Age & NAA+NAAAG - Scan 1 Right ACC	41	-0,343509	-2,28421	0,027885		
Age & Ins - Scan 1 Right ACC	41	0,107517	0,67536	0,503434		
Age & GPC+PCh - Scan 1 Right ACC	41	0,172011	1,09046	0,282203		
Age & Glu - Scan 1 Left ACC	42	-0,229238	-1,48949	0,144202		
Age & Glu+Gln - Scan 1 Left ACC	42	-0,113385	-0,72176	0,474638		
Age & NAA - Scan 1 Left ACC	42	-0,143439	-0,91667	0,364811		
Age & NAA+NAAAG - Scan 1 Left ACC	42	-0,251740	-1,64513	0,107781		
Age & Ins - Scan 1 Left ACC	42	0,063197	0,40049	0,690925		
Age & GPC+PCh - Scan 1 Left ACC	42	0,050198	0,31788	0,752231		
Age & Glu - Scan 1 Right DLPFC	36	0,055043	0,32144	0,749846		
Age & Glu+Gln - Scan 1 Right DLPFC	36	0,043285	0,25263	0,802077		
Age & NAA - Scan 1 Right DLPFC	39	-0,383934	-2,52922	0,015824		
Age & NAA+NAAAG - Scan 1 Right DLPFC	39	-0,507520	-3,58285	0,000974		
Age & Ins - Scan 1 Right DLPFC	38	0,191973	1,17367	0,248234		
Age & GPC+PCh - Scan 1 Right DLPFC	39	-0,252808	-1,58940	0,120480		
Age & Glu - Scan 1 Left DLPFC	36	0,049833	0,29093	0,772870		
Age & Glu+Gln - Scan 1 Left DLPFC	36	0,043040	0,25120	0,803174		
Age & NAA - Scan 1 Left DLPFC	40	-0,340154	-2,22982	0,031745		
Age & NAA+NAAAG - Scan 1 Left DLPFC	40	-0,293519	-1,89274	0,066028		
Age & Ins - Scan 1 Left DLPFC	39	0,046537	0,28338	0,778465		
Age & GPC+PCh - Scan 1 Left DLPFC	40	-0,004006	-0,02469	0,980430		
Age started taking MA & Glu - Scan 1 Right ACC	40	0,042813	0,26416	0,793086		
Age started taking MA & Glu+Gln - Scan 1 Right ACC	39	0,031289	0,19042	0,850022		
Age started taking MA & NAA - Scan 1 Right ACC	40	-0,221613	-1,40095	0,169343		
Age started taking MA & NAA+NAAAG - Scan 1 Right ACC	41	-0,257722	-1,66575	0,103778		

Age started taking MA & Ins - Scan 1 Right ACC	41	0,299056	1,95717	0,057512
Age started taking MA & GPC+PCh - Scan 1 Right ACC	41	0,074227	0,46483	0,644637
Age started taking MA & Glu - Scan 1 Left ACC	42	-0,078318	-0,49685	0,622014
Age started taking MA & Glu+Gln - Scan 1 Left ACC	42	-0,045286	-0,28671	0,775818
Age started taking MA & NAA - Scan 1 Left ACC	42	-0,010161	-0,06427	0,949079
Age started taking MA & NAA+NAAG - Scan 1 Left ACC	42	-0,165726	-1,06284	0,294229
Age started taking MA & Ins - Scan 1 Left ACC	42	-0,177982	-1,14392	0,259457
Age started taking MA & GPC+PCh - Scan 1 Left ACC	42	-0,028737	-0,18183	0,856637
Age started taking MA & Glu - Scan 1 Right DLPFC	36	-0,237362	-1,42476	0,163340
Age started taking MA & Glu+Gln - Scan 1 Right DLPFC	36	-0,252136	-1,51928	0,137938
Age started taking MA & NAA - Scan 1 Right DLPFC	39	-0,212429	-1,32234	0,194173
Age started taking MA & NAA+NAAG - Scan 1 Right DLPFC	39	-0,268242	-1,69372	0,098722
Age started taking MA & Ins - Scan 1 Right DLPFC	38	-0,130934	-0,79243	0,433303
Age started taking MA & GPC+PCh - Scan 1 Right DLPFC	39	-0,071937	-0,43871	0,663422
Age started taking MA & Glu - Scan 1 Left DLPFC	36	0,195601	1,16301	0,252925
Age started taking MA & Glu+Gln - Scan 1 Left DLPFC	36	0,108132	0,63423	0,530174
Age started taking MA & NAA - Scan 1 Left DLPFC	40	-0,280926	-1,80441	0,079098
Age started taking MA & NAA+NAAG - Scan 1 Left DLPFC	40	-0,275143	-1,76419	0,085738
Age started taking MA & Ins - Scan 1 Left DLPFC	39	-0,106355	-0,65062	0,519312
Age started taking MA & GPC+PCh - Scan 1 Left DLPFC	40	0,002004	0,01236	0,990207
Length of drug taking & Glu - Scan 1 Right ACC	40	0,122200	0,75898	0,452548
Length of drug taking & Glu+Gln - Scan 1 Right ACC	39	0,189580	1,17447	0,247710
Length of drug taking & NAA - Scan 1 Right ACC	40	-0,240221	-1,52549	0,135417
Length of drug taking & NAA+NAAG - Scan 1 Right ACC	41	-0,308394	-2,02460	0,049795
Length of drug taking & Ins - Scan 1 Right ACC	41	0,164637	1,04238	0,303655
Length of drug taking & GPC+PCh - Scan 1 Right ACC	41	0,128827	0,81129	0,422125
Length of drug taking & Glu - Scan 1 Left ACC	42	-0,101375	-0,64447	0,522947
Length of drug taking & Glu+Gln - Scan 1 Left ACC	42	-0,037397	-0,23669	0,814107
Length of drug taking & NAA - Scan 1 Left ACC	42	-0,072603	-0,46039	0,647726
Length of drug taking & NAA+NAAG - Scan 1 Left ACC	42	-0,153535	-0,98269	0,331665
Length of drug taking & Ins - Scan 1 Left ACC	42	-0,252871	-1,65302	0,106155

Length of drug taking & GPC+PCh - Scan 1 Left ACC	42	-0,002061	-0,01304	0,989664
Length of drug taking & Glu - Scan 1 Right DLPFC	36	-0,218557	-1,30597	0,200330
Length of drug taking & Glu+Gln - Scan 1 Right DLPFC	36	-0,295925	-1,80643	0,079709
Length of drug taking & NAA - Scan 1 Right DLPFC	39	-0,115362	-0,70643	0,484343
Length of drug taking & NAA+NAAAG - Scan 1 Right DLPFC	39	-0,232485	-1,45399	0,154379
Length of drug taking & Ins - Scan 1 Right DLPFC	38	-0,093609	-0,56413	0,576165
Length of drug taking & GPC+PCh - Scan 1 Right DLPFC	39	-0,098925	-0,60470	0,549069
Length of drug taking & Glu - Scan 1 Left DLPFC	36	0,009488	0,05533	0,956203
Length of drug taking & Glu+Gln - Scan 1 Left DLPFC	36	-0,034696	-0,20243	0,840783
Length of drug taking & NAA - Scan 1 Left DLPFC	40	-0,373552	-2,48243	0,017582
Length of drug taking & NAA+NAAAG - Scan 1 Left DLPFC	40	-0,311813	-2,02300	0,050150
Length of drug taking & Ins - Scan 1 Left DLPFC	39	-0,245702	-1,54181	0,131630
Length of drug taking & GPC+PCh - Scan 1 Left DLPFC	40	-0,037827	-0,23335	0,816744
Duration of abstinence Scan 2 & Glu - Scan 1 Right ACC	40	0,061356	0,37894	0,706843
Duration of abstinence Scan 2 & Glu+Gln - Scan 1 Right ACC	39	0,100812	0,61635	0,541435
Duration of abstinence Scan 2 & NAA - Scan 1 Right ACC	40	-0,237946	-1,51017	0,139272
Duration of abstinence Scan 2 & NAA+NAAAG - Scan 1 Right ACC	41	-0,309457	-2,03231	0,048972
Duration of abstinence Scan 2 & Ins - Scan 1 Right ACC	41	0,335346	2,22296	0,032085
Duration of abstinence Scan 2 & GPC+PCh - Scan 1 Right ACC	41	0,219095	1,40232	0,168730
Duration of abstinence Scan 2 & Glu - Scan 1 Left ACC	42	-0,056929	-0,36064	0,720269
Duration of abstinence Scan 2 & Glu+Gln - Scan 1 Left ACC	42	-0,117402	-0,74769	0,459023
Duration of abstinence Scan 2 & NAA - Scan 1 Left ACC	42	-0,023366	-0,14782	0,883227
Duration of abstinence Scan 2 & NAA+NAAAG - Scan 1 Left ACC	42	-0,166989	-1,07117	0,290512
Duration of abstinence Scan 2 & Ins - Scan 1 Left ACC	42	-0,046203	-0,29253	0,771394
Duration of abstinence Scan 2 & GPC+PCh - Scan 1 Left ACC	42	0,047886	0,30321	0,763305
Duration of abstinence Scan 2 & Glu - Scan 1 Right DLPFC	36	-0,258695	-1,56160	0,127643
Duration of abstinence Scan 2 & Glu+Gln - Scan 1 Right DLPFC	36	-0,269510	-1,63188	0,111934

Duration of abstinence Scan 2 & NAA - Scan 1 Right DLPFC	39	-0,154837	-0,95333	0,346609
Duration of abstinence Scan 2 & NAA+NAAAG - Scan 1 Right DLPFC	39	-0,189731	-1,17544	0,247329
Duration of abstinence Scan 2 & Ins - Scan 1 Right DLPFC	38	0,009654	0,05793	0,954126
Duration of abstinence Scan 2 & GPC+PCh - Scan 1 Right DLPFC	39	-0,000541	-0,00329	0,997390
Duration of abstinence Scan 2 & Glu - Scan 1 Left DLPFC	36	0,026006	0,15169	0,880328
Duration of abstinence Scan 2 & Glu+Gln - Scan 1 Left DLPFC	36	-0,050309	-0,29372	0,770755
Duration of abstinence Scan 2 & NAA - Scan 1 Left DLPFC	40	-0,265790	-1,69957	0,097385
Duration of abstinence Scan 2 & NAA+NAAAG - Scan 1 Left DLPFC	40	-0,292321	-1,88429	0,067193
Duration of abstinence Scan 2 & Ins - Scan 1 Left DLPFC	39	-0,162408	-1,00118	0,323243
Duration of abstinence Scan 2 & GPC+PCh - Scan 1 Left DLPFC	40	0,106950	0,66309	0,511276

Full dataset - Acute to short-term abstinence

[illegible]

T-tests

NAA – right ACC

Variable	T-test for Dependent Samples (Acute to short term abstinence (2).sta) Marked differences are significant at p < ,05000									
	Mean	Std.Dv.	N	Diff.	Std.Dv. Diff.	t	df	p	Confidence -95,000%	Confidence +95,000%
NAA - Scan 1 Right ACC	1,144750	0,099523								
NAA - Scan 2 Right ACC	1,091875	0,107250	16	0,052875	0,088572	2,387880	15	0,030539	0,005678	0,100072

NAA+NAAG – right ACC

Variable	T-test for Dependent Samples (Acute to short term abstinence (2).sta) Marked differences are significant at p < ,05000									
	Mean	Std.Dv.	N	Diff.	Std.Dv. Diff.	t	df	p	Confidence -95,000%	Confidence +95,000%
NAA+NAAG - Scan 1 Right ACC	1,230529	0,145402								
NAA+NAAG - Scan 2 Right ACC	1,152882	0,118695	17	0,077647	0,124789	2,565511	16	0,020742	0,013487	0,141808

Ins – right ACC

Variable	T-test for Dependent Samples (Acute to short term abstinence (2).sta) Marked differences are significant at p < ,05000									
	Mean	Std.Dv.	N	Diff.	Std.Dv. Diff.	t	df	p	Confidence -95,000%	Confidence +95,000%
Ins - Scan 1 Right ACC	0,975824	0,128204								
Ins - Scan 2 Right ACC	1,078235	0,134930	17	-0,102412	0,175455	-2,40662	16	0,028541	-0,192623	-0,012201

GPC+pCh right ACC

Variable	T-test for Dependent Samples (Acute to short term abstinence (2).sta) Marked differences are significant at p < ,05000									
	Mean	Std.Dv.	N	Diff.	Std.Dv. Diff.	t	df	p	Confidence -95,000%	Confidence +95,000%
GPC+pCh - Scan 1 Right ACC	0,277118	0,028816								
GPC+pCh - Scan 2 Right ACC	0,286529	0,033971	17	-0,009412	0,030249	-1,28287	16	0,217810	-0,024964	0,006141

Glu - left ACC

T-test for Dependent Samples (Acute to short term abstinence (2).sta) Marked differences are significant at p < ,05000										
Variable	Mean	Std.Dv.	N	Diff.	Std.Dv. Diff.	t	df	p	Confidence -95,000%	Confidence +95,000%
Glu - Scan 1 Left ACC	1,362533	0,170881								
Glu - Scan 2 Left ACC	1,308667	0,153863	15	0,053867	0,257129	0,811361	14	0,430737	-0,088527	0,196260

Glu+Gln - left ACC

	T-test for Dependent Samples (Acute to short term abstinence (2).sta) Marked differences are significant at p < ,05000									
Variable	Mean	Std.Dv.	N	Diff.	Std.Dv. Diff.	t	df	p	Confidence -95,000%	Confidence +95,000%
Glu+Gln - Scan 1 Left ACC	1,510333	0,291420								
Glu+Gln - Scan 2 Left ACC	1,496400	0,248159	15	0,013933	0,405831	0,132971	14	0,896109	-0,210808	0,238675

NAA - left ACC

T-test for Dependent Samples (Acute to short term abstinence (2).sta) Marked differences are significant at p < ,05000										
Variable	Mean	Std.Dv.	N	Diff.	Std.Dv. Diff.	t	df	p	Confidence -95,000%	Confidence +95,000%
NAA - Scan 1 Left ACC	1,131600	0,135547								
NAA - Scan 2 Left ACC	1,186600	0,135842	15	-0,055000	0,137449	-1,54977	14	0,143502	-0,131117	0,021117

NAA+NAAG - left ACC

T-test for Dependent Samples (Acute to short term abstinence (2).sta) Marked differences are significant at p < ,05000										
Variable	Mean	Std.Dv.	N	Diff.	Std.Dv. Diff.	t	df	p	Confidence -95,000%	Confidence +95,000%
NAA+NAAG - Scan 1 Left ACC	1,199467	0,164588								
NAA+NAAG - Scan 2 Left ACC	1,252867	0,135236	15	-0,053400	0,146788	-1,40895	14	0,180671	-0,134688	0,027888

Ins - left ACC

T-test for Dependent Samples (Acute to short term abstinence (2).sta) Marked differences are significant at p < ,05000										
Variable	Mean	Std.Dv.	N	Diff.	Std.Dv. Diff.	t	df	p	Confidence -95,000%	Confidence +95,000%
Ins - Scan 1 Left ACC	1,021000	0,110545								
Ins - Scan 2 Left ACC	1,013200	0,151398	15	0,007800	0,178349	0,169383	14	0,867919	-0,090967	0,106567

GPC+PCh – left ACC

T-test for Dependent Samples (Acute to short term abstinence (2).sta) Marked differences are significant at p < ,05000										
Variable	Mean	Std.Dv.	N	Diff.	Std.Dv. Diff.	t	df	p	Confidence -95,000%	Confidence +95,000%
GPC+PCh - Scan 1 Left ACC	0,282267	0,024488								
GPC+PCh - Scan 2 Left ACC	0,293467	0,031904	15	-0,011200	0,033281	-1,30338	14	0,213472	-0,029630	0,007230

Glu – right DLPFC

T-test for Dependent Samples (Acute to short term abstinence (2).sta) Marked differences are significant at p < ,05000										
Variable	Mean	Std.Dv.	N	Diff.	Std.Dv. Diff.	t	df	p	Confidence -95,000%	Confidence +95,000%
Glu - Scan 1 Right DLPFC	1,321692	0,213437								
Glu - Scan 2 Right DLPFC	1,333769	0,285953	13	-0,012077	0,285317	-0,152616	12	0,881237	-0,184492	0,160339

Glu+Gln – right DLPFC

T-test for Dependent Samples (Acute to short term abstinence (2).sta) Marked differences are significant at p < ,05000										
Variable	Mean	Std.Dv.	N	Diff.	Std.Dv. Diff.	t	df	p	Confidence -95,000%	Confidence +95,000%
Glu+Gln - Scan 1 Right DLPFC	1,585769	0,227705								
Glu+Gln - Scan 2 Right DLPFC	1,426308	0,345321	13	0,159462	0,274370	2,095518	12	0,058005	-0,006338	0,325262

NAA – right DLPFC

T-test for Dependent Samples (Acute to short term abstinence (2).sta) Marked differences are significant at p < ,05000										
Variable	Mean	Std.Dv.	N	Diff.	Std.Dv. Diff.	t	df	p	Confidence -95,000%	Confidence +95,000%
NAA - Scan 1 Right DLPFC	1,319286	0,136339								
NAA - Scan 2 Right DLPFC	1,353143	0,148953	14	-0,033857	0,200429	-0,632054	13	0,538309	-0,149581	0,081867

NAA+NAAG – right DLPFC

T-test for Dependent Samples (Acute to short term abstinence (2).sta) Marked differences are significant at p < ,05000										
Variable	Mean	Std.Dv.	N	Diff.	Std.Dv. Diff.	t	df	p	Confidence -95,000%	Confidence +95,000%
NAA+NAAG - Scan 1 Right DLPFC	1,336800	0,173814								
NAA+NAAG - Scan 2 Right DLPFC	1,399667	0,129407	15	-0,062867	0,183409	-1,32754	14	0,205573	-0,164435	0,038702

Ins - right DLPFC

Variable	T-test for Dependent Samples (Acute to short term abstinence (2).sta) Marked differences are significant at p < ,05000							
	Mean	Std.Dv.	N	Diff.	Std.Dv. Diff.	t	df	p
Ins - Scan 1 Right DLPFC	0,932643	0,111850						
Ins - Scan 2 Right DLPFC	0,980571	0,189253	14	-0,047929	0,175294	-1,02304	13	0,324952
								0,053283

GPC+PCh - right DLPFC

Variable	T-test for Dependent Samples (Acute to short term abstinence (2).sta) Marked differences are significant at p < ,05000							
	Mean	Std.Dv.	N	Diff.	Std.Dv. Diff.	t	df	p
GPC+PCh - Scan 1 Right DLPFC	0,228667	0,031357						
GPC+PCh - Scan 2 Right DLPFC	0,244267	0,039100	15	-0,015600	0,055876	-1,08130	14	0,297839
								0,015343

Glu - left DLPFC

Variable	T-test for Dependent Samples (Acute to short term abstinence (2).sta) Marked differences are significant at p < ,05000							
	Mean	Std.Dv.	N	Diff.	Std.Dv. Diff.	t	df	p
Glu - Scan 1 Left DLPFC	1,269714	0,215110						
Glu - Scan 2 Left DLPFC	1,313929	0,268306	14	-0,044214	0,348035	-0,475340	13	0,642432
								0,156735

Glu+Gln - left DLPFC

Variable	T-test for Dependent Samples (Acute to short term abstinence (2).sta) Marked differences are significant at p < ,05000							
	Mean	Std.Dv.	N	Diff.	Std.Dv. Diff.	t	df	p
Glu+Gln - Scan 1 Left DLPFC	1,487786	0,368371						
Glu+Gln - Scan 2 Left DLPFC	1,408357	0,355107	14	0,079429	0,552972	0,537449	13	0,600037
								0,398705

NAA - left DLPFC

Variable	T-test for Dependent Samples (Acute to short term abstinence (2).sta) Marked differences are significant at p < ,05000							
	Mean	Std.Dv.	N	Diff.	Std.Dv. Diff.	t	df	p
NAA - Scan 1 Left DLPFC	1,326750	0,134020						
NAA - Scan 2 Left DLPFC	1,298875	0,155179	16	0,027875	0,172787	0,645302	15	0,528479
								0,119947

NAA+NAAG - left DLPFC

T-test for Dependent Samples (Acute to short term abstinence (2).sta) Marked differences are significant at p < ,05000										
Variable	Mean	Std.Dv.	N	Diff.	Std.Dv. Diff.	t	df	p	Confidence -95,000%	Confidence +95,000%
NAA+NAAG - Scan 1 Left DLPFC	1,411250	0,138254								
NAA+NAAG - Scan 2 Left DLPFC	1,372625	0,137834	16	0,038625	0,177270	0,871554	15	0,397188	-0,055835	0,133085

Ins - left DLPFC

T-test for Dependent Samples (Acute to short term abstinence (2).sta) Marked differences are significant at p < ,05000										
Variable	Mean	Std.Dv.	N	Diff.	Std.Dv. Diff.	t	df	p	Confidence -95,000%	Confidence +95,000%
Ins - Scan 1 Left DLPFC	0,933133	0,138751								
Ins - Scan 2 Left DLPFC	0,931067	0,210721	15	0,002067	0,257509	0,031083	14	0,975642	-0,140537	0,144671

GPC+PCh - left DLPFC

T-test for Dependent Samples (Acute to short term abstinence (2).sta) Marked differences are significant at p < ,05000										
Variable	Mean	Std.Dv.	N	Diff.	Std.Dv. Diff.	t	df	p	Confidence -95,000%	Confidence +95,000%
GPC+PCh - Scan 1 Left DLPFC	0,243400	0,034100								
GPC+PCh - Scan 2 Left DLPFC	0,240800	0,041715	15	0,002600	0,053196	0,189295	14	0,852579	-0,026859	0,032059

Summary - Relative metabolite concentrations – Acute vs Short-term abstinence

	MA dependent n = 19			
	Time point 1		Time point 2	
	Mean	Stdev	Mean	Stdev
<i>Anterior cingulate cortex</i>				
Right hemisphere				
Glutamate (Glu)	1.32	0.3	1.32	0.2
Glutamate + Glutamine (Glu+Gln)	1.48	0.4	1.54	0.3
N-acetyl-aspartate (NAA)	* 1.16	0.1	1.09	0.1
N-acetyl-aspartyl + N-acetyl-aspartyl-glutamate (NAA+NAAG) #	1.23	0.1	1.16	0.1
Myo-inositol (Ins)	@ 0.98	0.1	1.07	0.1
Glycerophosphocholine + phosphocholine (GPC+PCh)	0.28	0.0	0.28	0.0
Left hemisphere				
Glutamate (Glu)	1.34	0.2	1.29	0.2
Glutamate + Glutamine (Glu+Gln)	1.49	0.3	1.47	0.2
N-acetyl-aspartate (NAA)	1.13	0.1	1.17	0.1
N-acetyl-aspartyl + N-acetyl-aspartyl-glutamate (NAA+NAAG)	1.19	0.2	1.23	0.1
Myo-inositol (Ins)	1.01	0.1	1.02	0.1
Glycerophosphocholine + phosphocholine (GPC+PCh)	0.28	0.0	0.29	0.0
<i>Dorsolateral prefrontal cortex</i>				
Right hemisphere				
Glutamate (Glu)	1.33	0.2	1.29	0.3
Glutamate + Glutamine (Glu+Gln)	1.56	0.2	1.43	0.3
N-acetyl-aspartate (NAA)	1.31	0.1	1.34	0.2
N-acetyl-aspartyl + N-acetyl-aspartyl-glutamate (NAA+NAAG)	1.33	0.2	1.40	0.1
Myo-inositol (Ins)	0.94	0.1	0.95	0.2
Glycerophosphocholine + phosphocholine (GPC+PCh)	0.23	0.0	0.24	0.0
Left hemisphere				
Glutamate (Glu)	1.25	0.2	1.31	0.3
Glutamate + Glutamine (Glu+Gln)	1.47	0.3	1.42	0.3
N-acetyl-aspartate (NAA)	* 1.31	0.1	1.27	0.2
N-acetyl-aspartyl + N-acetyl-aspartyl-glutamate (NAA+NAAG) *	1.39	0.2	1.35	0.2
Myo-inositol (Ins)	0.93	0.1	0.93	0.2
Glycerophosphocholine + phosphocholine (GPC+PCh)	0.24	0.0	0.24	0.0

Significant differences of acute to short-term abstinence in brain metabolites using ^1H -MRS CSI. Lower concentrations in short-term abstinence were seen, when compared to acute abstinence concentrations: *n-acetyl-aspartate (NAA)_(p < 0.05), #n-acetyl-aspartate + n-acetyl-aspartyl glutamate (NAA+NAAG)_(p < 0.05). Higher concentration of @myo-inositol (Ins)_(p < 0.05) was seen in short-term abstinence.

Appendix II

Full dataset - Time point 1

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Descriptive statistics Demographics

Variable	Descriptive Statistics (MethKi database final time 1.sta)				
	Valid N	Mean	Minimum	Maximum	Std.Dev.
S1 - Age	28	6,45214	6,00000	7,08000	0,355573
MA Frequency 1st Tri	23	2,30435	1,00000	5,00000	1,743424
MA Frequency 2nd Tri	23	2,26087	1,00000	5,00000	1,684620
MA Frequency 3rd Tri	23	2,26087	1,00000	5,00000	1,684620
Smoke Frequency 1st Tri	25	2,24000	1,00000	5,00000	1,331666
Smoke Frequency 2nd Tri	25	2,24000	1,00000	5,00000	1,331666
Smoke Frequency 3rd Tri	25	2,24000	1,00000	5,00000	1,331666
Alcohol Frequency 1st Tri	27	1,29630	1,00000	5,00000	0,953327
Alcohol Frequency 2nd Tri	27	1,25926	1,00000	5,00000	0,944319
Alcohol Frequency 3rd Tri	27	1,25926	1,00000	5,00000	0,944319
Child weight Scan 1	27	19,44444	16,00000	27,40000	2,859711
Child height Scan 1	26	1,05192	0,92000	1,18000	0,075367
BMI Scan 1	26	17,75918	12,41873	25,78179	3,092280

Neurocognitive tasks

Variable	Descriptive Statistics (MethKi database final time 1.sta)				
	Valid N	Mean	Minimum	Maximum	Std.Dev.
Block Counting RS S1	16	9,25000	2,00000	15,00000	4,17133
Block Counting SCS S1	16	8,93750	5,00000	13,00000	2,61964
Pattern Reasoning RS No Tmpt S1	28	5,92857	1,00000	11,00000	3,36572
Pattern Reasoning SCS No Tmpt S1	28	6,89286	2,00000	14,00000	3,42474
Atlantis RS S1	28	52,10714	21,00000	90,00000	21,57389
Atlantis SCS S1	28	6,96429	3,00000	13,00000	2,79526
Atlantis Delay RS S1	28	11,10714	3,00000	22,00000	4,96163
Atlantis Delay SCS S1	28	8,17857	4,00000	15,00000	2,49523
Total BNT S1	28	7,00000	3,00000	13,00000	2,09054

Metabolite concentrations

Variable	Descriptive Statistics (MethKi database final time 1.sta)				
	Valid N	Mean	Minimum	Maximum	Std.Dev.
S1 - Cr	26	2,450538	1,724000	3,43400	0,425565
S1 - PCr	25	2,753160	2,191000	3,55000	0,348194
S1 - Glu	28	8,538036	7,176000	9,62200	0,569568
S1 - GPC	28	1,109929	0,876000	1,37400	0,140398
S1 - Ins	28	5,125786	3,793000	6,05700	0,636696
S1 - NAA	28	6,111786	4,897000	6,80000	0,413008
S1 - GPC+PCh	28	1,109929	0,876000	1,37400	0,140398
S1 - NAA+NAAG	28	6,395571	5,356000	7,21600	0,415687
S1 - Cr+PCr	28	5,113000	4,164000	5,58300	0,345365
S1 - Glu+Gln	28	9,882929	8,382000	11,77900	0,956228

Frequency tables Demographics Age

Category	Frequency table: S1 - Age (MethKi database final time 1.sta) Shapiro-Wilk W=,90821, p=,01790				
	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases
5,800000<x<=6,000000	4	4	14,28571	14,2857	14,28571
6,000000<x<=6,200000	4	8	14,28571	28,5714	14,28571
6,200000<x<=6,400000	7	15	25,00000	53,5714	25,00000
6,400000<x<=6,600000	5	20	17,85714	71,4286	17,85714
6,600000<x<=6,800000	2	22	7,14286	78,5714	7,14286
6,800000<x<=7,000000	5	27	17,85714	96,4286	17,85714
7,000000<x<=7,200000	1	28	3,57143	100,0000	3,57143
Missing	0	28	0,00000		0,00000

Weight

Frequency table: Child weight Scan 1 (MethKi database final time 1.sta) Shapiro-Wilk W=,88805, p=,00720						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
14,00000<x<=16,00000	1	1	3,70370	3,7037	3,57143	3,5714
16,00000<x<=18,00000	9	10	33,33333	37,0370	32,14286	35,7143
18,00000<x<=20,00000	9	19	33,33333	70,3704	32,14286	67,8571
20,00000<x<=22,00000	4	23	14,81481	85,1852	14,28571	82,1429
22,00000<x<=24,00000	2	25	7,40741	92,5926	7,14286	89,2857
24,00000<x<=26,00000	0	25	0,00000	92,5926	0,00000	89,2857
26,00000<x<=28,00000	2	27	7,40741	100,0000	7,14286	96,4286
Missing	1	28	3,70370		3,57143	100,0000

Height

Frequency table: Child height Scan 1 (MethKi database final time 1.sta) Shapiro-Wilk W=,96274, p=,44830						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
,8000000<x<=,9000000	0	0	0,00000	0,0000	0,00000	0,0000
,9000000<x<=1,000000	8	8	30,76923	30,7692	28,57143	28,5714
1,000000<x<=1,100000	11	19	42,30769	73,0769	39,28571	67,8571
1,100000<x<=1,200000	7	26	26,92308	100,0000	25,00000	92,8571
Missing	2	28	7,69231		7,14286	100,0000

BMI

Frequency table: BMI Scan 1 (MethKi database final time 1.sta) Shapiro-Wilk W=,95009, p=,23300						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
10,00000<x<=12,00000	0	0	0,00000	0,0000	0,00000	0,0000
12,00000<x<=14,00000	3	3	11,53846	11,5385	10,71429	10,7143
14,00000<x<=16,00000	5	8	19,23077	30,7692	17,85714	28,5714
16,00000<x<=18,00000	4	12	15,38462	46,1538	14,28571	42,8571
18,00000<x<=20,00000	8	20	30,76923	76,9231	28,57143	71,4286
20,00000<x<=22,00000	4	24	15,38462	92,3077	14,28571	85,7143
22,00000<x<=24,00000	1	25	3,84615	96,1538	3,57143	89,2857
24,00000<x<=26,00000	1	26	3,84615	100,0000	3,57143	92,8571
Missing	2	28	7,69231		7,14286	100,0000

Neurocognitive tasks
Block Counting raw score

Frequency table: Block Counting RS S1 (MethKi database final time 1.sta) Shapiro-Wilk W=,91768, p=,15478						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
0,000000<x<=2,000000	2	2	12,50000	12,5000	7,14286	7,1429
2,000000<x<=4,000000	1	3	6,25000	18,7500	3,57143	10,7143
4,000000<x<=6,000000	0	3	0,00000	18,7500	0,00000	10,7143
6,000000<x<=8,000000	4	7	25,00000	43,7500	14,28571	25,0000
8,000000<x<=10,00000	2	9	12,50000	56,2500	7,14286	32,1429
10,00000<x<=12,00000	4	13	25,00000	81,2500	14,28571	46,4286
12,00000<x<=14,00000	1	14	6,25000	87,5000	3,57143	50,0000
14,00000<x<=16,00000	2	16	12,50000	100,0000	7,14286	57,1429
Missing	12	28	75,00000		42,85714	100,0000

Block Counting scaled score

Frequency table: Block Counting SCS S1 (MethKi database final time 1.sta) Shapiro-Wilk W=,94900, p=,47397						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
4,000000<x<=5,000000	2	2	12,50000	12,5000	7,14286	7,1429
5,000000<x<=6,000000	1	3	6,25000	18,7500	3,57143	10,7143
6,000000<x<=7,000000	2	5	12,50000	31,2500	7,14286	17,8571
7,000000<x<=8,000000	3	8	18,75000	50,0000	10,71429	28,5714
8,000000<x<=9,000000	1	9	6,25000	56,2500	3,57143	32,1429
9,000000<x<=10,00000	2	11	12,50000	68,7500	7,14286	39,2857
10,000000<x<=11,00000	2	13	12,50000	81,2500	7,14286	46,4286
11,000000<x<=12,00000	1	14	6,25000	87,5000	3,57143	50,0000
12,000000<x<=13,00000	2	16	12,50000	100,0000	7,14286	57,1429
Missing	12	28	75,00000		42,85714	100,0000

Pattern Reasoning raw score

Frequency table: Pattern Reasoning RS No Tmpt S1 (MethKi database final time 1.sta) Shapiro-Wilk W=,89007, p=,00675						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
0,000000<x<=2,000000	6	6	21,42857	21,4286	21,42857	21,4286
2,000000<x<=4,000000	6	12	21,42857	42,8571	21,42857	42,8571
4,000000<x<=6,000000	3	15	10,71429	53,5714	10,71429	53,5714
6,000000<x<=8,000000	3	18	10,71429	64,2857	10,71429	64,2857
8,000000<x<=10,00000	9	27	32,14286	96,4286	32,14286	96,4286
10,000000<x<=12,00000	1	28	3,57143	100,0000	3,57143	100,0000
Missing	0	28	0,00000		0,00000	100,0000

Pattern Reasoning scaled score

Frequency table: Pattern Reasoning SCS No Tmpt S1 (MethKi database final time 1.sta) Shapiro-Wilk W=,93035, p=,06290						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
0,000000<x<=2,000000	1	1	3,57143	3,5714	3,57143	3,5714
2,000000<x<=4,000000	8	9	28,57143	32,1429	28,57143	32,1429
4,000000<x<=6,000000	5	14	17,85714	50,0000	17,85714	50,0000
6,000000<x<=8,000000	5	19	17,85714	67,8571	17,85714	67,8571
8,000000<x<=10,00000	3	22	10,71429	78,5714	10,71429	78,5714
10,00000<x<=12,00000	5	27	17,85714	96,4286	17,85714	96,4286
12,00000<x<=14,00000	1	28	3,57143	100,0000	3,57143	100,0000
Missing	0	28	0,00000		0,00000	100,0000

Atlantis raw score

Frequency table: Atlantis RS S1 (MethKi database final time 1.sta) Shapiro-Wilk W=,93406, p=,07811						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
10,00000<x<=20,00000	0	0	0,00000	0,0000	0,00000	0,00000
20,00000<x<=30,00000	8	8	28,57143	28,5714	28,57143	28,5714
30,00000<x<=40,00000	1	9	3,57143	32,1429	3,57143	32,1429
40,00000<x<=50,00000	4	13	14,28571	46,4286	14,28571	46,4286
50,00000<x<=60,00000	5	18	17,85714	64,2857	17,85714	64,2857
60,00000<x<=70,00000	5	23	17,85714	82,1429	17,85714	82,1429
70,00000<x<=80,00000	1	24	3,57143	85,7143	3,57143	85,7143
80,00000<x<=90,00000	4	28	14,28571	100,0000	14,28571	100,0000
Missing	0	28	0,00000		0,00000	100,0000

Atlantis scaled score

Frequency table: Atlantis SCS S1 (MethKi database final time 1.sta) Shapiro-Wilk W= .93935, p=,10639						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
0,000000<x<=2,000000	0	0	0,00000	0,0000	0,00000	0,0000
2,000000<x<=4,000000	7	7	25,00000	25,0000	25,00000	25,0000
4,000000<x<=6,000000	6	13	21,42857	46,4286	21,42857	46,4286
6,000000<x<=8,000000	8	21	28,57143	75,0000	28,57143	75,0000
8,000000<x<=10,00000	3	24	10,71429	85,7143	10,71429	85,7143
10,00000<x<=12,00000	3	27	10,71429	96,4286	10,71429	96,4286
12,00000<x<=14,00000	1	28	3,57143	100,0000	3,57143	100,0000
Missing	0	28	0,00000		0,00000	100,0000

Atlantis Delayed raw score

Frequency table: Atlantis Delayed RS S1 (MethKi database final time 1.sta) Shapiro-Wilk W= .97397, p=,68995						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
0,000000<x<=5,000000	4	4	14,28571	14,2857	14,28571	14,2857
5,000000<x<=10,00000	8	12	28,57143	42,8571	28,57143	42,8571
10,00000<x<=15,00000	10	22	35,71429	78,5714	35,71429	78,5714
15,00000<x<=20,00000	5	27	17,85714	96,4286	17,85714	96,4286
20,00000<x<=25,00000	1	28	3,57143	100,0000	3,57143	100,0000
Missing	0	28	0,00000		0,00000	100,0000

Atlantis Delayed scaled score

Frequency table: Atlantis Delay SCS S1 (MethKi database final time 1.sta) Shapiro-Wilk W=,93905, p=,10457						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
2,000000<x<=4,000000	3	3	10,71429	10,7143	10,71429	10,7143
4,000000<x<=6,000000	2	5	7,14286	17,8571	7,14286	17,8571
6,000000<x<=8,000000	12	17	42,85714	60,7143	42,85714	60,7143
8,000000<x<=10,00000	8	25	28,57143	89,2857	28,57143	89,2857
10,00000<x<=12,00000	1	26	3,57143	92,8571	3,57143	92,8571
12,00000<x<=14,00000	1	27	3,57143	96,4286	3,57143	96,4286
14,00000<x<=16,00000	1	28	3,57143	100,0000	3,57143	100,0000
Missing	0	28	0,00000		0,00000	100,0000

Boston Naming Test – total score

Frequency table: Total BNT S1 (MethKi database final time 1.sta) Shapiro-Wilk W=,93899, p=,10419						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
0,000000<x<=2,000000	0	0	0,00000	0,0000	0,00000	0,0000
2,000000<x<=4,000000	3	3	10,71429	10,7143	10,71429	10,7143
4,000000<x<=6,000000	7	10	25,00000	35,7143	25,00000	35,7143
6,000000<x<=8,000000	14	24	50,00000	85,7143	50,00000	85,7143
8,000000<x<=10,00000	3	27	10,71429	96,4286	10,71429	96,4286
10,00000<x<=12,00000	0	27	0,00000	96,4286	0,00000	96,4286
12,00000<x<=14,00000	1	28	3,57143	100,0000	3,57143	100,0000
Missing	0	28	0,00000		0,00000	100,0000

Metabolite concentrations

Cr

Frequency table: S1 -Cr (MethKi database final time 1.sta) Shapiro-Wilk W=,92886, p=,07281						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
1,500000<x<=2,000000	1	1	3,84615	3,8462	3,57143	3,5714
2,000000<x<=2,500000	14	15	53,84615	57,6923	50,00000	53,5714
2,500000<x<=3,000000	8	23	30,76923	88,4615	28,57143	82,1429
3,000000<x<=3,500000	3	26	11,53846	100,0000	10,71429	92,8571
Missing	2	28	7,69231		7,14286	100,0000

PCr

Frequency table: S1 - PCr (MethKi database final time 1.sta) Shapiro-Wilk W=,97113, p=,67384						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
2,000000<x<=2,200000	1	1	4,00000	4,0000	3,57143	3,5714
2,200000<x<=2,400000	3	4	12,00000	16,0000	10,71429	14,2857
2,400000<x<=2,600000	5	9	20,00000	36,0000	17,85714	32,1429
2,600000<x<=2,800000	6	15	24,00000	60,0000	21,42857	53,5714
2,800000<x<=3,000000	4	19	16,00000	76,0000	14,28571	67,8571
3,000000<x<=3,200000	4	23	16,00000	92,0000	14,28571	82,1429
3,200000<x<=3,400000	1	24	4,00000	96,0000	3,57143	85,7143
3,400000<x<=3,600000	1	25	4,00000	100,0000	3,57143	89,2857
Missing	3	28	12,00000		10,71429	100,0000

Glu

Frequency table: S1 - Glu (MethKi database final time 1.sta) Shapiro-Wilk W=,97179, p=,62925					
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases
6,500000<x<=7,000000	0	0	0,00000	0,0000	0,00000
7,000000<x<=7,500000	1	1	3,57143	3,5714	3,57143
7,500000<x<=8,000000	4	5	14,28571	17,8571	14,28571
8,000000<x<=8,500000	9	14	32,14286	50,0000	32,14286
8,500000<x<=9,000000	10	24	35,71429	85,7143	35,71429
9,000000<x<=9,500000	2	26	7,14286	92,8571	7,14286
9,500000<x<=10,00000	2	28	7,14286	100,0000	7,14286
Missing	0	28	0,00000		0,00000

GPC

Frequency table: S1 - GPC (MethKi database final time 1.sta) Shapiro-Wilk W=,95540, p=,27000					
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases
,8000000<x<=,9000000	1	1	3,57143	3,5714	3,57143
,9000000<x<=1,000000	8	9	28,57143	32,1429	28,57143
1,000000<x<=1,100000	5	14	17,85714	50,0000	17,85714
1,100000<x<=1,200000	6	20	21,42857	71,4286	21,42857
1,200000<x<=1,300000	5	25	17,85714	89,2857	17,85714
1,300000<x<=1,400000	3	28	10,71429	100,0000	10,71429
Missing	0	28	0,00000		0,00000

Ins

Frequency table: S1 - Ins (MethKi database final time 1.sta) Shapiro-Wilk W=,95351, p=,24250						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
3,500000<x<=4,000000	1	1	3,57143	3,5714	3,57143	3,5714
4,000000<x<=4,500000	4	5	14,28571	17,8571	14,28571	17,8571
4,500000<x<=5,000000	7	12	25,00000	42,8571	25,00000	42,8571
5,000000<x<=5,500000	7	19	25,00000	67,8571	25,00000	67,8571
5,500000<x<=6,000000	8	27	28,57143	96,4286	28,57143	96,4286
6,000000<x<=6,500000	1	28	3,57143	100,0000	3,57143	100,0000
Missing	0	28	0,00000		0,00000	100,0000

NAA

Frequency table: S1 - NAA (MethKi database final time 1.sta) Shapiro-Wilk W=,94897, p=,18662						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
4,500000<x<=5,000000	1	1	3,57143	3,5714	3,57143	3,5714
5,000000<x<=5,500000	0	1	0,00000	3,5714	0,00000	3,5714
5,500000<x<=6,000000	8	9	28,57143	32,1429	28,57143	32,1429
6,000000<x<=6,500000	15	24	53,57143	85,7143	53,57143	85,7143
6,500000<x<=7,000000	4	28	14,28571	100,0000	14,28571	100,0000
Missing	0	28	0,00000		0,00000	100,0000

GPC+PCh

Frequency table: S1 - GPC+PCh (MethKi database final time 1.sta) Shapiro-Wilk W=,95540, p=,27000						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
,8000000<x<=,90000000	1	1	3,57143	3,5714	3,57143	3,5714
,9000000<x<=1,000000	8	9	28,57143	32,1429	28,57143	32,1429
1,000000<x<=1,100000	5	14	17,85714	50,0000	17,85714	50,0000
1,100000<x<=1,200000	6	20	21,42857	71,4286	21,42857	71,4286
1,200000<x<=1,300000	5	25	17,85714	89,2857	17,85714	89,2857
1,300000<x<=1,400000	3	28	10,71429	100,0000	10,71429	100,0000
Missing	0	28	0,00000		0,00000	100,0000

NAA+NAAG

Frequency table: S1 - NAA+NAAG (MethKi database final time 1.sta) Shapiro-Wilk W=,95558, p=,27273						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
5,000000<x<=5,500000	1	1	3,57143	3,5714	3,57143	3,5714
5,500000<x<=6,000000	2	3	7,14286	10,7143	7,14286	10,7143
6,000000<x<=6,500000	14	17	50,00000	60,7143	50,00000	60,7143
6,500000<x<=7,000000	10	27	35,71429	96,4286	35,71429	96,4286
7,000000<x<=7,500000	1	28	3,57143	100,0000	3,57143	100,0000
Missing	0	28	0,00000		0,00000	100,0000

Cr+PCr

Frequency table: S1 - Cr+PCr (MethKi database final time 1.sta) Shapiro-Wilk W=.85765, p=.00134					
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases
4,000000<x<=4,200000	2	2	7,14286	7,1429	7,14286
4,200000<x<=4,400000	0	2	0,00000	7,1429	0,00000
4,400000<x<=4,600000	0	2	0,00000	7,1429	0,00000
4,600000<x<=4,800000	2	4	7,14286	14,2857	7,14286
4,800000<x<=5,000000	3	7	10,71429	25,0000	10,71429
5,000000<x<=5,200000	9	16	32,14286	57,1429	32,14286
5,200000<x<=5,400000	9	25	32,14286	89,2857	32,14286
5,400000<x<=5,600000	3	28	10,71429	100,0000	10,71429
Missing	0	28	0,00000		0,00000

Glu+Gln

Frequency table: S1 - Glu+Gln (MethKi database final time 1.sta) Shapiro-Wilk W=.94869, p=.18367					
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases
8,000000<x<=8,500000	1	1	3,57143	3,5714	3,57143
8,500000<x<=9,000000	6	7	21,42857	25,0000	21,42857
9,000000<x<=9,500000	3	10	10,71429	35,7143	10,71429
9,500000<x<=10,00000	4	14	14,28571	50,0000	14,28571
10,00000<x<=10,50000	8	22	28,57143	78,5714	28,57143
10,50000<x<=11,00000	1	23	3,57143	82,1429	3,57143
11,00000<x<=11,50000	3	26	10,71429	92,8571	10,71429
11,50000<x<=12,00000	2	28	7,14286	100,0000	7,14286
Missing	0	28	0,00000		0,00000

Mann-Whitney U test – Demographics

Age & weight

variable	Mann-Whitney U Test (w/ continuity correction) (MethKi database final time 1.sta) By variable Main Diagnosis Marked tests are significant at p <,05000									
	Rank Sum Control	Rank Sum Meth	U	Z	p-value	Z adjusted	p-value	Valid N Control	Valid N Meth	2*1sided exact p
S1 - Age	231,5000	174,5000	69,50000	1,286535	0,198257	1,294710	0,195421	14	14	0,193579
Child weight Scan 1	192,0000	186,0000	81,00000	0,460999	0,644800	0,461421	0,644497	13	14	0,650036

ANOVA – demographics

Univariate Results for Each DV (MethKi database final time 1.sta) Sigma-restricted parameterization Effective hypothesis decomposition											
Effect	Degr. of Freedom	Child height SS	Child height MS	Child height F	Child height p	BMI Scan 1 SS	BMI Scan 1 MS	BMI Scan 1 F	BMI Scan 1	BMI Scan 1 p	BMI Scan 1
Intercept	1	28,77010	28,77010	4865,714	0,000000	8200,105	8200,105	825,1086	8200,105	0,000000	0,000000
Main Diagnosis	1	0,00010	0,00010	0,016	0,899590	0,538	0,538	0,0541	0,538	0,818021	0,818021
Error	24	0,14191	0,00591			238,517	9,938				
Total	25	0,14200				239,055					

Mann-Whitney U test – Neurocognitive tasks

Pattern Reasoning raw score

variable	Mann-Whitney U Test (w/ continuity correction) (MethKi database final time 1.sta) By variable Main Diagnosis Marked tests are significant at p <,05000									
	Rank Sum Control	Rank Sum Meth	U	Z	p-value	Z adjusted	p-value	Valid N Control	Valid N Meth	2*1sided exact p
Pattern Reasoning RS No Tmpt S1	290,0000	116,0000	11,00000	3,974474	0,000071	4,004172	0,000062	14	14	0,000010

ANOVA - Neurocognitive tasks

Univariate Results for Each DV (MethKi database final time 1.sta) Sigma-restricted parameterization Effective hypothesis decomposition

[illegible]Mann-Whitney U test – metabolites
Cr+PCr

	Mann-Whitney U Test	U Test (w/ continuity correction)	(MethKi database final time 1.sta)	By variable	Main Diagnosis	Marked tests are significant at p < 0.050000

variable	Rank Sum Control	Rank Sum Meth	U	Z	p-value	Z adjusted	p-value	Valid N Control	Valid N Meth	2*1sided exact p
S1 - Cr+PCr	222,0000	184,0000	79,00000	0,850032	0,395308	0,850032	0,395308	14	14	0,401263

ANOVA - metabolites

Univariate Results for Each DV (MethKi database final time 1.sta) Sigma-restricted parameterization Effective hypothesis decomposition

[illegible]

Spearman Rank Order correlations – demographics

Both groups

Pair of Variables	Spearman Rank Order Correlations (MethKi database final time 1.sta) MD pairwise deleted Marked correlations are significant at p <,05000			
	Valid N	Spearman R	t(N-2)	p-value
S1 - Age & S1 - Cr	26	-0,021013	-0,102967	0,918845
S1 - Age & S1 - PCr	25	0,230133	1,134121	0,268427
S1 - Age & S1 - Glu	28	0,049299	0,251681	0,803266
S1 - Age & S1 - GPC	28	0,524935	3,144777	0,004130
S1 - Age & S1 - Ins	28	0,325444	1,754981	0,091041
S1 - Age & S1 - NAA	28	0,518050	3,088259	0,004745
S1 - Age & S1 - GPC+PCh	28	0,524935	3,144777	0,004130
S1 - Age & S1 - NAA+NAA	28	0,422482	2,376776	0,025112
S1 - Age & S1 - Cr+PCr	28	0,200500	1,043543	0,306303
S1 - Age & S1 - Glu+Gln	28	0,069128	0,353332	0,726688
Child weight Scan 1 & S1 - Cr	25	-0,118191	-0,570823	0,573655
Child weight Scan 1 & S1 - PCr	24	0,254189	1,232745	0,230682
Child weight Scan 1 & S1 - Glu	27	0,068439	0,342998	0,734467
Child weight Scan 1 & S1 - GPC	27	0,542927	3,232557	0,003431
Child weight Scan 1 & S1 - Ins	27	0,162567	0,823793	0,417847
Child weight Scan 1 & S1 - NAA	27	0,271311	1,409419	0,171030
Child weight Scan 1 & S1 - GPC+PCh	27	0,542927	3,232557	0,003431
Child weight Scan 1 & S1 - NAA+NAA	27	0,096853	0,486553	0,630814
Child weight Scan 1 & S1 - Cr+PCr	27	-0,092270	-0,463327	0,647138
Child weight Scan 1 & S1 - Glu+Gln	27	0,262145	1,358224	0,186524
Child height Scan 1 & S1 - Cr	24	-0,204011	-0,977454	0,338971
Child height Scan 1 & S1 - PCr	23	0,441419	2,254353	0,034979
Child height Scan 1 & S1 - Glu	26	0,122645	0,605406	0,550592
Child height Scan 1 & S1 - GPC	26	0,051388	0,252080	0,803126
Child height Scan 1 & S1 - Ins	26	0,004797	0,023501	0,981445
Child height Scan 1 & S1 - NAA	26	0,110997	0,547154	0,589325

Child height Scan 1 & S1 - GPC+PCh	26	0,051388	0,252080	0,803126
Child height Scan 1 & S1 - NAA+NAAG	26	0,173347	0,862280	0,397068
Child height Scan 1 & S1 - Cr+PCr	26	-0,100034	-0,492537	0,626815
Child height Scan 1 & S1 - Glu+Gln	26	0,276123	1,407436	0,172118
BMI Scan 1 & S1 -Cr	24	0,011304	0,053025	0,958190
BMI Scan 1 & S1 - PCr	23	-0,132411	-0,612174	0,546995
BMI Scan 1 & S1 - Glu	26	-0,186325	-0,929071	0,362103
BMI Scan 1 & S1 - GPC	26	0,382564	2,028482	0,053747
BMI Scan 1 & S1 - Ins	26	0,182937	0,911589	0,371051
BMI Scan 1 & S1 - NAA	26	0,113846	0,561380	0,579743
BMI Scan 1 & S1 - GPC+PCh	26	0,382564	2,028482	0,053747
BMI Scan 1 & S1 - NAA+NAAG	26	-0,076923	-0,377964	0,708779
BMI Scan 1 & S1 - Cr+PCr	26	-0,030427	-0,149132	0,882696
BMI Scan 1 & S1 - Glu+Gln	26	-0,109060	-0,537488	0,595880

Control group

Pair of Variables	Main Diagnosis=Control Spearman Rank Order Correlations (MethKi database final time 1.sta) MD pairwise deleted Marked correlations are significant at p <,05000			
	Valid N	Spearman R	t(N-2)	p-value
S1 - Age & S1 -Cr	13	-0,294331	-1,02143	0,328990
S1 - Age & S1 - PCr	13	0,343137	1,21162	0,251044
S1 - Age & S1 - Glu	14	-0,072011	-0,25010	0,806738
S1 - Age & S1 - GPC	14	0,360055	1,33694	0,206037
S1 - Age & S1 - Ins	14	0,130520	0,45604	0,656507
S1 - Age & S1 - NAA	14	0,364556	1,35619	0,200008
S1 - Age & S1 - GPC+PCh	14	0,360055	1,33694	0,206037
S1 - Age & S1 - NAA+NAAG	14	0,436567	1,68096	0,118591

S1 - Age & S1 - Cr+PCr	14	-0,249788	-0,89362	0,389096
S1 - Age & S1 - Glu+Gln	14	-0,137271	-0,48007	0,639813
Child weight Scan 1 & S1 - Cr	12	-0,245184	-0,79975	0,442438
Child weight Scan 1 & S1 - PCr	12	0,553416	2,10115	0,061958
Child weight Scan 1 & S1 - Glu	13	0,440165	1,62583	0,132265
Child weight Scan 1 & S1 - GPC	13	0,657497	2,89422	0,014595
Child weight Scan 1 & S1 - Ins	13	0,291610	1,01110	0,333690
Child weight Scan 1 & S1 - NAA	13	0,310867	1,08478	0,301223
Child weight Scan 1 & S1 - GPC+PCh	13	0,657497	2,89422	0,014595
Child weight Scan 1 & S1 - NAA+NAAG	13	0,002751	0,00912	0,992883
Child weight Scan 1 & S1 - Cr+PCr	13	0,008253	0,02737	0,978652
Child weight Scan 1 & S1 - Glu+Gln	13	0,525448	2,04826	0,065171
Child height Scan 1 & S1 - Cr	12	-0,253527	-0,82880	0,426556
Child height Scan 1 & S1 - PCr	12	0,809879	4,36597	0,001408
Child height Scan 1 & S1 - Glu	13	0,143649	0,48142	0,639651
Child height Scan 1 & S1 - GPC	13	-0,005525	-0,01832	0,985708
Child height Scan 1 & S1 - Ins	13	-0,127074	-0,42490	0,679102
Child height Scan 1 & S1 - NAA	13	0,088399	0,29434	0,773979
Child height Scan 1 & S1 - GPC+PCh	13	-0,005525	-0,01832	0,985708
Child height Scan 1 & S1 - NAA+NAAG	13	0,060774	0,20194	0,843650
Child height Scan 1 & S1 - Cr+PCr	13	-0,088399	-0,29434	0,773979
Child height Scan 1 & S1 - Glu+Gln	13	0,287297	0,99480	0,341215
BMI Scan 1 & S1 - Cr	12	-0,125874	-0,40124	0,696683
BMI Scan 1 & S1 - PCr	12	-0,258741	-0,84706	0,416775
BMI Scan 1 & S1 - Glu	13	-0,164835	-0,55428	0,590479
BMI Scan 1 & S1 - GPC	13	0,318681	1,11508	0,288583
BMI Scan 1 & S1 - Ins	13	0,456044	1,69955	0,117283

BMI Scan 1 & S1 - NAA	13	0,197802	0,66926	0,517131
BMI Scan 1 & S1 - GPC+PCh	13	0,318681	1,11508	0,288583
BMI Scan 1 & S1 - NAA+NAAAG	13	0,000000	0,00000	1,000000
BMI Scan 1 & S1 - Cr+PCr	13	-0,016484	-0,05468	0,957376
BMI Scan 1 & S1 - Glu+Gln	13	-0,027473	-0,09115	0,929012

MA group

Pair of Variables	Main Diagnosis=Meth Spearman Rank Order Correlations (MethKi database final time 1.sta) MD pairwise deleted Marked correlations are significant at p <,05000			
	Valid N	Spearman R	t(N-2)	p-value
S1 - Age & S1 - Cr	13	0,376744	1,34891	0,204479
S1 - Age & S1 - PCr	12	0,112480	0,35796	0,727811
S1 - Age & S1 - Glu	14	-0,024337	-0,08433	0,934184
S1 - Age & S1 - GPC	14	0,630545	2,81423	0,015626
S1 - Age & S1 - Ins	14	0,296467	1,07533	0,303371
S1 - Age & S1 - NAA	14	0,654882	3,00183	0,011029
S1 - Age & S1 - GPC+PCh	14	0,630545	2,81423	0,015626
S1 - Age & S1 - NAA+NAAAG	14	0,429213	1,64618	0,125645
S1 - Age & S1 - Cr+PCr	14	0,502223	2,01188	0,067237
S1 - Age & S1 - Glu+Gln	14	0,269917	0,97106	0,350683
Child weight Scan 1 & S1 - Cr	13	-0,066025	-0,21946	0,830312
Child weight Scan 1 & S1 - PCr	12	0,007005	0,02215	0,982762
Child weight Scan 1 & S1 - Glu	14	-0,444445	-1,71868	0,111339
Child weight Scan 1 & S1 - GPC	14	0,396040	1,49409	0,160975
Child weight Scan 1 & S1 - Ins	14	0,077008	0,26756	0,793583
Child weight Scan 1 & S1 - NAA	14	0,204621	0,72415	0,482854
Child weight Scan 1 & S1 - GPC+PCh	14	0,396040	1,49409	0,160975
Child weight Scan 1 & S1 - NAA+NAAAG	14	0,125413	0,43790	0,669238
Child weight Scan 1 & S1 - Cr+PCr	14	-0,277228	-0,99952	0,337271

Child weight Scan 1 & S1 - Glu+Gln	14	0,035204	0,12202	0,904899
Child height Scan 1 & S1 - Cr	12	-0,077330	-0,24527	0,811206
Child height Scan 1 & S1 - PCr	11	0,018265	0,05480	0,957492
Child height Scan 1 & S1 - Glu	13	0,030345	0,10069	0,921609
Child height Scan 1 & S1 - GPC	13	0,091035	0,30319	0,767403
Child height Scan 1 & S1 - Ins	13	0,088277	0,29393	0,774285
Child height Scan 1 & S1 - NAA	13	-0,011035	-0,03660	0,971460
Child height Scan 1 & S1 - GPC+PCh	13	0,091035	0,30319	0,767403
Child height Scan 1 & S1 - NAA+NAAg	13	0,242761	0,82997	0,424200
Child height Scan 1 & S1 - Cr+PCr	13	-0,104828	-0,34960	0,733238
Child height Scan 1 & S1 - Glu+Gln	13	0,176553	0,59491	0,563943
BMI Scan 1 & S1 - Cr	12	0,118881	0,37862	0,712884
BMI Scan 1 & S1 - PCr	11	-0,109091	-0,32924	0,749509
BMI Scan 1 & S1 - Glu	13	-0,280220	-0,96817	0,353764
BMI Scan 1 & S1 - GPC	13	0,252747	0,86640	0,404774
BMI Scan 1 & S1 - Ins	13	-0,098901	-0,32963	0,747868
BMI Scan 1 & S1 - NAA	13	0,148352	0,49753	0,628609
BMI Scan 1 & S1 - GPC+PCh	13	0,252747	0,86640	0,404774
BMI Scan 1 & S1 - NAA+NAAg	13	-0,016484	-0,05468	0,957376
BMI Scan 1 & S1 - Cr+PCr	13	-0,082418	-0,27428	0,788951
BMI Scan 1 & S1 - Glu+Gln	13	-0,120879	-0,40387	0,694047

Spearman Rank Order correlations – neurocognitive tasks

Both groups

Spearman Rank Order Correlations (MethKi database final time 1.sta) MD pairwise deleted Marked correlations are significant at p <,05000						
Pair of Variables	Valid N	Spearman R	t(N-2)	p-value		
Block Counting RS S1 & S1 - Cr	14	0,190482	0,67216	0,514218		
Block Counting RS S1 & S1 - PCr	14	-0,367932	-1,37070	0,195561		
Block Counting RS S1 & S1 - Glu	16	-0,248156	-0,95850	0,354074		
Block Counting RS S1 & S1 - GPC	16	-0,294221	-1,15186	0,268671		
Block Counting RS S1 & S1 - Ins	16	-0,267474	-1,03864	0,316580		
Block Counting RS S1 & S1 - NAA	16	-0,166428	-0,63152	0,537874		
Block Counting RS S1 & S1 - GPC+PCh	16	-0,294221	-1,15186	0,268671		
Block Counting RS S1 & S1 - NAA+NAAG	16	-0,090644	-0,34056	0,738491		
Block Counting RS S1 & S1 - Cr+PCr	16	-0,427958	-1,77171	0,098197		
Block Counting RS S1 & S1 - Glu+Gln	16	-0,435388	-1,80959	0,091875		
Block Counting SCS S1 & S1 - Cr	14	0,154698	0,54242	0,597458		
Block Counting SCS S1 & S1 - PCr	14	-0,279390	-1,00798	0,333359		
Block Counting SCS S1 & S1 - Glu	16	-0,279799	-1,09047	0,293921		
Block Counting SCS S1 & S1 - GPC	16	-0,297564	-1,16621	0,263013		
Block Counting SCS S1 & S1 - Ins	16	-0,272397	-1,05927	0,307410		
Block Counting SCS S1 & S1 - NAA	16	-0,161366	-0,61179	0,550482		
Block Counting SCS S1 & S1 - GPC+PCh	16	-0,297564	-1,16621	0,263013		
Block Counting SCS S1 & S1 - NAA+NAAG	16	-0,105110	-0,39548	0,698453		
Block Counting SCS S1 & S1 - Cr+PCr	16	-0,398232	-1,62441	0,126581		
Block Counting SCS S1 & S1 - Glu+Gln	16	-0,455969	-1,91695	0,075883		
Pattern Reasoning RS No Tmpt S1 & S1 - Cr	26	0,340584	1,77461	0,088650		
Pattern Reasoning RS No Tmpt S1 & S1 - PCr	25	-0,243996	-1,20664	0,239837		
Pattern Reasoning RS No Tmpt S1 & S1 - Glu	28	-0,062036	-0,31694	0,753823		
Pattern Reasoning RS No Tmpt S1 & S1 - GPC	28	0,089608	0,45876	0,650219		
Pattern Reasoning RS No Tmpt S1 & S1 - Ins	28	0,202542	1,05463	0,301299		
Pattern Reasoning RS No Tmpt S1 & S1 - NAA	28	0,218368	1,14100	0,264271		

Pattern Reasoning RS No Tmpt S1 & S1 - GPC+PCh	28	0,089608	0,45876	0,650219
Pattern Reasoning RS No Tmpt S1 & S1 - NAA+NAAG	28	0,252282	1,32939	0,195267
Pattern Reasoning RS No Tmpt S1 & S1 - Cr+PCr	28	0,178665	0,92591	0,363006
Pattern Reasoning RS No Tmpt S1 & S1 - Glu+Gln	28	0,030880	0,15753	0,876040
Pattern Reasoning SCS No Tmpt S1 & S1 - Cr	26	0,307064	1,58066	0,127045
Pattern Reasoning SCS No Tmpt S1 & S1 - PCr	25	-0,198882	-0,97324	0,340557
Pattern Reasoning SCS No Tmpt S1 & S1 - Glu	28	-0,187108	-0,97122	0,340387
Pattern Reasoning SCS No Tmpt S1 & S1 - GPC	28	-0,014605	-0,07448	0,941200
Pattern Reasoning SCS No Tmpt S1 & S1 - Ins	28	0,164397	0,84982	0,403180
Pattern Reasoning SCS No Tmpt S1 & S1 - NAA	28	0,282454	1,50137	0,145308
Pattern Reasoning SCS No Tmpt S1 & S1 - GPC+PCh	28	-0,014605	-0,07448	0,941200
Pattern Reasoning SCS No Tmpt S1 & S1 - NAA+NAAG	28	0,306703	1,64307	0,112408
Pattern Reasoning SCS No Tmpt S1 & S1 - Cr+PCr	28	0,158450	0,81827	0,420637
Pattern Reasoning SCS No Tmpt S1 & S1 - Glu+Gln	28	-0,078260	-0,40028	0,692221
Atlantis RS S1 & S1 -Cr	26	0,248028	1,25427	0,221821
Atlantis RS S1 & S1 - PCr	25	-0,132459	-0,64090	0,527923
Atlantis RS S1 & S1 - Glu	28	0,169027	0,87446	0,389877
Atlantis RS S1 & S1 - GPC	28	0,417209	2,34081	0,027185
Atlantis RS S1 & S1 - Ins	28	0,160667	0,83003	0,414081
Atlantis RS S1 & S1 - NAA	28	0,169302	0,87592	0,389095
Atlantis RS S1 & S1 - GPC+PCh	28	0,417209	2,34081	0,027185
Atlantis RS S1 & S1 - NAA+NAAG	28	0,104714	0,53689	0,595907
Atlantis RS S1 & S1 - Cr+PCr	28	0,144841	0,74642	0,462111
Atlantis RS S1 & S1 - Glu+Gln	28	0,065687	0,33566	0,739818
Atlantis SCS S1 & S1 -Cr	26	0,279272	1,42484	0,167079
Atlantis SCS S1 & S1 - PCr	25	-0,163539	-0,79501	0,434737
Atlantis SCS S1 & S1 - Glu	28	0,147591	0,76090	0,453562
Atlantis SCS S1 & S1 - GPC	28	0,295734	1,57856	0,126528

Atlantis SCS S1 & S1 - Ins	28	0,186514	0,96803	0,341950
Atlantis SCS S1 & S1 - NAA	28	0,164143	0,84848	0,403916
Atlantis SCS S1 & S1 - GPC+PCh	28	0,295734	1,57856	0,126528
Atlantis SCS S1 & S1 - NAA+NAAG	28	0,124694	0,64082	0,527250
Atlantis SCS S1 & S1 - Cr+PCr	28	0,177661	0,92054	0,365753
Atlantis SCS S1 & S1 - Glu+Gln	28	0,105659	0,54179	0,592578
Atlantis Delay RS S1 & S1 - Cr	26	-0,047015	-0,23058	0,819596
Atlantis Delay RS S1 & S1 - PCr	25	0,212053	1,04064	0,308861
Atlantis Delay RS S1 & S1 - Glu	28	0,007418	0,03782	0,970117
Atlantis Delay RS S1 & S1 - GPC	28	0,228024	1,19416	0,243198
Atlantis Delay RS S1 & S1 - Ins	28	0,276139	1,46500	0,154910
Atlantis Delay RS S1 & S1 - NAA	28	0,235716	1,23677	0,227228
Atlantis Delay RS S1 & S1 - GPC+PCh	28	0,228024	1,19416	0,243198
Atlantis Delay RS S1 & S1 - NAA+NAAG	28	0,184342	0,95635	0,347702
Atlantis Delay RS S1 & S1 - Cr+PCr	28	0,118407	0,60804	0,548436
Atlantis Delay RS S1 & S1 - Glu+Gln	28	-0,134616	-0,69272	0,494629
Atlantis Delay SCS S1 & S1 - Cr	26	-0,067764	-0,33274	0,742219
Atlantis Delay SCS S1 & S1 - PCr	25	0,202719	0,99282	0,331129
Atlantis Delay SCS S1 & S1 - Glu	28	-0,059384	-0,30334	0,764047
Atlantis Delay SCS S1 & S1 - GPC	28	0,157340	0,81240	0,423938
Atlantis Delay SCS S1 & S1 - Ins	28	0,297100	1,58656	0,124701
Atlantis Delay SCS S1 & S1 - NAA	28	0,219777	1,14873	0,261125
Atlantis Delay SCS S1 & S1 - GPC+PCh	28	0,157340	0,81240	0,423938
Atlantis Delay SCS S1 & S1 - NAA+NAAG	28	0,176210	0,91278	0,369744
Atlantis Delay SCS S1 & S1 - Cr+PCr	28	0,072704	0,37170	0,713126
Atlantis Delay SCS S1 & S1 - Glu+Gln	28	-0,138748	-0,71439	0,481352
Total BNT S1 & S1 - Cr	26	-0,025835	-0,12661	0,900307
Total BNT S1 & S1 - PCr	25	0,219041	1,07663	0,292810
Total BNT S1 & S1 - Glu	28	0,068603	0,35063	0,728689
Total BNT S1 & S1 - GPC	28	0,100673	0,51596	0,610246
Total BNT S1 & S1 - Ins	28	0,317122	1,70501	0,100114
Total BNT S1 & S1 - NAA	28	0,284171	1,51130	0,142772

Total BNT S1 & S1 - GPC+PCr	28	0,100673	0,51596	0,610246
Total BNT S1 & S1 - NAA+NAAG	28	0,233695	1,22555	0,231353
Total BNT S1 & S1 - Cr+PCr	28	0,233974	1,22710	0,230781
Total BNT S1 & S1 - Glu+Gln	28	0,152543	0,78703	0,438379

Control group

Pair of Variables	Main Diagnosis=Control Spearman Rank Order Correlations (MethKi database final time 1.sta) MD pairwise deleted Marked correlations are significant at p <,05000			
	Valid N	Spearman R	t(N-2)	p-value
Block Counting RS S1 & S1 - Cr	9	0,100844	0,26817	0,796296
Block Counting RS S1 & S1 - PCr	9	-0,434141	-1,27506	0,242975
Block Counting RS S1 & S1 - Glu	10	-0,332347	-0,99667	0,348111
Block Counting RS S1 & S1 - GPC	10	-0,264647	-0,77621	0,459956
Block Counting RS S1 & S1 - Ins	10	-0,123091	-0,35082	0,734780
Block Counting RS S1 & S1 - NAA	10	0,116937	0,33303	0,747670
Block Counting RS S1 & S1 - GPC+PCh	10	-0,264647	-0,77621	0,459956
Block Counting RS S1 & S1 - NAA+NAAG	10	0,381584	1,16763	0,276575
Block Counting RS S1 & S1 - Cr+PCr	10	-0,012309	-0,03482	0,973078
Block Counting RS S1 & S1 - Glu+Gln	10	-0,578530	-2,00614	0,079754
Block Counting SCS S1 & S1 - Cr	9	0,100844	0,26817	0,796296
Block Counting SCS S1 & S1 - PCr	9	-0,329140	-0,92221	0,387101
Block Counting SCS S1 & S1 - Glu	10	-0,348639	-1,05211	0,323487
Block Counting SCS S1 & S1 - GPC	10	-0,379221	-1,15918	0,279809
Block Counting SCS S1 & S1 - Ins	10	-0,152912	-0,43765	0,673218
Block Counting SCS S1 & S1 - NAA	10	0,073398	0,20816	0,840305
Block Counting SCS S1 & S1 - GPC+PCh	10	-0,379221	-1,15918	0,279809
Block Counting SCS S1 & S1 - NAA+NAAG	10	0,354755	1,07320	0,314484
Block Counting SCS S1 & S1 - Cr+PCr	10	0,006116	0,01730	0,986621
Block Counting SCS S1 & S1 - Glu+Gln	10	-0,538249	-1,80639	0,108488

Pattern Reasoning RS No Tmpt S1 & S1 -Cr	13	0,207813	0,70462	0,495695
Pattern Reasoning RS No Tmpt S1 & S1 -PCr	13	-0,401392	-1,45350	0,174013
Pattern Reasoning RS No Tmpt S1 & S1 -Glu	14	-0,251828	-0,90141	0,385107
Pattern Reasoning RS No Tmpt S1 & S1 -GPC	14	0,088480	0,30771	0,763578
Pattern Reasoning RS No Tmpt S1 & S1 -Ins	14	0,083943	0,29182	0,775411
Pattern Reasoning RS No Tmpt S1 & S1 -NAA	14	0,501387	2,00740	0,067768
Pattern Reasoning RS No Tmpt S1 & S1 -GPC+PCr	14	0,088480	0,30771	0,763578
Pattern Reasoning RS No Tmpt S1 & S1 -NAA+NAAG	14	0,419713	1,60185	0,135170
Pattern Reasoning RS No Tmpt S1 & S1 -Cr+PCr	14	0,338039	1,24425	0,237164
Pattern Reasoning RS No Tmpt S1 & S1 -Glu+Gln	14	-0,297202	-1,07826	0,302116
Pattern Reasoning SCS No Tmpt S1 & S1 -Cr	13	0,216376	0,73505	0,477687
Pattern Reasoning SCS No Tmpt S1 & S1 -PCr	13	-0,232048	-0,79121	0,445546
Pattern Reasoning SCS No Tmpt S1 & S1 -Glu	14	-0,343310	-1,26622	0,229463
Pattern Reasoning SCS No Tmpt S1 & S1 -GPC	14	0,208201	0,73739	0,475058
Pattern Reasoning SCS No Tmpt S1 & S1 -Ins	14	0,093026	0,32366	0,751770
Pattern Reasoning SCS No Tmpt S1 & S1 -NAA	14	0,655612	3,00770	0,010909
Pattern Reasoning SCS No Tmpt S1 & S1 -GPC+PCr	14	0,208201	0,73739	0,475058
Pattern Reasoning SCS No Tmpt S1 & S1 -NAA+NAAG	14	0,478420	1,88730	0,083539
Pattern Reasoning SCS No Tmpt S1 & S1 -Cr+PCr	14	0,301227	1,09431	0,295299

Pattern Reasoning SCS No Tmpt S1 & S1 - Glu+Gln	14	-0,343310	-1,26622	0,229463
Atlantis RS S1 & S1 - Cr	13	0,300277	1,04409	0,318848
Atlantis RS S1 & S1 - PCr	13	-0,344831	-1,21840	0,248557
Atlantis RS S1 & S1 - Glu	14	0,273430	0,98472	0,344202
Atlantis RS S1 & S1 - GPC	14	0,575527	2,43791	0,031277
Atlantis RS S1 & S1 - Ins	14	-0,041897	-0,14526	0,886916
Atlantis RS S1 & S1 - NAA	14	0,467478	1,83188	0,091891
Atlantis RS S1 & S1 - GPC+PCh	14	0,575527	2,43791	0,031277
Atlantis RS S1 & S1 - NAA+NAAG	14	0,277841	1,00192	0,336160
Atlantis RS S1 & S1 - Cr+PCr	14	0,295481	1,07142	0,305058
Atlantis RS S1 & S1 - Glu+Gln	14	0,041897	0,14526	0,886916
Atlantis SCS S1 & S1 - Cr	13	0,378459	1,35607	0,202259
Atlantis SCS S1 & S1 - PCr	13	-0,395034	-1,42617	0,181576
Atlantis SCS S1 & S1 - Glu	14	0,320447	1,17186	0,263996
Atlantis SCS S1 & S1 - GPC	14	0,472935	1,85938	0,087656
Atlantis SCS S1 & S1 - Ins	14	-0,024310	-0,08424	0,934257
Atlantis SCS S1 & S1 - NAA	14	0,373486	1,39472	0,188381
Atlantis SCS S1 & S1 - GPC+PCh	14	0,472935	1,85938	0,087656
Atlantis SCS S1 & S1 - NAA+NAAG	14	0,167958	0,59021	0,565999
Atlantis SCS S1 & S1 - Cr+PCr	14	0,397796	1,50196	0,158958
Atlantis SCS S1 & S1 - Glu+Gln	14	0,090609	0,31518	0,758042
Atlantis Delay RS S1 & S1 - Cr	13	-0,160670	-0,53990	0,600027
Atlantis Delay RS S1 & S1 - PCr	13	0,008369	0,02776	0,978352
Atlantis Delay RS S1 & S1 - Glu	14	-0,100232	-0,34897	0,733159
Atlantis Delay RS S1 & S1 - GPC	14	0,055684	0,19320	0,850037
Atlantis Delay RS S1 & S1 - Ins	14	-0,296240	-1,07443	0,303758
Atlantis Delay RS S1 & S1 - NAA	14	0,347470	1,28365	0,223497
Atlantis Delay RS S1 & S1 - GPC+PCh	14	0,055684	0,19320	0,850037
Atlantis Delay RS S1 & S1 - NAA+NAAG	14	0,171508	0,60306	0,557698
Atlantis Delay RS S1 & S1 - Cr+PCr	14	-0,169280	-0,59499	0,562902
Atlantis Delay RS S1 & S1 - Glu+Gln	14	-0,343015	-1,26499	0,229890

Atlantis Delay SCS S1 & S1 - Cr	13	-0,168340	-0,56640	0,582490
Atlantis Delay SCS S1 & S1 - PCr	13	0,005587	0,01853	0,985547
Atlantis Delay SCS S1 & S1 - Glu	14	-0,190622	-0,67267	0,513904
Atlantis Delay SCS S1 & S1 - GPC	14	-0,026911	-0,09326	0,927238
Atlantis Delay SCS S1 & S1 - Ins	14	-0,260143	-0,93329	0,369068
Atlantis Delay SCS S1 & S1 - NAA	14	0,396942	1,49813	0,159937
Atlantis Delay SCS S1 & S1 - GPC+PCh	14	-0,026911	-0,09326	0,927238
Atlantis Delay SCS S1 & S1 - NAA+NAAG	14	0,248930	0,89034	0,390782
Atlantis Delay SCS S1 & S1 - Cr+PCr	14	-0,174924	-0,61544	0,549757
Atlantis Delay SCS S1 & S1 - Glu+Gln	14	-0,352090	-1,30312	0,216985
Total BNT S1 & S1 - Cr	13	-0,244223	-0,83529	0,421327
Total BNT S1 & S1 - PCr	13	0,022944	0,07612	0,940693
Total BNT S1 & S1 - Glu	14	-0,094926	-0,33033	0,746849
Total BNT S1 & S1 - GPC	14	0,370444	1,38155	0,192292
Total BNT S1 & S1 - Ins	14	-0,180591	-0,63604	0,536690
Total BNT S1 & S1 - NAA	14	0,497784	1,98821	0,070089
Total BNT S1 & S1 - GPC+PCh	14	0,370444	1,38155	0,192292
Total BNT S1 & S1 - NAA+NAAG	14	0,356552	1,32202	0,210808
Total BNT S1 & S1 - Cr+PCr	14	-0,050936	-0,17668	0,862709
Total BNT S1 & S1 - Glu+Gln	14	-0,245419	-0,87698	0,397716

MA group

Main Diagnosis=Meth Spearman Rank Order Correlations (MethKi database final time 1.sta) MD pairwise deleted Marked correlations are significant at p <,05000				
Pair of Variables	Valid N	Spearman R	t(N-2)	p-value
Block Counting RS S1 & S1 - Cr	5	0,359092	0,66641	0,552815
Block Counting RS S1 & S1 - PCr	5	-0,153897	-0,26977	0,804829
Block Counting RS S1 & S1 - Glu	6	-0,057977	-0,11615	0,913132
Block Counting RS S1 & S1 - GPC	6	0,318874	0,67287	0,537901
Block Counting RS S1 & S1 - Ins	6	-0,347863	-0,74207	0,499253
Block Counting RS S1 & S1 - NAA	6	-0,724714	-2,10352	0,103243
Block Counting RS S1 & S1 - GPC+PCh	6	0,318874	0,67287	0,537901
Block Counting RS S1 & S1 - NAA+NAAG	6	-0,695725	-1,93712	0,124789
Block Counting RS S1 & S1 - Cr+PCr	6	-0,869657	-3,52332	0,024377
Block Counting RS S1 & S1 - Glu+Gln	6	-0,405840	-0,88811	0,424663
Block Counting SCS S1 & S1 - Cr	5	0,359092	0,66641	0,552815
Block Counting SCS S1 & S1 - PCr	5	-0,153897	-0,26977	0,804829
Block Counting SCS S1 & S1 - Glu	6	-0,057977	-0,11615	0,913132
Block Counting SCS S1 & S1 - GPC	6	0,318874	0,67287	0,537901
Block Counting SCS S1 & S1 - Ins	6	-0,347863	-0,74207	0,499253
Block Counting SCS S1 & S1 - NAA	6	-0,724714	-2,10352	0,103243
Block Counting SCS S1 & S1 - GPC+PCh	6	0,318874	0,67287	0,537901
Block Counting SCS S1 & S1 - NAA+NAAG	6	-0,695725	-1,93712	0,124789
Block Counting SCS S1 & S1 - Cr+PCr	6	-0,869657	-3,52332	0,024377
Block Counting SCS S1 & S1 - Glu+Gln	6	-0,405840	-0,88811	0,424663
Pattern Reasoning RS No Tmpt S1 & S1 -Cr	13	0,443932	1,64314	0,128602
Pattern Reasoning RS No Tmpt S1 & S1 - PCr	12	-0,434628	-1,52609	0,157973
Pattern Reasoning RS No Tmpt S1 & S1 - Glu	14	-0,107769	-0,37551	0,713836
Pattern Reasoning RS No Tmpt S1 & S1 - GPC	14	0,249215	0,89143	0,390222
Pattern Reasoning RS No Tmpt S1 & S1 - Ins	14	0,069601	0,24169	0,813101

Pattern Reasoning RS No Tmpt S1 & S1 - NAA	14	0,096543	0,33600	0,742671
Pattern Reasoning RS No Tmpt S1 & S1 - GPC+PCh	14	0,249215	0,89143	0,390222
Pattern Reasoning RS No Tmpt S1 & S1 - NAA+NAAG	14	0,505165	2,02769	0,065394
Pattern Reasoning RS No Tmpt S1 & S1 - Cr+PCr	14	-0,163898	-0,57554	0,575558
Pattern Reasoning RS No Tmpt S1 & S1 - Glu+Gln	14	0,042658	0,14791	0,884872
Pattern Reasoning SCS No Tmpt S1 & S1 - Cr	13	0,210727	0,71496	0,489531
Pattern Reasoning SCS No Tmpt S1 & S1 - PCr	12	-0,379351	-1,29653	0,223914
Pattern Reasoning SCS No Tmpt S1 & S1 - Glu	14	-0,176547	-0,62134	0,546001
Pattern Reasoning SCS No Tmpt S1 & S1 - GPC	14	-0,165230	-0,58035	0,572416
Pattern Reasoning SCS No Tmpt S1 & S1 - Ins	14	-0,022634	-0,07843	0,938781
Pattern Reasoning SCS No Tmpt S1 & S1 - NAA	14	-0,061112	-0,21210	0,835592
Pattern Reasoning SCS No Tmpt S1 & S1 - GPC+PCh	14	-0,165230	-0,58035	0,572416
Pattern Reasoning SCS No Tmpt S1 & S1 - NAA+NAAG	14	0,330460	1,21289	0,248510
Pattern Reasoning SCS No Tmpt S1 & S1 - Cr+PCr	14	-0,242186	-0,86470	0,404158
Pattern Reasoning SCS No Tmpt S1 & S1 - Glu+Gln	14	-0,013581	-0,04705	0,963248
Atlantis RS S1 & S1 - Cr	13	0,232068	0,79129	0,445504
Atlantis RS S1 & S1 - PCr	12	-0,096275	-0,30587	0,765977
Atlantis RS S1 & S1 - Glu	14	-0,022503	-0,07797	0,939134
Atlantis RS S1 & S1 - GPC	14	0,594092	2,55843	0,025074
Atlantis RS S1 & S1 - Ins	14	0,288044	1,04198	0,317961
Atlantis RS S1 & S1 - NAA	14	0,042757	0,14825	0,884608

Atlantis RS S1 & S1 - GPC+PCh	14	0,594092	2,55843	0,025074
Atlantis RS S1 & S1 - NAA+NAAG	14	0,297046	1,07764	0,302382
Atlantis RS S1 & S1 - Cr+PCr	14	-0,112517	-0,39226	0,701742
Atlantis RS S1 & S1 - Glu+Gln	14	-0,247538	-0,88504	0,393523
Atlantis SCS S1 & S1 - Cr	13	0,165112	0,55523	0,589847
Atlantis SCS S1 & S1 - PCr	12	-0,086207	-0,27363	0,789938
Atlantis SCS S1 & S1 - Glu	14	-0,040742	-0,14125	0,890016
Atlantis SCS S1 & S1 - GPC	14	0,387045	1,45410	0,171571
Atlantis SCS S1 & S1 - Ins	14	0,420997	1,60780	0,133856
Atlantis SCS S1 & S1 - NAA	14	0,083747	0,29113	0,775923
Atlantis SCS S1 & S1 - GPC+PCh	14	0,387045	1,45410	0,171571
Atlantis SCS S1 & S1 - NAA+NAAG	14	0,380255	1,42423	0,179862
Atlantis SCS S1 & S1 - Cr+PCr	14	-0,065639	-0,22787	0,823582
Atlantis SCS S1 & S1 - Glu+Gln	14	-0,219552	-0,77957	0,450745
Atlantis Delay RS S1 & S1 - Cr	13	-0,049794	-0,16535	0,871666
Atlantis Delay RS S1 & S1 - PCr	12	0,275143	0,90501	0,386745
Atlantis Delay RS S1 & S1 - Glu	14	0,030940	0,10723	0,916379
Atlantis Delay RS S1 & S1 - GPC	14	0,503875	2,02075	0,066198
Atlantis Delay RS S1 & S1 - Ins	14	0,654154	2,99599	0,011149
Atlantis Delay RS S1 & S1 - NAA	14	0,167958	0,59021	0,565999
Atlantis Delay RS S1 & S1 - GPC+PCh	14	0,503875	2,02075	0,066198
Atlantis Delay RS S1 & S1 - NAA+NAAG	14	0,386746	1,45277	0,171930
Atlantis Delay RS S1 & S1 - Cr+PCr	14	0,251938	0,90183	0,384892
Atlantis Delay RS S1 & S1 - Glu+Gln	14	-0,011050	-0,03828	0,970094
Atlantis Delay SCS S1 & S1 - Cr	13	-0,180340	-0,60809	0,555476
Atlantis Delay SCS S1 & S1 - PCr	12	0,278125	0,91564	0,381408
Atlantis Delay SCS S1 & S1 - Glu	14	-0,096432	-0,33562	0,742956
Atlantis Delay SCS S1 & S1 - GPC	14	0,412640	1,56926	0,142568
Atlantis Delay SCS S1 & S1 - Ins	14	0,663812	3,07463	0,009634
Atlantis Delay SCS S1 & S1 - NAA	14	0,109888	0,38298	0,708431
Atlantis Delay SCS S1 & S1 - GPC+PCh	14	0,412640	1,56926	0,142568
Atlantis Delay SCS S1 & S1 - NAA+NAAG	14	0,311723	1,13647	0,277948

Atlantis Delay SCS S1 & S1 - Cr+PCr	14	0,094190	0,32774	0,748756
Atlantis Delay SCS S1 & S1 - Glu+Gln	14	-0,091947	-0,31987	0,754568
Total BNT S1 & S1 - Cr	13	-0,080902	-0,26920	0,792755
Total BNT S1 & S1 - PCr	12	0,471679	1,69157	0,121603
Total BNT S1 & S1 - Glu	14	0,182439	0,64277	0,532461
Total BNT S1 & S1 - GPC	14	0,135717	0,47453	0,643643
Total BNT S1 & S1 - Ins	14	0,658559	3,03153	0,010437
Total BNT S1 & S1 - NAA	14	0,280332	1,01166	0,331663
Total BNT S1 & S1 - GPC+PCh	14	0,135717	0,47453	0,643643
Total BNT S1 & S1 - NAA+NAAG	14	0,278108	1,00296	0,335676
Total BNT S1 & S1 - Cr+PCr	14	0,351528	1,30075	0,217770
Total BNT S1 & S1 - Glu+Gln	14	0,382676	1,43485	0,176877

Spearman Rank Order correlations – metabolites

Both groups

Spearman Rank Order Correlations (MethKi database final time 1. sta) MD pairwise deleted Marked correlations are significant at p < ,05000				
Pair of Variables	Valid N	Spearman R	t(N-2)	p-value
S1 -Cr & S1 -Cr				
S1 -Cr & S1 - PCr	24	-0,626087	-3,76607	0,001065
S1 -Cr & S1 - Glu	26	0,158291	0,78536	0,439925
S1 -Cr & S1 - GPC	26	-0,005128	-0,02512	0,980164
S1 -Cr & S1 - Ins	26	0,058472	0,28694	0,776620
S1 -Cr & S1 - NAA	26	0,147350	0,72983	0,472556
S1 -Cr & S1 - GPC+PCh	26	-0,005128	-0,02512	0,980164
S1 -Cr & S1 - NAA+NAAG	26	0,221880	1,11477	0,275986
S1 -Cr & S1 - Cr+PCr	26	0,612308	3,79409	0,000885
S1 -Cr & S1 - Glu+Gln	26	0,139829	0,69182	0,495692
S1 - PCr & S1 -Cr	24	-0,626087	-3,76607	0,001065

S1 - PCr & S1 - PCr					
S1 - PCr & S1 - Glu	25	0,214615	1,05381		0,302913
S1 - PCr & S1 - GPC	25	0,199231	0,97502		0,339693
S1 - PCr & S1 - Ins	25	0,258511	1,28340		0,212132
S1 - PCr & S1 - NAA	25	0,211538	1,03799		0,310063
S1 - PCr & S1 - GPC+PCh	25	0,199231	0,97502		0,339693
S1 - PCr & S1 - NAA+NAAg	25	-0,007692	-0,03689		0,970889
S1 - PCr & S1 - Cr+PCr	25	0,156923	0,76202		0,453794
S1 - PCr & S1 - Glu+Gln	25	0,180769	0,88146		0,387188
S1 - Glu & S1 - Cr	26	0,158291	0,78536		0,439925
S1 - Glu & S1 - PCr	25	0,214615	1,05381		0,302913
S1 - Glu & S1 - Glu					
S1 - Glu & S1 - GPC	28	0,257800	1,36051		0,185347
S1 - Glu & S1 - Ins	28	0,127275	0,65430		0,518665
S1 - Glu & S1 - NAA	28	-0,201970	-1,05152		0,302695
S1 - Glu & S1 - GPC+PCh	28	0,257800	1,36051		0,185347
S1 - Glu & S1 - NAA+NAAg	28	-0,222770	-1,16519		0,254523
S1 - Glu & S1 - Cr+PCr	28	0,348659	1,89685		0,069010
S1 - Glu & S1 - Glu+Gln	28	0,546251	3,32530		0,002636
S1 - GPC & S1 - Cr	26	-0,005128	-0,02512		0,980164
S1 - GPC & S1 - PCr	25	0,199231	0,97502		0,339693
S1 - GPC & S1 - Glu	28	0,257800	1,36051		0,185347
S1 - GPC & S1 - GPC					
S1 - GPC & S1 - Ins	28	0,388395	2,14916		0,041105
S1 - GPC & S1 - NAA	28	0,439518	2,49502		0,019273
S1 - GPC & S1 - GPC+PCh	28	1,000000			
S1 - GPC & S1 - NAA+NAAg	28	0,303777	1,62579		0,116055
S1 - GPC & S1 - Cr+PCr	28	0,142857	0,73598		0,468331
S1 - GPC & S1 - Glu+Gln	28	0,031746	0,16196		0,872593
S1 - Ins & S1 - Cr	26	0,058472	0,28694		0,776620
S1 - Ins & S1 - PCr	25	0,258511	1,28340		0,212132
S1 - Ins & S1 - Glu	28	0,127275	0,65430		0,518665

S1 - Ins & S1 - GPC	28	0,388395	2,14916	0,041105
S1 - Ins & S1 - Ins				
S1 - Ins & S1 - NAA	28	0,321336	1,73026	0,095439
S1 - Ins & S1 - GPC+PCh	28	0,388395	2,14916	0,041105
S1 - Ins & S1 - NAA+NAAG	28	0,286848	1,52681	0,138884
S1 - Ins & S1 - Cr+PCr	28	0,424524	2,39079	0,024344
S1 - Ins & S1 - Glu+Gln	28	0,345970	1,88022	0,071327
S1 - NAA & S1 - Cr	26	0,147350	0,72983	0,472556
S1 - NAA & S1 - PCr	25	0,211538	1,03799	0,310063
S1 - NAA & S1 - Glu	28	-0,201970	-1,05152	0,302695
S1 - NAA & S1 - GPC	28	0,439518	2,49502	0,019273
S1 - NAA & S1 - Ins	28	0,321336	1,73026	0,095439
S1 - NAA & S1 - NAA				
S1 - NAA & S1 - GPC+PCh	28	0,439518	2,49502	0,019273
S1 - NAA & S1 - NAA+NAAG	28	0,819923	7,30306	0,000000
S1 - NAA & S1 - Cr+PCr	28	0,406678	2,26983	0,031743
S1 - NAA & S1 - Glu+Gln	28	-0,076081	-0,38907	0,700395
S1 - GPC+PCh & S1 - Cr	26	-0,005128	-0,02512	0,980164
S1 - GPC+PCh & S1 - PCr	25	0,199231	0,97502	0,339693
S1 - GPC+PCh & S1 - Glu	28	0,257800	1,36051	0,185347
S1 - GPC+PCh & S1 - GPC	28	1,000000		
S1 - GPC+PCh & S1 - Ins	28	0,388395	2,14916	0,041105
S1 - GPC+PCh & S1 - NAA	28	0,439518	2,49502	0,019273
S1 - GPC+PCh & S1 - GPC+PCh				
S1 - GPC+PCh & S1 - NAA+NAAG	28	0,303777	1,62579	0,116055
S1 - GPC+PCh & S1 - Cr+PCr	28	0,142857	0,73598	0,468331
S1 - GPC+PCh & S1 - Glu+Gln	28	0,031746	0,16196	0,872593
S1 - NAA+NAAG & S1 - Cr	26	0,221880	1,11477	0,275986
S1 - NAA+NAAG & S1 - PCr	25	-0,007692	-0,03689	0,970889
S1 - NAA+NAAG & S1 - Glu	28	-0,222770	-1,16519	0,254523
S1 - NAA+NAAG & S1 - GPC	28	0,303777	1,62579	0,116055
S1 - NAA+NAAG & S1 - Ins	28	0,286848	1,52681	0,138884

S1 - NAA+NAAG & S1 - NAA	28	0,819923	7,30306	0,000000
S1 - NAA+NAAG & S1 - GPC+PCh	28	0,303777	1,62579	0,116055
S1 - NAA+NAAG & S1 - NAA+NAAG				
S1 - NAA+NAAG & S1 - Cr+PCr	28	0,251232	1,32348	0,197196
S1 - NAA+NAAG & S1 - Glu+Gln	28	-0,190476	-0,98936	0,331608
S1 - Cr+PCr & S1 - Cr	26	0,612308	3,79409	0,000885
S1 - Cr+PCr & S1 - PCr	25	0,156923	0,76202	0,453794
S1 - Cr+PCr & S1 - Glu	28	0,348659	1,89685	0,069010
S1 - Cr+PCr & S1 - GPC	28	0,142857	0,73598	0,468331
S1 - Cr+PCr & S1 - Ins	28	0,424524	2,39079	0,024344
S1 - Cr+PCr & S1 - NAA	28	0,406678	2,26983	0,031743
S1 - Cr+PCr & S1 - GPC+PCh	28	0,142857	0,73598	0,468331
S1 - Cr+PCr & S1 - NAA+NAAG	28	0,251232	1,32348	0,197196
S1 - Cr+PCr & S1 - Cr+PCr				
S1 - Cr+PCr & S1 - Glu+Gln	28	0,287356	1,52975	0,138154
S1 - Glu+Gln & S1 - Cr	26	0,139829	0,69182	0,495692
S1 - Glu+Gln & S1 - PCr	25	0,180769	0,88146	0,387188
S1 - Glu+Gln & S1 - Glu	28	0,546251	3,32530	0,002636
S1 - Glu+Gln & S1 - GPC	28	0,031746	0,16196	0,872593
S1 - Glu+Gln & S1 - Ins	28	0,345970	1,88022	0,071327
S1 - Glu+Gln & S1 - NAA	28	-0,076081	-0,38907	0,700395
S1 - Glu+Gln & S1 - GPC+PCh	28	0,031746	0,16196	0,872593
S1 - Glu+Gln & S1 - NAA+NAAG	28	-0,190476	-0,98936	0,331608
S1 - Glu+Gln & S1 - Cr+PCr	28	0,287356	1,52975	0,138154
S1 - Glu+Gln & S1 - Glu+Gln				

Control group

Main Diagnosis=Control Spearman Rank Order Correlations (MethKi database final time 1.sta) MD pairwise deleted Marked correlations are significant at p <,05000				
Pair of Variables	Valid N	Spearman R	t(N-2)	p-value
S1 -Cr & S1 -Cr				
S1 -Cr & S1 - PCr	12	-0,790210	-4,07754	0,002223
S1 -Cr & S1 - Glu	13	-0,010989	-0,03645	0,971578
S1 -Cr & S1 - GPC	13	-0,181319	-0,61150	0,553295
S1 -Cr & S1 - Ins	13	-0,027473	-0,09115	0,929012
S1 -Cr & S1 - NAA	13	-0,005495	-0,01822	0,985787
S1 -Cr & S1 - GPC+PCr	13	-0,181319	-0,61150	0,553295
S1 -Cr & S1 - NAA+NAAG	13	0,115385	0,38526	0,707390
S1 -Cr & S1 - Cr+PCr	13	0,802198	4,45616	0,000969
S1 -Cr & S1 - Glu+Gln	13	-0,104396	-0,34814	0,734304
S1 - PCr & S1 -Cr	12	-0,790210	-4,07754	0,002223
S1 - PCr & S1 - PCr				
S1 - PCr & S1 - Glu	13	0,208791	0,70809	0,493622
S1 - PCr & S1 - GPC	13	0,087912	0,29270	0,775195
S1 - PCr & S1 - Ins	13	0,120879	0,40387	0,694047
S1 - PCr & S1 - NAA	13	0,043956	0,14593	0,886619
S1 - PCr & S1 - GPC+PCr	13	0,087912	0,29270	0,775195
S1 - PCr & S1 - NAA+NAAG	13	-0,131868	-0,44121	0,667608
S1 - PCr & S1 - Cr+PCr	13	-0,252747	-0,86640	0,404774
S1 - PCr & S1 - Glu+Gln	13	0,456044	1,69955	0,117283
S1 - Glu & S1 -Cr	13	-0,010989	-0,03645	0,971578
S1 - Glu & S1 - PCr	13	0,208791	0,70809	0,493622
S1 - Glu & S1 - Glu				
S1 - Glu & S1 - GPC	14	0,402198	1,52176	0,153974
S1 - Glu & S1 - Ins	14	0,107692	0,37524	0,714031
S1 - Glu & S1 - NAA	14	-0,226374	-0,80508	0,436435
S1 - Glu & S1 - GPC+PCr	14	0,402198	1,52176	0,153974
S1 - Glu & S1 - NAA+NAAG	14	-0,432967	-1,66388	0,122010

S1 - Glu & S1 - Cr+PCr	14	0,186813	0,65874	0,522504
S1 - Glu & S1 - Glu+Gln	14	0,683516	3,24381	0,007037
S1 - GPC & S1 - Cr	13	-0,181319	-0,61150	0,553295
S1 - GPC & S1 - PCr	13	0,087912	0,29270	0,775195
S1 - GPC & S1 - Glu	14	0,402198	1,52176	0,153974
S1 - GPC & S1 - GPC				
S1 - GPC & S1 - Ins	14	0,230769	0,82158	0,427336
S1 - GPC & S1 - NAA	14	0,529670	2,16320	0,051417
S1 - GPC & S1 - GPC+PCh	14	1,000000		
S1 - GPC & S1 - NAA+NAAG	14	0,274725	0,98976	0,341830
S1 - GPC & S1 - Cr+PCr	14	-0,019780	-0,06853	0,946489
S1 - GPC & S1 - Glu+Gln	14	0,441758	1,70576	0,113777
S1 - Ins & S1 - Cr	13	-0,027473	-0,09115	0,929012
S1 - Ins & S1 - PCr	13	0,120879	0,40387	0,694047
S1 - Ins & S1 - Glu	14	0,107692	0,37524	0,714031
S1 - Ins & S1 - GPC	14	0,230769	0,82158	0,427336
S1 - Ins & S1 - Ins				
S1 - Ins & S1 - NAA	14	0,112088	0,39075	0,702833
S1 - Ins & S1 - GPC+PCh	14	0,230769	0,82158	0,427336
S1 - Ins & S1 - NAA+NAAG	14	0,125275	0,43741	0,669582
S1 - Ins & S1 - Cr+PCr	14	0,305495	1,11140	0,288170
S1 - Ins & S1 - Glu+Gln	14	0,472527	1,85732	0,087967
S1 - NAA & S1 - Cr	13	-0,005495	-0,01822	0,985787
S1 - NAA & S1 - PCr	13	0,043956	0,14593	0,886619
S1 - NAA & S1 - Glu	14	-0,226374	-0,80508	0,436435
S1 - NAA & S1 - GPC	14	0,529670	2,16320	0,051417
S1 - NAA & S1 - Ins	14	0,112088	0,39075	0,702833
S1 - NAA & S1 - NAA				
S1 - NAA & S1 - GPC+PCh	14	0,529670	2,16320	0,051417
S1 - NAA & S1 - NAA+NAAG	14	0,872527	6,18653	0,000047
S1 - NAA & S1 - Cr+PCr	14	0,142857	0,50000	0,626117
S1 - NAA & S1 - Glu+Gln	14	-0,156044	-0,54726	0,594235

S1 - GPC+PCh & S1 -Cr	13	-0,181319	-0,61150	0,553295
S1 - GPC+PCh & S1 - PCr	13	0,087912	0,29270	0,775195
S1 - GPC+PCh & S1 - Glu	14	0,402198	1,52176	0,153974
S1 - GPC+PCh & S1 - GPC	14	1,000000		
S1 - GPC+PCh & S1 - Ins	14	0,230769	0,82158	0,427336
S1 - GPC+PCh & S1 - NAA	14	0,529670	2,16320	0,051417
S1 - GPC+PCh & S1 - GPC+PCh				
S1 - GPC+PCh & S1 - NAA+NAA	14	0,274725	0,98976	0,341830
S1 - GPC+PCh & S1 - Cr+PCr	14	-0,019780	-0,06853	0,946489
S1 - GPC+PCh & S1 - Glu+Gln	14	0,441758	1,70576	0,113777
S1 - NAA+NAA & S1 - Cr	13	0,115385	0,38526	0,707390
S1 - NAA+NAA & S1 - PCr	13	-0,131868	-0,44121	0,667608
S1 - NAA+NAA & S1 - Glu	14	-0,432967	-1,66388	0,122010
S1 - NAA+NAA & S1 - GPC	14	0,274725	0,98976	0,341830
S1 - NAA+NAA & S1 - Ins	14	0,125275	0,43741	0,669582
S1 - NAA+NAA & S1 - NAA	14	0,872527	6,18653	0,000047
S1 - NAA+NAA & S1 - GPC+PCh	14	0,274725	0,98976	0,341830
S1 - NAA+NAA & S1 - NAA+NAA				
S1 - NAA+NAA & S1 - Cr+PCr	14	0,081319	0,28263	0,782275
S1 - NAA+NAA & S1 - Glu+Gln	14	-0,340659	-1,25515	0,233316
S1 - Cr+PCr & S1 - Cr	13	0,802198	4,45616	0,000969
S1 - Cr+PCr & S1 - PCr	13	-0,252747	-0,86640	0,404774
S1 - Cr+PCr & S1 - Glu	14	0,186813	0,65874	0,522504
S1 - Cr+PCr & S1 - GPC	14	-0,019780	-0,06853	0,946489
S1 - Cr+PCr & S1 - Ins	14	0,305495	1,11140	0,288170
S1 - Cr+PCr & S1 - NAA	14	0,142857	0,50000	0,626117
S1 - Cr+PCr & S1 - GPC+PCh	14	-0,019780	-0,06853	0,946489
S1 - Cr+PCr & S1 - NAA+NAA	14	0,081319	0,28263	0,782275

S1 - Cr+PCr & S1 - Cr+PCr				
S1 - Cr+PCr & S1 - Glu+Gln	14	0,164835	0,57892	0,573346
S1 - Glu+Gln & S1 - Cr	13	-0,104396	-0,34814	0,734304
S1 - Glu+Gln & S1 - PCr	13	0,456044	1,69955	0,117283
S1 - Glu+Gln & S1 - Glu	14	0,683516	3,24381	0,007037
S1 - Glu+Gln & S1 - GPC	14	0,441758	1,70576	0,113777
S1 - Glu+Gln & S1 - Ins	14	0,472527	1,85732	0,087967
S1 - Glu+Gln & S1 - NAA	14	-0,156044	-0,54726	0,594235
S1 - Glu+Gln & S1 - GPC+PCh	14	0,441758	1,70576	0,113777
S1 - Glu+Gln & S1 - NAA+NAAG	14	-0,340659	-1,25515	0,233316
S1 - Glu+Gln & S1 - Cr+PCr	14	0,164835	0,57892	0,573346
S1 - Glu+Gln & S1 - Glu+Gln				

MA group

Pair of Variables	Main Diagnosis=Meth Spearman Rank Order Correlations (MethKi database final time 1.sta) MD pairwise deleted Marked correlations are significant at p <,05000			
	Valid N	Spearman R	t(N-2)	p-value
S1 -Cr & S1 -Cr				
S1 -Cr & S1 - PCr	12	-0,552448	-2,09585	0,062511
S1 -Cr & S1 - Glu	13	0,445055	1,64832	0,127524
S1 -Cr & S1 - GPC	13	0,153846	0,51640	0,615799
S1 -Cr & S1 - Ins	13	0,049451	0,16421	0,872544
S1 -Cr & S1 - NAA	13	0,131868	0,44121	0,667608
S1 -Cr & S1 - GPC+PCh	13	0,153846	0,51640	0,615799
S1 -Cr & S1 - NAA+NAAG	13	0,313187	1,09375	0,297438

S1 - Cr & S1 - Cr+PCr	13	0,362637	1,29058	0,223316
S1 - Cr & S1 - Glu+Gln	13	0,593407	2,44515	0,032524
S1 - PCr & S1 - Cr	12	-0,552448	-2,09585	0,062511
S1 - PCr & S1 - PCr				
S1 - PCr & S1 - Glu	12	0,132867	0,42392	0,680598
S1 - PCr & S1 - GPC	12	0,328671	1,10049	0,296904
S1 - PCr & S1 - Ins	12	0,370629	1,26190	0,235621
S1 - PCr & S1 - NAA	12	0,482517	1,74207	0,112109
S1 - PCr & S1 - GPC+PCh	12	0,328671	1,10049	0,296904
S1 - PCr & S1 - NAA+NAAG	12	0,020979	0,06636	0,948402
S1 - PCr & S1 - Cr+PCr	12	0,531469	1,98406	0,075362
S1 - PCr & S1 - Glu+Gln	12	-0,391608	-1,34587	0,208063
S1 - Glu & S1 - Cr	13	0,445055	1,64832	0,127524
S1 - Glu & S1 - PCr	12	0,132867	0,42392	0,680598
S1 - Glu & S1 - Glu				
S1 - Glu & S1 - GPC	14	0,063736	0,22124	0,828626
S1 - Glu & S1 - Ins	14	0,164835	0,57892	0,573346
S1 - Glu & S1 - NAA	14	-0,221978	-0,78863	0,445630
S1 - Glu & S1 - GPC+PCh	14	0,063736	0,22124	0,828626
S1 - Glu & S1 - NAA+NAAG	14	-0,112088	-0,39075	0,702833
S1 - Glu & S1 - Cr+PCr	14	0,472527	1,85732	0,087967
S1 - Glu & S1 - Glu+Gln	14	0,292308	1,05883	0,310526
S1 - GPC & S1 - Cr	13	0,153846	0,51640	0,615799
S1 - GPC & S1 - PCr	12	0,328671	1,10049	0,296904
S1 - GPC & S1 - Glu	14	0,063736	0,22124	0,828626
S1 - GPC & S1 - GPC				
S1 - GPC & S1 - Ins	14	0,498901	1,99415	0,069364
S1 - GPC & S1 - NAA	14	0,380220	1,42407	0,179906
S1 - GPC & S1 - GPC+PCh	14	1,000000		
S1 - GPC & S1 - NAA+NAAG	14	0,393407	1,48233	0,164032
S1 - GPC & S1 - Cr+PCr	14	0,265934	0,95563	0,358113
S1 - GPC & S1 - Glu+Gln	14	-0,292308	-1,05883	0,310526

S1 - Ins & S1 - Cr	13	0,049451	0,16421	0,872544
S1 - Ins & S1 - PCr	12	0,370629	1,26190	0,235621
S1 - Ins & S1 - Glu	14	0,164835	0,57892	0,573346
S1 - Ins & S1 - GPC	14	0,498901	1,99415	0,069364
S1 - Ins & S1 - Ins				
S1 - Ins & S1 - NAA	14	0,415385	1,58186	0,139666
S1 - Ins & S1 - GPC+PCh	14	0,498901	1,99415	0,069364
S1 - Ins & S1 - NAA+NAAG	14	0,516484	2,08940	0,058637
S1 - Ins & S1 - Cr+PCr	14	0,503297	2,01764	0,066560
S1 - Ins & S1 - Glu+Gln	14	0,142857	0,50000	0,626117
S1 - NAA & S1 - Cr	13	0,131868	0,44121	0,667608
S1 - NAA & S1 - PCr	12	0,482517	1,74207	0,112109
S1 - NAA & S1 - Glu	14	-0,221978	-0,78863	0,445630
S1 - NAA & S1 - GPC	14	0,380220	1,42407	0,179906
S1 - NAA & S1 - Ins	14	0,415385	1,58186	0,139666
S1 - NAA & S1 - NAA				
S1 - NAA & S1 - GPC+PCh	14	0,380220	1,42407	0,179906
S1 - NAA & S1 - NAA+NAAG	14	0,679121	3,20498	0,007562
S1 - NAA & S1 - Cr+PCr	14	0,578022	2,45377	0,030383
S1 - NAA & S1 - Glu+Gln	14	0,116484	0,40628	0,691691
S1 - GPC+PCh & S1 - Cr	13	0,153846	0,51640	0,615799
S1 - GPC+PCh & S1 - PCr	12	0,328671	1,10049	0,296904
S1 - GPC+PCh & S1 - Glu	14	0,063736	0,22124	0,828626
S1 - GPC+PCh & S1 - GPC	14	1,000000		
S1 - GPC+PCh & S1 - Ins	14	0,498901	1,99415	0,069364
S1 - GPC+PCh & S1 - NAA	14	0,380220	1,42407	0,179906
S1 - GPC+PCh & S1 - GPC+PCh				
S1 - GPC+PCh & S1 - NAA+NAAG	14	0,393407	1,48233	0,164032
S1 - GPC+PCh & S1 - Cr+PCr	14	0,265934	0,95563	0,358113
S1 - GPC+PCh & S1 - Glu+Gln	14	-0,292308	-1,05883	0,310526
S1 - NAA+NAAG & S1 - Cr	13	0,313187	1,09375	0,297438

S1 - NAA+NAAG & S1 - PCr	12	0,020979	0,06636	0,948402
S1 - NAA+NAAG & S1 - Glu	14	-0,112088	-0,39075	0,702833
S1 - NAA+NAAG & S1 - GPC	14	0,393407	1,48233	0,164032
S1 - NAA+NAAG & S1 - Ins	14	0,516484	2,08940	0,058637
S1 - NAA+NAAG & S1 - NAA	14	0,679121	3,20498	0,007562
S1 - NAA+NAAG & S1 - GPC+PCh	14	0,393407	1,48233	0,164032
S1 - NAA+NAAG & S1 - NAA+NAAG				
S1 - NAA+NAAG & S1 - Cr+PCr	14	0,446154	1,72692	0,109807
S1 - NAA+NAAG & S1 - Glu+Gln	14	0,068132	0,23657	0,816984
S1 - Cr+PCr & S1 - Cr	13	0,362637	1,29058	0,223316
S1 - Cr+PCr & S1 - PCr	12	0,531469	1,98406	0,075362
S1 - Cr+PCr & S1 - Glu	14	0,472527	1,85732	0,087967
S1 - Cr+PCr & S1 - GPC	14	0,265934	0,95563	0,358113
S1 - Cr+PCr & S1 - Ins	14	0,503297	2,01764	0,066560
S1 - Cr+PCr & S1 - NAA	14	0,578022	2,45377	0,030383
S1 - Cr+PCr & S1 - GPC+PCh	14	0,265934	0,95563	0,358113
S1 - Cr+PCr & S1 - NAA+NAAG	14	0,446154	1,72692	0,109807
S1 - Cr+PCr & S1 - Cr+PCr				
S1 - Cr+PCr & S1 - Glu+Gln	14	0,292308	1,05883	0,310526
S1 - Glu+Gln & S1 - Cr	13	0,593407	2,44515	0,032524
S1 - Glu+Gln & S1 - PCr	12	-0,391608	-1,34587	0,208063
S1 - Glu+Gln & S1 - Glu	14	0,292308	1,05883	0,310526
S1 - Glu+Gln & S1 - GPC	14	-0,292308	-1,05883	0,310526
S1 - Glu+Gln & S1 - Ins	14	0,142857	0,50000	0,626117
S1 - Glu+Gln & S1 - NAA	14	0,116484	0,40628	0,691691
S1 - Glu+Gln & S1 - GPC+PCh	14	-0,292308	-1,05883	0,310526
S1 - Glu+Gln & S1 - NAA+NAAG	14	0,068132	0,23657	0,816984
S1 - Glu+Gln & S1 - Cr+PCr	14	0,292308	1,05883	0,310526
S1 - Glu+Gln & S1 - Glu+Gln				

Full dataset – time point 2

Participant ID	Main Diagnosis	S2 - Age	Gender	MA Freque ncy 1st Tri	MA Freque ncy 3rd Tri	MA Freque ncy 3rd Tri	Smoke Freque ncy 1st Tri	Smoke Freque ncy 2nd Tri	Smoke Freque ncy 3rd Tri	Alcohol Freque ncy 1st Tri	Alcohol Freque ncy 2nd Tri	Alcohol Freque ncy 3rd Tri	Child weight Scan 2	Child height Scan 2	BMI Scan 2	Child head circumference Scan 2	Block Counting RS S2	Block Counting SCS S2	Pattern Reason ing RS Tmpt S2	Pattern Reason ing SCS Tmpt S2	Pattern Reason ing SCS No Tmpt S2	Atlantis RS S2	Atlantis SCS S2	Atlantis Delay RS S2	Atlantis Delay SCS S2	Total BNT S2	S2 - Cr	S2 - PCr	S2 - Glu	S2 - GPC	S2 - Ins	S2 - NAA	S2 - GPC+P Ch	S2 - NAA+N AAG	S2 - Cr+PCr	S2 - Glu+Gln	
CON7	Control	8,660	F	1	1	1	1	1	1	1	1	1	22	1.2	15.6	51.3	20	13	11	10	7	7	57	6	5	4	7	2,598	2,880	8,448	1,170	5,881	6,203	1,170	6,379	5,478	9,454
CON13	Control	8,630	F	1	1	1	2	2	2	1	1	1	24	1.3	13.8	54.5	15	11	10	10	7	7	68	7	14	9	6	2,235	3,010	9,678	1,138	4,962	6,041	1,138	6,041	5,246	10,925
CON14	Control	8,380	F	1	1	1	1	1	1	1	1	1	29	1.4	15.4	57.5	18	12	13	11	8	7	94	12	6	5	8	2,783	3,130	8,586	1,254	6,055	6,451	1,254	6,914	5,914	9,472
CON15	Control	8,020	M	1	1	1	3	3	3	1	1	1	22	1.1	16.5	51.0	14	11	11	11	8	8	38	4	4	4	8	2,577	2,986	9,085		5,858	6,502	1,097	6,544	5,563	10,738
CON16	Control	8,220	F	1	1	1	3	3	3	1	1	1	25	1.2	16.4	51.2	30	15	12	11	8	8	68	8	12	8	9	3,120	2,444	9,980	1,108	5,681	6,789	1,108	6,965	5,564	11,601
CON17	Control	7,850	F	1	1	1	1	1	1	1	1	1	23	1.3	13.1	50.0	10	8	4	4	5	4	67	8	10	7	7	2,840	2,584	9,963		5,014	6,742	1,020	6,918	5,424	11,735
CON18	Control	7,400	F	1	1	1	1	1	1	1	1	1	20	1.2	13.3	51.0	2	5	10	10	8	8	57	7	16	10	7	2,492	2,943	8,226	1,031	5,458	6,533	1,031	6,680	5,435	9,177
CON19	Control	8,350	F	1	1	1	1	1	1	1	1	1	22	1.3	14.0		14	11	10	9	7	6	65	7	4	4	9	2,462	2,685	9,170	1,188	5,484	6,522	1,188	6,754	5,146	10,736
CON21	Control	8,040	M	1	1	1	3	3	3	1	1	1	21	1.2	13.7	50.9	5	6	10	8	7	6	65	7	6	5	7	2,276	2,878	7,644	1,017	4,493	6,420	1,017	6,420	5,153	8,871
CON24	Control	7,670	M	1	1	1	4	4	4	2	2	2	25	1.3	14.3	51.5	15	11	10	9	7	6	67	7	10	7	9	2,515	3,047	8,854	1,085	6,082	7,061	1,085	7,176	5,563	10,876
CON27	Control	7,780	F	1	1	1				1	1	1	22	1.2	15.9	50.6	6	7	3	3	4	3	65	8	14	9	8	2,605	2,842	10,168	1,087	5,871	6,144	1,087	6,514	5,447	11,918
MET2	Meth	8,680	M	5	5	5	3	3	3	1	1	1	32	1.2	20.6	53.8	12	9	7	7	5	5	75	8	10	7	9	2,801	2,417	8,159	1,122	5,435	6,702	1,122	6,702	5,218	9,801
MET6	Meth	8,210	M	4	4	4	5	5	5	1	1	1	24	1.2	15.3	53.5	16	12	10	10	7	7	82	10	10	10	8	2,000	2,959	8,692	0,950	4,836	6,419	0,950	6,546	4,959	10,863
MET10	Meth	7,400	F				3	3	3	4	4	4	24	1.2	15.8	53.3	11	10	12	10	9	8	71	9	17	10	10	2,412	2,950	8,841	1,021	5,514	6,631	1,021	6,847	5,362	9,871
MET12	Meth	7,860	F	4	4	4	4	4	4	1	1	1	21	1.2	15.1	51.6	2	1	11	10	8	8	70	8	9	7	7	2,454	3,414	9,413	1,033	5,076	6,216	1,033	6,386	5,868	11,795
MET13	Meth	7,320	M										21	1.2	13.5	49.6	2	5	10	9	8	7	92	12	13	8	8	2,155	2,872	9,237	1,050	5,071	6,265	1,050	6,545	5,027	9,797
MET14	Meth	8,280	F	5	5	5	3	3	3	5	5	5	23	1.2	16.2	50.3	5	6	12	10	8	7	78	9	8	6	6	2,749	2,510	8,913	1,211	6,177	6,349	1,211	6,712	5,259	10,760
MET16	Meth	8,630	M	5	4	4	5	5	5	1	1	1	21	1.2	14.5	51.1	12	9	6	6	5	4	66	7	14	9	9	2,204	2,953	7,982	1,188	5,585	6,262	1,188	6,262	5,157	9,472
MET19	Meth	7,630	F	3	3	3	3	3	3	1	1	1	20	1.2	12.7	50.8	9	8	16	13	12	10	73	9	11	8	9	2,746	3,080	9,559	1,174	5,420	6,509	1,174	7,251	5,826	11,680
MET21	Meth	7,440	F	3	3	3	3	3	3	1	1	1	22	1.3	14.0	50.1	1	3	4	4	4	3	65	7	15	9	8	2,983	2,281	9,142	0,969	5,372	6,222	0,969	6,700	5,263	10,526
MET22	Meth	7,590	M										23	1.2	16.4	52.1	10	9	14	11	11	9	73	9	7	6	8	2,658	2,160	8,155	1,084	5,476	6,518	1,084	6,762	4,818	9,143
MET23	Meth	8,110	M				3	3	3	3	3	3	16	1.2	12.4	48.6	8	7	11	10	8	7	74	8	8	6	9	3,157	2,528	8,435	1,135	5,015	6,360	1,135	6,623	5,685	9,847
MET24	Meth	8,450	M				5	5	5	1	1	1	21	1.3	13.5	51.9	0	1	5	5	4	4	74	8	17	10	7	2,617	3,099	9,574	1,077	6,303	6,301	1,077	6,728	5,716	10,702
MET25	Meth	9,460	M				5	5	5	3	3	3	22	1.3	13.5	52.8	14	10	5	5	3	3	38	4	18	10	8	2,659	2,190	7,987	1,008	5,221	6,156	1,008	6,156	4,848	9,044

Descriptive statistics
Demographics

Variable	Descriptive Statistics (MethKi database final time 2.sta)				
	Valid N	Mean	Minimum	Maximum	Std. Dev.
S2 - Age	24	8,08583	7,32000	9,46000	0,523424
MA Frequency 1st Tri	18	2,22222	1,00000	5,00000	1,664705
MA Frequency 2nd Tri	18	2,16667	1,00000	5,00000	1,581139
MA Frequency 3rd Tri	18	2,16667	1,00000	5,00000	1,581139
Smoke Frequency 1st Tri	21	2,95238	1,00000	5,00000	1,395571
Smoke Frequency 2nd Tri	21	2,95238	1,00000	5,00000	1,395571
Smoke Frequency 3rd Tri	21	2,95238	1,00000	5,00000	1,395571
Alcohol Frequency 1st Tri	22	1,54545	1,00000	5,00000	1,143398
Alcohol Frequency 2nd Tri	22	1,54545	1,00000	5,00000	1,143398
Alcohol Frequency 3rd Tri	22	1,54545	1,00000	5,00000	1,143398
Child weight Scan 2	24	22,57500	16,40000	31,60000	2,999601
Child height Scan 2	24	1,23500	1,14000	1,37000	0,055795
BMI Scan 2	24	14,80419	12,40076	20,55151	1,756555

Neurocognitive tasks

Variable	Descriptive Statistics (MethKi database final time 2.sta)				
	Valid N	Mean	Minimum	Maximum	Std. Dev.
Block Counting RS S2	24	10,45833	0,00000	30,00000	7,05863
Block Counting SCS S2	24	8,33333	1,00000	15,00000	3,61959
Pattern Reasonin RS Tmpt S2	24	9,45833	3,00000	16,00000	3,40050
Pattern Reasoning RS No Tmpt S2	24	8,58333	3,00000	13,00000	2,70131
Pattern Reasoning SCS Tmpt S2	24	7,00000	3,00000	12,00000	2,16695
Pattern Reasoning SCS No Tmpt S2	24	6,33333	3,00000	10,00000	1,97080
Atlantis RS S2	24	68,41667	38,00000	94,00000	12,87369
Atlantis SCS S2	24	7,87500	4,00000	12,00000	1,89536
Atlantis Delay RS S2	24	10,75000	4,00000	18,00000	4,26564
Atlantis Delay SCS S2	24	7,41667	4,00000	10,00000	2,06243
Total BNT S2	24	7,95833	6,00000	10,00000	1,04170

Metabolites

Variable	Descriptive Statistics (MethKi database final time 2.sta)				
	Valid N	Mean	Minimum	Maximum	Std.Dev.
S2 - Cr	24	2,58742	2,000000	3,15700	0,291463
S2 - PCr	24	2,78508	2,160000	3,41400	0,325816
S2 - Glu	24	8,91213	7,644000	10,16800	0,701467
S2 - GPC	22	1,09545	0,950000	1,25400	0,081313
S2 - Ins	24	5,47250	4,493000	6,30300	0,460149
S2 - NAA	24	6,42992	6,041000	7,06100	0,238656
S2 - GPC+PCh	24	1,09238	0,950000	1,25400	0,079212
S2 - NAA+NAAG	24	6,64688	6,041000	7,25100	0,292693
S2 - Cr+PCr	24	5,37246	4,818000	5,91400	0,307603
S2 - Glu+Gln	24	10,36683	8,871000	11,91800	0,965606

Frequency tables

Demographics

Age

Category	Frequency table: S2 - Age (MethKi database final time 2.sta) Shapiro-Wilk W=,95318, p=,31700					
	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
7,000000<x<=7,500000	4	4	16,66667	16,6667	16,66667	16,6667
7,500000<x<=8,000000	6	10	25,00000	41,6667	25,00000	41,6667
8,000000<x<=8,500000	9	19	37,50000	79,1667	37,50000	79,1667
8,500000<x<=9,000000	4	23	16,66667	95,8333	16,66667	95,8333
9,000000<x<=9,500000	1	24	4,16667	100,0000	4,16667	100,0000
Missing	0	24	0,00000		0,00000	100,0000

Weight

Frequency table: Child weight Scan 2 (MethKi database final time 2.sta) Shapiro-Wilk W=,88175, p=,00902						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
14,00000<x<=16,00000	0	0	0,00000	0,0000	0,00000	0,0000
16,00000<x<=18,00000	1	1	4,16667	4,1667	4,16667	4,1667
18,00000<x<=20,00000	2	3	8,33333	12,5000	8,33333	12,5000
20,00000<x<=22,00000	8	11	33,33333	45,8333	33,33333	45,8333
22,00000<x<=24,00000	9	20	37,50000	83,3333	37,50000	83,3333
24,00000<x<=26,00000	2	22	8,33333	91,6667	8,33333	91,6667
26,00000<x<=28,00000	0	22	0,00000	91,6667	0,00000	91,6667
28,00000<x<=30,00000	1	23	4,16667	95,8333	4,16667	95,8333
30,00000<x<=32,00000	1	24	4,16667	100,0000	4,16667	100,0000
Missing	0	24	0,00000		0,00000	100,0000

Height

Frequency table: Child height Scan 2 (MethKi database final time 2.sta) Shapiro-Wilk W=,95962, p=,43080						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
1,100000<x<=1,150000	2	2	8,33333	8,3333	8,33333	8,3333
1,150000<x<=1,200000	6	8	25,00000	33,3333	25,00000	33,3333
1,200000<x<=1,250000	9	17	37,50000	70,8333	37,50000	70,8333
1,250000<x<=1,300000	3	20	12,50000	83,3333	12,50000	83,3333
1,300000<x<=1,350000	3	23	12,50000	95,8333	12,50000	95,8333
1,350000<x<=1,400000	1	24	4,16667	100,0000	4,16667	100,0000
Missing	0	24	0,00000		0,00000	100,0000

BMI

Frequency table: BMI Scan 2 (MethKi database final time 2.sta) Shapiro-Wilk W=,88114, p=,00876						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
11,00000<x<=12,00000	0	0	0,00000	0,0000	0,00000	0,0000
12,00000<x<=13,00000	2	2	8,33333	8,3333	8,33333	8,3333
13,00000<x<=14,00000	8	10	33,33333	41,6667	33,33333	41,6667
14,00000<x<=15,00000	3	13	12,50000	54,1667	12,50000	54,1667
15,00000<x<=16,00000	6	19	25,00000	79,1667	25,00000	79,1667
16,00000<x<=17,00000	4	23	16,66667	95,8333	16,66667	95,8333
17,00000<x<=18,00000	0	23	0,00000	95,8333	0,00000	95,8333
18,00000<x<=19,00000	0	23	0,00000	95,8333	0,00000	95,8333
19,00000<x<=20,00000	0	23	0,00000	95,8333	0,00000	95,8333
20,00000<x<=21,00000	1	24	4,16667	100,0000	4,16667	100,0000
Missing	0	24	0,00000		0,00000	100,0000

Frequency tables - Neurocognitive Tasks

Block Counting raw score

Frequency table: Block Counting RS S2 (MethKi database final time 2.sta) Shapiro-Wilk W=,94602, p=,22179						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
-5,00000<x<=0,000000	1	1	4,16667	4,1667	4,16667	4,1667
0,000000<x<=5,000000	6	7	25,00000	29,1667	25,00000	29,1667
5,000000<x<=10,00000	5	12	20,83333	50,0000	20,83333	50,0000
10,00000<x<=15,00000	8	20	33,33333	83,3333	33,33333	83,3333
15,00000<x<=20,00000	3	23	12,50000	95,8333	12,50000	95,8333
20,00000<x<=25,00000	0	23	0,00000	95,8333	0,00000	95,8333
25,00000<x<=30,00000	1	24	4,16667	100,0000	4,16667	100,0000
Missing	0	24	0,00000		0,00000	100,0000

Block Counting scaled score

Frequency table: Block Counting SCS S2 (MethKi database final time 2.sta) Shapiro-Wilk W=,96432, p=,53111						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
-2,00000<x<=0,000000	0	0	0,00000	0,0000	0,00000	0,0000
0,000000<x<=2,000000	2	2	8,33333	8,3333	8,33333	8,3333
2,000000<x<=4,000000	1	3	4,16667	12,5000	4,16667	12,5000
4,000000<x<=6,000000	4	7	16,66667	29,1667	16,66667	29,1667
6,000000<x<=8,000000	4	11	16,66667	45,8333	16,66667	45,8333
8,000000<x<=10,00000	5	16	20,83333	66,6667	20,83333	66,6667
10,00000<x<=12,00000	6	22	25,00000	91,6667	25,00000	91,6667
12,00000<x<=14,00000	1	23	4,16667	95,8333	4,16667	95,8333
14,00000<x<=16,00000	1	24	4,16667	100,0000	4,16667	100,0000
Missing	0	24	0,00000		0,00000	100,0000

Pattern Reasoning raw score

Frequency table: Pattern Reasoning RS No Tmpt S2 (MethKi database final time 2.sta) Shapiro-Wilk W=,88114, p=,00876						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
0,000000<x<=2,000000	0	0	0,00000	0,0000	0,00000	0,0000
2,000000<x<=4,000000	3	3	12,50000	12,5000	12,50000	12,5000
4,000000<x<=6,000000	3	6	12,50000	25,0000	12,50000	25,0000
6,000000<x<=8,000000	2	8	8,33333	33,3333	8,33333	33,3333
8,000000<x<=10,00000	11	19	45,83333	79,1667	45,83333	79,1667
10,00000<x<=12,00000	4	23	16,66667	95,8333	16,66667	95,8333
12,00000<x<=14,00000	1	24	4,16667	100,0000	4,16667	100,0000
Missing	0	24	0,00000		0,00000	100,0000

Pattern Reasoning scaled score

Frequency table: Pattern Reasoning SCS No Tmpt S2 (MethKi database final time 2.sta) Shapiro-Wilk W=,92158, p=,06330						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
2,000000<x<=3,000000	3	3	12,50000	12,5000	12,50000	12,5000
3,000000<x<=4,000000	3	6	12,50000	25,0000	12,50000	25,0000
4,000000<x<=5,000000	1	7	4,16667	29,1667	4,16667	29,1667
5,000000<x<=6,000000	3	10	12,50000	41,6667	12,50000	41,6667
6,000000<x<=7,000000	7	17	29,16667	70,8333	29,16667	70,8333
7,000000<x<=8,000000	5	22	20,83333	91,6667	20,83333	91,6667
8,000000<x<=9,000000	1	23	4,16667	95,8333	4,16667	95,8333
9,000000<x<=10,00000	1	24	4,16667	100,0000	4,16667	100,0000
Missing	0	24	0,00000		0,00000	100,0000

Atlantis raw score

Frequency table: Atlantis RS S2 (MethKi database final time 2.sta) Shapiro-Wilk W=,90614, p=,02910						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
30,00000<x<=40,00000	2	2	8,33333	8,3333	8,33333	8,3333
40,00000<x<=50,00000	0	2	0,00000	8,3333	0,00000	8,3333
50,00000<x<=60,00000	2	4	8,33333	16,6667	8,33333	16,6667
60,00000<x<=70,00000	10	14	41,66667	58,3333	41,66667	58,3333
70,00000<x<=80,00000	7	21	29,16667	87,5000	29,16667	87,5000
80,00000<x<=90,00000	1	22	4,16667	91,6667	4,16667	91,6667
90,00000<x<=100,0000	2	24	8,33333	100,0000	8,33333	100,0000
Missing	0	24	0,00000		0,00000	100,0000

Atlantis scaled score

Frequency table: Atlantis SCS S2 (MethKi database final time 2.sta) Shapiro-Wilk W= .91090, p=.03689						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
3,000000<x<=4,000000	2	2	8,33333	8,3333	8,33333	8,3333
4,000000<x<=5,000000	0	2	0,00000	8,3333	0,00000	8,3333
5,000000<x<=6,000000	1	3	4,16667	12,5000	4,16667	12,5000
6,000000<x<=7,000000	7	10	29,16667	41,6667	29,16667	41,6667
7,000000<x<=8,000000	7	17	29,16667	70,8333	29,16667	70,8333
8,000000<x<=9,000000	4	21	16,66667	87,5000	16,66667	87,5000
9,000000<x<=10,00000	1	22	4,16667	91,6667	4,16667	91,6667
10,00000<x<=11,00000	0	22	0,00000	91,6667	0,00000	91,6667
11,00000<x<=12,00000	2	24	8,33333	100,0000	8,33333	100,0000
Missing	0	24	0,00000		0,00000	100,0000

Atlantis Delayed raw score

Frequency table: Atlantis Delayed RS S2 (MethKi database final time 2.sta) Shapiro-Wilk W= .95693, p=.37985						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
2,000000<x<=4,000000	2	2	8,33333	8,3333	8,33333	8,3333
4,000000<x<=6,000000	3	5	12,50000	20,8333	12,50000	20,8333
6,000000<x<=8,000000	3	8	12,50000	33,3333	12,50000	33,3333
8,000000<x<=10,00000	5	13	20,83333	54,1667	20,83333	54,1667
10,00000<x<=12,00000	2	15	8,33333	62,5000	8,33333	62,5000
12,00000<x<=14,00000	4	19	16,66667	79,1667	16,66667	79,1667
14,00000<x<=16,00000	2	21	8,33333	87,5000	8,33333	87,5000
16,00000<x<=18,00000	3	24	12,50000	100,0000	12,50000	100,0000
Missing	0	24	0,00000		0,00000	100,0000

Atlantis Delayed scaled score

Frequency table: Atlantis Delay SCS S2 (MethKi database final time 2.sta) Shapiro-Wilk W=,91152, p=,03806						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
3,000000<x<=4,000000	3	3	12,50000	12,5000	12,50000	12,5000
4,000000<x<=5,000000	2	5	8,33333	20,8333	8,33333	20,8333
5,000000<x<=6,000000	3	8	12,50000	33,3333	12,50000	33,3333
6,000000<x<=7,000000	4	12	16,66667	50,0000	16,66667	50,0000
7,000000<x<=8,000000	3	15	12,50000	62,5000	12,50000	62,5000
8,000000<x<=9,000000	4	19	16,66667	79,1667	16,66667	79,1667
9,000000<x<=10,00000	5	24	20,83333	100,0000	20,83333	100,0000
Missing	0	24	0,00000		0,00000	100,0000

Boston Naming Test - total score

Frequency table: Total BNT S2 (MethKi database final time 2.sta) Shapiro-Wilk W=,91533, p=,04609						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
5,500000<x<=6,000000	2	2	8,33333	8,3333	8,33333	8,3333
6,000000<x<=6,500000	0	2	0,00000	8,3333	0,00000	8,3333
6,500000<x<=7,000000	6	8	25,00000	33,3333	25,00000	33,3333
7,000000<x<=7,500000	0	8	0,00000	33,3333	0,00000	33,3333
7,500000<x<=8,000000	8	16	33,33333	66,6667	33,33333	66,6667
8,000000<x<=8,500000	0	16	0,00000	66,6667	0,00000	66,6667
8,500000<x<=9,000000	7	23	29,16667	95,8333	29,16667	95,8333
9,000000<x<=9,500000	0	23	0,00000	95,8333	0,00000	95,8333
9,500000<x<=10,00000	1	24	4,16667	100,0000	4,16667	100,0000
Missing	0	24	0,00000		0,00000	100,0000

Frequency tables - metabolites

Cr

Frequency table: S2 - Cr (MethKi database final time 2.sta) Shapiro-Wilk W=,98305, p=,94476					
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases
1,800000<x<=2,000000	1	1	4,16667	4,1667	4,16667
2,000000<x<=2,200000	1	2	4,16667	8,3333	4,16667
2,200000<x<=2,400000	3	5	12,50000	20,8333	12,50000
2,400000<x<=2,600000	7	12	29,16667	50,0000	29,16667
2,600000<x<=2,800000	7	19	29,16667	79,1667	29,16667
2,800000<x<=3,000000	3	22	12,50000	91,6667	12,50000
3,000000<x<=3,200000	2	24	8,33333	100,0000	8,33333
Missing	0	24	0,00000		0,00000

PCr

Frequency table: S2 - PCr (MethKi database final time 2.sta) Shapiro-Wilk W=,93830, p=,14950					
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases
2,000000<x<=2,200000	2	2	8,33333	8,3333	8,33333
2,200000<x<=2,400000	1	3	4,16667	12,5000	4,16667
2,400000<x<=2,600000	5	8	20,83333	33,3333	20,83333
2,600000<x<=2,800000	1	9	4,16667	37,5000	4,16667
2,800000<x<=3,000000	9	18	37,50000	75,0000	37,50000
3,000000<x<=3,200000	5	23	20,83333	95,8333	20,83333
3,200000<x<=3,400000	0	23	0,00000	95,8333	0,00000
3,400000<x<=3,600000	1	24	4,16667	100,0000	4,16667
Missing	0	24	0,00000		0,00000

Glu

Frequency table: S2 - Glu (MethKi database final time 2.sta) Shapiro-Wilk W=,97396, p=,76425						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
7,000000<x<=7,500000	0	0	0,00000	0,0000	0,00000	0,0000
7,500000<x<=8,000000	3	3	12,50000	12,5000	12,50000	12,5000
8,000000<x<=8,500000	5	8	20,83333	33,3333	20,83333	33,3333
8,500000<x<=9,000000	5	13	20,83333	54,1667	20,83333	54,1667
9,000000<x<=9,500000	5	18	20,83333	75,0000	20,83333	75,0000
9,500000<x<=10,00000	5	23	20,83333	95,8333	20,83333	95,8333
10,00000<x<=10,50000	1	24	4,16667	100,0000	4,16667	100,0000
Missing	0	24	0,00000		0,00000	100,0000

GPC

Frequency table: S2 - GPC (MethKi database final time 2.sta) Shapiro-Wilk W=,97977, p=,91234						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
,9000000<x<=,9500000	1	1	4,54545	4,5455	4,16667	4,1667
,9500000<x<=1,000000	1	2	4,54545	9,0909	4,16667	8,3333
1,000000<x<=1,050000	6	8	27,27273	36,3636	25,00000	33,3333
1,050000<x<=1,100000	4	12	18,18182	54,5455	16,66667	50,0000
1,100000<x<=1,150000	4	16	18,18182	72,7273	16,66667	66,6667
1,150000<x<=1,200000	4	20	18,18182	90,9091	16,66667	83,3333
1,200000<x<=1,250000	1	21	4,54545	95,4545	4,16667	87,5000
1,250000<x<=1,300000	1	22	4,54545	100,0000	4,16667	91,6667
Missing	2	24	9,09091		8,33333	100,0000

Ins

Frequency table: S2 - Ins (MethKi database final time 2.sta) Shapiro-Wilk W=,97775, p=,85097						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
4,000000<x<=4,500000	1	1	4,16667	4,1667	4,1667	4,1667
4,500000<x<=5,000000	2	3	8,33333	12,5000	8,33333	12,5000
5,000000<x<=5,500000	11	14	45,83333	58,3333	45,83333	58,3333
5,500000<x<=6,000000	6	20	25,00000	83,3333	25,00000	83,3333
6,000000<x<=6,500000	4	24	16,66667	100,0000	16,66667	100,0000
Missing	0	24	0,00000		0,00000	100,0000

NAA

Frequency table: S2 - NAA (MethKi database final time 2.sta) Shapiro-Wilk W=,95988, p=,43609						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
5,800000<x<=6,000000	0	0	0,00000	0,0000	0,00000	0,0000
6,000000<x<=6,200000	3	3	12,50000	12,5000	12,50000	12,5000
6,200000<x<=6,400000	8	11	33,33333	45,8333	33,33333	45,8333
6,400000<x<=6,600000	8	19	33,33333	79,1667	33,33333	79,1667
6,600000<x<=6,800000	4	23	16,66667	95,8333	16,66667	95,8333
6,800000<x<=7,000000	0	23	0,00000	95,8333	0,00000	95,8333
7,000000<x<=7,200000	1	24	4,16667	100,0000	4,16667	100,0000
Missing	0	24	0,00000		0,00000	100,0000

GPC+PCh

Frequency table: S2 - GPC+PCh (MethKi database final time 2.sta) Shapiro-Wilk W=,97847, p=,86615						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
,9000000<x<=,9500000	1	1	4,16667	4,1667	4,16667	4,1667
,9500000<x<=1,000000	1	2	4,16667	8,3333	4,16667	8,3333
1,000000<x<=1,050000	7	9	29,16667	37,5000	29,16667	37,5000
1,050000<x<=1,100000	5	14	20,83333	58,3333	20,83333	58,3333
1,100000<x<=1,150000	4	18	16,66667	75,0000	16,66667	75,0000
1,150000<x<=1,200000	4	22	16,66667	91,6667	16,66667	91,6667
1,200000<x<=1,250000	1	23	4,16667	95,8333	4,16667	95,8333
1,250000<x<=1,300000	1	24	4,16667	100,0000	4,16667	100,0000
Missing	0	24	0,00000		0,00000	100,0000

NAA+NAAG

Frequency table: S2 - NAA+NAAG (MethKi database final time 2.sta) Shapiro-Wilk W=,98474, p=,96480						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
5,800000<x<=6,000000	0	0	0,00000	0,0000	0,00000	0,0000
6,000000<x<=6,200000	2	2	8,33333	8,3333	8,33333	8,3333
6,200000<x<=6,400000	3	5	12,50000	20,8333	12,50000	20,8333
6,400000<x<=6,600000	5	10	20,83333	41,6667	20,83333	41,6667
6,600000<x<=6,800000	8	18	33,33333	75,0000	33,33333	75,0000
6,800000<x<=7,000000	4	22	16,66667	91,6667	16,66667	91,6667
7,000000<x<=7,200000	1	23	4,16667	95,8333	4,16667	95,8333
7,200000<x<=7,400000	1	24	4,16667	100,0000	4,16667	100,0000
Missing	0	24	0,00000		0,00000	100,0000

Cr+PCr

Frequency table: S2 - Cr+PCr (MethKi database final time 2.sta) Shapiro-Wilk W=,97542, p=,79895					
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases
4,600000<x<=4,800000	0	0	0,00000	0,0000	0,00000
4,800000<x<=5,000000	3	3	12,50000	12,5000	12,50000
5,000000<x<=5,200000	4	7	16,66667	29,1667	16,66667
5,200000<x<=5,400000	5	12	20,83333	50,0000	20,83333
5,400000<x<=5,600000	7	19	29,16667	79,1667	29,16667
5,600000<x<=5,800000	2	21	8,33333	87,5000	8,33333
5,800000<x<=6,000000	3	24	12,50000	100,0000	12,50000
Missing	0	24	0,00000		0,00000

Glu+Gln

Frequency table: S2 - Glu+Gln (MethKi database final time 2.sta) Shapiro-Wilk W=,92819, p=,08880					
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases
8,500000<x<=9,000000	1	1	4,16667	4,1667	4,1667
9,000000<x<=9,500000	6	7	25,00000	29,1667	25,00000
9,500000<x<=10,00000	4	11	16,66667	45,8333	16,66667
10,00000<x<=10,50000	0	11	0,00000	45,8333	0,00000
10,50000<x<=11,00000	8	19	33,33333	79,1667	33,33333
11,00000<x<=11,50000	0	19	0,00000	79,1667	0,00000
11,50000<x<=12,00000	5	24	20,83333	100,0000	20,83333
Missing	0	24	0,00000		0,00000

Mann-Whitney U test – demographics

variable	Mann-Whitney U Test (w/ continuity correction) (MethKi database final time 2.sta) By variable Main Diagnosis Marked tests are significant at p <,05000									
	Rank Sum Control	Rank Sum Meth	U	Z	p-value	Z adjusted	p-value	Valid N Control	Valid N Meth	2*1sided exact p
Child weight Scan 2	157,0000	143,0000	52,00000	1,100794	0,270987	1,101513	0,270674	11	13	0,276668
BMI Scan 2	142,0000	158,0000	67,00000	0,231746	0,816735	0,231746	0,816735	11	13	0,820139

ANOVA – demographics

Effect	Univariate Results for Each DV (MethKi database final time 2.sta) Sigma-restricted parameterization Effective hypothesis decomposition									
	Degr. of Freedom	S2 - Age SS	S2 - Age MS	S2 - Age F	S2 - Age p	Child height SS	Child height Scan 2 MS	Child height Scan 2 F	Child height Scan 2 Valid N	Child height Scan 2 p
Intercept	1	1558,391	1558,391	5441,256	0,000000	36,43152	36,43152	12289,42	11	0,000000
Main Diagnosis	1	0,001	0,001	0,002	0,966294	0,00638	0,00638	2,15	13	0,156464
Error	22	6,301	0,286			0,06522	0,00296			
Total	23	6,301				0,07160				

Mann-Whitney U test – neurocognitive tasks

variable	Mann-Whitney U Test (w/ continuity correction) (MethKi database final time 2.sta) By variable Main Diagnosis Marked tests are significant at p <,05000									
	Rank Sum Control	Rank Sum Meth	U	Z	p-value	Z adjusted	p-value	Valid N Control	Valid N Meth	2*1sided exact p
Pattern Reasoning RS No Tmpt S2	142,5000	157,5000	66,50000	0,26071	0,794313	0,26657	0,789797	11	13	0,776211
Atlantis RS S2	98,0000	202,0000	32,00000	-2,25953	0,023851	-2,26743	0,023365	11	13	0,021754
Atlantis SCS S2	105,0000	195,0000	39,00000	-1,85397	0,063744	-1,90606	0,056643	11	13	0,062918
Atlantis Delay SCS S2	107,0000	193,0000	41,00000	-1,73810	0,082195	-1,75848	0,078668	11	13	0,082130
Total BNT S2	121,0000	179,0000	55,00000	-0,92698	0,353935	-0,96463	0,334733	11	13	0,360704

ANOVA – neurocognitive tasks

Univariate Results for Each DV (MethKi database final time 2.sta) Sigma-restricted parameterization Effective hypothesis decomposition																
Effect	Degr. of Freedom	Block Counting RS S2 SS	Block Counting RS S2 MS	Block Counting RS S2 F	Block Counting RS S2 p	Block Counting RS S2 MS	Block Counting RS S2 F	Block Counting RS S2 p	Block Counting RS S2 MS	Block Counting RS S2 F	Block Counting RS S2 p	Pattern Reasoning SCS Tmpt S2 MS	Pattern Reasoning SCS Tmpt S2 MS	Pattern Reasoning SCS Tmpt S2 F	Pattern Reasoning SCS Tmpt S2 MS	Pattern Reasoning SCS Tmpt S2 F
Intercept	1	2726,5 39	2726,5 39	62,980 49	0,0000 00	1706,4 10	1706,4 10	153,27 68	0,0000 00	2132,0 00	2132,0 00	176,35 87	0,0000 00	1165,5 01	1165,5 01	237,78 64
Main Diagnosis	1	193,53 9	193,53 9	4,4705 6	0,0460 49	56,410 00	56,410 00	5,0670 11	0,0347 11	0,0000 00	0,0000 00	0,168 27	0,168 27	0,0342 90	0,8548 90	0,0342 90
Error	22	952,42 0	43,292			244,92 3	11,133			265,95 8	12,089	107,83 2	4,901		89,314 7	368,55 9
Total	23	1145,9 58				301,33 3	265,95 8			108,00 0					89,333 3	418,50 0

ANOVA – metabolites

Univariate Results for Each DV (MethKi database final time 2.sta) Sigma-restricted parameterization Effective hypothesis decomposition																														
Effect	Degr. of Freedom	S2 - Cr SS	S2 - Cr MS	S2 - Cr p	S2 - PCr MS	S2 - PCr F	S2 - PCr p	S2 - GPC MS	S2 - GPC SS	S2 - GPC p	S2 - GPC F	S2 - GPC MS	S2 - GPC SS	S2 - GPC p	S2 - GPC F	S2 - GPC MS	S2 - GPC SS	S2 - GPC p	S2 - GPC F	S2 - GPC MS	S2 - GPC SS	S2 - GPC p	S2 - GPC F	S2 - GPC MS	S2 - GPC SS	S2 - GPC p	S2 - GPC F	S2 - GPC MS	S2 - GPC SS	S2 - GPC p
Intercept	1	141,0154	141,1495	0,00	166,0000	166,0000	1486,0000	25,7	25,7	25,7	25,7	25,7	25,7	25,7	25,7	25,7	25,7	25,7	25,7	25,7	25,7	25,7	25,7	25,7	25,7	25,7	25,7	25,7	25,7	25,7
Main Diagnosis	1	0,00	0,00	0,02	0,88	0,11	1,05	0,52	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
Error	20	1,88	0,09	2,24	0,11	25	21	0,12	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
Total	21	1,88	2,36	0,08				0,13	885	885	885	885	885	885	885	885	885	885	885	885	885	885	885	885	885	885	885	885	885	885

Spearman Rank Order correlations – demographics

Both groups

Pair of Variables	Spearman Rank Order Correlations (MethKi database final time 2.sta) MD pairwise deleted Marked correlations are significant at p <,05000			
	Valid N	Spearman R	t(N-2)	p-value
S2 - Age & S2 - Cr	24	0,107003	0,50479	0,618728
S2 - Age & S2 - PCr	24	-0,018269	-0,08570	0,932478
S2 - Age & S2 - Glu	24	-0,212266	-1,01883	0,319356
S2 - Age & S2 - GPC	22	0,409438	2,00700	0,058457
S2 - Age & S2 - Ins	24	0,147020	0,69716	0,493003
S2 - Age & S2 - NAA	24	-0,290996	-1,42663	0,167725
S2 - Age & S2 - GPC+PCh	24	0,411355	2,11682	0,045819
S2 - Age & S2 - NAA+NAAg	24	-0,361462	-1,81835	0,082653
S2 - Age & S2 - Cr+PCr	24	-0,061779	-0,29033	0,774286
S2 - Age & S2 - Glu+Gln	24	-0,155536	-0,73852	0,468006
Child weight Scan 2 & S2 - Cr	24	0,148358	0,70365	0,489034
Child weight Scan 2 & S2 - PCr	24	-0,090929	-0,42827	0,672619
Child weight Scan 2 & S2 - Glu	24	0,114858	0,54232	0,593051
Child weight Scan 2 & S2 - GPC	22	0,159412	0,72215	0,478563
Child weight Scan 2 & S2 - Ins	24	0,251468	1,21865	0,235883
Child weight Scan 2 & S2 - NAA	24	0,319774	1,58299	0,127695
Child weight Scan 2 & S2 - GPC+PCh	24	0,131419	0,62180	0,540464
Child weight Scan 2 & S2 - NAA+NAAg	24	0,333696	1,66034	0,111033
Child weight Scan 2 & S2 - Cr+PCr	24	-0,080505	-0,37883	0,708445
Child weight Scan 2 & S2 - Glu+Gln	24	0,194082	0,92797	0,363493
Child height Scan 2 & S2 - Cr	24	0,029303	0,13750	0,891885
Child height Scan 2 & S2 - PCr	24	0,163572	0,77769	0,445033
Child height Scan 2 & S2 - Glu	24	0,162697	0,77342	0,447505
Child height Scan 2 & S2 - GPC	22	-0,059461	-0,26639	0,792667
Child height Scan 2 & S2 - Ins	24	-0,123335	-0,58294	0,565860
Child height Scan 2 & S2 - NAA	24	0,153075	0,72655	0,475163

Child height Scan 2 & S2 - GPC+PCh	24	-0,131017	-0,61987	0,541713
Child height Scan 2 & S2 - NAA+NAAG	24	0,281658	1,37683	0,182414
Child height Scan 2 & S2 - Cr+PCr	24	-0,045714	-0,21464	0,832024
Child height Scan 2 & S2 - Glu+Gln	24	0,035871	0,16836	0,867839
BMI Scan 2 & S2 - Cr	24	0,045217	0,21231	0,833823
BMI Scan 2 & S2 - PCr	24	-0,160870	-0,76450	0,452691
BMI Scan 2 & S2 - Glu	24	-0,076522	-0,35997	0,722299
BMI Scan 2 & S2 - GPC	22	0,164925	0,74781	0,463279
BMI Scan 2 & S2 - Ins	24	0,458261	2,41831	0,024318
BMI Scan 2 & S2 - NAA	24	0,116522	0,55028	0,587669
BMI Scan 2 & S2 - GPC+PCh	24	0,210915	1,01205	0,322517
BMI Scan 2 & S2 - NAA+NAAG	24	0,018261	0,08567	0,932507
BMI Scan 2 & S2 - Cr+PCr	24	-0,078713	-0,37034	0,714667
BMI Scan 2 & S2 - Glu+Gln	24	0,047402	0,22258	0,825913

Control group

Pair of Variables	Main Diagnosis=Control Spearman Rank Order Correlations (MethKi database final time 2.sta) MD pairwise deleted Marked correlations are significant at p <,05000			
	Valid N	Spearman R	t(N-2)	p-value
S2 - Age & S2 - Cr	11	-0,063636	-0,19130	0,852539
S2 - Age & S2 - PCr	11	0,063636	0,19130	0,852539
S2 - Age & S2 - Glu	11	-0,036364	-0,10916	0,915468
S2 - Age & S2 - GPC	9	0,766667	3,15929	0,015944
S2 - Age & S2 - Ins	11	-0,018182	-0,05455	0,957685
S2 - Age & S2 - NAA	11	-0,509091	-1,77443	0,109737
S2 - Age & S2 - GPC+PCh	11	0,736364	3,26506	0,009760
S2 - Age & S2 - NAA+NAAG	11	-0,427273	-1,41775	0,189944

S2 - Age & S2 - Cr+PCr	11	-0,013667	-0,04101	0,968186
S2 - Age & S2 - Glu+Gln	11	-0,172727	-0,52609	0,611542
Child weight Scan 2 & S2 - Cr	11	0,409091	1,34497	0,211545
Child weight Scan 2 & S2 - PCr	11	0,254545	0,78965	0,450037
Child weight Scan 2 & S2 - Glu	11	0,309091	0,97502	0,355028
Child weight Scan 2 & S2 - GPC	9	0,566667	1,81961	0,111633
Child weight Scan 2 & S2 - Ins	11	0,481818	1,64955	0,133434
Child weight Scan 2 & S2 - NAA	11	0,227273	0,70014	0,501536
Child weight Scan 2 & S2 - GPC+PCh	11	0,481818	1,64955	0,133434
Child weight Scan 2 & S2 - NAA+NAAG	11	0,481818	1,64955	0,133434
Child weight Scan 2 & S2 - Cr+PCr	11	0,523919	1,84529	0,098083
Child weight Scan 2 & S2 - Glu+Gln	11	0,381818	1,23935	0,246560
Child height Scan 2 & S2 - Cr	11	0,004556	0,01367	0,989393
Child height Scan 2 & S2 - PCr	11	0,264238	0,82193	0,432354
Child height Scan 2 & S2 - Glu	11	-0,045558	-0,13682	0,894187
Child height Scan 2 & S2 - GPC	9	0,316667	0,88328	0,406397
Child height Scan 2 & S2 - Ins	11	0,000000	0,00000	1,000000
Child height Scan 2 & S2 - NAA	11	0,282461	0,88335	0,400026
Child height Scan 2 & S2 - GPC+PCh	11	0,109340	0,33000	0,748953
Child height Scan 2 & S2 - NAA+NAAG	11	0,455582	1,53534	0,159074
Child height Scan 2 & S2 - Cr+PCr	11	-0,015982	-0,04795	0,962802
Child height Scan 2 & S2 - Glu+Gln	11	0,041002	0,12311	0,904725
BMI Scan 2 & S2 - Cr	11	0,400000	1,30931	0,222868
BMI Scan 2 & S2 - PCr	11	0,045455	0,13650	0,894427
BMI Scan 2 & S2 - Glu	11	0,309091	0,97502	0,355028
BMI Scan 2 & S2 - GPC	9	0,400000	1,15470	0,286105
BMI Scan 2 & S2 - Ins	11	0,618182	2,35937	0,042646

BMI Scan 2 & S2 - NAA	11	-0,100000	-0,30151	0,769875
BMI Scan 2 & S2 - GPC+PCh	11	0,463636	1,56983	0,150901
BMI Scan 2 & S2 - NAA+NAAg	11	0,018182	0,05455	0,957685
BMI Scan 2 & S2 - Cr+PCr	11	0,660594	2,63976	0,026924
BMI Scan 2 & S2 - Glu+Gln	11	0,245455	0,75960	0,466922

MA group

Pair of Variables	Main Diagnosis=Meth Spearman Rank Order Correlations (MethKi database final time 2.sta) MD pairwise deleted Marked correlations are significant at p <,05000			
	Valid N	Spearman R	t(N-2)	p-value
S2 - Age & S2 - Cr	13	0,164835	0,55428	0,590479
S2 - Age & S2 - PCr	13	-0,043956	-0,14593	0,886619
S2 - Age & S2 - Glu	13	-0,428571	-1,57321	0,143971
S2 - Age & S2 - GPC	13	0,241758	0,82633	0,426176
S2 - Age & S2 - Ins	13	0,225275	0,76686	0,459305
S2 - Age & S2 - NAA	13	-0,159341	-0,53531	0,603088
S2 - Age & S2 - GPC+PCh	13	0,241758	0,82633	0,426176
S2 - Age & S2 - NAA+NAAg	13	-0,368132	-1,31317	0,215857
S2 - Age & S2 - Cr+PCr	13	-0,159341	-0,53531	0,603088
S2 - Age & S2 - Glu+Gln	13	-0,181319	-0,61150	0,553295
Child weight Scan 2 & S2 - Cr	13	-0,080001	-0,26619	0,795020
Child weight Scan 2 & S2 - PCr	13	-0,344831	-1,21840	0,248557
Child weight Scan 2 & S2 - Glu	13	-0,226209	-0,77021	0,457395
Child weight Scan 2 & S2 - GPC	13	-0,375176	-1,34237	0,206523
Child weight Scan 2 & S2 - Ins	13	0,168277	0,56619	0,582633
Child weight Scan 2 & S2 - NAA	13	0,438624	1,61878	0,133784
Child weight Scan 2 & S2 - GPC+PCh	13	-0,375176	-1,34237	0,206523

Child weight Scan 2 & S2 - NAA+NAAG	13	0,226209	0,77021	0,457395
Child weight Scan 2 & S2 - Cr+PCr	13	-0,386210	-1,38866	0,192412
Child weight Scan 2 & S2 - Glu+Gln	13	-0,022069	-0,07321	0,942951
Child height Scan 2 & S2 - Cr	13	-0,058835	-0,19547	0,848588
Child height Scan 2 & S2 - PCr	13	0,011207	0,03717	0,971015
Child height Scan 2 & S2 - Glu	13	0,274563	0,94702	0,363971
Child height Scan 2 & S2 - GPC	13	-0,518307	-2,01010	0,069588
Child height Scan 2 & S2 - Ins	13	-0,002802	-0,00929	0,992752
Child height Scan 2 & S2 - NAA	13	-0,282968	-0,97849	0,348862
Child height Scan 2 & S2 - GPC+PCh	13	-0,518307	-2,01010	0,069588
Child height Scan 2 & S2 - NAA+NAAG	13	-0,089653	-0,29855	0,770849
Child height Scan 2 & S2 - Cr+PCr	13	-0,070041	-0,23287	0,820136
Child height Scan 2 & S2 - Glu+Gln	13	0,000000	0,00000	1,000000
BMI Scan 2 & S2 - Cr	13	-0,093407	-0,31115	0,761500
BMI Scan 2 & S2 - PCr	13	-0,307692	-1,07253	0,306447
BMI Scan 2 & S2 - Glu	13	-0,368132	-1,31317	0,215857
BMI Scan 2 & S2 - GPC	13	-0,016484	-0,05468	0,957376
BMI Scan 2 & S2 - Ins	13	0,346154	1,22372	0,246625
BMI Scan 2 & S2 - NAA	13	0,417582	1,52422	0,155675
BMI Scan 2 & S2 - GPC+PCh	13	-0,016484	-0,05468	0,957376
BMI Scan 2 & S2 - NAA+NAAG	13	0,175824	0,59237	0,565580
BMI Scan 2 & S2 - Cr+PCr	13	-0,362637	-1,29058	0,223316
BMI Scan 2 & S2 - Glu+Gln	13	-0,071429	-0,23751	0,816628

Spearman Rank Order correlations – neurocognitive tasks

Both groups

Pair of Variables		Spearman Rank Order Correlations (MethKi database final time 2.sta) MD pairwise deleted Marked correlations are significant at p <,05000				
		Valid N	Spearman R	t(N-2)	p-value	
Block Counting RS S2 & S2 - Cr		24	-0,017437	-0,08180	0,935547	
Block Counting RS S2 & S2 - PCr		24	0,059285	0,27856	0,783182	
Block Counting RS S2 & S2 - Glu		24	-0,094159	-0,44362	0,661653	
Block Counting RS S2 & S2 - GPC		22	0,347015	1,65472	0,113590	
Block Counting RS S2 & S2 - Ins		24	0,145162	0,68816	0,498546	
Block Counting RS S2 & S2 - NAA		24	0,210550	1,01021	0,323376	
Block Counting RS S2 & S2 - GPC+PCh		24	0,334642	1,66564	0,109962	
Block Counting RS S2 & S2 - NAA+NAAg		24	0,057978	0,27240	0,787857	
Block Counting RS S2 & S2 - Cr+PCr		24	-0,031611	-0,14834	0,883423	
Block Counting RS S2 & S2 - Glu+Gln		24	0,024635	0,11558	0,909032	
Block Counting SCS S2 & S2 - Cr		24	-0,031885	-0,14963	0,882420	
Block Counting SCS S2 & S2 - PCr		24	0,037563	0,17631	0,861662	
Block Counting SCS S2 & S2 - Glu		24	-0,078184	-0,36784	0,716507	
Block Counting SCS S2 & S2 - GPC		22	0,312449	1,47096	0,156862	
Block Counting SCS S2 & S2 - Ins		24	0,179080	0,85376	0,402437	
Block Counting SCS S2 & S2 - NAA		24	0,250712	1,21474	0,237342	
Block Counting SCS S2 & S2 - GPC+PCh		24	0,318264	1,57467	0,129604	
Block Counting SCS S2 & S2 - NAA+NAAg		24	0,112690	0,53195	0,600092	
Block Counting SCS S2 & S2 - Cr+PCr		24	-0,056794	-0,26682	0,792095	
Block Counting SCS S2 & S2 - Glu+Gln		24	0,007208	0,03381	0,973332	
Pattern Reasoning RS No Tmpt S2 & S2 - Cr		24	0,025784	0,12098	0,904806	
Pattern Reasoning RS No Tmpt S2 & S2 - PCr		24	0,277846	1,35663	0,188657	
Pattern Reasoning RS No Tmpt S2 & S2 - Glu		24	-0,032897	-0,15438	0,878714	
Pattern Reasoning RS No Tmpt S2 & S2 - GPC		22	0,320880	1,51514	0,145383	
Pattern Reasoning RS No Tmpt S2 & S2 - Ins		24	0,105359	0,49695	0,624158	
Pattern Reasoning RS No Tmpt S2 & S2 - NAA		24	0,273401	1,33316	0,196122	

Pattern Reasoning RS No Tmpt S2 & S2 - GPC+PCh	24	0,380177	1,92795	0,066868
Pattern Reasoning RS No Tmpt S2 & S2 - NAA+NAAG	24	0,274290	1,33784	0,194613
Pattern Reasoning RS No Tmpt S2 & S2 - Cr+PCr	24	0,309699	1,52773	0,140830
Pattern Reasoning RS No Tmpt S2 & S2 - Glu+Gln	24	0,022010	0,10326	0,918690
Pattern Reasoning SCS No Tmpt S2 & S2 - Cr	24	-0,104630	-0,49347	0,626574
Pattern Reasoning SCS No Tmpt S2 & S2 - PCr	24	0,264235	1,28504	0,212142
Pattern Reasoning SCS No Tmpt S2 & S2 - Glu	24	0,024827	0,11649	0,908324
Pattern Reasoning SCS No Tmpt S2 & S2 - GPC	22	0,106487	0,47895	0,637171
Pattern Reasoning SCS No Tmpt S2 & S2 - Ins	24	-0,007980	-0,03743	0,970478
Pattern Reasoning SCS No Tmpt S2 & S2 - NAA	24	0,318323	1,57499	0,129530
Pattern Reasoning SCS No Tmpt S2 & S2 - GPC+PCh	24	0,181812	0,86723	0,395179
Pattern Reasoning SCS No Tmpt S2 & S2 - NAA+NAAG	24	0,262461	1,27578	0,215340
Pattern Reasoning SCS No Tmpt S2 & S2 - Cr+PCr	24	0,255867	1,24145	0,227515
Pattern Reasoning SCS No Tmpt S2 & S2 - Glu+Gln	24	0,059865	0,28130	0,781113
Atlantis RS S2 & S2 - Cr	24	0,075917	0,35711	0,724411
Atlantis RS S2 & S2 - PCr	24	0,156196	0,74173	0,466096
Atlantis RS S2 & S2 - Glu	24	0,095550	0,45023	0,656949
Atlantis RS S2 & S2 - GPC	22	0,216333	0,99093	0,333556
Atlantis RS S2 & S2 - Ins	24	-0,021379	-0,10030	0,921016
Atlantis RS S2 & S2 - NAA	24	0,135690	0,64238	0,527262
Atlantis RS S2 & S2 - GPC+PCh	24	0,205325	0,98403	0,335802
Atlantis RS S2 & S2 - NAA+NAAG	24	0,372166	1,88071	0,073314
Atlantis RS S2 & S2 - Cr+PCr	24	0,089025	0,41923	0,679114
Atlantis RS S2 & S2 - Glu+Gln	24	0,124810	0,59002	0,561187
Atlantis SCS S2 & S2 - Cr	24	0,061686	0,28988	0,774619
Atlantis SCS S2 & S2 - PCr	24	0,090741	0,42738	0,673260
Atlantis SCS S2 & S2 - Glu	24	0,200256	0,95870	0,348127
Atlantis SCS S2 & S2 - GPC	22	0,093672	0,42077	0,678413

Atlantis SCS S2 & S2 - Ins	24	-0,023244	-0,10905	0,914149
Atlantis SCS S2 & S2 - NAA	24	0,193551	0,92533	0,364834
Atlantis SCS S2 & S2 - GPC+PCh	24	0,069747	0,32794	0,746057
Atlantis SCS S2 & S2 - NAA+NAAG	24	0,473372	2,52061	0,019469
Atlantis SCS S2 & S2 - Cr+PCr	24	0,072653	0,34168	0,735837
Atlantis SCS S2 & S2 - Glu+Gln	24	0,192475	0,91999	0,367556
Atlantis Delay RS S2 & S2 - Cr	24	-0,064165	-0,30158	0,765804
Atlantis Delay RS S2 & S2 - PCr	24	-0,035356	-0,16594	0,869721
Atlantis Delay RS S2 & S2 - Glu	24	0,164122	0,78038	0,443483
Atlantis Delay RS S2 & S2 - GPC	22	-0,458925	-2,31000	0,031683
Atlantis Delay RS S2 & S2 - Ins	24	-0,058490	-0,27481	0,786024
Atlantis Delay RS S2 & S2 - NAA	24	-0,203843	-0,97661	0,339379
Atlantis Delay RS S2 & S2 - GPC+PCh	24	-0,411922	-2,12033	0,045492
Atlantis Delay RS S2 & S2 - NAA+NAAG	24	-0,085553	-0,40275	0,691015
Atlantis Delay RS S2 & S2 - Cr+PCr	24	-0,086008	-0,40491	0,689451
Atlantis Delay RS S2 & S2 - Glu+Gln	24	0,040384	0,18957	0,851381
Atlantis Delay SCS S2 & S2 - Cr	24	-0,208503	-0,99994	0,328210
Atlantis Delay SCS S2 & S2 - PCr	24	0,062903	0,29563	0,770288
Atlantis Delay SCS S2 & S2 - Glu	24	0,130644	0,61807	0,542873
Atlantis Delay SCS S2 & S2 - GPC	22	-0,554231	-2,97778	0,007438
Atlantis Delay SCS S2 & S2 - Ins	24	-0,150879	-0,71588	0,481595
Atlantis Delay SCS S2 & S2 - NAA	24	-0,183430	-0,87521	0,390913
Atlantis Delay SCS S2 & S2 - GPC+PCh	24	-0,496073	-2,67976	0,013685
Atlantis Delay SCS S2 & S2 - NAA+NAAG	24	-0,103372	-0,48747	0,630749
Atlantis Delay SCS S2 & S2 - Cr+PCr	24	-0,146292	-0,69363	0,495172
Atlantis Delay SCS S2 & S2 - Glu+Gln	24	0,094155	0,44360	0,661667
Total BNT S2 & S2 - Cr	24	0,125325	0,59250	0,559558
Total BNT S2 & S2 - PCr	24	-0,125325	-0,59250	0,559558
Total BNT S2 & S2 - Glu	24	-0,128945	-0,60990	0,548179
Total BNT S2 & S2 - GPC	22	0,104539	0,47009	0,643379
Total BNT S2 & S2 - Ins	24	0,111300	0,52531	0,604625
Total BNT S2 & S2 - NAA	24	0,456962	2,40964	0,024777

Total BNT S2 & S2 - GPC+PCh	24	0,153410	0,72818	0,474186
Total BNT S2 & S2 - NAA+NAAG	24	0,406742	2,08834	0,048555
Total BNT S2 & S2 - Cr+PCr	24	0,015160	0,07111	0,943949
Total BNT S2 & S2 - Glu+Gln	24	0,003847	0,01804	0,985768

Control group

Pair of Variables	Main Diagnosis=Control Spearman Rank Order Correlations (MethKi database final time 2.sta) MD pairwise deleted Marked correlations are significant at p <,05000			
	Valid N	Spearman R	t(N-2)	p-value
Block Counting RS S2 & S2 - Cr	11	0,388132	1,26344	0,238175
Block Counting RS S2 & S2 - PCr	11	0,127855	0,38674	0,707934
Block Counting RS S2 & S2 - Glu	11	0,200915	0,61529	0,553599
Block Counting RS S2 & S2 - GPC	9	0,610884	2,04144	0,080542
Block Counting RS S2 & S2 - Ins	11	0,506855	1,76393	0,111569
Block Counting RS S2 & S2 - NAA	11	0,077626	0,23358	0,820534
Block Counting RS S2 & S2 - GPC+PCh	11	0,694071	2,89234	0,017816
Block Counting RS S2 & S2 - NAA+NAAG	11	0,200915	0,61529	0,553599
Block Counting RS S2 & S2 - Cr+PCr	11	0,590391	2,19444	0,055845
Block Counting RS S2 & S2 - Glu+Gln	11	0,173518	0,52857	0,609888
Block Counting SCS S2 & S2 - Cr	11	0,423370	1,40196	0,194463
Block Counting SCS S2 & S2 - PCr	11	0,055829	0,16775	0,870490
Block Counting SCS S2 & S2 - Glu	11	0,204707	0,62741	0,545979
Block Counting SCS S2 & S2 - GPC	9	0,678064	2,44079	0,044707
Block Counting SCS S2 & S2 - Ins	11	0,507114	1,76515	0,111356
Block Counting SCS S2 & S2 - NAA	11	0,088396	0,26623	0,796061
Block Counting SCS S2 & S2 - GPC+PCh	11	0,744387	3,34432	0,008601
Block Counting SCS S2 & S2 - NAA+NAAG	11	0,204707	0,62741	0,545979
Block Counting SCS S2 & S2 - Cr+PCr	11	0,582879	2,15201	0,059840

Block Counting SCS S2 & S2 - Glu+Gln	11	0,139573	0,42286	0,682324
Pattern Reasoning RS No Tmpt S2 & S2 - Cr	11	0,167090	0,50842	0,623388
Pattern Reasoning RS No Tmpt S2 & S2 - PCr	11	0,366669	1,18236	0,267358
Pattern Reasoning RS No Tmpt S2 & S2 - Glu	11	-0,176373	-0,53754	0,603926
Pattern Reasoning RS No Tmpt S2 & S2 - GPC	9	0,487340	1,47659	0,183300
Pattern Reasoning RS No Tmpt S2 & S2 - Ins	11	0,259917	0,80751	0,440194
Pattern Reasoning RS No Tmpt S2 & S2 - NAA	11	0,102110	0,30794	0,765135
Pattern Reasoning RS No Tmpt S2 & S2 - GPC+PCh	11	0,547683	1,96376	0,081152
Pattern Reasoning RS No Tmpt S2 & S2 - NAA+NAAG	11	0,083545	0,25151	0,807066
Pattern Reasoning RS No Tmpt S2 & S2 - Cr+PCr	11	0,621038	2,37708	0,041425
Pattern Reasoning RS No Tmpt S2 & S2 - Glu+Gln	11	-0,250635	-0,77669	0,457265
Pattern Reasoning SCS No Tmpt S2 & S2 - Cr	11	0,009349	0,02805	0,978235
Pattern Reasoning SCS No Tmpt S2 & S2 - PCr	11	0,243086	0,75181	0,471368
Pattern Reasoning SCS No Tmpt S2 & S2 - Glu	11	-0,280484	-0,87664	0,403473
Pattern Reasoning SCS No Tmpt S2 & S2 - GPC	9	0,112640	0,29993	0,772945
Pattern Reasoning SCS No Tmpt S2 & S2 - Ins	11	0,028048	0,08418	0,934757
Pattern Reasoning SCS No Tmpt S2 & S2 - NAA	11	0,140242	0,42493	0,680869
Pattern Reasoning SCS No Tmpt S2 & S2 - GPC+PCh	11	0,271135	0,84506	0,419975
Pattern Reasoning SCS No Tmpt S2 & S2 - NAA+NAAG	11	-0,028048	-0,08418	0,934757

Pattern Reasoning SCS No Tmpt S2 & S2 - Cr+PCr	11	0,431056	1,43315	0,185623
Pattern Reasoning SCS No Tmpt S2 & S2 - Glu+Gln	11	-0,355280	-1,14023	0,283625
Atlantis RS S2 & S2 - Cr	11	0,258694	0,80343	0,442426
Atlantis RS S2 & S2 - PCr	11	0,097010	0,29241	0,776602
Atlantis RS S2 & S2 - Glu	11	0,346466	1,10802	0,296583
Atlantis RS S2 & S2 - GPC	9	0,376192	1,07422	0,318351
Atlantis RS S2 & S2 - Ins	11	0,041576	0,12484	0,903398
Atlantis RS S2 & S2 - NAA	11	0,110869	0,33467	0,745541
Atlantis RS S2 & S2 - GPC+PCh	11	0,263314	0,81884	0,434024
Atlantis RS S2 & S2 - NAA+NAAG	11	0,383422	1,24545	0,244414
Atlantis RS S2 & S2 - Cr+PCr	11	0,238449	0,73659	0,480128
Atlantis RS S2 & S2 - Glu+Gln	11	0,374183	1,21048	0,256923
Atlantis SCS S2 & S2 - Cr	11	0,568254	2,07177	0,068168
Atlantis SCS S2 & S2 - PCr	11	-0,211891	-0,65044	0,531657
Atlantis SCS S2 & S2 - Glu	11	0,433414	1,44280	0,182962
Atlantis SCS S2 & S2 - GPC	9	0,192669	0,51949	0,619438
Atlantis SCS S2 & S2 - Ins	11	0,067420	0,20272	0,843862
Atlantis SCS S2 & S2 - NAA	11	0,144471	0,43801	0,671704
Atlantis SCS S2 & S2 - GPC+PCh	11	0,048157	0,14464	0,888183
Atlantis SCS S2 & S2 - NAA+NAAG	11	0,462308	1,56411	0,152230
Atlantis SCS S2 & S2 - Cr+PCr	11	0,241335	0,74606	0,474668
Atlantis SCS S2 & S2 - Glu+Gln	11	0,433414	1,44280	0,182962
Atlantis Delay RS S2 & S2 - Cr	11	0,027524	0,08260	0,935975
Atlantis Delay RS S2 & S2 - PCr	11	-0,027524	-0,08260	0,935975
Atlantis Delay RS S2 & S2 - Glu	11	0,261479	0,81271	0,437353
Atlantis Delay RS S2 & S2 - GPC	9	-0,504219	-1,54479	0,166313
Atlantis Delay RS S2 & S2 - Ins	11	-0,215605	-0,66240	0,524316
Atlantis Delay RS S2 & S2 - NAA	11	-0,004587	-0,01376	0,989320
Atlantis Delay RS S2 & S2 - GPC+PCh	11	-0,362401	-1,16650	0,273392
Atlantis Delay RS S2 & S2 - NAA+NAAG	11	0,009175	0,02753	0,978641
Atlantis Delay RS S2 & S2 - Cr+PCr	11	-0,004598	-0,01379	0,989296

Atlantis Delay RS S2 & S2 - Glu+Gln	11	0,339464	1,08268	0,307102
Atlantis Delay SCS S2 & S2 - Cr	11	0,004620	0,01386	0,989245
Atlantis Delay SCS S2 & S2 - PCr	11	-0,032337	-0,09706	0,924805
Atlantis Delay SCS S2 & S2 - Glu	11	0,295651	0,92846	0,377399
Atlantis Delay SCS S2 & S2 - GPC	9	-0,497930	-1,51911	0,172532
Atlantis Delay SCS S2 & S2 - Ins	11	-0,244836	-0,75756	0,468082
Atlantis Delay SCS S2 & S2 - NAA	11	0,027717	0,08318	0,935526
Atlantis Delay SCS S2 & S2 - GPC+PCh	11	-0,374183	-1,21048	0,256923
Atlantis Delay SCS S2 & S2 - NAA+NAAG	11	0,046195	0,13873	0,892715
Atlantis Delay SCS S2 & S2 - Cr+PCr	11	-0,025465	-0,07642	0,940756
Atlantis Delay SCS S2 & S2 - Glu+Gln	11	0,364944	1,17594	0,269788
Total BNT S2 & S2 - Cr	11	0,346287	1,10737	0,296849
Total BNT S2 & S2 - PCr	11	-0,151797	-0,46073	0,655923
Total BNT S2 & S2 - Glu	11	0,298850	0,93948	0,372010
Total BNT S2 & S2 - GPC	9	0,181956	0,48958	0,639397
Total BNT S2 & S2 - Ins	11	0,573982	2,10284	0,064819
Total BNT S2 & S2 - NAA	11	0,569238	2,07708	0,067585
Total BNT S2 & S2 - GPC+PCh	11	0,270388	0,84255	0,421306
Total BNT S2 & S2 - NAA+NAAG	11	0,702061	2,95763	0,016021
Total BNT S2 & S2 - Cr+PCr	11	0,413639	1,36298	0,206011
Total BNT S2 & S2 - Glu+Gln	11	0,237183	0,73245	0,482533

MA group

Pair of Variables	Main Diagnosis=Meth Spearman Rank Order Correlations (MethKi database final time 2.sta) MD pairwise deleted Marked correlations are significant at p <,05000			
	Valid N	Spearman R	t(N-2)	p-value
Block Counting RS S2 & S2 - Cr	13	-0,239670	-0,81876	0,430304
Block Counting RS S2 & S2 - PCr	13	-0,223141	-0,75922	0,463681
Block Counting RS S2 & S2 - Glu	13	-0,754824	-3,81668	0,002860
Block Counting RS S2 & S2 - GPC	13	-0,088155	-0,29352	0,774590
Block Counting RS S2 & S2 - Ins	13	-0,176309	-0,59406	0,564491
Block Counting RS S2 & S2 - NAA	13	0,308541	1,07580	0,305045
Block Counting RS S2 & S2 - GPC+PCh	13	-0,088155	-0,29352	0,774590
Block Counting RS S2 & S2 - NAA+NAAG	13	-0,212122	-0,71991	0,486594
Block Counting RS S2 & S2 - Cr+PCr	13	-0,573005	-2,31888	0,040658
Block Counting RS S2 & S2 - Glu+Gln	13	-0,355373	-1,26095	0,233415
Block Counting SCS S2 & S2 - Cr	13	-0,252086	-0,86398	0,406046
Block Counting SCS S2 & S2 - PCr	13	-0,296409	-1,02934	0,325424
Block Counting SCS S2 & S2 - Glu	13	-0,700855	-3,25874	0,007616
Block Counting SCS S2 & S2 - GPC	13	-0,180062	-0,60712	0,556096
Block Counting SCS S2 & S2 - Ins	13	-0,127428	-0,42611	0,678250
Block Counting SCS S2 & S2 - NAA	13	0,418297	1,52738	0,154896
Block Counting SCS S2 & S2 - GPC+PCh	13	-0,180062	-0,60712	0,556096
Block Counting SCS S2 & S2 - NAA+NAAG	13	-0,027702	-0,09191	0,928421
Block Counting SCS S2 & S2 - Cr+PCr	13	-0,601129	-2,49479	0,029781
Block Counting SCS S2 & S2 - Glu+Gln	13	-0,382285	-1,37211	0,197360
Pattern Reasoning RS No Tmpt S2 & S2 - Cr	13	-0,073583	-0,24471	0,811186
Pattern Reasoning RS No Tmpt S2 & S2 - PCr	13	0,181127	0,61083	0,553723
Pattern Reasoning RS No Tmpt S2 & S2 - Glu	13	0,104714	0,34922	0,733520
Pattern Reasoning RS No Tmpt S2 & S2 - GPC	13	0,311311	1,08649	0,300496
Pattern Reasoning RS No Tmpt S2 & S2 - Ins	13	-0,135845	-0,45476	0,658124

Pattern Reasoning RS No Tmpt S2 & S2 - NAA	13	0,557530	2,22743	0,047740
Pattern Reasoning RS No Tmpt S2 & S2 - GPC+PCh	13	0,311311	1,08649	0,300496
Pattern Reasoning RS No Tmpt S2 & S2 - NAA+NAAG	13	0,483948	1,83417	0,093799
Pattern Reasoning RS No Tmpt S2 & S2 - Cr+PCr	13	0,133015	0,44512	0,664868
Pattern Reasoning RS No Tmpt S2 & S2 - Glu+Gln	13	0,339612	1,19754	0,256264
Pattern Reasoning SCS No Tmpt S2 & S2 - Cr	13	-0,167860	-0,56474	0,583583
Pattern Reasoning SCS No Tmpt S2 & S2 - PCr	13	0,276969	0,95600	0,359610
Pattern Reasoning SCS No Tmpt S2 & S2 - Glu	13	0,262981	0,90403	0,385351
Pattern Reasoning SCS No Tmpt S2 & S2 - GPC	13	0,226611	0,77166	0,456575
Pattern Reasoning SCS No Tmpt S2 & S2 - Ins	13	-0,086728	-0,28873	0,778156
Pattern Reasoning SCS No Tmpt S2 & S2 - NAA	13	0,534354	2,09669	0,059943
Pattern Reasoning SCS No Tmpt S2 & S2 - GPC+PCh	13	0,226611	0,77166	0,456575
Pattern Reasoning SCS No Tmpt S2 & S2 - NAA+NAAG	13	0,534354	2,09669	0,059943
Pattern Reasoning SCS No Tmpt S2 & S2 - Cr+PCr	13	0,240599	0,82213	0,428465
Pattern Reasoning SCS No Tmpt S2 & S2 - Glu+Gln	13	0,369292	1,31796	0,214302
Atlantis RS S2 & S2 - Cr	13	-0,179064	-0,60364	0,558322
Atlantis RS S2 & S2 - PCr	13	0,148761	0,49894	0,627652
Atlantis RS S2 & S2 - Glu	13	0,250690	0,85887	0,408739
Atlantis RS S2 & S2 - GPC	13	0,203858	0,69062	0,504116
Atlantis RS S2 & S2 - Ins	13	-0,146006	-0,48949	0,634108
Atlantis RS S2 & S2 - NAA	13	0,471076	1,77122	0,104190

Atlantis RS S2 & S2 - GPC+PCh	13	0,203858	0,69062	0,504116
Atlantis RS S2 & S2 - NAA+NAAG	13	0,214877	0,72971	0,480818
Atlantis RS S2 & S2 - Cr+PCr	13	-0,104684	-0,34911	0,733595
Atlantis RS S2 & S2 - Glu+Gln	13	0,212122	0,71991	0,486594
Atlantis SCS S2 & S2 - Cr	13	-0,430176	-1,58044	0,142313
Atlantis SCS S2 & S2 - PCr	13	0,203767	0,69030	0,504308
Atlantis SCS S2 & S2 - Glu	13	0,331122	1,16386	0,269103
Atlantis SCS S2 & S2 - GPC	13	0,019811	0,06572	0,948782
Atlantis SCS S2 & S2 - Ins	13	-0,164146	-0,55190	0,592055
Atlantis SCS S2 & S2 - NAA	13	0,532059	2,08412	0,061260
Atlantis SCS S2 & S2 - GPC+PCh	13	0,019811	0,06572	0,948782
Atlantis SCS S2 & S2 - NAA+NAAG	13	0,421685	1,54241	0,151235
Atlantis SCS S2 & S2 - Cr+PCr	13	-0,107544	-0,35876	0,726563
Atlantis SCS S2 & S2 - Glu+Gln	13	0,291501	1,01069	0,333879
Atlantis Delay RS S2 & S2 - Cr	13	-0,228967	-0,78012	0,451778
Atlantis Delay RS S2 & S2 - PCr	13	0,113104	0,37755	0,712950
Atlantis Delay RS S2 & S2 - Glu	13	0,091035	0,30319	0,767403
Atlantis Delay RS S2 & S2 - GPC	13	-0,430349	-1,58122	0,142135
Atlantis Delay RS S2 & S2 - Ins	13	0,187588	0,63340	0,539417
Atlantis Delay RS S2 & S2 - NAA	13	-0,350348	-1,24060	0,240562
Atlantis Delay RS S2 & S2 - GPC+PCh	13	-0,430349	-1,58122	0,142135
Atlantis Delay RS S2 & S2 - NAA+NAAG	13	-0,154484	-0,51859	0,614318
Atlantis Delay RS S2 & S2 - Cr+PCr	13	0,027586	0,09153	0,928718
Atlantis Delay RS S2 & S2 - Glu+Gln	13	-0,193105	-0,65274	0,527328
Atlantis Delay SCS S2 & S2 - Cr	13	-0,492405	-1,87636	0,087371
Atlantis Delay SCS S2 & S2 - PCr	13	0,284188	0,98308	0,346697
Atlantis Delay SCS S2 & S2 - Glu	13	0,070344	0,23388	0,819372
Atlantis Delay SCS S2 & S2 - GPC	13	-0,619024	-2,61413	0,024079
Atlantis Delay SCS S2 & S2 - Ins	13	0,033765	0,11205	0,912803
Atlantis Delay SCS S2 & S2 - NAA	13	-0,216658	-0,73606	0,477099
Atlantis Delay SCS S2 & S2 - GPC+PCh	13	-0,619024	-2,61413	0,024079
Atlantis Delay SCS S2 & S2 - NAA+NAAG	13	-0,149128	-0,50020	0,626792

Atlantis Delay SCS S2 & S2 - Cr+PCr	13	-0,075971	-0,25270	0,805162
Atlantis Delay SCS S2 & S2 - Glu+Gln	13	-0,002814	-0,00933	0,992721
Total BNT S2 & S2 - Cr	13	0,060318	0,20042	0,844812
Total BNT S2 & S2 - PCr	13	-0,071807	-0,23877	0,815671
Total BNT S2 & S2 - Glu	13	-0,384886	-1,38307	0,194073
Total BNT S2 & S2 - GPC	13	0,109147	0,36417	0,722631
Total BNT S2 & S2 - Ins	13	-0,083296	-0,27723	0,786747
Total BNT S2 & S2 - NAA	13	0,502649	1,92842	0,080001
Total BNT S2 & S2 - GPC+PCh	13	0,109147	0,36417	0,722631
Total BNT S2 & S2 - NAA+NAAG	13	0,189571	0,64035	0,535059
Total BNT S2 & S2 - Cr+PCr	13	0,008617	0,02858	0,977712
Total BNT S2 & S2 - Glu+Gln	13	-0,298717	-1,03813	0,321490

Spearman Rank Order correlations – metabolites
Both groups

Pair of Variables	Spearman Rank Order Correlations (MethKi database final time 2.sta) MD pairwise deleted Marked correlations are significant at p <,05000			
	Valid N	Spearman R	t(N-2)	p-value
S2 - Cr & S2 - Cr				
S2 - Cr & S2 - PCr	24	-0,463478	-2,45332	0,022545
S2 - Cr & S2 - Glu	24	0,130435	0,61707	0,543526
S2 - Cr & S2 - GPC	22	0,262073	1,21447	0,238712
S2 - Cr & S2 - Ins	24	0,215652	1,03587	0,311514
S2 - Cr & S2 - NAA	24	0,235652	1,13734	0,267634
S2 - Cr & S2 - GPC+PCh	24	0,181344	0,86492	0,396417
S2 - Cr & S2 - NAA+NAAG	24	0,462609	2,44746	0,022833
S2 - Cr & S2 - Cr+PCr	24	0,386606	1,96623	0,062016
S2 - Cr & S2 - Glu+Gln	24	0,094803	0,44668	0,659473
S2 - PCr & S2 - Cr	24	-0,463478	-2,45332	0,022545
S2 - PCr & S2 - PCr				
S2 - PCr & S2 - Glu	24	0,217391	1,04464	0,307533
S2 - PCr & S2 - GPC	22	0,136685	0,61706	0,544155

S2 - PCr & S2 - Ins	24	0,162609	0,77299	0,447754
S2 - PCr & S2 - NAA	24	-0,080000	-0,37644	0,710196
S2 - PCr & S2 - GPC+PCh	24	0,168297	0,80081	0,431807
S2 - PCr & S2 - NAA+NAAG	24	-0,010435	-0,04895	0,961404
S2 - PCr & S2 - Cr+PCr	24	0,557513	3,14992	0,004648
S2 - PCr & S2 - Glu+Gln	24	0,291803	1,43095	0,166496
S2 - Glu & S2 - Cr	24	0,130435	0,61707	0,543526
S2 - Glu & S2 - PCr	24	0,217391	1,04464	0,307533
S2 - Glu & S2 - Glu				
S2 - Glu & S2 - GPC	22	0,132166	0,59630	0,557667
S2 - Glu & S2 - Ins	24	0,108696	0,51287	0,613156
S2 - Glu & S2 - NAA	24	-0,046957	-0,22049	0,827524
S2 - Glu & S2 - GPC+PCh	24	0,060883	0,28610	0,777481
S2 - Glu & S2 - NAA+NAAG	24	0,266087	1,29473	0,208836
S2 - Glu & S2 - Cr+PCr	24	0,410524	2,11167	0,046303
S2 - Glu & S2 - Glu+Gln	24	0,849315	7,54640	0,000000
S2 - GPC & S2 - Cr	22	0,262073	1,21447	0,238712
S2 - GPC & S2 - PCr	22	0,136685	0,61706	0,544155
S2 - GPC & S2 - Glu	22	0,132166	0,59630	0,557667
S2 - GPC & S2 - GPC				
S2 - GPC & S2 - Ins	22	0,477266	2,42888	0,024697
S2 - GPC & S2 - NAA	22	0,048009	0,21495	0,831982
S2 - GPC & S2 - GPC+PCh	22	1,000000		
S2 - GPC & S2 - NAA+NAAG	22	0,206721	0,94490	0,355989
S2 - GPC & S2 - Cr+PCr	22	0,313471	1,47629	0,155438
S2 - GPC & S2 - Glu+Gln	22	0,160734	0,72830	0,474874
S2 - Ins & S2 - Cr	24	0,215652	1,03587	0,311514
S2 - Ins & S2 - PCr	24	0,162609	0,77299	0,447754
S2 - Ins & S2 - Glu	24	0,108696	0,51287	0,613156
S2 - Ins & S2 - GPC	22	0,477266	2,42888	0,024697
S2 - Ins & S2 - Ins				
S2 - Ins & S2 - NAA	24	0,126087	0,59616	0,557154

S2 - Ins & S2 - GPC+PCh	24	0,500978	2,71509	0,012643
S2 - Ins & S2 - NAA+NAAG	24	0,320870	1,58903	0,126322
S2 - Ins & S2 - Cr+PCr	24	0,398347	2,03701	0,053858
S2 - Ins & S2 - Glu+Gln	24	0,045662	0,21440	0,832212
S2 - NAA & S2 - Cr	24	0,235652	1,13734	0,267634
S2 - NAA & S2 - PCr	24	-0,080000	-0,37644	0,710196
S2 - NAA & S2 - Glu	24	-0,046957	-0,22049	0,827524
S2 - NAA & S2 - GPC	22	0,048009	0,21495	0,831982
S2 - NAA & S2 - Ins	24	0,126087	0,59616	0,557154
S2 - NAA & S2 - NAA				
S2 - NAA & S2 - GPC+PCh	24	-0,003044	-0,01428	0,988737
S2 - NAA & S2 - NAA+NAAG	24	0,794783	6,14252	0,000003
S2 - NAA & S2 - Cr+PCr	24	0,103066	0,48601	0,631766
S2 - NAA & S2 - Glu+Gln	24	0,051750	0,24306	0,810214
S2 - GPC+PCh & S2 - Cr	24	0,181344	0,86492	0,396417
S2 - GPC+PCh & S2 - PCr	24	0,168297	0,80081	0,431807
S2 - GPC+PCh & S2 - Glu	24	0,060883	0,28610	0,777481
S2 - GPC+PCh & S2 - GPC	22	1,000000		
S2 - GPC+PCh & S2 - Ins	24	0,500978	2,71509	0,012643
S2 - GPC+PCh & S2 - NAA	24	-0,003044	-0,01428	0,988737
S2 - GPC+PCh & S2 - GPC+PCh				
S2 - GPC+PCh & S2 - NAA+NAAG	24	0,127854	0,60465	0,551597
S2 - GPC+PCh & S2 - Cr+PCr	24	0,307960	1,51825	0,143192
S2 - GPC+PCh & S2 - Glu+Gln	24	0,085037	0,40031	0,692790
S2 - NAA+NAAG & S2 - Cr	24	0,462609	2,44746	0,022833
S2 - NAA+NAAG & S2 - PCr	24	-0,010435	-0,04895	0,961404
S2 - NAA+NAAG & S2 - Glu	24	0,266087	1,29473	0,208836
S2 - NAA+NAAG & S2 - GPC	22	0,206721	0,94490	0,355989
S2 - NAA+NAAG & S2 - Ins	24	0,320870	1,58903	0,126322
S2 - NAA+NAAG & S2 - NAA	24	0,794783	6,14252	0,000003
S2 - NAA+NAAG & S2 - GPC+PCh	24	0,127854	0,60465	0,551597
S2 - NAA+NAAG & S2 - NAA+NAAG				

S2 - NAA+NAAG & S2 - Cr+PCr	24	0,323114	1,60144	0,123542
S2 - NAA+NAAG & S2 - Glu+Gln	24	0,263101	1,27912	0,214183
S2 - Cr+PCr & S2 - Cr	24	0,386606	1,96623	0,062016
S2 - Cr+PCr & S2 - PCr	24	0,557513	3,14992	0,004648
S2 - Cr+PCr & S2 - Glu	24	0,410524	2,11167	0,046303
S2 - Cr+PCr & S2 - GPC	22	0,313471	1,47629	0,155438
S2 - Cr+PCr & S2 - Ins	24	0,398347	2,03701	0,053858
S2 - Cr+PCr & S2 - NAA	24	0,103066	0,48601	0,631766
S2 - Cr+PCr & S2 - GPC+PCh	24	0,307960	1,51825	0,143192
S2 - Cr+PCr & S2 - NAA+NAAG	24	0,323114	1,60144	0,123542
S2 - Cr+PCr & S2 - Cr+PCr				
S2 - Cr+PCr & S2 - Glu+Gln	24	0,424532	2,19925	0,038666
S2 - Glu+Gln & S2 - Cr	24	0,094803	0,44668	0,659473
S2 - Glu+Gln & S2 - PCr	24	0,291803	1,43095	0,166496
S2 - Glu+Gln & S2 - Glu	24	0,849315	7,54640	0,000000
S2 - Glu+Gln & S2 - GPC	22	0,160734	0,72830	0,474874
S2 - Glu+Gln & S2 - Ins	24	0,045662	0,21440	0,832212
S2 - Glu+Gln & S2 - NAA	24	0,051750	0,24306	0,810214
S2 - Glu+Gln & S2 - GPC+PCh	24	0,085037	0,40031	0,692790
S2 - Glu+Gln & S2 - NAA+NAAG	24	0,263101	1,27912	0,214183
S2 - Glu+Gln & S2 - Cr+PCr	24	0,424532	2,19925	0,038666
S2 - Glu+Gln & S2 - Glu+Gln				

Control group

Pair of Variables	Main Diagnosis=Control Spearman Rank Order Correlations (MethKi database final time 2.sta) MD pairwise deleted Marked correlations are significant at p <,05000			
	Valid N	Spearman R	t(N-2)	p-value
S2 - Cr & S2 - Cr				
S2 - Cr & S2 - PCr	11	-0,345455	-1,10435	0,298089
S2 - Cr & S2 - Glu	11	0,445455	1,49264	0,169733
S2 - Cr & S2 - GPC	9	0,283333	0,78166	0,460030
S2 - Cr & S2 - Ins	11	0,445455	1,49264	0,169733
S2 - Cr & S2 - NAA	11	0,354545	1,13753	0,284693
S2 - Cr & S2 - GPC+PCh	11	0,100000	0,30151	0,769875
S2 - Cr & S2 - NAA+NAAG	11	0,536364	1,90654	0,088953
S2 - Cr & S2 - Cr+PCr	11	0,669706	2,70542	0,024178
S2 - Cr & S2 - Glu+Gln	11	0,472727	1,60936	0,141999
S2 - PCr & S2 - Cr	11	-0,345455	-1,10435	0,298089
S2 - PCr & S2 - PCr				
S2 - PCr & S2 - Glu	11	-0,472727	-1,60936	0,141999
S2 - PCr & S2 - GPC	9	0,100000	0,26591	0,797972
S2 - PCr & S2 - Ins	11	0,400000	1,30931	0,222868
S2 - PCr & S2 - NAA	11	-0,209091	-0,64145	0,537221
S2 - PCr & S2 - GPC+PCh	11	0,236364	0,72977	0,484091
S2 - PCr & S2 - NAA+NAAG	11	-0,136364	-0,41295	0,689309
S2 - PCr & S2 - Cr+PCr	11	0,337131	1,07428	0,310652
S2 - PCr & S2 - Glu+Gln	11	-0,336364	-1,07153	0,311824
S2 - Glu & S2 - Cr	11	0,445455	1,49264	0,169733
S2 - Glu & S2 - PCr	11	-0,472727	-1,60936	0,141999
S2 - Glu & S2 - Glu				
S2 - Glu & S2 - GPC	9	0,300000	0,83205	0,432845
S2 - Glu & S2 - Ins	11	0,027273	0,08185	0,936558
S2 - Glu & S2 - NAA	11	0,036364	0,10916	0,915468
S2 - Glu & S2 - GPC+PCh	11	0,136364	0,41295	0,689309
S2 - Glu & S2 - NAA+NAAG	11	0,218182	0,67070	0,519248

S2 - Glu & S2 - Cr+PCr	11	0,068337	0,20549	0,841760
S2 - Glu & S2 - Glu+Gln	11	0,954545	9,60741	0,000005
S2 - GPC & S2 - Cr	9	0,283333	0,78166	0,460030
S2 - GPC & S2 - PCr	9	0,100000	0,26591	0,797972
S2 - GPC & S2 - Glu	9	0,300000	0,83205	0,432845
S2 - GPC & S2 - GPC				
S2 - GPC & S2 - Ins	9	0,383333	1,09809	0,308495
S2 - GPC & S2 - NAA	9	-0,200000	-0,54006	0,605901
S2 - GPC & S2 - GPC+PCh	9	1,000000		
S2 - GPC & S2 - NAA+NAAG	9	0,033333	0,08824	0,932157
S2 - GPC & S2 - Cr+PCr	9	0,250000	0,68313	0,516490
S2 - GPC & S2 - Glu+Gln	9	0,216667	0,58719	0,575515
S2 - Ins & S2 - Cr	11	0,445455	1,49264	0,169733
S2 - Ins & S2 - PCr	11	0,400000	1,30931	0,222868
S2 - Ins & S2 - Glu	11	0,027273	0,08185	0,936558
S2 - Ins & S2 - GPC	9	0,383333	1,09809	0,308495
S2 - Ins & S2 - Ins				
S2 - Ins & S2 - NAA	11	0,181818	0,55470	0,592615
S2 - Ins & S2 - GPC+PCh	11	0,436364	1,45492	0,179665
S2 - Ins & S2 - NAA+NAAG	11	0,372727	1,20501	0,258926
S2 - Ins & S2 - Cr+PCr	11	0,756266	3,46771	0,007074
S2 - Ins & S2 - Glu+Gln	11	0,109091	0,32924	0,749509
S2 - NAA & S2 - Cr	11	0,354545	1,13753	0,284693
S2 - NAA & S2 - PCr	11	-0,209091	-0,64145	0,537221
S2 - NAA & S2 - Glu	11	0,036364	0,10916	0,915468
S2 - NAA & S2 - GPC	9	-0,200000	-0,54006	0,605901
S2 - NAA & S2 - Ins	11	0,181818	0,55470	0,592615
S2 - NAA & S2 - NAA				
S2 - NAA & S2 - GPC+PCh	11	-0,272727	-0,85042	0,417141
S2 - NAA & S2 - NAA+NAAG	11	0,909091	6,54654	0,000106
S2 - NAA & S2 - Cr+PCr	11	0,277905	0,86790	0,407993
S2 - NAA & S2 - Glu+Gln	11	0,100000	0,30151	0,769875

S2 - GPC+PCh & S2 - Cr	11	0,10000	0,30151	0,769875
S2 - GPC+PCh & S2 - PCr	11	0,236364	0,72977	0,484091
S2 - GPC+PCh & S2 - Glu	11	0,136364	0,41295	0,689309
S2 - GPC+PCh & S2 - GPC	9	1,00000		
S2 - GPC+PCh & S2 - Ins	11	0,436364	1,45492	0,179665
S2 - GPC+PCh & S2 - NAA	11	-0,272727	-0,85042	0,417141
S2 - GPC+PCh & S2 - GPC+PCh				
S2 - GPC+PCh & S2 - NAA+NAA	11	-0,081818	-0,24628	0,810990
S2 - GPC+PCh & S2 - Cr+PCr	11	0,291573	0,91445	0,384324
S2 - GPC+PCh & S2 - Glu+Gln	11	-0,018182	-0,05455	0,957685
S2 - NAA+NAA & S2 - Cr	11	0,536364	1,90654	0,088953
S2 - NAA+NAA & S2 - PCr	11	-0,136364	-0,41295	0,689309
S2 - NAA+NAA & S2 - Glu	11	0,218182	0,67070	0,519248
S2 - NAA+NAA & S2 - GPC	9	0,033333	0,08824	0,932157
S2 - NAA+NAA & S2 - Ins	11	0,372727	1,20501	0,258926
S2 - NAA+NAA & S2 - NAA	11	0,909091	6,54654	0,000106
S2 - NAA+NAA & S2 - GPC+PCh	11	-0,081818	-0,24628	0,810990
S2 - NAA+NAA & S2 - NAA+NAA				
S2 - NAA+NAA & S2 - Cr+PCr	11	0,437359	1,45902	0,178561
S2 - NAA+NAA & S2 - Glu+Gln	11	0,281818	0,88117	0,401145
S2 - Cr+PCr & S2 - Cr	11	0,669706	2,70542	0,024178
S2 - Cr+PCr & S2 - PCr	11	0,337131	1,07428	0,310652
S2 - Cr+PCr & S2 - Glu	11	0,068337	0,20549	0,841760
S2 - Cr+PCr & S2 - GPC	9	0,250000	0,68313	0,516490
S2 - Cr+PCr & S2 - Ins	11	0,756266	3,46771	0,007074
S2 - Cr+PCr & S2 - NAA	11	0,277905	0,86790	0,407993
S2 - Cr+PCr & S2 - GPC+PCh	11	0,291573	0,91445	0,384324
S2 - Cr+PCr & S2 - NAA+NAA	11	0,437359	1,45902	0,178561

S2 - Cr+PCr & S2 - Cr+PCr				
S2 - Cr+PCr & S2 - Glu+Gln	11	0,150342	0,45621	0,659047
S2 - Glu+Gln & S2 - Cr	11	0,472727	1,60936	0,141999
S2 - Glu+Gln & S2 - PCr	11	-0,336364	-1,07153	0,311824
S2 - Glu+Gln & S2 - Glu	11	0,954545	9,60741	0,000005
S2 - Glu+Gln & S2 - GPC	9	0,216667	0,58719	0,575515
S2 - Glu+Gln & S2 - Ins	11	0,109091	0,32924	0,749509
S2 - Glu+Gln & S2 - NAA	11	0,100000	0,30151	0,769875
S2 - Glu+Gln & S2 - GPC+PCh	11	-0,018182	-0,05455	0,957685
S2 - Glu+Gln & S2 - NAA+NAAG	11	0,281818	0,88117	0,401145
S2 - Glu+Gln & S2 - Cr+PCr	11	0,150342	0,45621	0,659047
S2 - Glu+Gln & S2 - Glu+Gln				

MA group

Pair of Variables	Main Diagnosis=Meth Spearman Rank Order Correlations (MethKi database final time 2.sta) MD pairwise deleted Marked correlations are significant at p <,05000			
	Valid N	Spearman R	t(N-2)	p-value
S2 - Cr & S2 - Cr				
S2 - Cr & S2 - PCr	13	-0,478022	-1,80500	0,098490
S2 - Cr & S2 - Glu	13	-0,027473	-0,09115	0,929012
S2 - Cr & S2 - GPC	13	0,313187	1,09375	0,297438
S2 - Cr & S2 - Ins	13	0,071429	0,23751	0,816628
S2 - Cr & S2 - NAA	13	0,087912	0,29270	0,775195
S2 - Cr & S2 - GPC+PCh	13	0,313187	1,09375	0,297438
S2 - Cr & S2 - NAA+NAAG	13	0,258242	0,88656	0,394284
S2 - Cr & S2 - Cr+PCr	13	0,269231	0,92717	0,373733
S2 - Cr & S2 - Glu+Gln	13	-0,016484	-0,05468	0,957376

S2 - PCr & S2 - Cr	13	-0,478022	-1,80500	0,098490
S2 - PCr & S2 - PCr				
S2 - PCr & S2 - Glu	13	0,598901	2,48036	0,030554
S2 - PCr & S2 - GPC	13	0,032967	0,10940	0,914856
S2 - PCr & S2 - Ins	13	-0,005495	-0,01822	0,985787
S2 - PCr & S2 - NAA	13	-0,082418	-0,27428	0,788951
S2 - PCr & S2 - GPC+PCh	13	0,032967	0,10940	0,914856
S2 - PCr & S2 - NAA+NAAg	13	0,021978	0,07291	0,943186
S2 - PCr & S2 - Cr+PCr	13	0,653846	2,86609	0,015349
S2 - PCr & S2 - Glu+Gln	13	0,697802	3,23102	0,008001
S2 - Glu & S2 - Cr	13	-0,027473	-0,09115	0,929012
S2 - Glu & S2 - PCr	13	0,598901	2,48036	0,030554
S2 - Glu & S2 - Glu				
S2 - Glu & S2 - GPC	13	-0,082418	-0,27428	0,788951
S2 - Glu & S2 - Ins	13	0,032967	0,10940	0,914856
S2 - Glu & S2 - NAA	13	-0,082418	-0,27428	0,788951
S2 - Glu & S2 - GPC+PCh	13	-0,082418	-0,27428	0,788951
S2 - Glu & S2 - NAA+NAAg	13	0,384615	1,38193	0,194413
S2 - Glu & S2 - Cr+PCr	13	0,703297	3,28117	0,007319
S2 - Glu & S2 - Glu+Gln	13	0,741758	3,66819	0,003701
S2 - GPC & S2 - Cr	13	0,313187	1,09375	0,297438
S2 - GPC & S2 - PCr	13	0,032967	0,10940	0,914856
S2 - GPC & S2 - Glu	13	-0,082418	-0,27428	0,788951
S2 - GPC & S2 - GPC				
S2 - GPC & S2 - Ins	13	0,489011	1,85935	0,089913
S2 - GPC & S2 - NAA	13	0,247253	0,84632	0,415405
S2 - GPC & S2 - GPC+PCh	13	1,000000		
S2 - GPC & S2 - NAA+NAAg	13	0,252747	0,86640	0,404774
S2 - GPC & S2 - Cr+PCr	13	0,192308	0,64994	0,529068
S2 - GPC & S2 - Glu+Gln	13	-0,043956	-0,14593	0,886619
S2 - Ins & S2 - Cr	13	0,071429	0,23751	0,816628
S2 - Ins & S2 - PCr	13	-0,005495	-0,01822	0,985787

S2 - Ins & S2 - Glu	13	0,032967	0,10940	0,914856
S2 - Ins & S2 - GPC	13	0,489011	1,85935	0,089913
S2 - Ins & S2 - Ins				
S2 - Ins & S2 - NAA	13	0,181319	0,61150	0,553295
S2 - Ins & S2 - GPC+PCh	13	0,489011	1,85935	0,089913
S2 - Ins & S2 - NAA+NAAG	13	0,467033	1,75176	0,107609
S2 - Ins & S2 - Cr+PCr	13	0,115385	0,38526	0,707390
S2 - Ins & S2 - Glu+Gln	13	-0,082418	-0,27428	0,788951
S2 - NAA & S2 - Cr	13	0,087912	0,29270	0,775195
S2 - NAA & S2 - PCr	13	-0,082418	-0,27428	0,788951
S2 - NAA & S2 - Glu	13	-0,082418	-0,27428	0,788951
S2 - NAA & S2 - GPC	13	0,247253	0,84632	0,415405
S2 - NAA & S2 - Ins	13	0,181319	0,61150	0,553295
S2 - NAA & S2 - NAA				
S2 - NAA & S2 - GPC+PCh	13	0,247253	0,84632	0,415405
S2 - NAA & S2 - NAA+NAAG	13	0,736264	3,60859	0,004108
S2 - NAA & S2 - Cr+PCr	13	-0,032967	-0,10940	0,914856
S2 - NAA & S2 - Glu+Gln	13	0,043956	0,14593	0,886619
S2 - GPC+PCh & S2 - Cr	13	0,313187	1,09375	0,297438
S2 - GPC+PCh & S2 - PCr	13	0,032967	0,10940	0,914856
S2 - GPC+PCh & S2 - Glu	13	-0,082418	-0,27428	0,788951
S2 - GPC+PCh & S2 - GPC	13	1,000000		
S2 - GPC+PCh & S2 - Ins	13	0,489011	1,85935	0,089913
S2 - GPC+PCh & S2 - NAA	13	0,247253	0,84632	0,415405
S2 - GPC+PCh & S2 - GPC+PCh				
S2 - GPC+PCh & S2 - NAA+NAAG	13	0,252747	0,86640	0,404774
S2 - GPC+PCh & S2 - Cr+PCr	13	0,192308	0,64994	0,529068
S2 - GPC+PCh & S2 - Glu+Gln	13	-0,043956	-0,14593	0,886619
S2 - NAA+NAAG & S2 - Cr	13	0,258242	0,88656	0,394284
S2 - NAA+NAAG & S2 - PCr	13	0,021978	0,07291	0,943186
S2 - NAA+NAAG & S2 - Glu	13	0,384615	1,38193	0,194413

S2 - NAA+NAAG & S2 - GPC	13	0,252747	0,86640	0,404774
S2 - NAA+NAAG & S2 - Ins	13	0,467033	1,75176	0,107609
S2 - NAA+NAAG & S2 - NAA	13	0,736264	3,60859	0,004108
S2 - NAA+NAAG & S2 - GPC+PCh	13	0,252747	0,86640	0,404774
S2 - NAA+NAAG & S2 - NAA+NAAG				
S2 - NAA+NAAG & S2 - Cr+PCr	13	0,313187	1,09375	0,297438
S2 - NAA+NAAG & S2 - Glu+Gln	13	0,296703	1,03046	0,324922
S2 - Cr+PCr & S2 - Cr	13	0,269231	0,92717	0,373733
S2 - Cr+PCr & S2 - PCr	13	0,653846	2,86609	0,015349
S2 - Cr+PCr & S2 - Glu	13	0,703297	3,28117	0,007319
S2 - Cr+PCr & S2 - GPC	13	0,192308	0,64994	0,529068
S2 - Cr+PCr & S2 - Ins	13	0,115385	0,38526	0,707390
S2 - Cr+PCr & S2 - NAA	13	-0,032967	-0,10940	0,914856
S2 - Cr+PCr & S2 - GPC+PCh	13	0,192308	0,64994	0,529068
S2 - Cr+PCr & S2 - NAA+NAAG	13	0,313187	1,09375	0,297438
S2 - Cr+PCr & S2 - Cr+PCr				
S2 - Cr+PCr & S2 - Glu+Gln	13	0,714286	3,38502	0,006088
S2 - Glu+Gln & S2 - Cr	13	-0,016484	-0,05468	0,957376
S2 - Glu+Gln & S2 - PCr	13	0,697802	3,23102	0,008001
S2 - Glu+Gln & S2 - Glu	13	0,741758	3,66819	0,003701
S2 - Glu+Gln & S2 - GPC	13	-0,043956	-0,14593	0,886619
S2 - Glu+Gln & S2 - Ins	13	-0,082418	-0,27428	0,788951
S2 - Glu+Gln & S2 - NAA	13	0,043956	0,14593	0,886619
S2 - Glu+Gln & S2 - GPC+PCh	13	-0,043956	-0,14593	0,886619
S2 - Glu+Gln & S2 - NAA+NAAG	13	0,296703	1,03046	0,324922
S2 - Glu+Gln & S2 - Cr+PCr	13	0,714286	3,38502	0,006088
S2 - Glu+Gln & S2 - Glu+Gln				

Full dataset – differences between the two time points

[illegible]

Atlantis RS S1		16	48,06250	21,00000	87,00000	17,56310
Atlantis RS S2		16	68,50000	38,00000	94,00000	12,25833
Atlantis SCS S1		16	6,56250	3,00000	13,00000	2,52900
Atlantis SCS S2		16	7,93750	4,00000	12,00000	1,80624
Atlantis Delay RS S1		16	11,00000	4,00000	22,00000	4,25833
Atlantis Delay RS S2		16	9,50000	4,00000	17,00000	4,21110
Atlantis Delay SCS S1		16	8,31250	4,00000	15,00000	2,27211
Atlantis Delay SCS S2		16	6,93750	4,00000	10,00000	2,20511
Total BNT S1		16	7,06250	5,00000	9,00000	1,23659
Total BNT S2		16	7,93750	6,00000	10,00000	1,06262

Metabolites

Variable	Descriptive Statistics (MethKi database final time 3.sta)					
	Valid N	Mean	Minimum	Maximum	Std.Dev.	
S1 - Cr	15	2,56187	2,035000	3,43400	0,449706	
S1 - PCr	15	2,79007	2,191000	3,55000	0,389590	
S1 - Glu	16	8,56663	7,762000	9,34800	0,443486	
S1 - GPC	16	1,10544	0,876000	1,37400	0,130817	
S1 - Ins	16	5,34000	4,660000	5,85200	0,387154	
S1 - NAA	16	6,16888	5,655000	6,62700	0,255243	
S1 - GPC+PCh	16	1,10544	0,876000	1,37400	0,130817	
S1 - NAA+NAAG	16	6,48525	6,076000	7,21600	0,297096	
S1 - Cr+PCr	16	5,25006	4,966000	5,58300	0,185430	
S1 - Glu+Gln	16	9,95019	8,382000	11,77900	0,957029	
S2 - Cr	16	2,56469	2,000000	2,98300	0,260103	
S2 - PCr	16	2,80063	2,160000	3,41400	0,333930	
S2 - Glu	16	8,74863	7,644000	9,96300	0,630076	
S2 - GPC	14	1,10086	0,950000	1,25400	0,097929	
S2 - Ins	16	5,44588	4,493000	6,17700	0,439754	
S2 - NAA	16	6,45006	6,203000	6,74200	0,167246	
S2 - GPC+PCh	16	1,09556	0,950000	1,25400	0,093372	

S2 - NAA+NAAG	16	6,67356	6,262000	7,25100	0,249611
S2 - Cr+PCr	16	5,36519	4,818000	5,91400	0,313130
S2 - Glu+Gln	16	10,25588	8,871000	11,79500	0,976075

Frequency tables
Demographics
Age - time point 1

Frequency table: S1 - Age (MethKi database final time 3.sta) Shapiro-Wilk W=,89944, p=,07874						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
5,800000<x<=6,000000	2	2	12,50000	12,5000	12,50000	12,5000
6,000000<x<=6,200000	3	5	18,75000	31,2500	18,75000	31,2500
6,200000<x<=6,400000	4	9	25,00000	56,2500	25,00000	56,2500
6,400000<x<=6,600000	2	11	12,50000	68,7500	12,50000	68,7500
6,600000<x<=6,800000	1	12	6,25000	75,0000	6,25000	75,0000
6,800000<x<=7,000000	3	15	18,75000	93,7500	18,75000	93,7500
7,000000<x<=7,200000	1	16	6,25000	100,0000	6,25000	100,0000
Missing	0	16	0,00000		0,00000	100,0000

Age - time point 2

Frequency table: S2 - Age (MethKi database final time 3.sta) Shapiro-Wilk W=,92732, p=,22101						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
7,200000<x<=7,400000	2	2	12,50000	12,5000	12,50000	12,5000
7,400000<x<=7,600000	2	4	12,50000	25,0000	12,50000	25,0000
7,600000<x<=7,800000	1	5	6,25000	31,2500	6,25000	31,2500
7,800000<x<=8,000000	2	7	12,50000	43,7500	12,50000	43,7500
8,000000<x<=8,200000	2	9	12,50000	56,2500	12,50000	56,2500
8,200000<x<=8,400000	4	13	25,00000	81,2500	25,00000	81,2500
8,400000<x<=8,600000	0	13	0,00000	81,2500	0,00000	81,2500
8,600000<x<=8,800000	3	16	18,75000	100,0000	18,75000	100,0000
Missing	0	16	0,00000		0,00000	100,0000

Weight - time point 1

Frequency table: Child weight Scan 1 (MethKi database final time 3.sta) Shapiro-Wilk W=,89404, p=,06456						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
14,00000<x<=16,00000	1	1	6,25000	6,2500	6,25000	6,2500
16,00000<x<=18,00000	6	7	37,50000	43,7500	37,50000	43,7500
18,00000<x<=20,00000	5	12	31,25000	75,0000	31,25000	75,0000
20,00000<x<=22,00000	2	14	12,50000	87,5000	12,50000	87,5000
22,00000<x<=24,00000	1	15	6,25000	93,7500	6,25000	93,7500
24,00000<x<=26,00000	0	15	0,00000	93,7500	0,00000	93,7500
26,00000<x<=28,00000	1	16	6,25000	100,0000	6,25000	100,0000
Missing	0	16	0,00000		0,00000	100,0000

Weight - time point 2

Frequency table: Child weight Scan 2 (MethKi database final time 3.sta) Shapiro-Wilk W=,78760, p=,00187						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
18,00000<x<=20,00000	2	2	12,50000	12,5000	12,50000	12,5000
20,00000<x<=22,00000	5	7	31,25000	43,7500	31,25000	43,7500
22,00000<x<=24,00000	7	14	43,75000	87,5000	43,75000	87,5000
24,00000<x<=26,00000	0	14	0,00000	87,5000	0,00000	87,5000
26,00000<x<=28,00000	0	14	0,00000	87,5000	0,00000	87,5000
28,00000<x<=30,00000	1	15	6,25000	93,7500	6,25000	93,7500
30,00000<x<=32,00000	1	16	6,25000	100,0000	6,25000	100,0000
Missing	0	16	0,00000		0,00000	100,0000

Height – time point 1

Frequency table: Child height Scan 1 (MethKi database final time 3.sta) Shapiro-Wilk W=,93091, p=,25205						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
,8000000<x<=,9000000	0	0	0,00000	0,0000	0,00000	0,0000
,9000000<x<=1,000000	5	5	31,25000	31,2500	31,25000	31,2500
1,000000<x<=1,100000	5	10	31,25000	62,5000	31,25000	62,5000
1,100000<x<=1,200000	6	16	37,50000	100,0000	37,50000	100,0000
Missing	0	16	0,00000		0,00000	100,0000

Height – time point 2

Frequency table: Child height Scan 2 (MethKi database final time 3.sta) Shapiro-Wilk W=,91040, p=,11812						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
1,100000<x<=1,150000	1	1	6,25000	6,2500	6,25000	6,2500
1,150000<x<=1,200000	5	6	31,25000	37,5000	31,25000	37,5000
1,200000<x<=1,250000	7	13	43,75000	81,2500	43,75000	81,2500
1,250000<x<=1,300000	1	14	6,25000	87,5000	6,25000	87,5000
1,300000<x<=1,350000	1	15	6,25000	93,7500	6,25000	93,7500
1,350000<x<=1,400000	1	16	6,25000	100,0000	6,25000	100,0000
Missing	0	16	0,00000		0,00000	100,0000

BMI time point 1

Category	Frequency table: BMI Scan 1 (MethKi database final time 3.sta) Shapiro-Wilk W=,93430, p=,28493					
	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
10,00000<x<=12,00000	0	0	0,00000	0,0000	0,00000	0,0000
12,00000<x<=14,00000	2	2	12,50000	12,5000	12,50000	12,5000
14,00000<x<=16,00000	5	7	31,25000	43,7500	31,25000	43,7500
16,00000<x<=18,00000	2	9	12,50000	56,2500	12,50000	56,2500
18,00000<x<=20,00000	3	12	18,75000	75,0000	18,75000	75,0000
20,00000<x<=22,00000	3	15	18,75000	93,7500	18,75000	93,7500
22,00000<x<=24,00000	0	15	0,00000	93,7500	0,00000	93,7500
24,00000<x<=26,00000	1	16	6,25000	100,0000	6,25000	100,0000
Missing	0	16	0,00000		0,00000	100,0000

BMI time point 2

Category	Frequency table: BMI Scan 2 (MethKi database final time 3.sta) Shapiro-Wilk W=,87372, p=,03102					
	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
11,00000<x<=12,00000	0	0	0,00000	0,0000	0,00000	0,0000
12,00000<x<=13,00000	1	1	6,25000	6,2500	6,25000	6,2500
13,00000<x<=14,00000	4	5	25,00000	31,2500	25,00000	31,2500
14,00000<x<=15,00000	3	8	18,75000	50,0000	18,75000	50,0000
15,00000<x<=16,00000	4	12	25,00000	75,0000	25,00000	75,0000
16,00000<x<=17,00000	3	15	18,75000	93,7500	18,75000	93,7500
17,00000<x<=18,00000	0	15	0,00000	93,7500	0,00000	93,7500
18,00000<x<=19,00000	0	15	0,00000	93,7500	0,00000	93,7500
19,00000<x<=20,00000	0	15	0,00000	93,7500	0,00000	93,7500
20,00000<x<=21,00000	1	16	6,25000	100,0000	6,25000	100,0000
Missing	0	16	0,00000		0,00000	100,0000

Frequency tables – neurocognitive tasks
Block Counting raw score – time point 1

Frequency table: Block Counting RS S1 (MethKi database final time 3.sta) Shapiro-Wilk W=,86885, p=,11952						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
0,000000<x<=2,000000	2	2	22,22222	22,2222	12,50000	12,5000
2,000000<x<=4,000000	1	3	11,11111	33,3333	6,25000	18,7500
4,000000<x<=6,000000	0	3	0,00000	33,3333	0,00000	18,7500
6,000000<x<=8,000000	2	5	22,22222	55,5556	12,50000	31,2500
8,000000<x<=10,00000	1	6	11,11111	66,6667	6,25000	37,5000
10,00000<x<=12,00000	0	6	0,00000	66,6667	0,00000	37,5000
12,00000<x<=14,00000	1	7	11,11111	77,7778	6,25000	43,7500
14,00000<x<=16,00000	2	9	22,22222	100,0000	12,50000	56,2500
Missing	7	16	77,77778		43,75000	100,0000

Block Counting raw score – time point 2

Frequency table: Block Counting RS S2 (MethKi database final time 3.sta) Shapiro-Wilk W=,95625, p=,59459						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
-5,000000<x<=0,000000	0	0	0,00000	0,0000	0,00000	0,0000
0,000000<x<=5,000000	5	5	31,25000	31,2500	31,25000	31,2500
5,000000<x<=10,00000	3	8	18,75000	50,0000	18,75000	50,0000
10,00000<x<=15,00000	5	13	31,25000	81,2500	31,25000	81,2500
15,00000<x<=20,00000	3	16	18,75000	100,0000	18,75000	100,0000
Missing	0	16	0,00000		0,00000	100,0000

Block Counting scaled score – time point 1

Frequency table: Block Counting SCS S1 (MethKi database final time 3.sta) Shapiro-Wilk W=,85861, p=,09260						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
4,000000<x<=5,000000	2	2	22,22222	22,2222	12,50000	12,5000
5,000000<x<=6,000000	1	3	11,11111	33,3333	6,25000	18,7500
6,000000<x<=7,000000	0	3	0,00000	33,3333	0,00000	18,7500
7,000000<x<=8,000000	3	6	33,33333	66,6667	18,75000	37,5000
8,000000<x<=9,000000	0	6	0,00000	66,6667	0,00000	37,5000
9,000000<x<=10,00000	0	6	0,00000	66,6667	0,00000	37,5000
10,00000<x<=11,00000	0	6	0,00000	66,6667	0,00000	37,5000
11,00000<x<=12,00000	1	7	11,11111	77,7778	6,25000	43,7500
12,00000<x<=13,00000	2	9	22,22222	100,0000	12,50000	56,2500
Missing	7	16	77,77778		43,75000	100,0000

Block Counting scaled score – time point 2

Frequency table: Block Counting SCS S2 (MethKi database final time 3.sta) Shapiro-Wilk W=,94772, p=,45448						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
-2,000000<x<=0,000000	0	0	0,00000	0,0000	0,00000	0,0000
0,000000<x<=2,000000	1	1	6,25000	6,2500	6,25000	6,2500
2,000000<x<=4,000000	1	2	6,25000	12,5000	6,25000	12,5000
4,000000<x<=6,000000	3	5	18,75000	31,2500	18,75000	31,2500
6,000000<x<=8,000000	2	7	12,50000	43,7500	12,50000	43,7500
8,000000<x<=10,00000	4	11	25,00000	68,7500	25,00000	68,7500
10,00000<x<=12,00000	4	15	25,00000	93,7500	25,00000	93,7500
12,00000<x<=14,00000	1	16	6,25000	100,0000	6,25000	100,0000
Missing	0	16	0,00000		0,00000	100,0000

Pattern Reasoning raw score - time point 1

Frequency table: Pattern Reasoning RS No Tmpt S1 (MethKi database final time 3.sta) Shapiro-Wilk W=,87993, p=,03871						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
0,000000<x<=2,000000	3	3	18,75000	18,7500	18,75000	18,7500
2,000000<x<=4,000000	4	7	25,00000	43,7500	25,00000	43,7500
4,000000<x<=6,000000	2	9	12,50000	56,2500	12,50000	56,2500
6,000000<x<=8,000000	1	10	6,25000	62,5000	6,25000	62,5000
8,000000<x<=10,00000	6	16	37,50000	100,0000	37,50000	100,0000
Missing	0	16	0,00000		0,00000	100,0000

Pattern Reasoning raw score - time point 2

Frequency table: Pattern Reasoning RS No Tmpt S2 (MethKi database final time 3.sta) Shapiro-Wilk W=,87867, p=,03700						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
2,000000<x<=4,000000	2	2	12,50000	12,5000	12,50000	12,5000
4,000000<x<=6,000000	1	3	6,25000	18,7500	6,25000	18,7500
6,000000<x<=8,000000	2	5	12,50000	31,2500	12,50000	31,2500
8,000000<x<=10,00000	7	12	43,75000	75,0000	43,75000	75,0000
10,00000<x<=12,00000	3	15	18,75000	93,7500	18,75000	93,7500
12,00000<x<=14,00000	1	16	6,25000	100,0000	6,25000	100,0000
Missing	0	16	0,00000		0,00000	100,0000

Pattern Reasoning scaled score - time point 1

Frequency table: Pattern Reasoning SCS No Tmpt S1 (MethKi database final time 3.sta) Shapiro-Wilk W=,90380, p=,09248						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
2,000000<x<=4,000000	5	5	31,25000	31,2500	31,25000	31,2500
4,000000<x<=6,000000	3	8	18,75000	50,0000	18,75000	50,0000
6,000000<x<=8,000000	5	13	31,25000	81,2500	31,25000	81,2500
8,000000<x<=10,00000	0	13	0,00000	81,2500	0,00000	81,2500
10,00000<x<=12,00000	3	16	18,75000	100,0000	18,75000	100,0000
Missing	0	16	0,00000		0,00000	100,0000

Pattern Reasoning scaled score - time point 2

Frequency table: Pattern Reasoning SCS No Tmpt S2 (MethKi database final time 3.sta) Shapiro-Wilk W=,95202, p=,52238						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
2,000000<x<=3,000000	1	1	6,25000	6,2500	6,25000	6,2500
3,000000<x<=4,000000	2	3	12,50000	18,7500	12,50000	18,7500
4,000000<x<=5,000000	1	4	6,25000	25,0000	6,25000	25,0000
5,000000<x<=6,000000	2	6	12,50000	37,5000	12,50000	37,5000
6,000000<x<=7,000000	4	10	25,00000	62,5000	25,00000	62,5000
7,000000<x<=8,000000	4	14	25,00000	87,5000	25,00000	87,5000
8,000000<x<=9,000000	1	15	6,25000	93,7500	6,25000	93,7500
9,000000<x<=10,00000	1	16	6,25000	100,0000	6,25000	100,0000
Missing	0	16	0,00000		0,00000	100,0000

Atlantis raw score - time point 1

Frequency table: Atlantis RS S1 (MethKi database final time 3.sta) Shapiro-Wilk W=,95110, p=,50724					
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases
10,00000<x<=20,00000	0	0	0,00000	0,0000	0,00000
20,00000<x<=30,00000	4	4	25,00000	25,0000	25,00000
30,00000<x<=40,00000	1	5	6,25000	31,2500	6,25000
40,00000<x<=50,00000	4	9	25,00000	56,2500	25,00000
50,00000<x<=60,00000	3	12	18,75000	75,0000	18,75000
60,00000<x<=70,00000	3	15	18,75000	93,7500	18,75000
70,00000<x<=80,00000	0	15	0,00000	93,7500	0,00000
80,00000<x<=90,00000	1	16	6,25000	100,0000	6,25000
Missing	0	16	0,00000		0,00000
					100,0000

Atlantis raw score - time point 2

Frequency table: Atlantis RS S2 (MethKi database final time 3.sta) Shapiro-Wilk W=,94239, p=,37932					
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases
30,00000<x<=40,00000	1	1	6,25000	6,2500	6,25000
40,00000<x<=50,00000	0	1	0,00000	6,2500	0,00000
50,00000<x<=60,00000	2	3	12,50000	18,7500	12,50000
60,00000<x<=70,00000	6	9	37,50000	56,2500	37,50000
70,00000<x<=80,00000	5	14	31,25000	87,5000	31,25000
80,00000<x<=90,00000	1	15	6,25000	93,7500	6,25000
90,00000<x<=100,0000	1	16	6,25000	100,0000	6,25000
Missing	0	16	0,00000		0,00000
					100,0000

Atlantis scaled score - time point 1

Frequency table: Atlantis SCS S1 (MethKi database final time 3.sta) Shapiro-Wilk W= 92472, p=,20081						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
0,000000<x<=2,000000	0	0	0,00000	0,0000	0,00000	0,0000
2,000000<x<=4,000000	3	3	18,75000	18,7500	18,75000	18,7500
4,000000<x<=6,000000	5	8	31,25000	50,0000	31,25000	50,0000
6,000000<x<=8,000000	6	14	37,50000	87,5000	37,50000	87,5000
8,000000<x<=10,00000	1	15	6,25000	93,7500	6,25000	93,7500
10,00000<x<=12,00000	0	15	0,00000	93,7500	0,00000	93,7500
12,00000<x<=14,00000	1	16	6,25000	100,0000	6,25000	100,0000
Missing	0	16	0,00000		0,00000	100,0000

Atlantis scaled score - time point 2

Frequency table: Atlantis SCS S2 (MethKi database final time 3.sta) Shapiro-Wilk W= 94588, p=,42736						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
3,000000<x<=4,000000	1	1	6,25000	6,2500	6,25000	6,2500
4,000000<x<=5,000000	0	1	0,00000	6,2500	0,00000	6,2500
5,000000<x<=6,000000	1	2	6,25000	12,5000	6,25000	12,5000
6,000000<x<=7,000000	5	7	31,25000	43,7500	31,25000	43,7500
7,000000<x<=8,000000	3	10	18,75000	62,5000	18,75000	62,5000
8,000000<x<=9,000000	4	14	25,00000	87,5000	25,00000	87,5000
9,000000<x<=10,00000	1	15	6,25000	93,7500	6,25000	93,7500
10,00000<x<=11,00000	0	15	0,00000	93,7500	0,00000	93,7500
11,00000<x<=12,00000	1	16	6,25000	100,0000	6,25000	100,0000
Missing	0	16	0,00000		0,00000	100,0000

Atlantis Delayed raw score - time point 1

Frequency table: Atlantis Delayed RS S1 (MethKi database final time 3.sta) Shapiro-Wilk W=,93811, p=,32653						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
0,000000<x<=5,000000	1	1	6,25000	6,2500	6,25000	6,2500
5,000000<x<=10,00000	6	7	37,50000	43,7500	37,50000	43,7500
10,00000<x<=15,00000	7	14	43,75000	87,5000	43,75000	87,5000
15,00000<x<=20,00000	1	15	6,25000	93,7500	6,25000	93,7500
20,00000<x<=25,00000	1	16	6,25000	100,0000	6,25000	100,0000
Missing	0	16	0,00000		0,00000	100,0000

Atlantis Delayed raw score - time point 2

Frequency table: Atlantis Delay RS S2 (MethKi database final time 3.sta) Shapiro-Wilk W=,93330, p=,27486						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
2,000000<x<=4,000000	2	2	12,50000	12,5000	12,50000	12,5000
4,000000<x<=6,000000	3	5	18,75000	31,2500	18,75000	31,2500
6,000000<x<=8,000000	2	7	12,50000	43,7500	12,50000	43,7500
8,000000<x<=10,00000	4	11	25,00000	68,7500	25,00000	68,7500
10,00000<x<=12,00000	1	12	6,25000	75,0000	6,25000	75,0000
12,00000<x<=14,00000	1	13	6,25000	81,2500	6,25000	81,2500
14,00000<x<=16,00000	2	15	12,50000	93,7500	12,50000	93,7500
16,00000<x<=18,00000	1	16	6,25000	100,0000	6,25000	100,0000
Missing	0	16	0,00000		0,00000	100,0000

Atlantis Delayed scaled score - time point 1

Frequency table: Atlantis Delay SCS S1 (MethKi database final time 3.sta) Shapiro-Wilk W=,82266, p=,00554						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
2,000000<x<=4,000000	1	1	6,25000	6,2500	6,25000	6,2500
4,000000<x<=6,000000	0	1	0,00000	6,2500	0,00000	6,2500
6,000000<x<=8,000000	10	11	62,50000	68,7500	62,50000	68,7500
8,000000<x<=10,00000	4	15	25,00000	93,7500	25,00000	93,7500
10,000000<x<=12,00000	0	15	0,00000	93,7500	0,00000	93,7500
12,000000<x<=14,00000	0	15	0,00000	93,7500	0,00000	93,7500
14,000000<x<=16,00000	1	16	6,25000	100,0000	6,25000	100,0000
Missing	0	16	0,00000		0,00000	100,0000

Atlantis Delayed scaled score - time point 2

Frequency table: Atlantis Delay SCS S2 (MethKi database final time 3.sta) Shapiro-Wilk W=,90723, p=,10499						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
3,000000<x<=4,000000	3	3	18,75000	18,7500	18,75000	18,7500
4,000000<x<=5,000000	2	5	12,50000	31,2500	12,50000	31,2500
5,000000<x<=6,000000	2	7	12,50000	43,7500	12,50000	43,7500
6,000000<x<=7,000000	3	10	18,75000	62,5000	18,75000	62,5000
7,000000<x<=8,000000	1	11	6,25000	68,7500	6,25000	68,7500
8,000000<x<=9,000000	2	13	12,50000	81,2500	12,50000	81,2500
9,000000<x<=10,00000	3	16	18,75000	100,0000	18,75000	100,0000
Missing	0	16	0,00000		0,00000	100,0000

Boston Naming Test – total score – time point 1

Frequency table: Total BNT S1 (MethKi database final time 3.sta) Shapiro-Wilk W=,93101, p=,25297						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
4,500000<x<=5,000000	2	2	12,50000	12,5000	12,50000	12,5000
5,000000<x<=5,500000	0	2	0,00000	12,5000	0,00000	12,5000
5,500000<x<=6,000000	3	5	18,75000	31,2500	18,75000	31,2500
6,000000<x<=6,500000	0	5	0,00000	31,2500	0,00000	31,2500
6,500000<x<=7,000000	5	10	31,25000	62,5000	31,25000	62,5000
7,000000<x<=7,500000	0	10	0,00000	62,5000	0,00000	62,5000
7,500000<x<=8,000000	4	14	25,00000	87,5000	25,00000	87,5000
8,000000<x<=8,500000	0	14	0,00000	87,5000	0,00000	87,5000
8,500000<x<=9,000000	2	16	12,50000	100,0000	12,50000	100,0000
Missing	0	16	0,00000		0,00000	100,0000

Boston Naming Test – total score – time point 2

Frequency table: Total BNT S2 (MethKi database final time 3.sta) Shapiro-Wilk W=,92690, p=,21762						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
5,500000<x<=6,000000	1	1	6,25000	6,2500	6,25000	6,2500
6,000000<x<=6,500000	0	1	0,00000	6,2500	0,00000	6,2500
6,500000<x<=7,000000	5	6	31,25000	37,5000	31,25000	37,5000
7,000000<x<=7,500000	0	6	0,00000	37,5000	0,00000	37,5000
7,500000<x<=8,000000	5	11	31,25000	68,7500	31,25000	68,7500
8,000000<x<=8,500000	0	11	0,00000	68,7500	0,00000	68,7500
8,500000<x<=9,000000	4	15	25,00000	93,7500	25,00000	93,7500
9,000000<x<=9,500000	0	15	0,00000	93,7500	0,00000	93,7500
9,500000<x<=10,00000	1	16	6,25000	100,0000	6,25000	100,0000
Missing	0	16	0,00000		0,00000	100,0000

Frequency tables - metabolites

Cr - time point 1

Frequency table: S1 -Cr (MethKi database final time 3.sta) Shapiro-Wilk W=,90869, p=,12928						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
1,800000<x<=2,000000	0	0	0,00000	0,0000	0,00000	0,0000
2,000000<x<=2,200000	5	5	33,33333	33,3333	31,25000	31,2500
2,200000<x<=2,400000	2	7	13,33333	46,6667	12,50000	43,7500
2,400000<x<=2,600000	1	8	6,66667	53,3333	6,25000	50,0000
2,600000<x<=2,800000	3	11	20,00000	73,3333	18,75000	68,7500
2,800000<x<=3,000000	1	12	6,66667	80,0000	6,25000	75,0000
3,000000<x<=3,200000	1	13	6,66667	86,6667	6,25000	81,2500
3,200000<x<=3,400000	1	14	6,66667	93,3333	6,25000	87,5000
3,400000<x<=3,600000	1	15	6,66667	100,0000	6,25000	93,7500
Missing	1	16	6,66667		6,25000	100,0000

Cr - time point 2

Frequency table: S2 - Cr (MethKi database final time 3.sta) Shapiro-Wilk W=,96982, p=,83574						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
1,800000<x<=2,000000	1	1	6,25000	6,2500	6,25000	6,2500
2,000000<x<=2,200000	0	1	0,00000	6,2500	0,00000	6,2500
2,200000<x<=2,400000	2	3	12,50000	18,7500	12,50000	18,7500
2,400000<x<=2,600000	6	9	37,50000	56,2500	37,50000	56,2500
2,600000<x<=2,800000	4	13	25,00000	81,2500	25,00000	81,2500
2,800000<x<=3,000000	3	16	18,75000	100,0000	18,75000	100,0000
Missing	0	16	0,00000		0,00000	100,0000

PCr - time point 1

Frequency table: S1 - PCr (MethKi database final time 3.sta) Shapiro-Wilk W = .98011, p = .97024						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
2,000000<x<=2,200000	1	1	6,66667	6,6667	6,25000	6,2500
2,200000<x<=2,400000	2	3	13,33333	20,0000	12,50000	18,7500
2,400000<x<=2,600000	2	5	13,33333	33,3333	12,50000	31,2500
2,600000<x<=2,800000	3	8	20,00000	53,3333	18,75000	50,0000
2,800000<x<=3,000000	3	11	20,00000	73,3333	18,75000	68,7500
3,000000<x<=3,200000	2	13	13,33333	86,6667	12,50000	81,2500
3,200000<x<=3,400000	1	14	6,66667	93,3333	6,25000	87,5000
3,400000<x<=3,600000	1	15	6,66667	100,0000	6,25000	93,7500
Missing	1	16	6,66667		6,25000	100,0000

PCr - time point 2

Frequency table: S2 - PCr (MethKi database final time 3.sta) Shapiro-Wilk W = .94843, p = .46524						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
2,000000<x<=2,200000	1	1	6,25000	6,2500	6,25000	6,2500
2,200000<x<=2,400000	1	2	6,25000	12,5000	6,25000	12,5000
2,400000<x<=2,600000	3	5	18,75000	31,2500	18,75000	31,2500
2,600000<x<=2,800000	1	6	6,25000	37,5000	6,25000	37,5000
2,800000<x<=3,000000	7	13	43,75000	81,2500	43,75000	81,2500
3,000000<x<=3,200000	2	15	12,50000	93,7500	12,50000	93,7500
3,200000<x<=3,400000	0	15	0,00000	93,7500	0,00000	93,7500
3,400000<x<=3,600000	1	16	6,25000	100,0000	6,25000	100,0000
Missing	0	16	0,00000		0,00000	100,0000

Glu - time point 1

Frequency table: S1 - Glu (MethKi database final time 3.sta) Shapiro-Wilk W=,96533, p=,75850						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
7,600000<x<=7,800000	1	1	6,25000	6,2500	6,25000	6,2500
7,800000<x<=8,000000	1	2	6,25000	12,5000	6,25000	12,5000
8,000000<x<=8,200000	1	3	6,25000	18,7500	6,25000	18,7500
8,200000<x<=8,400000	3	6	18,75000	37,5000	18,75000	37,5000
8,400000<x<=8,600000	2	8	12,50000	50,0000	12,50000	50,0000
8,600000<x<=8,800000	3	11	18,75000	68,7500	18,75000	68,7500
8,800000<x<=9,000000	3	14	18,75000	87,5000	18,75000	87,5000
9,000000<x<=9,200000	1	15	6,25000	93,7500	6,25000	93,7500
9,200000<x<=9,400000	1	16	6,25000	100,0000	6,25000	100,0000
Missing	0	16	0,00000		0,00000	100,0000

Glu - time point 2

Frequency table: S2 - Glu (MethKi database final time 3.sta) Shapiro-Wilk W=,98629, p=,99453						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
7,000000<x<=7,500000	0	0	0,00000	0,0000	0,00000	0,0000
7,500000<x<=8,000000	2	2	12,50000	12,5000	12,50000	12,5000
8,000000<x<=8,500000	4	6	25,00000	37,5000	25,00000	37,5000
8,500000<x<=9,000000	4	10	25,00000	62,5000	25,00000	62,5000
9,000000<x<=9,500000	4	14	25,00000	87,5000	25,00000	87,5000
9,500000<x<=10,00000	2	16	12,50000	100,0000	12,50000	100,0000
Missing	0	16	0,00000		0,00000	100,0000

GPC - time point 1

Frequency table: S1 - GPC (MethKi database final time 3.sta) Shapiro-Wilk W=,97274, p=,88080						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
,8000000<x<=,9000000	1	1	6,25000	6,2500	6,25000	6,2500
,9000000<x<=1,000000	3	4	18,75000	25,0000	18,75000	25,0000
1,000000<x<=1,100000	4	8	25,00000	50,0000	25,00000	50,0000
1,100000<x<=1,200000	4	12	25,00000	75,0000	25,00000	75,0000
1,200000<x<=1,300000	3	15	18,75000	93,7500	18,75000	93,7500
1,300000<x<=1,400000	1	16	6,25000	100,0000	6,25000	100,0000
Missing	0	16	0,00000		0,00000	100,0000

GPC - time point 2

Frequency table: S2 - GPC (MethKi database final time 3.sta) Shapiro-Wilk W=,93114, p=,31651						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
,9000000<x<=,9500000	1	1	7,14286	7,1429	6,25000	6,2500
,9500000<x<=1,000000	1	2	7,14286	14,2857	6,25000	12,5000
1,000000<x<=1,050000	4	6	28,57143	42,8571	25,00000	37,5000
1,050000<x<=1,100000	1	7	7,14286	50,0000	6,25000	43,7500
1,100000<x<=1,150000	1	8	7,14286	57,1429	6,25000	50,0000
1,150000<x<=1,200000	4	12	28,57143	85,7143	25,00000	75,0000
1,200000<x<=1,250000	1	13	7,14286	92,8571	6,25000	81,2500
1,250000<x<=1,300000	1	14	7,14286	100,0000	6,25000	87,5000
Missing	2	16	14,28571		12,50000	100,0000

Ins – time point 1

Frequency table: S1 - Ins (MethKi database final time 3.sta) Shapiro-Wilk W=,93701, p=,31394						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
4,400000<x<=4,600000	0	0	0,00000	0,0000	0,00000	0,0000
4,600000<x<=4,800000	1	1	6,25000	6,2500	6,25000	6,2500
4,800000<x<=5,000000	3	4	18,75000	25,0000	18,75000	25,0000
5,000000<x<=5,200000	2	6	12,50000	37,5000	12,50000	37,5000
5,200000<x<=5,400000	2	8	12,50000	50,0000	12,50000	50,0000
5,400000<x<=5,600000	3	11	18,75000	68,7500	18,75000	68,7500
5,600000<x<=5,800000	2	13	12,50000	81,2500	12,50000	81,2500
5,800000<x<=6,000000	3	16	18,75000	100,0000	18,75000	100,0000
Missing	0	16	0,00000		0,00000	100,0000

Ins – time point 2

Frequency table: S2 - Ins (MethKi database final time 3.sta) Shapiro-Wilk W=,95707, p=,60909						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
4,000000<x<=4,500000	1	1	6,25000	6,2500	6,25000	6,2500
4,500000<x<=5,000000	1	2	6,25000	12,5000	6,25000	12,5000
5,000000<x<=5,500000	8	10	50,00000	62,5000	50,00000	62,5000
5,500000<x<=6,000000	4	14	25,00000	87,5000	25,00000	87,5000
6,000000<x<=6,500000	2	16	12,50000	100,0000	12,50000	100,0000
Missing	0	16	0,00000		0,00000	100,0000

NAA – time point 1

Frequency table: S1 - NAA (MethKi database final time 3.sta) Shapiro-Wilk W=,96305, p=,71730						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
5,400000<x<=5,600000	0	0	0,00000	0,0000	0,00000	0,0000
5,600000<x<=5,800000	1	1	6,25000	6,2500	6,25000	6,2500
5,800000<x<=6,000000	3	4	18,75000	25,0000	18,75000	25,0000
6,000000<x<=6,200000	7	11	43,75000	68,7500	43,75000	68,7500
6,200000<x<=6,400000	2	13	12,50000	81,2500	12,50000	81,2500
6,400000<x<=6,600000	2	15	12,50000	93,7500	12,50000	93,7500
6,600000<x<=6,800000	1	16	6,25000	100,0000	6,25000	100,0000
Missing	0	16	0,00000		0,00000	100,0000

NAA – time point 2

Frequency table: S2 - NAA (MethKi database final time 3.sta) Shapiro-Wilk W=,94394, p=,40007						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
6,100000<x<=6,200000	0	0	0,00000	0,0000	0,00000	0,0000
6,200000<x<=6,300000	4	4	25,00000	25,0000	25,00000	25,0000
6,300000<x<=6,400000	1	5	6,25000	31,2500	6,25000	31,2500
6,400000<x<=6,500000	3	8	18,75000	50,0000	18,75000	50,0000
6,500000<x<=6,600000	5	13	31,25000	81,2500	31,25000	81,2500
6,600000<x<=6,700000	1	14	6,25000	87,5000	6,25000	87,5000
6,700000<x<=6,800000	2	16	12,50000	100,0000	12,50000	100,0000
Missing	0	16	0,00000		0,00000	100,0000

GPC+PCh - time point 1

Frequency table: S1 - GPC+PCh (MethKi database final time 3.sta) Shapiro-Wilk W=,97274, p=,88080						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
,8000000<x<=,9000000	1	1	6,25000	6,2500	6,25000	6,2500
,9000000<x<=1,000000	3	4	18,75000	25,0000	18,75000	25,0000
1,000000<x<=1,100000	4	8	25,00000	50,0000	25,00000	50,0000
1,100000<x<=1,200000	4	12	25,00000	75,0000	25,00000	75,0000
1,200000<x<=1,300000	3	15	18,75000	93,7500	18,75000	93,7500
1,300000<x<=1,400000	1	16	6,25000	100,0000	6,25000	100,0000
Missing	0	16	0,00000		0,00000	100,0000

GPC+PCh - time point 2

Frequency table: S2 - GPC+PCh (MethKi database final time 3.sta) Shapiro-Wilk W=,94043, p=,35431						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
,9000000<x<=,9500000	1	1	6,25000	6,2500	6,25000	6,2500
,9500000<x<=1,000000	1	2	6,25000	12,5000	6,25000	12,5000
1,000000<x<=1,050000	5	7	31,25000	43,7500	31,25000	43,7500
1,050000<x<=1,100000	2	9	12,50000	56,2500	12,50000	56,2500
1,100000<x<=1,150000	1	10	6,25000	62,5000	6,25000	62,5000
1,150000<x<=1,200000	4	14	25,00000	87,5000	25,00000	87,5000
1,200000<x<=1,250000	1	15	6,25000	93,7500	6,25000	93,7500
1,250000<x<=1,300000	1	16	6,25000	100,0000	6,25000	100,0000
Missing	0	16	0,00000		0,00000	100,0000

NAA+NAAG – time point 1

Frequency table: S1 - NAA+NAAG (MethKi database final time 3.sta) Shapiro-Wilk W=,90689, p=,10368						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
5,800000<x<=6,000000	0	0	0,00000	0,0000	0,00000	0,0000
6,000000<x<=6,200000	1	1	6,25000	6,2500	6,25000	6,2500
6,200000<x<=6,400000	6	7	37,50000	43,7500	37,50000	43,7500
6,400000<x<=6,600000	5	12	31,25000	75,0000	31,25000	75,0000
6,600000<x<=6,800000	2	14	12,50000	87,5000	12,50000	87,5000
6,800000<x<=7,000000	1	15	6,25000	93,7500	6,25000	93,7500
7,000000<x<=7,200000	0	15	0,00000	93,7500	0,00000	93,7500
7,200000<x<=7,400000	1	16	6,25000	100,0000	6,25000	100,0000
Missing	0	16	0,00000		0,00000	100,0000

NAA+NAAG – time point 2

Frequency table: S2 - NAA+NAAG (MethKi database final time 3.sta) Shapiro-Wilk W=,96080, p=,67636						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
6,000000<x<=6,200000	0	0	0,00000	0,0000	0,00000	0,0000
6,200000<x<=6,400000	3	3	18,75000	18,7500	18,75000	18,7500
6,400000<x<=6,600000	3	6	18,75000	37,5000	18,75000	37,5000
6,600000<x<=6,800000	6	12	37,50000	75,0000	37,50000	75,0000
6,800000<x<=7,000000	3	15	18,75000	93,7500	18,75000	93,7500
7,000000<x<=7,200000	0	15	0,00000	93,7500	0,00000	93,7500
7,200000<x<=7,400000	1	16	6,25000	100,0000	6,25000	100,0000
Missing	0	16	0,00000		0,00000	100,0000

Cr+PCr - time point 1

Frequency table: S1 - Cr+PCr (MethKi database final time 3.sta) Shapiro-Wilk W=,97068, p=,84948					
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases
4,900000<x<=5,000000	2	2	12,50000	12,5000	12,50000
5,000000<x<=5,100000	2	4	12,50000	25,0000	12,50000
5,100000<x<=5,200000	3	7	18,75000	43,7500	18,75000
5,200000<x<=5,300000	3	10	18,75000	62,5000	18,75000
5,300000<x<=5,400000	3	13	18,75000	81,2500	18,75000
5,400000<x<=5,500000	1	14	6,25000	87,5000	6,25000
5,500000<x<=5,600000	2	16	12,50000	100,0000	12,50000
Missing	0	16	0,00000		0,00000
					100,0000

Cr+PCr - time point 2

Frequency table: S2 - Cr+PCr (MethKi database final time 3.sta) Shapiro-Wilk W=,95341, p=,54552					
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases
4,600000<x<=4,800000	0	0	0,00000	0,0000	0,00000
4,800000<x<=5,000000	2	2	12,50000	12,5000	12,50000
5,000000<x<=5,200000	3	5	18,75000	31,2500	18,75000
5,200000<x<=5,400000	4	9	25,00000	56,2500	25,00000
5,400000<x<=5,600000	4	13	25,00000	81,2500	25,00000
5,600000<x<=5,800000	0	13	0,00000	81,2500	0,00000
5,800000<x<=6,000000	3	16	18,75000	100,0000	18,75000
Missing	0	16	0,00000		0,00000
					100,0000

Glu+ Gln – time point 1

Frequency table: S1 - Glu+Gln (MethKi database final time 3.sta) Shapiro-Wilk W=,92916, p=,23639						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
8,000000<x<=8,500000	1	1	6,25000	6,2500	6,25000	6,2500
8,500000<x<=9,000000	3	4	18,75000	25,0000	18,75000	25,0000
9,000000<x<=9,500000	0	4	0,00000	25,0000	0,00000	25,0000
9,500000<x<=10,00000	3	7	18,75000	43,7500	18,75000	43,7500
10,00000<x<=10,50000	6	13	37,50000	81,2500	37,50000	81,2500
10,50000<x<=11,00000	1	14	6,25000	87,5000	6,25000	87,5000
11,00000<x<=11,50000	0	14	0,00000	87,5000	0,00000	87,5000
11,50000<x<=12,00000	2	16	12,50000	100,0000	12,50000	100,0000
Missing	0	16	0,00000		0,00000	100,0000

Glu+Gln – time point 2

Frequency table: S2 - Glu+Gln (MethKi database final time 3.sta) Shapiro-Wilk W=,91559, p=,14324						
Category	Count	Cumulative Count	Percent of Valid	Cumul % of Valid	% of all Cases	Cumulative % of All
8,500000<x<=9,000000	1	1	6,25000	6,2500	6,25000	6,2500
9,000000<x<=9,500000	5	6	31,25000	37,5000	31,25000	37,5000
9,500000<x<=10,00000	2	8	12,50000	50,0000	12,50000	50,0000
10,00000<x<=10,50000	0	8	0,00000	50,0000	0,00000	50,0000
10,50000<x<=11,00000	5	13	31,25000	81,2500	31,25000	81,2500
11,00000<x<=11,50000	0	13	0,00000	81,2500	0,00000	81,2500
11,50000<x<=12,00000	3	16	18,75000	100,0000	18,75000	100,0000
Missing	0	16	0,00000		0,00000	100,0000

Repeated measures ANOVA + Bonferroni correction (where applicable)
Demographics
Age

Repeated Measures Analysis of Variance (MethKi database final time 3.sta)		Sigma-restricted parameterization		Effective hypothesis decomposition	
Effect	SS	Degr. of Freedom	MS	F	p
Intercept	1654,197	1	1654,197	4992,724	0,000000
Main Diagnosis	0,000	1	0,000	0,001	0,974531
Error	4,639	14	0,331		
TIME	19,549	1	19,549	595,291	0,000000
TIME*Main Diagnosis	0,122	1	0,122	3,714	0,074508
Error	0,460	14	0,033		

Bonferroni test; variable DV_1 (MethKi database final time 3.sta) Probabilities for Post Hoc Tests Error: Within MS = ,03284, df = 14,000					
Cell No.	TIME		{1}	{2}	
			6,4662	8,0263	
	S1 - Age			0,000000	
2	S2 - Age		0,000000		

Weight

Repeated Measures Analysis of Variance (MethKi database final time 3.sta)		Sigma-restricted parameterization		Effective hypothesis decomposition	
Effect	SS	Degr. of Freedom	MS	F	p
Intercept	13826,48	1	13826,48	787,1327	0,000000
Main Diagnosis	3,72	1	3,72	0,2118	0,652443
Error	245,92	14	17,57		
TIME	107,25	1	107,25	145,0185	0,000000
TIME*Main Diagnosis	0,83	1	0,83	1,1164	0,308578
Error	10,35	14	0,74		

Bonferroni test; variable DV_1 (MethKi database final time 3.sta) Probabilities for Post Hoc Tests Error: Within MS = ,73959, df = 14,000			
Cell No.	TIME	{1} 19,169	{2} 22,819
1	Child weight Scan 1		0,000000
2	Child weight Scan 2	0,000000	

Height

Repeated Measures Analysis of Variance (MethKi database final time 3.sta) Sigma-restricted parameterization Effective hypothesis decomposition					
Effect	SS	Degr. of Freedom	MS	F	p
Intercept	41,43767	1	41,43767	5790,979	0,000000
Main Diagnosis	0,00204	1	0,00204	0,286	0,601397
Error	0,10018	14	0,00716		
TIME	0,22823	1	0,22823	59,643	0,000002
TIME*Main Diagnosis	0,00225	1	0,00225	0,588	0,455887
Error	0,05357	14	0,00383		

Bonferroni test; variable DV_1 (MethKi database final time 3.sta) Probabilities for Post Hoc Tests Error: Within MS = ,00383, df = 14,000			
Cell No.	TIME	{1} 1,0619	{2} 1,2300
1	Child height Scan 1		0,000002
2	Child height Scan 2	0,000002	

BMI

Repeated Measures Analysis of Variance (MethKi database final time 3.sta) Sigma-restricted parameterization Effective hypothesis decomposition					
Effect	SS	Degr. of Freedom	MS	F	p
Intercept	8175,508	1	8175,508	649,3770	0,000000
Main Diagnosis	7,458	1	7,458	0,5924	0,454302
Error	176,257	14	12,590		
TIME	37,134	1	37,134	12,7891	0,003039
TIME*Main Diagnosis	0,032	1	0,032	0,0110	0,917774
Error	40,650	14	2,904		

Bonferroni test; variable DV_1 (MethKi database final time 3.sta) Probabilities for Post Hoc Tests Error: Within MS = 2,9036, df = 14,000	
Cell No.	TIME
1	BMI Scan 1
2	BMI Scan 2

Repeated measures ANOVA + Bonferroni correction (where applicable)
 Neurocognitive tasks
 Block Counting raw score

Repeated Measures Analysis of Variance (MethKi database final time 3.sta) Sigma-restricted parameterization Effective hypothesis decomposition				
Effect	SS	Degr. of Freedom	MS	F
Intercept	1881,469	1	1881,469	39,08387
Main Diagnosis	119,025	1	119,025	2,47251
Error	336,975	7	48,139	
TIME	42,025	1	42,025	3,26952
TIME*Main Diagnosis	0,469	1	0,469	0,03652
Error	89,975	7	12,854	

Block Counting scaled score

Repeated Measures Analysis of Variance (MethKi database final time 3.sta) Sigma-restricted parameterization Effective hypothesis decomposition				
Effect	SS	Degr. of Freedom	MS	F
Intercept	1404,225	1	1404,225	75,16402
Main Diagnosis	39,336	1	39,336	2,10555
Error	130,775	7	18,682	
TIME	0,069	1	0,069	0,01457
TIME*Main Diagnosis	0,069	1	0,069	0,01457
Error	33,375	7	4,768	

Pattern Reasoning raw score

Repeated Measures Analysis of Variance (MethKi database final time 3.sta) Sigma-restricted parameterization Effective hypothesis decomposition					
Effect	SS	Degr. of Freedom	MS	F	p
Intercept	1819,060	1	1819,060	158,0233	0,000000
Main Diagnosis	34,310	1	34,310	2,9805	0,106261
Error	161,159	14	11,511		
TIME	61,810	1	61,810	31,8623	0,000060
TIME*Main Diagnosis	34,310	1	34,310	17,6864	0,000881
Error	27,159	14	1,940		

Bonferroni test; variable DV_1 (MethKi database final time 3.sta) Probabilities for Post Hoc Tests Error: Within MS = 1,9399, df = 14,000					
Cell No.	TIME		{1}	{2}	
1	Pattern Reasoning RS No Tmpt S1		5,9375		0,000022
2	Pattern Reasoning RS No Tmpt S2		0,000022		

Bonferroni test; variable DV_1 (MethKi database final time 3.sta) Probabilities for Post Hoc Tests Error: Between; Within; Pooled MS = 6,7256, df = 18,588						
Cell No.	Main Diagnosis	TIME	{1}	{2}	{3}	{4}
1	Control	Pattern Reasoning RS No Tmpt S1	8,2857	9,0000	4,1111	9,0000
2	Control	Pattern Reasoning RS No Tmpt S2	1,000000	1,000000	0,029251	1,000000
3	Meth	Pattern Reasoning RS No Tmpt S1	0,029251	0,008573		0,000019
4	Meth	Pattern Reasoning RS No Tmpt S2	1,000000	1,000000	0,000019	

Pattern Reasoning scaled score

Repeated Measures Analysis of Variance (MethKi database final time 3.sta) Sigma-restricted parameterization Effective hypothesis decomposition					
Effect	SS	Degr. of Freedom	MS	F	p
Intercept	1426,794	1	1426,794	174,9037	0,000000
Main Diagnosis	22,294	1	22,294	2,7329	0,120543
Error	114,206	14	8,158		
TIME	0,097	1	0,097	0,0442	0,836468
TIME*Main Diagnosis	28,097	1	28,097	12,7807	0,003046
Error	30,778	14	2,198		

Bonferroni test; variable DV_1 (MethKi database final time 3.sta) Probabilities for Post Hoc Tests Error: Between; Pooled MS = 5,1780, df = 21,035						
Cell No.	Main Diagnosis	TIME	{1}	{2}	{3}	{4}
1	Control	Pattern Reasoning SCS No Tmpt S1	8,5714	6,5714	5,0000	6,7778
2	Control	Pattern Reasoning SCS No Tmpt S2	0,146002	0,146002	0,031435	0,796276
3	Meth	Pattern Reasoning SCS No Tmpt S1	0,031435	1,000000	1,000000	1,000000
4	Meth	Pattern Reasoning SCS No Tmpt S2	0,796276	1,000000	0,140468	

Atlantis raw score

Repeated Measures Analysis of Variance (MethKi database final time 3.sta) Sigma-restricted parameterization Effective hypothesis decomposition					
Effect	SS	Degr. of Freedom	MS	F	p
Intercept	107406,4	1	107406,4	595,0827	0,000000
Main Diagnosis	25,1	1	25,1	0,1391	0,714734
Error	2526,9	14	180,5		
TIME	2859,5	1	2859,5	11,8919	0,003917
TIME*Main Diagnosis	962,5	1	962,5	4,0028	0,065203
Error	3366,4	14	240,5		

Bonferroni test; variable DV_1 (MethKi database final time 3.sta) Probabilities for Post Hoc Tests Error: Within MS = 240,46, df = 14,000					
Cell No.	TIME		{1}	{2}	
			48,063	68,500	
	Atlantis RS S1	Atlantis RS S2		0,002250	
1				0,002250	
2					

Atlantis scaled score

Repeated Measures Analysis of Variance (MethKi database final time 3.sta) Sigma-restricted parameterization Effective hypothesis decomposition					
Effect	SS	Degr. of Freedom	MS	F	p
Intercept	1664,794	1	1664,794	414,6704	0,000000
Main Diagnosis	0,794	1	0,794	0,1977	0,663393
Error	56,206	14	4,015		
TIME	11,161	1	11,161	2,2096	0,159325
TIME*Main Diagnosis	17,161	1	17,161	3,3975	0,086567
Error	70,714	14	5,051		

Atlantis Delayed raw score

Repeated Measures Analysis of Variance (MethKi database final time 3.sta) Sigma-restricted parameterization Effective hypothesis decomposition					
Effect	SS	Degr. of Freedom	MS	F	p
Intercept	3296,669	1	3296,669	284,5349	0,000000
Main Diagnosis	0,794	1	0,794	0,0685	0,797345
Error	162,206	14	11,586		
TIME	30,018	1	30,018	1,5458	0,234168
TIME*Main Diagnosis	103,143	1	103,143	5,3116	0,037019
Error	271,857	14	19,418		

Bonferroni test; variable DV_1 (MethKi database final time 3.sta) Probabilities for Post Hoc Tests Error: Between; Within; Pooled MS = 15,502, df = 26,320					
Cell No.	Main Diagnosis	TIME	{1} 12,857	{2} 7,2857	{3} 9,5556
1	Control	Atlantis Delay RS S1		0,197903	0,647933
2	Control	Atlantis Delay RS S2	0,197903		1,000000
3	Meth	Atlantis Delay RS S1	0,647933	1,000000	
4	Meth	Atlantis Delay RS S2	1,000000	0,346710	1,000000

Atlantis Delayed scaled score

Repeated Measures Analysis of Variance (MethKi database final time 3.sta) Sigma-restricted parameterization Effective hypothesis decomposition					
Effect	SS	Degr. of Freedom	MS	F	p
Intercept	1820,960	1	1820,960	525,2083	0,000000
Main Diagnosis	0,960	1	0,960	0,2770	0,606926
Error	48,540	14	3,467		
TIME	21,050	1	21,050	4,4099	0,054335
TIME*Main Diagnosis	34,050	1	34,050	7,1334	0,018270
Error	66,825	14	4,773		

Bonferroni test; variable DV_1 (MethKi database final time 3.sta) Probabilities for Post Hoc Tests Error: Between; Within; Pooled MS = 4,1202, df = 27,314						
Cell No.	Main Diagnosis	TIME	{1} 9,2857	{2} 5,5714	{3} 7,5556	{4} 8,0000
1	Control	Atlantis Delay SCS S1		0,040042	0,612884	1,000000
2	Control	Atlantis Delay SCS S2	0,040042		0,376890	0,149231
3	Meth	Atlantis Delay SCS S1	0,612884	0,376890		1,000000
4	Meth	Atlantis Delay SCS S2	1,000000	0,149231	1,000000	

Boston Naming Test - total score

Repeated Measures Analysis of Variance (MethKi database final time 3.sta) Sigma-restricted parameterization Effective hypothesis decomposition					
Effect	SS	Degr. of Freedom	MS	F	p
Intercept	1771,875	1	1771,875	1033,594	0,000000
Main Diagnosis		1			
Error	24,000	14	1,714		
TIME	4,960	1	4,960	5,538	0,033751
TIME*Main Diagnosis	3,335	1	3,335	3,724	0,074161
Error	12,540	14	0,896		

Bonferroni test; variable DV_1 (MethKi database final time 3.sta) Probabilities for Post Hoc Tests Error: Within MS = ,89569, df = 14,000	
Cell No.	TIME
1	Total BNT S1
2	Total BNT S2

Repeated measures ANOVA + Bonferroni correction (where applicable)
Metabolites
Cr

Repeated Measures Analysis of Variance (MethKi database final time 3.sta) Sigma-restricted parameterization Effective hypothesis decomposition					
Effect	SS	Degr. of Freedom	MS	F	p
Intercept	193,5706	1	193,5706	1467,138	0,000000
Main Diagnosis	0,2774	1	0,2774	2,102	0,170767
Error	1,7152	13	0,1319		
TIME	0,0001	1	0,0001	0,001	0,980012
TIME*Main Diagnosis	0,1166	1	0,1166	0,920	0,354956
Error	1,6480	13	0,1268		

PCr

Repeated Measures Analysis of Variance (MethKi database final time 3.sta) Sigma-restricted parameterization Effective hypothesis decomposition					
Effect	SS	Degr. of Freedom	MS	F	p
Intercept	223,8452	1	223,8452	1892,365	0,000000
Main Diagnosis	0,0090	1	0,0090	0,076	0,786977
Error	1,5378	13	0,1183		
TIME	0,0001	1	0,0001	0,000	0,985992
TIME*Main Diagnosis	0,0136	1	0,0136	0,084	0,777044
Error	2,1215	13	0,1632		

Glu

Repeated Measures Analysis of Variance (MethKi database final time 3.sta) Sigma-restricted parameterization Effective hypothesis decomposition					
Effect	SS	Degr. of Freedom	MS	F	p
Intercept	2358,081	1	2358,081	5188,511	0,000000
Main Diagnosis	0,060	1	0,060	0,133	0,720863
Error	6,363	14	0,454		
TIME	0,282	1	0,282	1,607	0,225620
TIME*Main Diagnosis	0,026	1	0,026	0,149	0,705722
Error	2,456	14	0,175		

GPC

Repeated Measures Analysis of Variance (MethKi database final time 3.sta) Sigma-restricted parameterization Effective hypothesis decomposition					
Effect	SS	Degr. of Freedom	MS	F	p
Intercept	30,98838	1	30,98838	1776,188	0,000000
Main Diagnosis	0,02341	1	0,02341	1,342	0,269255
Error	0,20936	12	0,01745		
TIME	0,00257	1	0,00257	0,518	0,485378
TIME*Main Diagnosis	0,07608	1	0,07608	15,316	0,002059
Error	0,05961	12	0,00497		

Bonferroni test; variable DV_1 (MethKi database final time 3.sta) Probabilities for Post Hoc Tests Error: Between; Within; Pooled MS = ,01121, df = 18,321					
Cell No.	Main Diagnosis	TIME	{1} 1,0032	{2} 1,1320	{3} 1,1723
1	Control	S1 - GPC		0,081532	0,061080
2	Control	S2 - GPC	0,081532		1,000000
3	Meth	S1 - GPC	0,061080	1,000000	
4	Meth	S2 - GPC	1,000000	1,000000	0,121996

Ins

Repeated Measures Analysis of Variance (MethKi database final time 3.sta) Sigma-restricted parameterization Effective hypothesis decomposition					
Effect	SS	Degr. of Freedom	MS	F	p
Intercept	914,3409	1	914,3409	4271,874	0,000000
Main Diagnosis	0,0565	1	0,0565	0,264	0,615370
Error	2,9965	14	0,2140		
TIME	0,1140	1	0,1140	0,802	0,385648
TIME*Main Diagnosis	0,1054	1	0,1054	0,741	0,403855
Error	1,9907	14	0,1422		

NAA

Repeated Measures Analysis of Variance (MethKi database final time 3.sta) Sigma-restricted parameterization Effective hypothesis decomposition					
Effect	SS	Degr. of Freedom	MS	F	p
Intercept	1253,013	1	1253,013	23692,24	0,000000
Main Diagnosis	0,012	1	0,012	0,23	0,636717
Error	0,740	14	0,053		
TIME	0,677	1	0,677	16,59	0,001141
TIME*Main Diagnosis	0,073	1	0,073	1,78	0,203256
Error	0,571	14	0,041		

Bonferroni test; variable DV_1 (MethKi database final time 3.sta) Probabilities for Post Hoc Tests Error: Within MS = ,04081, df = 14,000			
Cell No.	TIME	{1} 6,1689	{2} 6,4501
1	S1 - NAA		0,001490
2	S2 - NAA	0,001490	

GPC+PCh

Repeated Measures Analysis of Variance (MethKi database final time 3.sta) Sigma-restricted parameterization Effective hypothesis decomposition					
Effect	SS	Degr. of Freedom	MS	F	p
Intercept	37,87832	1	37,87832	2522,719	0,000000
Main Diagnosis	0,03099	1	0,03099	2,064	0,172797
Error	0,21021	14	0,01501		
TIME	0,00002	1	0,00002	0,003	0,959934
TIME*Main Diagnosis	0,06404	1	0,06404	10,901	0,005245
Error	0,08224	14	0,00587		

Bonferroni test; variable DV_1 (MethKi database final time 3.sta) Probabilities for Post Hoc Tests Error: Between; Within; Pooled MS = ,01044, df = 23,500						
Cell No.	Main Diagnosis	TIME	{1} 1,0194	{2} 1,1110	{3} 1,1723	{4} 1,0836
1	Control	S1 - GPC+PCh		0,253299	0,040656	1,000000
2	Control	S2 - GPC+PCh	0,253299		1,000000	1,000000
3	Meth	S1 - GPC+PCh	0,040656	1,000000		0,165969
4	Meth	S2 - GPC+PCh	1,000000	1,000000	0,165969	

NAA+NAAG

Repeated Measures Analysis of Variance (MethKi database final time 3.sta) Sigma-restricted parameterization Effective hypothesis decomposition					
Effect	SS	Degr. of Freedom	MS	F	p
Intercept	1360,616	1	1360,616	17346,37	0,000000
Main Diagnosis	0,104	1	0,104	1,33	0,268975
Error	1,098	14	0,078		
TIME	0,313	1	0,313	4,40	0,054595
TIME*Main Diagnosis	0,061	1	0,061	0,86	0,370232
Error	0,996	14	0,071		

Cr+PCr

Effect	Repeated Measures Analysis of Variance (MethKi database final time 3.sta) Sigma-restricted parameterization Effective hypothesis decomposition				
	SS	Degr. of Freedom	MS	F	p
Intercept	889,1784	1	889,1784	9003,427	0,000000
Main Diagnosis	0,0581	1	0,0581	0,588	0,455928
Error	1,3826	14	0,0988		
TIME	0,1173	1	0,1173	3,150	0,097682
TIME*Main Diagnosis	0,0243	1	0,0243	0,651	0,433138
Error	0,5215	14	0,0373		

Glu+Gln

Effect	Repeated Measures Analysis of Variance (MethKi database final time 3.sta) Sigma-restricted parameterization Effective hypothesis decomposition				
	SS	Degr. of Freedom	MS	F	p
Intercept	3206,867	1	3206,867	2137,883	0,000000
Main Diagnosis	0,350	1	0,350	0,233	0,636685
Error	21,000	14	1,500		
TIME	0,622	1	0,622	1,366	0,262009
TIME*Main Diagnosis	0,308	1	0,308	0,676	0,424671
Error	6,372	14	0,455		