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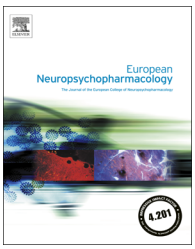

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Cluster analysis reveals abnormal hippocampal neurometabolic profiles in young people with mood disorders

Daniel F. Hermens*, Sharon L. Naismith, Kate M. Chitty, Rico S.C. Lee, Ashleigh Tickell, Shantel L. Duffy, Casey Paquola, Django White, Ian B. Hickie, Jim Lagopoulos

Clinical Research Unit, Brain and Mind Research Institute, University of Sydney, Australia

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Abstract
While numerous studies have employed magnetic resonance spectroscopy (MRS) to determine *in vivo* neurometabolite levels associated with mood disorders the findings in both unipolar depression and bipolar disorder have been mixed. Data-driven studies may shed new light on this literature by identifying distinct subgroups of patients who may benefit from different treatment strategies. The objective of the present study was to utilize hierarchical cluster analysis in order to generate new hypotheses with respect to neurometabolic profiling of mood disorder. Participants were 165 young persons (18–30 yrs) with a mood disorder and 40 healthy controls. Neurometabolite levels were recorded via proton-MRS (^{1}H MRS). The ratios (relative to creatine) of glutamate (GLU), N-acetyl aspartate (NAA) and *myo*-inositol (MI) measured within the hippocampus. Self-reported and clinician rated symptoms as well as cognition were also measured. The unipolar depression (N=90) and bipolar disorder (N=75) groups did not significantly differ (from each other or controls) in their levels of GLU, NAA or MI. Cluster analyses derived four subgroups of patients who were distinguished by all three metabolites. There was a pattern of positive association between NAA and GLU, whereby clusters were abnormally increased (clusters 1, 2) or normal (cluster 4) or abnormally decreased (cluster 3) in these neurometabolites. These findings suggest that there are neurometabolic abnormalities in subgroups of young people with mood disorder, which may occur despite diagnostic similarities. Such evidence highlights that the underlying neurobiology of mood disorder is complex and MRS may have unique utility in delineating underlying neurobiology and targeting treatment strategies.

*Correspondence to: Clinical Research Unit, Brain and Mind Research Institute, University of Sydney, 100 Mallett Street, Camperdown, NSW 2050, Australia. Tel.: +61 2 93510529; fax: +61 2 93510652.
E-mail address: daniel.hermens@sydney.edu.au (D.F. Hermens).

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1. Introduction

As a means to assess *in vivo* neurochemistry, proton magnetic resonance spectroscopy (^{1}H MRS) has provided unique insights into the neurobiology of psychiatric conditions (Bustillo, 2013), particularly at early stages (Hermens et al., 2012), since changes in neurometabolites often precede gross structural changes. Three of the most commonly examined neurometabolites in ^{1}H MRS-based studies of psychiatric illnesses are glutamate (GLU), N-acetylaspartate (NAA) and *myo*-inositol (MI). GLU is the most abundant amino acid in the brain and its primary function is to facilitate excitatory neurotransmission (Sanacora et al., 2012). The second most concentrated amino acid, NAA, is almost exclusively located within neurons and axons and is thought to reflect neuronal viability, integrity and/or functionality (Bustillo, 2013; Reynolds and Reynolds, 2011). In contrast, MI is found in glial cells and increased concentrations are thought to reflect neuroinflammation (Bustillo, 2013). These neurometabolites have been examined in numerous studies of mood disorder, although such studies have tended not to assess all three in the same individuals. This issue is further complicated by the fact that many of the earlier ^{1}H MRS studies which (for the most part) have utilized 1.5 T scanners have tended to report "GLX" (an overlapping resonance of GLU and its precursor glutamine) whereas the more recent literature, which typically involves 3 T systems, has predominantly reported GLU.

The GLU system is now being recognized as a primary mediator of mood disorder pathophysiology (Sanacora et al., 2012). Despite this, studies utilizing ^{1}H MRS in both depression and bipolar disorder have been mixed with respect to their findings of GLU (or GLX) levels in various brain structures. More specifically, ^{1}H MRS studies of depression have shown decreased frontal (Auer et al., 2000; Hasler et al., 2007; Merkl et al., 2011), normal frontal (Taylor et al., 2009) and increased occipital (Bhagwagar et al., 2007; Sanacora et al., 2004) levels of GLU (or GLX). A recent meta-analysis (Luykx et al., 2012) concluded that reduced levels of GLU (within the anterior cingulate cortex; ACC) in major depression may be state-dependent. Whereas evidence of elevated occipital GLU in young people with increased familial risk for major depression (Taylor et al., 2011), as well as in recovered patients with a history of recurrent depression (Bhagwagar et al., 2007), supports the notion of trait vulnerability.

In bipolar disorder, the ^{1}H MRS studies are also mixed, with evidence of increased frontal (Castillo et al., 2000; Frye et al., 2007; Ongür et al., 2008), increased occipital (Bhagwagar et al., 2007) and decreased frontal (Port et al., 2008) GLU (or GLX) levels while there have also been reports of null findings in frontal (Davanzo et al., 2003; Moore et al., 2007), hippocampal (Gigante et al., 2014; Zanetti et al., 2014) and occipital (Davanzo et al., 2003) regions. A recent review (Yuksel and Ongur, 2010) has suggested that GLU may distinguish depressive from manic episodes, with reduced levels found to be consistent with the former and increased levels consistent with the latter. Our previous findings (Hermens et al., 2012) suggest that there are subgroups of patients that differ in neurochemical profiles and not necessarily their symptomatology or diagnosis. As highlighted by Sanacora et al. (2012), when taken together, these ^{1}H MRS-GLU studies significantly vary according to brain region, subtype of mood disorder, course of illness progression and phase of illness.

There have also been mixed findings with regards to NAA. In depression, several studies have reported reduced NAA levels within various brain structures, including frontal (Järnum et al., 2011; Merkl et al., 2011; Portella et al., 2011), caudate (Vythilingam et al., 2003), hippocampal (Capizzano et al., 2007) and occipital (Bhagwagar et al., 2007) regions. Null findings for NAA have been reported in frontal (Auer et al., 2000; Tae et al., 2013; Zhong et al., 2014) and hippocampal (Ende et al., 2000; Milne et al., 2009; Wang et al., 2012; Zhong et al., 2014) structures. Stage of illness may assume an important role with evidence of increased NAA in the ACC of young adults with first-episode depression compared to controls and peers with chronic illness (Portella et al., 2011) and evidence of a negative correlation reported between NAA levels and duration of illness (Tae et al., 2013). As observed in depression, numerous studies of bipolar disorder have shown significantly decreased levels of NAA in frontal (Cecil et al., 2002; Molina et al., 2007; Yildiz-Yesiloglu and Ankerst, 2006a), hippocampal (Reynolds and Reynolds, 2011; Scherk et al., 2008) and occipital (Bhagwagar et al., 2007) regions. However, null findings have also been reported in frontal (Scherk et al., 2009; Zhong et al., 2014) and hippocampal (Gigante et al., 2014; Zanetti et al., 2014; Zhong et al., 2014) regions. In contrast, higher levels of NAA have been reported in frontal regions (ACC and lateral prefrontal cortex) of bipolar disorder adolescents (Patel et al., 2008).

Additionally, there is contradictory data for MI among studies of depression and bipolar disorder. In the former, MI has been found to be decreased in frontal (Chen et al., 2014; Coupland et al., 2005; Gruber et al., 2003; Järnum et al., 2011), hippocampal (Milne et al., 2009) and cerebellar (Chen et al., 2014) structures. Null findings however have been reported in the ACC (Auer et al., 2000) while increased MI has been shown in frontal regions of those with depression (Kumar et al., 2002; Taylor et al., 2009). In bipolar disorder, null findings have been reported in frontal regions (Moore et al., 2000; Ongür et al., 2008) as well as in the hippocampus (Gigante et al., 2014; Zanetti et al., 2014) and basal ganglia (Scherk et al., 2008). However, increased MI has also been reported in frontal (Davanzo et al., 2003; Scherk et al., 2009; Yildiz-Yesiloglu and Ankerst, 2006a) and left caudate (Port et al., 2008) regions.

Given the heterogeneous findings across these studies, data-driven approaches that utilize these potential biomarkers (Hermens et al., 2012) may be an optimal method for characterizing illness phenotypes. In this study, we performed a cluster analysis utilizing the three key neurometabolites (i.e. GLU, NAA, MI) measured within the hippocampus in a large sample of young adult outpatients diagnosed with a mood (i.e. depressive or bipolar) disorder. We particularly aimed to determine the utility of such clusters by examining how they relate to key clinical, neuropsychological or functional features.