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Subcortical volumetric differences between clinical stages of young people with affective and psychotic disorders

Peta S. Eggins*, Sean N. Hatton, Daniel F. Hermens, Ian B. Hickie, Jim Lagopoulos

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

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ABSTRACT

The aim of this study was to investigate differences in subcortical and hippocampal volumes between healthy controls, young people at an early stage of affective and psychotic disorders and those in more advanced stages, to identify markers associated with functional outcomes and illness severity. Young people presenting to youth mental health services with admixtures of depressive, manic and psychotic symptoms (n = 141), and healthy counterparts (n = 49), aged 18–25 were recruited. Participants underwent magnetic resonance imaging, clinical assessments and were rated as to their current clinical stage. Eighty-four patients were classified at the attenuated syndrome stage (Stage 1b) and 57 were classified as having discrete and persistent disorders (Stage 2+). Automated segmentation was performed using NeuroQuant® to determine volumes of subcortical and hippocampus structures which were compared between groups and correlated with clinical and functional outcomes. Compared to healthy controls, Stage 2+ patients showed significantly reduced right amygdala volumes. Whereas Stage 1b patients showed significantly reduced left caudate volumes compared to healthy controls. Smaller left caudate volume correlated with greater psychological distress and impaired functioning. This study shows a clinical application for an automated program to identify and track subcortical changes evident in young people with emerging psychopathology.

1. Introduction

Affective and psychotic disorders are amongst the most common forms of mental illness affecting young people (Paus et al., 2008), leading to serious long-term disability. Symptom onset during adolescence and young adulthood is associated with a number of psychological, social and cognitive impairments (Fergusson and Woodward, 2002; Leeson et al., 2011) and increased risk of developing severe psychiatric disorders in adulthood (Pine et al., 1999; Fergusson et al., 2007). Intervention strategies may reduce and prevent such impairments by targeting young people at the earliest stages of illness. To date, however, no objective markers for targeting or tracking the progression of illness in these young people exist.

Major depression (MD), bipolar disorder (BD) and schizophrenia (SZ) have a peak age of onset during mid-to-late adolescence and early adulthood (Häfner et al., 1994; Kessler et al., 2005). Structural neuroimaging studies have focused on these disorders in adults, specifically exploring subcortical volume differences. Recently, large mega-analytical approaches pooling sample sizes greater than 4000 subjects have attempted to characterise the neuroanatomical abnormalities in these disorders in adults. A common finding in adults with MD, BD and SZ has been a reduction in hippocampal volume (Schmaal et al., 2016; van Erp et al., 2015; Hibar et al., 2016) suggesting these disorders may share common pathophysiological mechanisms associated with subcortical volume reduction.

Additionally, subcortical regions that are commonly reported to be associated with affective and schizophrenia spectrum disorders include the amygdala (Lagopoulos et al., 2013), thalamus (Strakowski et al., 1999; Ellison-Wright et al., 2008), caudate (Haijma et al., 2013) and putamen (DelBello et al., 2004). The majority of studies in this area limit investigations to only one disorder such as schizophrenia (Haijma et al., 2013), depression (Schmaal et al., 2016; Videbech and Ravnkilde, 2004) and bipolar (DelBello et al., 2004; Pfeifer et al., 2008), despite similar and often overlapping findings between disorders. Nevertheless, research investigating disorder-specific changes have revealed inconsistencies with regards to which regions are involved, the directionality

Abbreviations: ANOVA, Analysis of Variance; BD, Bipolar Disorder; BOLD, Blood-Oxygen-Level Dependent; BPRS, Brief Psychiatric Rating Scale; DSM, Diagnostic and Statistical Manual of Mental Disorders; GM, Grey Matter; HDRS, Hamilton Depression Rating Scale; ICD, International Classification of Diseases; K10, Kessler-10; SOFAS, Social and Occupational Functioning Assessment Scale; LSTC, Limbic-Striatal-Thalamo-Cortical; MANCOVA, Multivariate Analysis of Covariance; MD, Major Depression; SPSS, Statistical Package for the Social Sciences; SZ, Schizophrenia; WHO-DAS, World Health Organisation Disability Assessment Scale; WHO-QoL, World Health Organisation Quality of Life

* Correspondence to: Brain and Mind Centre, University of Sydney, 94 Mallet Street, Camperdown, NSW, 2050, Australia.
E-mail address: peta.eggins@sydney.edu.au (P.S. Eggins).

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of volumetric or functional change in these regions, and the extent to which these regions show change. Without addressing these issues, and without further our understanding of the relationship between subcortical and hippocampus changes and the symptoms and features of affective and psychotic disorders remains limited.

An important consideration when studying young people with emerging affective and psychotic disorders is the significant overlap in symptom clusters, including depression, negative symptoms, functional impairment, mania and psychosis (Häfner et al., 2008). Current classification systems alone (DSM-IV and ICD-10) are unable to reliably distinguish between these clinical phenotypes leading to unreliable diagnoses and delayed treatment intervention (Scott et al., 2013). This is evidenced by reports of misdiagnosis rates over 50% in young people with an approximate 12.5 year delay until appropriate diagnosis was made (Berk et al., 2007). It is clear that categorising these disorders into distinct diseases early in the course of illness has been ineffective. As a result, clinical staging models have been developed to characterise young people who are at risk of developing major psychiatric disorders based on disease progression and illness duration, rather than prescribed diagnostic criteria. Within these models, early clinical phenotypes, often displaying non-specific symptoms of depression, are distinguished from more severe, recurrent and persistent disorders with the motivation to prevent the progression of disease using early, stage-specific intervention strategies (Hickie et al., 2013a, 2013b; McGorry et al., 2006).

Previous research from our group and others suggest that an important point of illness progression occurs when early staged patients (Stage 1b), who display symptoms or syndromes (symptom clusters) of depression, mania and/or psychosis, with moderate social and functional impairment, transition into more advanced stages where the syndrome is manifested into a discrete and persistent disorder (Stage 2+). Differences in the neurobiology, cognition and the neuropsychological profiles of Stage 1b and Stage 2+ patients have been reported (Lagopoulos et al., 2012, 2013; Naismith et al., 2012; Hermens et al., 2013) suggesting these distinctions may be useful in identifying early biomarkers of disease, as well as predicting disease trajectory. Additionally, evidence from these findings suggests that the overlap in early symptoms in young people with emerging affective and psychotic disorders may be mirrored by similar structural and functional abnormalities in these young people.

The aim of the current study was to use a standardised analytical approach to investigate subcortical and hippocampus volumes in young people with emerging affective and psychotic disorders. Using an automated neuroanatomical quantification approach, it was investigated whether differences in structural grey matter volumes, symptom severity and functioning in young people with emerging affective and psychotic disorders exist, and whether these could be distinguished in Stage 1b patients and Stage 2+ patients. We hypothesised that compared to healthy counterparts, the patient group would exhibit a reduction in subcortical and hippocampus volumes, and that Stage 2+ patients, with more advanced disorders, would show a greater extent of volume loss associated with transition from Stage 1b to Stage 2+.

2. Methods

2.1. Participants

One-hundred and forty-one young people presenting to youth mental health services with admixtures of depressive, manic and psychotic symptoms were recruited from a specialised out-patient care service, *Headspace*, located within the Brain and Mind Centre, Sydney, Australia, for assessment and early intervention of mental health problems in young people (Scott et al., 2012, 2013). Inclusion criteria for this study were: (i) persons aged 18–25 years seeking professional help primarily for significant depressive, hypomanic or psychotic symptoms, and (ii) willingness to participate in other longitudinal research within the Brain and Mind Centre related to clinical and neurobiological outcomes (Hermens et al., 2011; Lagopoulos et al., 2012). In addition, 49 healthy control subjects (aged 18–25 years) were also recruited from the general population.

Subjects were excluded if they did not have sufficient English-language skills or had insufficient intellectual capacity to participate in the neuropsychological aspects of concurrent studies (Hermens et al., 2010) or had current substance dependence (according to DSM-IV criteria). In line with previous clinical staging studies, the staging model primarily focuses on mood, anxiety and psychotic disorders, where a history of childhood behavioural problems and concurrent substance use are highly comorbid, whereas substance dependence is far less common. Therefore, comorbid or pre-existing conditions such as attention deficit hyperactivity disorder and conduct disorder, anxiety disorders, alcohol or other substance abuse or mild autistic spectrum disorders were not exclusion criteria (See Hickie et al., 2013a for further details). The Human Research Ethics Committee of the University of Sydney approved this study, and all participants gave prospective written informed consent for their clinical data to be used for research purposes.

2.2. Clinical assessment

A psychiatrist or trained research psychologist conducted the clinical assessment (in a semi-structured interview format) on all participants, to determine the nature and history of any mental health problems. The assessment also focuses on detailed criteria developed for the formal application of a clinical staging framework. These details include (but are not limited to): current major symptoms (severity, frequency and type); clinical course of illness prior to presentation; current level of risk of harm to illness; current levels of social, educational or employment functioning (see (Hickie et al., 2013a) for further details).

In this study, participants' education level was assessed as the cumulative completed number of years in school, university and/or advanced diploma course. The measures of interest included in the clinical assessment were: the Social and Occupational Functioning Scale (SOFAS) to assess general social and occupational functioning; the Brief Psychiatric Rating Scale (BPRS), to quantify current general psychiatric symptoms; and the Hamilton Depression Rating Scale (HAMD 17-item) to quantify current mood symptoms.

2.3. Self report

Patients also completed a self-report assessment that included: the Kessler-10 (K-10), a brief instrument designed to detect psychological distress; and the World Health Organisation Disability Assessment Scale (WHO-DAS) and Quality of Life Scale (WHO-QoL) to quantify functional disability and quality of life, with higher scores indicating greater functional disability, and greater quality of life, respectively.

2.4. Clinical staging

All participants involved in this clinical staging study were recruited from individuals who had previously entered into *Headspace* services. All patients at *Headspace* receive individualised care and are managed by one or more medically and/or psychologically trained health professionals. With the patient's consent, the detailed clinical records from these assessments were utilised to determine clinical staging. A psychiatrist or trained research psychologist conducted a standardised clinical interview focusing on the necessary details for staging.

The clinical staging model utilised in this study involved assigning participants to a clinical stage based on information gathered during the clinical assessments, self-report assessment and other relevant ancillary investigations (such as neuropsychological outcomes). Once this information is integrated, a clinical stage is then assigned according to sets of established criteria [see Appendices of Hickie et al., 2013a for