Journal of Psychiatric Research 62 (2015) 84–91

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/psychires

Prediction of pediatric unipolar depression using multiple neuromorphometric measurements: A pattern classification approach

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ARTICLE INFO

Article history:
Received 12 August 2014
Received in revised form
16 December 2014
Accepted 28 January 2015

Keywords:
Pediatric unipolar depression
Neuroimaging
Machine learning
Support vector machine

ABSTRACT

Background: Diagnosis of pediatric neuropsychiatric disorders such as unipolar depression is largely based on clinical judgment – without objective biomarkers to guide diagnostic process and subsequent therapeutic interventions. Neuroimaging studies have previously reported average *group-level* neuroanatomical differences between patients with pediatric unipolar depression and healthy controls. In the present study, we investigated the utility of multiple neuromorphometric indices in distinguishing pediatric unipolar depression patients from healthy controls at an individual subject level.

Methods: We acquired structural T_1-weighted scans from 25 pediatric unipolar depression patients and 26 demographically matched healthy controls. Multiple neuromorphometric indices such as cortical thickness, volume, and cortical folding patterns were obtained. A support vector machine pattern classification model was 'trained' to distinguish *individual* subjects with pediatric unipolar depression from healthy controls based on multiple neuromorphometric indices and model predictive validity (sensitivity and specificity) calculated.

Results: The model correctly identified 40 out of 51 subjects translating to 78.4% accuracy, 76.0% sensitivity and 80.8% specificity, chi-square p-value = 0.000049. Volumetric and cortical folding abnormalities in the right thalamus and right temporal pole respectively were most central in distinguishing individual patients with pediatric unipolar depression from healthy controls.

Conclusions: These findings provide evidence that a support vector machine pattern classification model using multiple neuromorphometric indices may qualify as diagnostic marker for pediatric unipolar depression. In addition, our results identified the most relevant neuromorphometric features in distinguishing PUD patients from healthy controls.

1. Introduction

Major depressive disorder (MDD) or Unipolar Depression has a lifetime prevalence of 16.2% in the adult population and affecting approximately 2.5% of children and 8.3% of adolescents in the United States (Lewinsohn et al., 1994). Longitudinal studies have reported that a diagnosis of pediatric unipolar depression (PUD) is associated with an increased risk of recurrence during adulthood and that approximately 57.2% of adult MDD cases may have started during childhood (Carballo et al., 2011) (Harrington et al., 1990; Rosso et al., 2005). In addition, PUD is associated with poor academic outcomes, impaired social functioning and elevated risks of substance abuse and other psychiatric comorbidities (Rao and Chen, 2009; Shad et al., 2012). These facts underscore the need to elucidate the pathophysiological mechanism of PUD and identify objective biomarkers able to assist in PUD diagnosis and guide treatment management.

In vivo neuroimaging studies have implicated multiple neuroanatomical structures in the pathophysiology of PUD. Notable findings include, reduced hippocampal (Caetano et al., 2007; MacMaster and Kusumakar, 2004; Rao et al., 2010), amygdala (Rosso et al., 2005), striatum (Matsuo et al., 2008), caudate (Matsuo et al., 2008; Shad et al., 2012) and increased left prefrontal cortex (Nolan et al., 2002) volumes. In addition, white matter abnormalities have also been reported in the corpus callosum (Caetano et al., 2008) and middle frontal gyrus (Ma et al., 2007). However, despite

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http://dx.doi.org/10.1016/j.jpsychires.2015.01.015
0022-3956/

these multiple studies, significant limitations still exist. First, a majority of these studies utilized pre-defined anatomical regions-of-interest whilst recent studies have shown that neuroanatomical alterations in neuropsychiatric disorders involves multiple circuits as opposed to single anatomical regions – which underlines potential benefits of using whole brain neuroimaging scan data (Ecker et al., 2010; Good et al., 2002). Second, previous studies have not investigated the predictive utility (high specificity and sensitivity) of *in vivo* neuroimaging scans in distinguishing PUD patients from healthy controls but largely reported *average* group-level differences. Notably, multiple studies in other neuropsychiatric disorders – including adult unipolar depression and pediatric bipolar disorder have shown great potential of *in vivo* neuroimaging scans together with pattern classification or machine learning algorithms in distinguishing individual patients with neuropsychiatric disorders from healthy controls (Costafreda et al., 2009; Fu et al., 2008; Johnston et al., 2013; Mwangi et al., 2012, 2014a, 2014b; Nouretdinov et al., 2011; Orrù et al., 2012; Sun et al., 2009; Zeng et al., 2012). Third, previous PUD studies have largely utilized single neuromorphometric measurements (e.g. volume alone) whilst combining multiple measurements (e.g. anatomical volume and cortical thickness) may offer a complimentary view of brain structure which may further improve prediction accuracy (Ecker et al., 2010).

In the present study, we set out to investigate the utility of multiple neuromorphometric measurements such as anatomical volume, cortical thickness, folding index, mean curvature, Gaussian curvature and intrinsic curvature index together with a machine learning algorithm in identifying individual subjects with PUD. These neuromorphometric measurements were extracted using Freesurfer software library (Fischl, 2012) and input into a support vector machine (SVM) (Vapnik, 1999) pattern classification model which was 'trained' to distinguish individual PUD patients from healthy controls. The model's ability to generalize from novel subjects' data was evaluated using a leave-one-out cross-validation (LOOCV) method which involved 'training' the model using all subjects but one – a process which was repeated until all subjects were left-out once. The 'left-out' subjects were used for estimating the model diagnostic accuracy, specificity, sensitivity, positive predictive value (PPV), negative predictive value (NPV), and an area under receiver operating characteristic curve (AUROC). A review of machine learning applications in psychiatric neuroimaging is given elsewhere (Ecker et al., 2010; Mwangi et al., 2012; Mwangi et al., 2014a; Mwangi et al., 2014b; Orrù et al., 2012).

In summary, the main objective of this study was to examine the predictive validity of multiple neuromorphometric measurements acquired from T_1-weighted scans in distinguishing individual subjects with PUD from healthy controls.

Table 1
Demographics.

	PUD mean (SD)	Healthy controls mean (SD)	p-value
Age (years)	13.07 (2.55)	13.18 (2.62)	0.876[a]
Female/total	10 (25)	10 (26)	0.45[c]
CDRS	41.36 (17.13)	17.46 (1.14)	$p < 0.0001$[a]
HDRS	11 (6)	0.5 (1.03)	$p < 0.0001$[a]
Hollingshead SES score	47.09 (13.82)	44.48 (13.70)	0.524[a]
Petersen pubertal development score	2.41 (0.83)	2.39 (0.94)	0.950[a]
Age of onset	10.12 (2.37)	–	–
Education	1.6 (0.5)	1.62 (0.50)	0.913[a]
ADHD	10	–	–
Panic disorder	1	–	–
Social phobia	3	–	–
OCD	1	–	–
ODD	5	–	–
GAD	9	–	–
Enuresis	4	–	–
Encopresis	2	–	–
Drug abuse	1	–	–
SAD	9	–	–
Specific/simple phobia	2	–	–
Agoraphobia	2	–	–
Conduct disorder	1	–	–
Binge eating disorder	1	–	–
Currently or previously taken any psychotropic medication	12	–	–
Handedness (left)	3	1	0.34[b]
White	11	6	0.14[b]
Black	2	1	0.61[b]
Hispanic	10	18	0.05[b]
Others	2	1	0.61[b]

PUD – pediatric unipolar depression, SD – standard deviation, OCD – obsessive compulsive disorder, ODD – opposition defiant disorder, GAD – generalized anxiety disorder, SAD – social anxiety disorder, ADHD – Attention deficit hyperactivity disorder, CDRS – child depression rating scale, HDRS – Hamilton depression rating scale, SES – social economic status.
[a] Student t-test.
[b] Fisher's exact test.
[c] Chi-square test.

2. Methods and materials

2.1. Participants

This study was approved by the local Institutional review board (IRB) at The University of Texas Health Science Center at San Antonio. Study participants included 25 children and adolescents with DSM-IV diagnosis of unipolar depression and 26 age, gender, ethnicity, and pubertal status matched healthy controls with age ranging (8.5–17.5 years old). The diagnosis of unipolar depression in patients and the absence of Axis I pathology in controls was established through the administration of the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime version (K-SADS-PL) by a trained psychiatrist. Subjects were excluded if they met criteria for substance abuse or dependence in the 6 months that preceded their participation in the study. Healthy controls were excluded if they had any history of psychiatric disorders, including substance abuse or dependence, neurological disorders or a history of any Axis I psychiatric disorders in first degree relatives. Additional exclusion criteria were positive pregnancy test, neurological disorders, head injury with loss of consciousness, family history of hereditary neurologic disorders and presence of metallic objects in the body. Patient and healthy control groups did not differ significantly in terms of age, gender, ethnicity, years of education, pubertal development scale and social economic status. Conversely, the patient group differed significantly on the child depression rating scale (CDRS) and the Hamilton depression rating scale (HDRS) as compared to Healthy controls and shown in Table 1.

2.2. Magnetic resonance imaging protocol

Structural T_1-weighted MRI images were acquired using a 1.5 T Philips Gyroscan Intera scanner using a three-dimensional spoiled gradient recalled echo protocol with the following parameters. Repetition time (TR) = 24 ms, echo time (TE) = 5 ms, flip angle = 40°, field of view (FOV) = 24 cm, Slice thickness = 1 mm, voxel dimension = $1 \times 1 \times 1$ mm^3 and matrix size = 256×256. Scans were acquired by a trained MRI technologist and there were no consistent problems in scanning children and adolescents.