Identification and individualized prediction of clinical phenotypes in bipolar disorders using neurocognitive data, neuroimaging scans and machine learning


Abstract

Diagnosis, clinical management and research of psychiatric disorders remain subjective — largely guided by historically developed categories which may not effectively capture underlying pathophysiological mechanisms of dysfunction. Here, we report a novel approach of identifying and validating distinct and biologically meaningful clinical phenotypes of bipolar disorders using both unsupervised and supervised machine learning techniques. First, neurocognitive data were analyzed using an unsupervised machine learning approach and two distinct clinical phenotypes identified namely; phenotype I and phenotype II. Second, diffusion weighted imaging scans were pre-processed using the tract-based spatial statistics (TBSS) method and ‘skeletonized’ white matter fractional anisotropy (FA) and mean diffusivity (MD) maps extracted. The ‘skeletonized’ white matter FA and MD maps were entered into the Elastic Net machine learning algorithm to distinguish individual subjects’ phenotypic labels (e.g. phenotype I vs. phenotype II). This calculation was performed to ascertain whether the identified clinical phenotypes were biologically distinct. Original neurocognitive measurements distinguished individual subjects’ phenotypic labels with 94% accuracy (sensitivity = 92%, specificity = 97%). TBSS derived FA and MD measurements predicted individual subjects’ phenotypic labels with 76% and 65% accuracy respectively. In addition, individual subjects belonging to phenotypes I and II were distinguished from healthy controls with 57% and 92% accuracy respectively. Neurocognitive task variables identified as most relevant in distinguishing phenotypic labels included; Affective Go/No-Go (AGN), Cambridge Gambling Task (CGT) coupled with inferior fronto-occipital fasciculus and callosal white matter pathways. These results suggest that there may exist two biologically distinct clinical phenotypes in bipolar disorders which can be identified from healthy controls with high accuracy and at an individual subject level. We suggest a strong clinical utility of the proposed approach in defining and validating biologically meaningful and less heterogeneous clinical sub-phenotypes of major psychiatric disorders.

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In line with this goal, the two main objectives of this study were:
first, to determine whether we can identify distinct clinical phenotypes
based on a composite representation of neurocognitive data. Second,
investigate whether neuroimaging measurements acquired from diffu-
sion weighted scans are predictive of identified phenotypes at an indi-
vidual subject level and with above chance level accuracy. Notably, in
this study we refer to disease phenotypes as subgroups or sub-
classifications of patient groups with unique patterns of neurocognitive
functioning. As a first step, this approach was applied on a sample of
patients with bipolar disorders and validated against matched healthy
controls.

Bipolar disorder (BD) is a common psychiatric disorder charac-
terized by mania or hypomania, mostly alternating with depression and
ranked among top 20 causes of disability worldwide (Hirschfeld &
Vornik; 2005; Murray et al., 2013; Rajkowska et al., 2001). BD is associ-
ated with a high socio-economic burden including suicidality, substance
abuse and comorbidity with other disorders (Galvez et al., 2014; 
Hirschfeld & Vornik; 2005; Muller-Oerlinghausen et al., 2002). Clini-
ically, BD is categorized into two main subtypes: 1) bipolar I disorder
(BD I) — characterized by one or more manic or mixed episodes,
accompanied by one or multiple depressive episodes (Association,
2000; Muller-Oerlinghausen et al., 2002), 2) Bipolar II disorder (BD
II) — characterized by one or more hypomanic episodes with recur-
rent depressive episodes (Association, 2000; Muller-Oerlinghausen
et al., 2002). Noticeably, these clinical subtypes are based on
observed and potentially heterogeneous ‘signs and symptoms’ as op-
aposed to measureable neurobiological or behavioral characteristics.
Consequently, the main motivation of this study was not to investi-
gate neurobiological differences across subtypes of BD but to investi-
gate distinct neurobiologically relevant phenotypes within the entire
bipolar disorder spectrum. Markedly, identifying neurobiologically dis-
tinct phenotypes may lead to development of more effective, better-
targeted treatments and most importantly personalized or individualized
treatments. Indeed, this is also inline with the recently proposed P4
(predictive, preventive, personalized and participatory) medicine
framework in investigating major medical conditions (Hood & Friend,
2011).

Multiple neurocognition studies have reported impaired cognition
in BD patients as compared to healthy individuals. For example, a recent
meta-analysis summarizing 42 studies observed significant impairments
in BD patients across multiple domains such as attention, working mem-
ory, verbal/non-verbal memory, visuospatial function, psychomotor
speed, language and executive function (Kurtz & Gerraty, 2009). Most re-
cently, several studies have successfully identified unique neurocognitive
subgroups using data-driven machine learning algorithms (Brodersen
et al., 2014; Burdick et al., 2014; Fair et al.; 2012; Heinrichs & Awad,
1993; Lee et al., 2014). Distinctively, a recent longitudinal study reported
a data-driven approach able to identify neurocognition subgroups which
proved to be useful in predicting longitudinal functional outcomes
(Hermens et al., 2011). However, while these studies have undoubtedly
offered significant insights on unique and objective phenotypes of psychi-
atric disorders — the association between these data-driven phenotypes
and other neurobiological measurements (e.g. white matter tissue
diffusivity) remains largely unexplored. Furthermore, a significant
advantage would be to demonstrate that neuroimaging measurements
are highly predictive of identified disease phenotypes albeit at an in-
dividual subject level. Notably though, there is active research work
in this area (Brodersen et al., 2014; Geisler et al., 2015; Karalunas
et al., 2014).

Multiple studies have recently demonstrated the utility of machine
learning or pattern recognition algorithms in making clinically relevant
predictions at an individual subject level (Johnston et al., 2014; 
Lavagnino et al., 2015; Mwangi et al., 2012a; Mwangi et al., 2012b; 
Mwangi et al., 2014b; Rocha-Rego et al., 2014). Specifically, previous
studies have attempted to discriminate DSM defined categories from
matched healthy controls using neuroanatomical scans (Mwangi et al.,
2012a; Oliveira et al., 2013; Schnack et al., 2014). However, while these
algorithms have been received within the neuropsychiatric community with great optimism, a major criticism has been that these
algorithms are ordinarily ‘trained’ to categorize patients based on symp-
tom-based DSM defined categories — an assumption which may lead to
circularity (Mwangi et al., 2014a; Savitz et al., 2013). In this study
though, we somewhat circumvent this limitation by first; identifying
distinct behavioral phenotypes using neurocognitive data and an unsu-
pervised machine-learning technique. Second, using diffusion weighted
neuroimaging scan data such as mean diffusivity (MD) and fractional
anisotropy (FA) we ‘train’ a machine learning algorithm to distinguish
individual subjects among clinical phenotypes as well as healthy con-
trols. Importantly, to allow inter-subject comparisons diffusion weight-
ed imaging FA and MD maps were pre-processed using the tract-based
statistical (TBSS) method (Smith et al., 2006). This entitled spatial
normalization of subjects’ FA and MD volumes into a standardized
template coupled with a ‘tract skeletonization’ process to account for
any residual misalignments and resulting FA and MD volumes used in
the machine learning analyses and phenotype validation.

Materials and methods

Subjects

This study was approved by the local Institutional Review Board
(IRB) at The University of North Carolina at Chapel Hill. Study partici-
ants included 70 patients with DSM-IV diagnosis of BD as shown in
Table 1. A diagnosis of BD in patients was established through admin-
istration of the structured clinical interview for the diagnostic and statis-
tical manual of mental disorders axis I (SCID I) (First et al., 2012).
Subjects were excluded if they met criteria for substance abuse or

Table 1
Demographic and clinical details.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (SD)</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>33.87 (13.02)</td>
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<tr>
<td>Female/total (N)</td>
<td>41 (70)</td>
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<tr>
<td>Age of onset (years)</td>
<td>16.98 (6.43)</td>
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<td>Education (number of years)</td>
<td>14.42 (2.67)</td>
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<td>YMRS</td>
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<td>MADRS</td>
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<tr>
<td>Hollinghead SES score</td>
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<td>BD subtype</td>
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<tr>
<td>DSM IV bipolar disorder I (N)</td>
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<tr>
<td>DSM IV bipolar disorder II (N)</td>
<td>12</td>
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<tr>
<td>DSM IV bipolar disorder NOS (N)</td>
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<tr>
<td>Comorbidities</td>
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<td>Panic disorder (N)</td>
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<tr>
<td>Social phobia (N)</td>
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<tr>
<td>Unknown (N)</td>
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</tbody>
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