

Impulsivity as a Clinical Marker for Bipolar Affective Disorder

Thesis

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

قالوا

لَسْبَدَانِكَ لَا نَعْلَمُ لَنَا
إِلَّا مَا عَلَّمْتَنَا إِنَّكَ أَنْتَ
الْعَلِيمُ الْعَظِيمُ

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List of Abbreviations

Abb.	Full term
<i>5HT</i>	<i>5 Hydroxy tryptamine</i>
<i>ACC</i>	<i>Anterior cingulate cortex</i>
<i>ADHD</i>	<i>Attention-deficit / hyperactivity disorder</i>
<i>ANNK1</i>	<i>Ankyrin repeat and kinase domain containing 1</i>
<i>BAS</i>	<i>Behavioral activation system</i>
<i>BD</i>	<i>Bipolar Disorder</i>
<i>BDNF</i>	<i>Brain derived neurotrophic factor</i>
<i>BIS</i>	<i>Behavioral inhibition system</i>
<i>BIS-11</i>	<i>Barrat impulsiveness scale.</i>
<i>DA</i>	<i>Dopamine</i>
<i>DAT1</i>	<i>Dopamine transporter 1</i>
<i>dlPFC</i>	<i>Dorsolateral prefrontal cortex</i>
<i>DRD4</i>	<i>Dopamine receptor D4</i>
<i>fMRI</i>	<i>Functional magnetic resonance imaging</i>
<i>GNG</i>	<i>Go / no-go task</i>
<i>GSK3β</i>	<i>Glycogen synthase kinase 3 beta</i>
<i>HTR1B</i>	<i>Hydroxy tryptamine receptor 1B</i>
<i>HTR2A</i>	<i>Hydroxy tryptamine receptor 2A</i>
<i>IFG</i>	<i>Inferior frontal gyrus</i>
<i>Imp</i>	<i>Impulsivity</i>
<i>MAOA</i>	<i>Monoamine oxidase A</i>
<i>MCQ</i>	<i>Monetary Choice Questionnaire</i>
<i>Msec</i>	<i>Millisecond</i>
<i>NAS</i>	<i>Nonspecific Arousal System</i>
<i>NRXN3</i>	<i>Neurexin-3-alpha</i>
<i>OFC</i>	<i>Orbitofrontal cortex</i>
<i>PET</i>	<i>positron emission tomography</i>

List of Abbreviations (Cont...)

Abb.	Full term
<i>SNAP25</i>	<i>Synaptosomal-associated protein 25</i>
<i>VDR</i>	<i>Vitamin D receptor gene</i>
<i>Vent</i>	<i>Venturesomeness</i>
<i>vmPFC</i>	<i>Ventromedial prefrontal cortex</i>
<i>WHI</i>	<i>White hyperintensities</i>

Abstract

Cases have higher overall impulsivity in comparison to relatives and controls, and relatives have significantly higher (BIS) total, motor and non-planning impulsivity than controls.

Our findings suggest that impulsivity measured by BIS-11, may be a potentially valuable candidate endophenotype for bipolar disorder as it's state independent and manifests in patient's relatives more than general population.

The Global Assessment of Function (GAF) scores of the study sample results reveal that cases have more disturbed GAF than relatives. While investigating predictors of impulsivity, family history of psychiatric illness appeared to be a significant predictor of increasing impulsivity in cases group, on the other hand, history of violence and history of drug use are significant predictors of increasing impulsivity in relatives' group, while unemployment is significant predictor of increasing impulsivity in control group.

Keywords: Anterior cingulate cortex - Attention-deficit/hyperactivity disorder - Bipolar Disorder

INTRODUCTION

Bipolar disorder (BD) is a highly heritable disease, the substantial genetic component estimates ranging from 70% to 80% (*Duffy et al., 2013*).

It is characterized by a chronic course and accompanying affective, cognitive, and somatic impairments (*Bora et al., 2009*).

It is important to identify psychological mechanisms that increase the risk to develop BD which allow detecting the disorder earlier and help in preventing it (*Keener and Phillips, 2007*).

The concept of endophenotype is considered a promising method to detect psychological risk factors. Characterized by being measurable, associated with the disorder in the population, heritable and state-independent (*Kendler, 2005*).

Impulsivity has been defined as a predisposition toward rapid, unplanned reactions to internal or external stimuli, without regard to the negative consequences (*Moeller et al., 2001*).

It is divided into two components: trait impulsivity which is the component of impulsivity that remains constant at different episodes of the disorder and state impulsivity which is the changing part due to the state of the disorder (*Celikeloglu et al., 2015*).

Available findings suggest that in BD, impulsivity is not only state-related (manic or depressive episode), but also a trait component of BD (continued pattern), which could represent a core feature of the illness (*Ekinici et al., 2011*).

Among bipolar patients, impulsivity appears to be especially important during manic episodes, but may also be found during euthymia and other mood phases (*Swann et al., 2003*). Trait impulsivity, as measured by the Barratt Impulsiveness Scale (BIS-11), is increased in bipolar patients comparing to healthy individuals (*Swann et al., 2008*). It remains elevated even in euthymic patients and does not differ from manic ones, these findings indicate that the impulsivity found among bipolar patients may be independent of mood state (*Swann et al., 2003*).

In addition, family, twin and adoption studies show that increased impulsivity is heritable, suggesting that impulsive behavior is under genetic control. Several studies reported that unaffected first-degree relatives of BD patients committed more response inhibition errors than controls without a family member with BD in tasks measuring impulsive behavior, such as the Stroop Word Colour Test or the Hayling Sentence Completion Test (*Schulze et al., 2011*).

Further, they also displayed more trait impulsivity as measured on the BIS-11, scoring on an intermediate level between BD patients and healthy controls which is also

reflected in shared abnormalities between bipolar disorder patients and their relatives in brain function and a functional connectivity within neural networks involved in inhibitory control. These findings suggest that increased impulsivity may be part of familial risk for the illness (*Lombardo et al., 2012*).

Rational of the study:

Impulsivity is carrying a deleterious influence. Various findings suggest that impulsivity in bipolar disorder could be associated with numerous potential complications including substantial morbidity, deterioration in the social, family, and employment realms, higher risk of accidents, violence, substance abuse, suicide and some eating behavior disorders. In addition, impulsivity was associated with a more severe course of illness. Motivated by this fact, the research team decided to investigate increased impulsivity as a potential endophenotype of and a clinical marker for BD in relatives of BD patients.

Hypothesis

We hypothesized that both euthymic individuals with bipolar disorder and their clinically unaffected first-degree relatives would have higher levels of trait impulsivity compared to healthy subjects.

AIM OF THE WORK

- 1- To measure impulsivity in both BD euthymic patients and in healthy first-degree relatives of BD patients and compare it to controls.
- 2- To assess the functional implications of impulsiveness on psychosocial functioning in bipolar disorder patients and first-degree relatives of BD patients.

Chapter 1

IMPULSIVITY: CONCEPTS & STUDYING APPROACHES

Impulsivity is a behavioral aspect which adds important color to everyday life. Most people, at some point of their life, have engaged in an impulsive behavior such as extra purchase at the supermarket. However, even if it is easy to identify examples of impulsive behavior, it is more difficult to define impulsivity precisely and there is a disagreement as to what differentiates socially acceptable impulsive behavior from the unacceptable that varies from one culture to another, from one era to another, and depends upon the age of the person involved. These differences do not usually matter so much for everyday life (except perhaps when cultures clash), but they do pose problems for the scientific study of impulsivity, and especially the study of the biological basis of that phenomenon (*Moeller et al., 2001*).

According to *Stedman's Medical Dictionary (1995)* the word impulsive indicates an act relating to or activated by an impulse rather than controlled by reason or careful deliberation. Which lead to different forms of impulsive behaviors. Most importantly, these might be influenced by different biological mechanisms, thus rendering fruitless the search for a single biological basis of impulsivity.