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"Intolerance of Uncertainty and Jumping to Conclusions in psychotic disorders"

Relatore
Prof. Andrea Escelsior
Correlatore
Dott. Alberto Inuggi

Candidato
Filippo Chiozza

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Sommario

INTRODUCTION

PSYCHOSIS

DEFINITION

In the field of neurologic and psychiatric practice, psychosis is a significant focus for examination and treatment since it is a frequent and functionally disruptive symptom of many psychiatric, neurodevelopmental, and medical diseases. In the DSM-5[1] and International Classification of Diseases, Tenth Revision (ICD-10)[2], hallucinations, delusions and delusional misidentification are core features of psychosis' definition.

The hallmark of schizophrenia spectrum disorders is psychosis, which is also a common but varied component of mood and substance use disorders and, at times, neurologic and medical conditions. Psychosis can act both as a cause to incapacity and an obstacle to participation and productivity in all these illnesses[3–5].

The American Psychiatric Association's (APA's) Diagnostic and Statistical Manual of Mental Disorders (DSM) description of psychosis, in its old versions, focused the attention on functional limitations brought on by "loss of ego boundaries", "gross impairment in reality testing", rather than the symptoms themselves[6]. This led to a too inclusive definition and to the need for more practicable one in the clinical, research and epidemiologic fields[2,7]. Currently APA's[1] focus in describing psychosis is on hallucinations and delusions, not excluding the concept of impaired reality testing, which remains a core feature of psychosis, by defining the signs that indicate such impairment. Formal thought disorders, such as disorganized thinking, tangentiality, perseveration, neologism, derailment (alone or combined), are also considered as a common symptom of psychotic disorders; to fit this DSM-5 diagnostic condition communication must be impaired.[6]

KEY FEATURES OF PSYCHOSIS

The core features of psychotic disorders in the fifth edition of the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM-5) are disorders in five different areas, namely (a) delusions, (b) hallucinations, (c) disorganized thinking (speech), (d) grossly disorganized or abnormal motor behavior (including catatonia), and (e) negative symptoms.[1]

DELUSIONS

Delusions are beliefs that are firmly held and resistant to change, even when faced with evidence that contradicts them. Delusions can encompass a range of different topics or ideas, including themes related to persecution, reference, physical health, religion, or grandiosity.[1]

Delusions can be categorized as bizarre or non-bizarre depending on whether they are improbable, difficult for peers from the same culture to comprehend, and independent of daily experiences. The idea that one's internal organs have been removed and replaced with someone else's organs without leaving any signs, thought withdrawal, insertion, the belief that one's body is acted by exogenous forces are illustrations of bizarre delusions. A non-bizarre delusion, on the other hand, can be the conviction that one is being watched by the authorities despite the absence of solid proof.[1]

HALLUCINATIONS

Hallucinations are unvoluntary experiences in which an individual perceives something, that feel as real as normal perceptions, that is not present in the external environment. They can involve any of the five senses, but auditory hallucinations (hearing voices or other sounds) are the most frequent in psychotic disorders. Voices, whether familiar or

new, that are perceived as separate from the individual's own thoughts are often how auditory hallucinations are experienced.[1]

Among "first-rank" symptoms of schizophrenia, Schneider referred to auditory hallucinations including hearing voices chatting with one another, providing running commentary on one's activities, and "thought echoes" (hallucinations in which the patient hears his or her own ideas uttered aloud).[6]

DISORGANIZED THINKING (SPEECH)

The formal thought disorder is another key aspect of psychosis. The speech is compromised with derailment or loose association, tangentiality and incoherence, namely "word salad" (when thinking is heavily disorganized and communication is impaired).[1]

GROSSLY DISORGANIZED OR ABNORMAI IVIOTOR BEHAVIOR (INCLUDING CATATONIA)

Grossly disorganized or abnormal motor behavior can include a range of conducts, from silly or inappropriate behavior to irrational and agitated demeanor, which may lead to difficulties in goal-directed actions, making it difficult to carry out regular duties.

Catatonia, on the other hand, features a significant reduction in response to the environment, including negativism, inappropriate or rigid posturing, inhibition of verbal and motor responses. Catatonic excitation is another term for purposeless, excessive motor activity without a clear reason. Stereotyped motions, grimacing, gazing, mutism, and verbal echoes are further characteristics.[1]

NEGATIVE SYMPTOMS

Negative symptoms manifest themselves in different ways, firstly as Diminished emotional expression (lessening of facial expression, eye contact, prosody and

movements during speech) and Avolition (decline in goal-directed actions and in interest in sociality); further manifestations are Alogia, Anhedonia and Asociality.

Among all the psychotic disorders, schizophrenia is the one in which these symptoms carry the greatest influence. [1]

UNITARY PSYCHOSIS

The uncertainty regarding the clinical and neurobiological borders of disorders questions taxonomic classification in psychiatry[8] and led to new proposals in psychiatric categorization that are grounded in empirical research and psychometric analysis by looking into neural and psychological mechanisms.[9–11]

The traditional Kraepelinian approach considered schizophrenia (dementia praecox) and bipolar disorder (manic depressive illness) as separate diagnoses, but recent research has contested this dichotomy[12,13] and considers psychosis as a transdiagnostic spectrum[12], where schizoaffective disorder serves as an intermediary disorder between bipolar disease and schizophrenia[10].

Bifactor model of psychosis considers a general factor which includes both affective and non-affective symptoms in patients with bipolar disorder, schizoaffective disorder, and schizophrenia, as well as five specific dimensions of psychosis: positive symptoms, negative symptoms, disorganized symptoms, manic symptoms, and depressive symptoms[12,13]. These five domains are considered as the key factors of the pentagonal model of psychosis[11].

Thus, psychosis is not specific for schizophrenia, indeed can occur in other disorders such as bipolar disorder, substance-induced psychotic disorder, schizoaffective disorder and

others[11]. Similarities in psychotic disorders can be found in symptoms, evolution over time[14], cognitive and neurobiological features and in drug treatments[15].

S. R. Aminoff et al., in a meta-analysis found that the lifetime prevalence of psychotic symptoms in bipolar disorder is 57%, reaching percentage of 67% when considering BD1 only.[16]

The duration and severity of symptoms, as well as the presence of other features such as mood symptoms and substance use, can help to distinguish between them.[11]

Genetic and environmental variables may be responsible for this overlap between different diagnostic categories[12,17–19], although research also assess the heterogeneity of psychosis' spectrum with findings of distinct risk factors[8,17,19].

In this respect the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP)[10,20] studied different endophenotypes. B-SNIP's phenotypic data led to definition of three different B-SNIP psychosis biotypes[14]. This outcome has been reached by collecting a large panel of biomarkers related to psychosis and brain functionality[14].

SCHIZOPHRENIA

DEFINITION

Schizophrenia is a complex disorder with various clinical presentations which can be categorized as positive and negative symptoms and cognitive impairments in different domains (i.e. working memory). Positive symptoms include content-thought and formal thought disorders such as delusions and disorganized speech, hallucinations, and abnormal behavior, while lack of normal behavior or emotion, social withdrawal, inability to feel pleasure, and decreased initiative and energy are the defining features of negative symptoms[21].

EPIDEMIOLOGY

Schizophrenia has a reported a mean lifetime prevalence of 11·9 per 1000, with a median of 7·2 per 1000[22]. The male-to-female incidence rate ratio is of 1·70 [95% CI 1·46–1·97], suggesting higher frequency in men.[23]

Most often the onset of schizophrenia is in early adult life, the highest incidence is in the early twenties and then decrease gradually.[24] Women experience a less noticeable peak and a less steep decrease, and beginning in their mid- to late-forties, new instances of the disease outnumber those of males.[24]

Individuals with schizophrenia tend to have a shorter lifespan compared to the general population, with suicide accounting for most deaths in the early stages of the illness and cardiovascular disease for the majority of deaths in the later years.[25] Life expectancy is about 15 years shorter and the life- time risk of death by suicide is 5% to 10%.[26]

The high prevalence of smoking, unhealthy lifestyles, and the effects of antipsychotic treatments, are blamed for this high death rate. These elements enhance the risk of metabolic syndrome, diabetes, and mortality from the heart and the lungs in people with schizophrenia.[21]

ETIOPATHOGENESIS

Structural and functional brain alterations feature schizophrenia.

Lateral ventricular enlargement is a frequent characteristic of schizophrenia, with an enlargement of the order of 25% by volume and a reduction in brain volume of around 2% assessed with over 300 MRI studies. The reduction of brain volume is mainly due to loss of gray matter, especially frontal lobe, temporal lobe and hippocampus.[27]

Hypofrontality and hyperfrontality are both possible presentations. The reduced activity involves particularly the dorsolateral prefrontal cortex, on the other hand hyperfrontality involves mainly the medial frontal cortex, but also some lateral areas.[24]

GENE-ENVIRONMENT INTERACTION

Schizophrenia is believed to be caused by a combination of genetic and environmental factors that affect brain development and the way individuals adapt to life experiences over time.[21]

While there is a strong genetic component to schizophrenia, with heritability estimated at around 80%,[28] it is not solely a genetic disorder. Genome-wide association studies, GWAS, have identified over 100 loci which significantly link with schizophrenia,[29] but even among identical twins, pairwise concordance for schizophrenia is only around 50%.[30] This suggests that environmental factors and their interactions with genetic factors play a crucial role in increasing the risk of developing schizophrenia.

Additionally, some genetic variants involving the deletion or duplication of DNA's parts are associated with a greatly increased risk of schizophrenia but are only found in a small percentage of people with the disorder (2-3%). A specific copy-number variant characterized by deletion at chromosome 22q11.2 has been associated to a lifetime risk for schizophrenia from 30% to 40%.[31,32]

Overall, schizophrenia is considered a polygenic disorder, with multiple genetic and environmental risk factors contributing to its development.[26]

GWAS findings have also been deepen highlighting the molecular pathways associated with significant genes in development of schizophrenia: regulation of the postsynaptic

membrane, synaptic transmission, and voltage-gated potassium channels are involved. Furthermore, these genetic components typically regard hippocampal pyramidal cells, medium spiny neurons, and cortical interneurons.[26]

Studies have found diminished density of synaptic proteins, dendritic spines, and markers for GABAergic and glutamatergic neurotransmission in the brains of individuals with schizophrenia compared to control participants.[33,34] Additionally, studies have implicated complement-mediated synaptic elimination by microglia as being disrupted in schizophrenia.[35,36]

These results may imply that aberrant synapse plasticity and function, with dendric spines' loss, may be involved in the pathophysiology of schizophrenia.[26]

EXCITATORY – INHIBITORY IMBALANCE

Cognitive impairments have been consistently found in individuals with schizophrenia, even before the full-blown illness.[26]

Overall, the neurodevelopmental hypothesis of schizophrenia posits that disruptions in early brain development lead to the structural and functional abnormalities observed in the disorder and ultimately to the cognitive deficits experienced by schizophrenic patients.[26]

Neuroimaging studies have shown reduced volume and abnormal activation in cortex. These abnormalities are thought to contribute to the cognitive impairments and other symptoms associated with the disorder.[26]

Gamma oscillations are the result of fluctuations of synchronized neural activities due to cognitive processes, particularly working memory, and are disrupted in schizophrenia (in both first-episode and chronic disturb), along with functional brain network organization.[26] This disruption is linked to alterations in the balance between inhibitory

and excitatory neurons, with GABAergic interneurons playing a central role in regulating high-frequency rhythms.[37,38]

Alterations such as lower dendritic spine levels, inhibitory neurons markers and GAD67 mRNA (which is a key enzyme in GABA synthesis) suggest an impairment in neural inhibitory-excitatory balance in favor of excitation.[39,40]

Furthermore, altered microglial markers in individuals with schizophrenia[41,42] suggest that disrupted synaptic pruning may contribute to these abnormalities, along with N-methyl-D-aspartate receptor function and glutamatergic signaling.[43] These disruptions may contribute to aberrant gamma oscillations and so to the development of cognitive deficits and primary negative symptoms in individuals with schizophrenia.[38,39]

SUBCORTICAL DOPAMINE DYSREGULATION

The dopamine hypothesis of schizophrenia was developed based on two key observations: the therapeutic effects of antipsychotic drugs, which work by blocking dopamine D2 receptors, and the similarity between the effects of amphetamines abuse, which elevate dopamine levels, and psychotic symptoms in schizophrenia.[24] Initially, the hypothesis implicated increased dopamine D2 receptor binding as the cause of functional dopamine excess in the brain, but subsequent neurochemical imaging studies with radiolabelled dopamine did not support this theory.[24]

The evidences showing that amphetamines, which stimulate the release dopamine, induce psychotic symptoms in healthy individuals and worsen symptoms in patients with schizophrenia[44,45] suggest that the dysregulation of subcortical dopamine plays a significant role in the development of psychosis. Molecular imaging studies have further refined our understanding of dopamine disruptions in schizophrenia, showing that

patients have higher striatal dopamine synthesis and release capacity compared to control participants. Additionally, greater release of dopamine after amphetamine administration is directly associated with the worsening of psychotic symptoms in patients.[26] Striatal dopamine synthesis is also elevated in the prodromal stages of the disease.[26]

The discrepancy between expected and actual rewards, namely reward prediction error signal, is linked to mesostriatal dopamine system; further researches demonstrated that dopamine neuron firing also encodes aversive and other non-rewarding stimuli and is involved in the updating of beliefs after meaningful stimuli.[26] Thus, dopamine neurons are thought to signal the salience of stimuli for learning and updating cognitive models of the world. Impairment in these mesostriatal neurons may cause irrelevant objects to be percieved as salient.[26]

Dopaminergic neuronal populations are not only part of mesostriatum, indeed the dorsal striatum, which associated with threat, features the greatest dopaminergic disruption in schizophrenia.[46,47]

THE GLUTAMATE HYPOTHESIS

Phencyclidine is an anesthetic drug which mainly acts as N-methyl-D-aspartate (NMDA) receptors antagonist, so blocking them ionotropic receptors: observation that recreational use of this drug can lead to the rise of actual psychotic experiences is the finding over which the glutamate theory developed. Thus, a deficient glutamate function is thought to be an etiological factor for schizophrenia in this theory.[24]

BIPOLAR AND RELATED DISORDERS

DEFINITION

Fluctuations in mood are a frequent occurrence in life, particularly when faced by stressful events. However, severe and persistent mood swings that result in psychological distress and behavioral impairment in different aspects of life may be symptomatic of an underlying affective disorder.[48]

As a bridge between the two diagnostic classifications in terms of symptoms, family history, and genetics, bipolar and related disorders are distinct diagnostic categories from depressive disorders in the DSM-5 and put between the chapters on schizophrenia spectrum and other psychotic disorders and depressive disorders.[1]

The definition of bipolar and related disorders involves different conditions: bipolar I disorder, bipolar II disorder, cyclothymic disorder, substance/medication-induced bipolar and related disorder, bipolar and related disorder due to another medical condition, other specified bipolar and related disorder, and unspecified bipolar and related disorder.[1]

The sole way the bipolar I disorder's diagnostic criteria differ from the old definition of the manic-depressive illness or affective psychosis is that neither psychosis nor having had a major depressive episode at some point in life are necessary to the diagnosis. Nevertheless, patients with full-blown disorder and psychotic features usually also meet the major depressive episode criterion.[1]

Bipolar II disorder is not a "milder" condition than bipolar I disorder, is charachterized by working and social impairment, requires the lifetime experience of at least one episode of major depression and at least one hypomanic episode.[1]

EPIDEMIOLOGY

Bipolar disorders, ranking as the 17th leading source of disability among all diseases, have a reported lifetime prevalence of 2.4% and a 12-month prevalence of 1.5%; if we only consider BDI the lifetime prevalence is around 0,6% and 0,4% for BDII only.[49,50] However, prevalence rates may vary by country due to methodological and cultural differences (i.e. in China the lifetime prevalence rate is of 0.11%).[51]

Bipolar I disorder has a similar prevalence rate among males and females, whereas bipolar II disorder occurs more frequently among females.

Bipolar disorder is also prevalent in primary care practices and may be underrecognized and undertreated.[51]

For example, the multicentre, transcultural BRIDGE study[52] found that 31% of patients with a diagnosis of major depressive disorder had subthreshold hypomanic or manic symptoms.

Bipolar disorder's first episode usually manifests in late adolescence or early adulthood, around the age of 20. A worse prognosis, longer treatment delays, more severe depression episodes, and greater prevalences of concomitant anxiety and substance use disorders are frequently linked to early onset.[1]

Around 6 to 7% of people with bipolar disease commit suicide, accounting for a 20 to 30 times higher suicide rate than general population.[51] Female sex, early onset of illness, depressive polarity of first episode, and of current or most recent episode, comorbid anxiety disorder, any substance misuse disorder, borderline personality disorder, and a first-degree family history of suicide are all factors that are significantly associated with suicide attempts.[48]

Psychiatric comorbidities are common: the percentage of anxiety in individuals with bipolar disorder is around 71%, substance-abuse, personality disorders attention deficit-hyperactivity disorder are respectively present in 56%, 36% and 10-20% of patients.[53,54] Other concomitant medical conditions are metabolic syndrome (37%), migraine (35%), obesity (21%) and type 2 diabetes mellitus (14%).[51]

As a result of both high suicide prevalence and medical comorbidities the risk of death is almost doubled in bipolar disorders.[51]

ETIOPATHOGENESIS

Bipolar disorder heritability estimates range from 70 to 90%.[51] Genome-wide association studies (GWAS) led to several speculative conclusions about the genetics components and neurobiologic pathways of these disorders. Several genes with small effect size have been discovered and though to take part in the development of the disorder.[51] Yet, the sum of these frequent genetic variations only accounts for around 25% of the disorder's total heritability.[55]

The kindling hypothesis suggests that exposure to stressors can sensitize the brain, leading to an increased susceptibility to future affective episodes of bipolar disorder, even in presence of unknown source of stress. Ambiental factors such as smoking or sedentary behavior, being non-medicated or using psychoactive drugs may fortify this kindling mechanism.[51]

Neuroprogression is a concept that refers to the gradual and irreversible changes in brain structure and function that occur during the development of bipolar disorder.[56] These changes may lead to the worsening cognitive and functional impairments seen in some

individuals with the disorder,[57] and they may also be partly responsible for a higher prevalence of coexisting medical conditions and premature death.[58]

The underlying molecular mechanisms that promote neuroprogression are manifold including epigenetic processes, mitochondrial dysfunction, pathways supporting neuroplasticity, inflammation, and an increase in oxidative and nitrosative stress.[51]

CLINICAL MANIFESTATIONS

MANIA, HYPOMANIA

Manic or hypomanic episodes are key features of bipolar disorder. Manic episodes are characterized by elevated mood, increased energy, and increased activity levels, often accompanied by grandiosity, decreased need for sleep, rapid speech, distractibility, and poor judgment. These symptoms must last for at least one week and cause significant impairment in social, occupational, or other areas of functioning, and can also include psychotic symptoms such as delusions or hallucinations (delusions can both occur mood-congruent and mood-incongruent).[48] Hypomanic episodes are similar to manic episodes but are less severe and shorter in duration, lasting at least four days and not causing significant impairment,[1] nay sometimes improving occupational functionality; hypomanic symptoms are frequently underdiagnosed and sometimes the hypomanic state is perceived as pleasant.[48]

DEPRESSION

In the DSM-5, bipolar and unipolar depression both meet the same diagnostic criteria for a major depressive episode, whose severity may be estimated with the Hamilton Depression Rating Scale (HDRS)[59] or the Montgomery-Asberg Depression Rating Scale (MADRS).[60]

While depressive episodes in both bipolar and unipolar depression fit the same criteria and have no pathognomonic traits, bipolar depression has typical characteristics which help to distinguish it from the unipolar one: often begins at a younger age, has more frequent, briefer-duration episodes, an abrupt start and offset, concurrent substance abuse and a higher postpartum risk. Atypical symptoms such as hypersomnia, lability, and weight instability and psychotic features are usual in bipolar depression, whereas unipolar depression is more likely to be characterized by somatic problems.[48]

COGNITIVE ALTERATIONS IN PSYCHOSES

Psychosis often displays cognitive deficits across various domains such as intellectual function, learning and memory, attention, working memory, language, and executive function.[61–65] In young individuals at clinical and familial high risk for psychosis cognitive impairments are predictive factors for fully developed psychotic episodes.[66]

In schizophrenia, processing speed, especially for coding tasks and category fluency, is significantly affected. Additionally, functional neuroimaging studies have indicated a significant prefrontal dysfunction in schizophrenia subjects during encoding and retrieval tasks related to episodic memory deficits.[67]

In bipolar disorder, cognitive alterations across many domains have been observed, even during the first episode, in healthy relatives and euthymic periods, suggesting that they may be trait-related markers of the disorder;[68–70] more precisely bipolar psychotic patients exhibit worse cognitive abilities in verbal memory, executive function, working memory, and processing speed compared to non-psychotic bipolar disorder subjects.[71]

Psychotic symptoms, particularly delusions, are thought to be manifestation of functional, and structural, brain impairments.[72]

Working memory, a crucial function that briefly retains information connecting perception, long-term memory, and action permitting a united and continual sense of Self in time,[73] is often compromised in individuals with psychosis,[74] and this may contribute to the rise of hallucinations (fragmentation of experiences).[75]

Coordinating cognitive processing, especially the integration of contextual information, is considered a core impaired feature of schizophrenia spectrum disorders.[76–78] The cognitive bias of "jumping to conclusions", which is connected to delusions, may also be explained by these disorders.[79,80]

PERCEPTUAL ALTERATIONS IN PSYCHOSIS

Overall, while cognitive deficits have been extensively studied in psychosis, less attention has been given to perceptual anomalies and their role in driving psychotic alterations of self-experience.[81]

Phenomenological psychiatrists and more recent research[82] suggest that alterations of perception may be a fundamental dysfunction in psychosis, particularly in schizophrenia, and can lead to a disconnection between self and the world, as well as anomalous experiences in which the elements of the world, usually implicit, are perceived as strange or hyper-significant. These perceptual disturbances may be related to the loss of the perceptual coherence and the over-focusing on details, resulting in a sense of meaninglessness of the observed stimulus.[82–85]

Alterations can be involved in auditory, visual and kinesthetic perception.[86]

RELATION BEETWEEN PERCEPTUAL AND CONGNITIVE ALTERATION (PREDICTIVE CODING MODEL OF PSYCHOSIS)

Perceptual anomalies may play an important role in the development of psychotic disorders, particularly in the early and prodromal stages. These perceptual disturbances are linked to the loss of coherence in the perceptual field, resulting in a disconnection between the self and the world. This disconnection can lead to anomalous experiences and a sense of detachment from the surrounding environment. Furthermore, the erosion of the perceptual field, which is consequence of a weakening of top-down inferences, can also result in delusional thought, with rigidity, intolerance to uncertainty, and loss of causal effect association.[84,87]

Perceptual disturbances are not a result of impairments in higher cognitive processes, but rather a fundamental disorder in sensory organization that can be linked to anatomical anomalies in cortical and subcortical structures. These perceptual anomalies have significant implications for social and occupational functioning and are a key factor in predicting the course and outcome of psychotic disorders.[85]

Overall, the model proposed by Fletcher and Frith, "perceiving is believing"[88] suggests that alterations in both perceptual processing and higher-level cognitive processes, such as reasoning and inference, may contribute to the development of positive symptoms of psychosis, including hallucinations and delusions. These alterations may be related to disruptions in frontoparietal brain networks and dysfunctional Bayesian predictive coding model, according to which prior beliefs have key role in perceiving reality.[89] Brain regions which are part of this network are thought to be involved in visual working memory,[90] perceptual decision making[91] and inhibitory control,[92] as well as in shifting spatial attention[93,94] and guiding eye movements.[95]

This predictive coding model suggests that disruptions in the balance between prior beliefs and incoming sensory signals, and the resulting prediction errors (decreased priors and increased likelihood), may contribute to the development of psychotic symptoms such as hallucinations and delusions.[96] This disruption in the balance may be related to aberrant encoding of precision, possibly due to neurobiological factors such as increased dopaminergic tone or hypofunction of N-methyl-D-aspartate receptors.[97]

Dopamine-dependent perceptual bias and hallucinations have been linked in unmedicated schizophrenic patients.[98]

Psychotic patients are less able to incorporate new information that contradicts their existing beliefs, leading to a persistence of those delusional beliefs. This impaired ability to update prior beliefs may be due to an imbalance in the precision of prior beliefs versus sensory information, leading to delusions heightening reliance on prior beliefs even in the face of contradictory evidence.

JUMPING TO CONCLUSIONS

Many mental disorders such as psychosis, addiction, eating disorders, depression, and anxiety disorders are characterized by dysfunctions in decision-making.[99]

According to the dual-process theory of reasoning there are two different kind of thinking and reasoning: Type 1 and Type 2.[99]

Processes involved in Type 1 are associative, heuristic, unchallenging.[99] These processes are supposed to be empirical and promote intuitive judgments. Conversely, the Type 2 system involves rule-based, conscious, effortful, analytic, and controlled processes, which are rational and support deliberative judgments.[99]

The reasoning processes of Type 1 and Type 2 may interact in this way: intuitive judgments emerging from Type 1 are assented by Type 2 analytic thinking.[99]

This theory has been applied to the psychosis' field[100,101] and hypothesised that "paranoid fears may be partly driven by rapid gut feeling intuitions that are not then kept in check by the application of effortful logical reasoning"[101] (p. 454). There are evidences linking sub-clinical paranoid ideas and a weaken Type 2 reasoning[100], and that perceiving data as hypersalient by deluded patients may head to more intuitive decisions.[102]

The proneness to make decisions with certainty based on insufficient information is known as "Jumping to conclusions" (JTC). Significant associations between JTC and delusions have been found. JTC is also considered, together with different processes, to be partly responsible for delusions' setting up and maintenance as people assess stimuli promptly reaching delusional conclusions based on little proofs.[99]

'The beads task' is an experimental task, originally designed upon Bayesian probabilistic inference, which analyses the JTC bias, that is one's reasoning style under ambiguous circumstances. This task assesses the JTC reasoning bias when decisions are taken after seeing two or fewer beads.[103]

Over the past twenty years, the body of literature related to JTC and delusions has grown. This rise has been fueled by the introduction of new experimental paradigms to evaluate the reasoning bias, the inclusion of both clinical and non-clinical groups, and the examination of more precise correlations between JTC and delusions.[99] It's significant to note that there is proof suggesting that individuals who have a higher inclination towards

JTC are less likely to experience improvement in their delusional experiences as time passes.[104–107]

The first meta-analysis about the relation between JTC and psychosis assessed that DTD (draw to decision) was significantly associated with delusions.[108] This meta-analysis reported a large effect size for DTD between patients who experience delusions and healthy individuals. The effect size was found to be smaller when comparing patients with delusions to psychiatric controls (non-psychotic disorders).[108]

In a more recent meta-analysis psychotic patients are confirmed to take prompter decisions than controls.[99] The study also focused on two different subgroups: patients with schizophrenia spectrum disorders (not necessarily deluded) and patients with delusions (any psychotic disorder); in both subgroups a hastier decision-making style has been found.[99]

The basis of jumping to conclusions reasoning style are not defined. Beyond impulsivity, two contributors to this decision-making style are a reduced capability in tolerating uncertainty and an impaired working-memory.[109]

INTOLERANCE OF UNCERTAINTY

IU, intolerance of uncertainty, has been defined as "an individual's dispositional incapacity to endure an aversive response triggered by the perceived absence of salient, key, or sufficient information, and sustained by the associated perception of uncertainty".[110] The fear of the unknown a fundamental issue in IU.[110] According to IU-based theories of worry, those who have high IU will be more likely to worry because high IU causes a chain reaction of worrying, harmful issue orientation, and cognitive

avoidance in addition to directly influencing problem orientation and cognitive avoidance.[111]

IU consists of both prospective and inhibitory parts: suffering from unknowable future and avoidance and immobility when faced with uncertainty.[112]

When levels of IU are high people are prone to be sensitive and receptive to ambiguous stimuli or situations, requiring less of such stimuli to feel uncertainty, to interpret those situations and stimuli as menacing, stressing, unmanageable.[112]

Levels of intolerance of uncertainty are evaluated with The Intolerance of Uncertainty Scale (IUS), which consists of 27 item.[113] This scale, based on the clinical evidence of IU being a core feature of GAD, was developed at Laval University and, albeit it has an atheoretical foundation, it achieved high level of performance in psychometric testing. Although its definition has changed over the years, the measurement of IU hasn't varied over time.[114]

Besides the 27-item IUS a shortened version of 12-item IUS has been developed.[115] This assessment includes two subscales: Prospective and Inhibitory IU. The first one judge the ache for uncertain events in the future, unpredictability and the commitment to pursuing information in order to raise levels of certainty: the second one judge the elusion of uncertainty when facing it.[112]

Delusional beliefs arise from the interaction between genetic, biological, psychological susceptibility and exogenous or endogenous stressors. The main emotion assumed to be involved in the formation of delusional ideas is anxiety. Worry, which is a way of thinking

related to anxiety that considers the prospective results of speculative future occurrences, is also believed to contribute to paranoid ideations by directly giving rise to the paranoid belief.[116,117]

Paranoia, a feature of schizophrenia spectrum and other psychotic disorders[1] which involves diverse delusional beliefs, and worry share physical, social or psychological concerns. In both clinical and non-clinical populations significative correlation between worry and paranoia has been found.[118]. The proneness to worry from the outset is found significantly linked to the development of new persecutory beliefs at 18-month follow-up and to an increased possibility of persistence of the old ones.[118]

The domains of paranoia where IU is most correlated are social reference and interpersonal suspiciousness, albeit persecutory beliefs and mistrust are also significantly linked. These results may suggest that IU is more related to paranoid thinking considering social evaluation issues than other motifs.[118]

Although existing models suggest that delusional beliefs are primarily influenced by the content of persistent worries, another study indicates that having difficulty tolerating uncertainty and experiencing intense negative emotions may have a greater impact on the development of paranoid thinking.[118]

Even after adjusting for anxiety and worry, current research, have found a correlation between IU and paranoid beliefs, such as social reference and persecutory beliefs, that suggests an independent relationship between IU and paranoia.[118] One possible mechanism by which IU is linked to paranoia is that conditions of protracted or intolerable uncertainty and anxiety may cause individuals who are high in IU to exhibit cognitive biases that are indicative of paranoid thinking, such as "jumping to conclusions (JTC)".[118]

One crucial drawback of IU's measures, such as Intolerance of Uncertainty Scale (IUS-12),[115] is that they heavily depend on self-report measures, which means that participants provide information about their own thoughts, feelings and behaviors. The association between self-report IU and performance on behavioral tasks involving uncertainty or ambiguity, however, has been quantified in research to assess laboratory paradigms as in vivo measures of IU.[119] The Beads Task, a probabilistic inference task, is a behavioral test which has been used to study IU not only as a self-report measure.[120] Self-report inhibitory IU (avoidance and paralysis) was linked to in vivo suffering during the Beads Task, but not prospective IU, perfectionism, or overall psychological distress. Beads Task distress may thus be capturing anxiety caused to immobility when attempting to make an unclear decision because it is specifically connected with inhibitory IU but not prospective IU. Given that uncertainty and perfectionism are related categories, the finding that anxiety on the Beads Task was linked with IU but not perfectionism is significant and underscores the task's particular relationships with IU.[112]

These findings may also be used to clarify the ways in which IU contributes to the anguish brought on by uncertainty: it's possible that some participants on the Beads Task hesitate between options, ask for more beads to feel more certain about their choice, and experience decision paralysis, whereas other participants have behavioral responses opposed to the emotional ones, using a more avoidant approach and make snappier decisions to alleviate the threat brought on by uncertainty.[119]

OBJECTIVES OF THE STUDY

This pilot case-control study aims to replicate the available literature that reported an increased intolerance to uncertainty in psychotic disorders using the Beads Task as a measurement tool to assess both JTC, IU and their linkage.

METHODS

STUDY DESIGN

Case-control pilot study. A comparison will be made between schizophrenia spectrum disorder patients, bipolar patients (considered as psychotic patients) and healthy controls.

STUDY POPULATION

We recruited 24 participants affected by schizophrenia spectrum disorders (n=7), bipolar disorder (n=17) with or without treatment with antipsychotic drugs, hospitalized or in charge mental health services. Furthermore, a group of healthy controls (n=55) has been selected.

PARTICIPANTS

Cases

Recruitment took place at the psychiatric facilities of the "San Martino" Hospital in Genoa (Psychiatric Clinic and SPDC).

Inclusion criteria: diagnosis of schizophrenia spectrum disorders or bipolar disorders (DSM5 criteria); age greater than 18 years; absence severe neurological or internal diseases (e.g epilepsy, Parkinson's disease, cancer) or substance use disorder; spoken language: Italian; willingness to participate to the study.

Exclusion criteria: clinical conditions that compromise the safety of the patient or staff in carrying out the procedures related to the study (e.g high suicidal risk, aggressiveness).

MEDICAL EXAMINATION AND EVALUATIONS

The medical examination took place at the Psychiatric Clinic of the San Martino Hospital and will be conducted by the medical staff of the Psychiatric Clinic.

Questionnaries and evaluations

During the recruitment part of the study patients were subjected to psychopathological assessments.

The psychopathological assessment involved: Positive and Negative Syndrome Scale (PANSS); Scale for the Assessment of Thought, Language, and Communication (TLC); Young Mania Rating Scale (YMRS); Hamilton Depression Rating Scale (HAM-D); Aberrant Salience Inventory (ASI); Perceptual Aberrant Scale (PAS). .

Cognitive Tasks

Jumping to conclusion: The beads task

The intolerance to uncertainty is a characteristic of cognitive processing in psychotic subjects as well as in subjects at risk for psychosis. One well-replicated paradigm able to assess this alteration is known as 'jumping to conclusions'.[112]

In this paradigm, subjects are exposed to two urns containing both green and yellow balls. Two conditions have been developed: low uncertainty (LU) and moderate uncertainty (MU).

In the first conditions (LU) the urns contain green and yellow balls in a 85%-15% proportions. In the MU condition the proportions of green and yellow balls are 60% and 40%.

In both LU and MU conditions the task is repeated 4 times.

At the beginning a ball is taken from one of the urns and the patient must decide which urn has been selected. The patient can request as many draws as he feels certain about the decision. The subsequent draws are always visible during the execution of the task.

Psychotic patients have a tendency to develop false beliefs despite contrasting evidence, thus evidencing an alteration of probabilistic learning and decision making.

In both LU and MU conditions 4 tests are done assessing the number of draws-to-decision, the time taken to decide and the correctness of the answers in each task.

For an extended description of the task see ‘‘Jumping to conclusions’ data-gathering bias in psychosis and other psychiatric disorders — Two meta-analyses of comparisons between patients and healthy individuals’.[99]

DATA MANAGEMENT

The data collected will be entered into an electronic database and subjected to a specific anonymization procedure with an alphanumeric code.

DATA ANALYSIS

Use of multivariate statistical models with R SOFTWARE to analyze the differences between patients (affected by schizophrenia or bipolar disorder) and healthy controls in:

1. number of beads used to make a decision (draws to decision);
2. mean time taken for each bead;
3. rate of successful decisions.

Further analysis have been made comparing the two groups considering the two LU and MU conditions separately.

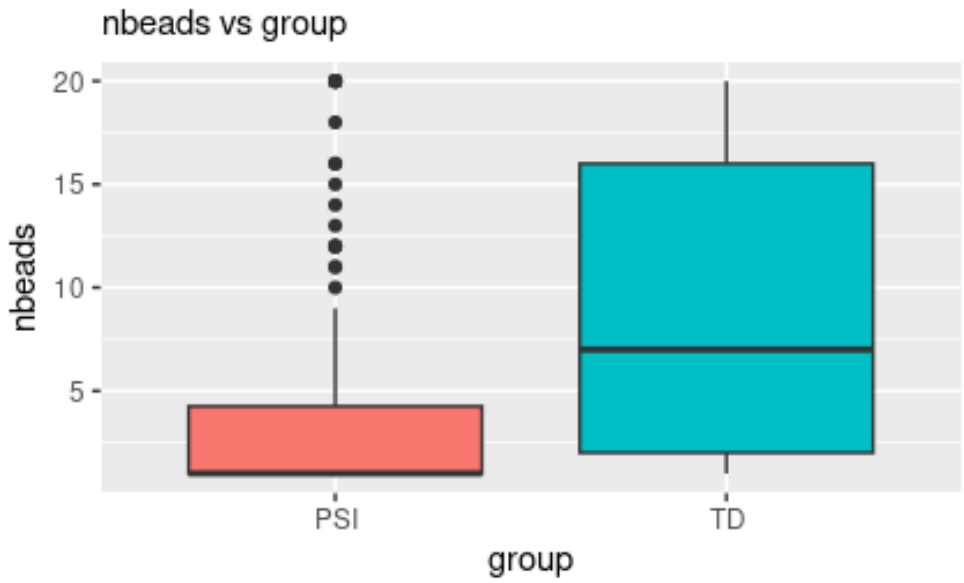
RESULTS

Draws to decision

The first parameter analyzed was the number of drawn beads needed to make the decision on whether the beads were from the first or the second jar (nbeads) in both LU and MU conditions.

We considered the mean number of beads used in both patients (PSI) and healthy controls (TD).

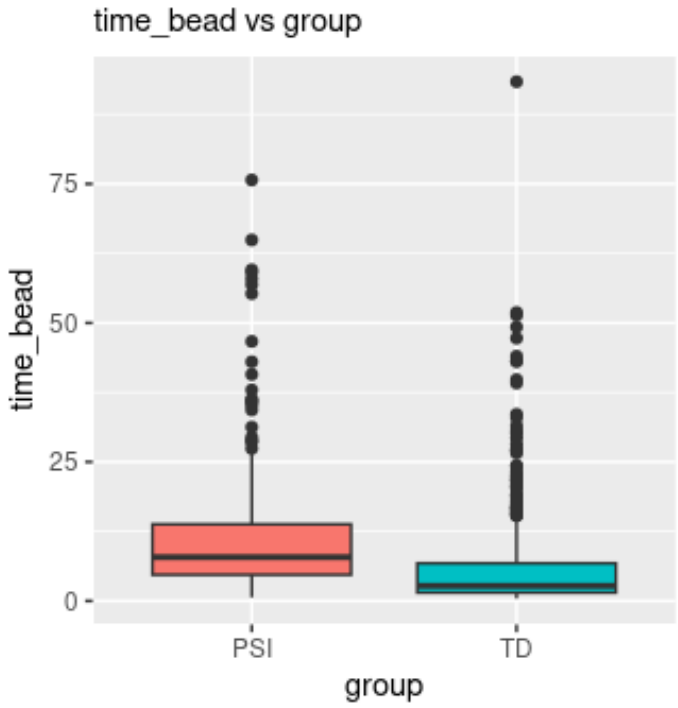
The average nbeads for the PSI group was 3.79 (SD=4.98), while the control group used an average of 8.8 beads (SD=7.13).



Mean time for each bead

The second analysis was about the average time taken to reason for each bead in both LU and MU conditions (time_bead).

The patient group (PSI) took on average 11.9 seconds (SD=12.7), while for healthy controls (TD) the mean time was 6.58 seconds (SD=9.75).

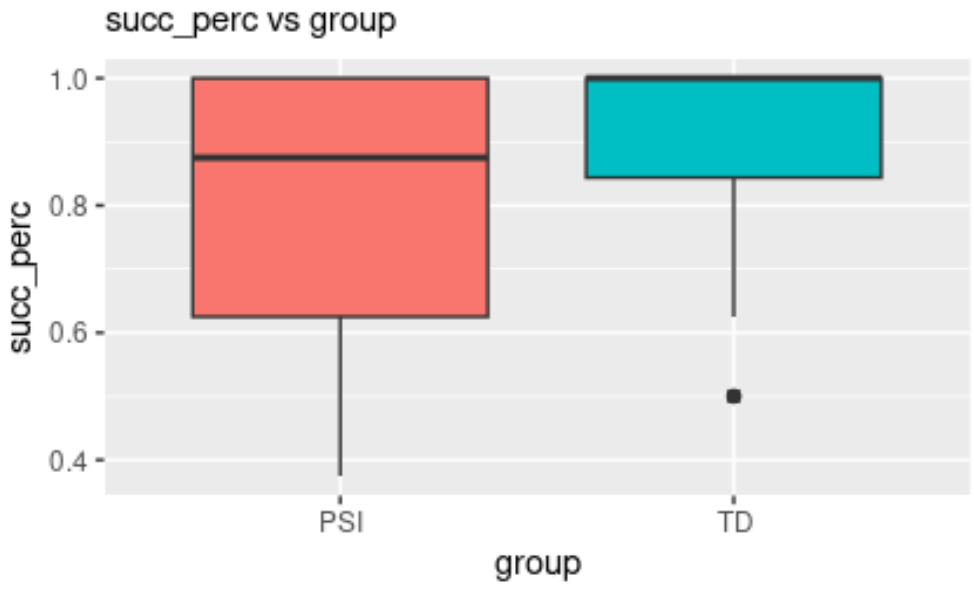


Rate of successful decisions

The third parameter which was analyzed has been the rate of right answers in both MU and LU conditions (msucc_perc).

The PSI group had 0.806 (SD=0.191) of correct answers.

The TD group had 0.897 (SD=0.149) of correct answers.



Gruppo	Media nbeads	SD	Media % risposte corrette	SD	Media tempo per bead	SD
PSI	3.79	4.88	0.806	0.191	11.9	12.7
TD	8.88	7.13	0.897	0.149	6.58	9.75

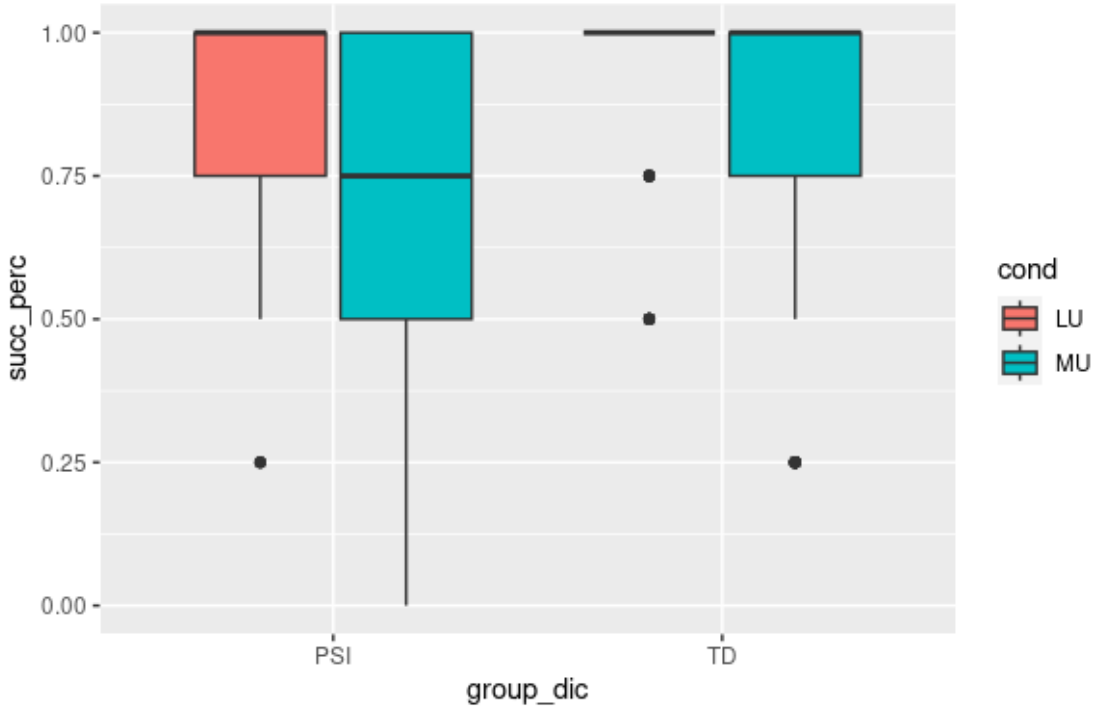
This table summarizes the findings descripted before (mean nbeads; mean succ_perc; mean time_bead).

Further analysis have been made comparing the LU and MU conditions in average draws to decisions, time spent reasoning on beads and rate of successful answers.

GRUPPO	CONDIZIONE	Media % risposte corrette	SD	Media nbeads	SD	Media tempo per bead	SD
PSI	**LU**	0.861	0.220	2.96	3.62	14.7	14.4
PSI	**MU**	0.75	0.273	4.61	5.78	9.13	10.1
TD	**LU**	0.962	0.124	7.77	7.01	7.99	10.2
TD	**MU**	0.832	0.248	9.99	7.10	5.18	9.04

This table summarizes the results of the LU – MU comparison between PSI and TD groups.

The only field of interest that had significant interaction between groups was the mean rate of successful answers.



The condition with low uncertainty levels (LU) had a 0.861 rate of successful answers (SD=0.220) in the PSI group, while the control group had a 0.962 (SD=0.124) rate.

In the MU condition the rate of successful answers was lower than the LU conditions in both PSI and TD groups, respectively 0.75 (SD=0.273) for the psychotic group and 0.832 (SD=0.248).

DISCUSSION

The first results results are consistent with the associations between psychosis and the jumping to conclusion bias as patients needed a significantly smaller number of beads to

take the decision: the average nbeads for the PSI group was 3.79 (SD=4.98), while the control group used an average of 8.8 beads (SD=7.13).
These results indicate a more impulsive, less analytic, reasoning style, in which less information are needed to make a decision with certainty.

Although the number of beads needed is significantly lower in the patients group, the average time taken for reasoning on each bead drawn is higher in the PSI group than the TD group: 11.9 seconds (SD=12.7) versus 6.58 seconds (SD=9.75).

This findings, together with the first ones about the number of beads requested, are consistent with the association between paranoid patients and Intolerance of Uncertainty with JTC reasoning bias being a mechanism by which IU and paranoia are linked[118]: as IU contributes to the anguish brought on by uncertainty it's possible that some participants on the Beads Task hesitate between options, ask for more beads to feel more certain about their choice, and experience decision paralysis (avoidance and paralysis are characteristic features of inhibitory IU).[112,119]

Finally, the analysis of successful answers in the two groups indicates that the cognitive bias in the psychotic patients, which is characterized by lesser required information and inhibitory intolerance of uncertainty, leads to more incorrect decisions compared to healthy controls: the PSI group had 0.806 (SD=0.191) of correct answers, while the TD group had 0.897 (SD=0.149) of correct answers (80.6% vs 89.7%).

From the confrontation of the two groups analyzing LU and MU conditions separately emerged a significant interaction only for the rate of successful answers, while for the analysis of the average number of beads drawn and the average time spent reasoning for each bead did not find any significant interaction between groups.

The first condition LU had a 0.861 rate of successful answers (SD=0.220) in the PSI group, while the control group had a rate of 0.962 (SD=0.124). The second condition MU had a 0.75 (SD=0.273) rate of successful answers in the PSI group, while the control group had a rate of 0.832 (SD=0.248).

These findings suggest that psychotic individuals (diagnosed with schizophrenia or bipolar disorder) during the Beads Task:

- Needed on average less beads to make a decision on whether the beads were drawn from the first or the second jar; this is consistent with the association between psychosis and the JTC bias.
- Used, on average, more time to reason for each bead drawn. This is consistent with the association between the paralysis of decision which is experienced with the inhibitory component of Intolerance of Uncertainty and the link between IU and JTC.
- The JTC reasoning bias and the IU led to less efficient answers, with a worsen outcome in the MU condition.

CONCLUSIONS

We considered psychosis with the bifactoral model (so included both patients with schizophrenia or bipolar disorder), the association between psychosis and JTC and IU and the JTC reasoning bias as a way in which IU emerges.

Using the Beads Task as an assessment of both JTC and inhibitory IU we analyzed the average number of beads used to make a decision, the average time used for each bead to reason and the mean rate of right answers.

The results highlight that less information are needed in psychotic individuals to make a decision, while the time spent reasoning on each bead is higher than the healthy control group. These findings may indicate that inhibitory IU, so paralysis in front of decisions, lead to jumping to conclusions to avoid uncertainty. The average rate of right answers is consistent with this hypothesis as it is not directly proportional to the time spent for each bead.

Overall, our preliminary results replicate previous literature, suggesting an alteration of the predictive reasoning in psychotic disorders.

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