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Visual multistable perception in psychosis: a pilot study

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Abstract

Binocular rivalry (BR) is a perceptual phenomenon characterized by fluctuating perceptual alternations between different images presented dichoptically. These alternations are regulated by neural circuits that modulate the suppression or enhancement of sensory stimuli. Impairments in BR have been observed in individuals with psychosis (PSI), but research on BR with interocular perceptual grouping (IO) and its neural correlates using functional magnetic resonance imaging (fMRI) is limited.

The objective of this pilot case-control study was to replicate previous findings of increased fusion images during BR in PSI, employing an ecological approach that utilized anaglyph glasses and natural images. Additionally, we aimed to investigate the effects of IO within the same methodological framework. A total of 52 (36 females,16 males) healthy controls (TD) and 37 PSI (11 females, 26 males) subjects participated in the study. Both groups underwent BR testing with and without IO. Consistent with prior research, PSI subjects exhibited a higher fusion time (43.8%, p=0.0007) during BR compared to TD (25.2%) individuals. However, the BR task with IO did not yield statistically significant differences.

In conclusion, our study successfully replicated previous literature findings of increased fusion during BR in PSI. Although preliminary, these results provide promising support for the applicability of simple and ecological approaches, particularly in an MRI environment, to investigate the neural correlates of this

perceptual abnormality in PSI. Further research is warranted to build upon these findings and gain a deeper understanding of the underlying mechanisms involved in perceptual abnormalities associated with psychosis.

Introduction

Section 1.01 Psychosis

(a) Definition

Psychosis' primary symptoms are hallucinations, delusions, disorganized speech (except for the ones caused by substance, medication or another condition), abnormal psychomotor behaviour, and negative symptoms, such as depression and mania[1].

Different conditions are defined within the DSM-5 where psychosis is a typical manifestation, such as delusional disorder, brief psychotic disorder, schizophreniform disorder, schizophrenia, schizoaffective disorder, substance/medication-induced psychotic disorder, psychotic disorder due to another medical condition and bipolar disorders too[1].

(b) History

The term "psychosis" was first coined by Karl Friedrich Canstatt[2] in 1841 as a synonymous of "psychic neurosis" so to underline the physic manifestation of a disease of the brain[3].

Throughout ancient history the illness was always connected to supernatural and religious causes and in this context was treaded, as even in the bible exorcism is used to heal a man whose symptoms were described in such a way that could fit our modern definition of the disease[4].

Even Hippocrates himself tackled a possible cause of the condition and thought it about being a dysregulation of human fluids, especially an increase of blood and yellow bile, according to the humoral theory present at the time[5].

The Kraepelinian dichotomy is a major milestone the in the disease's history as the endogenous psychosis (to be distinguished by exogenous psychosis that is triggered by outside stressor) is split into 2 diseases concepts: "dementia praecox" and "manic-depressive psychosis", respectively defined in our days as "schizophrenia" and "bipolar disorder"[6].

Kraepelin drastically changed the approach to psychiatric diseases with his "behavioral observation", but he didn't succeed to explain how psychosis comes to be, expressing hopes in future findings about the causes.

Jasper in 1913 more precisely defined endogenous psychosis's characteristic emphasizing the significance of delusions and hallucinations as core symptoms as well as establishing a new take on the pathology's diagnosis, based around the patients' subjective experience rather than just the symptoms themselves[7].

The Diagnostic and Statistical Manual of Mental Disorders, Second Edition (DSM-II) in 1968 defined psychosis as an advanced state of neurosis[8], in contrast to what Jasper defined being two different diseases[7].

Any standalone diagnosis called "psychosis" was removed in the DSM-III (1980) and psychotic disorders were classified under the broader category of "Schizophrenia and Other Psychotic Disorders"[9]. A new diagnostic approach was established, relying more and more on standardized research criteria rather than focusing on the presumed causes of mental disorders, thus granting consistency and reliability in diagnosing mental disorders[3].

DSM-IV (1994) broadened the disorders listed under the chapter "Schizophrenia and Other Psychotic Disorders", all characterized by strong psychotic symptoms, and “psychotic” is used to refer primarily to symptoms such as delusion and hallucinations[10], aligning more to Jasper’s ideology[7].

(c) Diagnosis

According to the DSM-5, the diagnosis and the consequential score both rely on the identification and evaluation of the most prominent features, which are:

- Hallucinations
- Delusions
- Disorganized speech
- Abnormal psychomotor behavior
- Negative symptoms (restricted emotional expression or avolition)

Another field of evaluation is added as it’s frequently present in patient with psychosis and it assists in predicting functional abilities. This field is:

- Impaired cognition

Additionally, two negative symptoms carry significant prognostic value as well as alert about possible mood pathology:

- Depression

- Mania

Other negative symptoms are apathy, impairment in productivity and fluency of speech, loss of initiative, poverty of ideation, difficulty in maintaining attention and impairment of interpersonal relationships, social functioning, and occupational functioning.

To each of the 8 total domain is assigned a score ranging from 0 (none) to 4 (present and severe) according to the individual's available information and the severity of the present condition.

For every disorder characterized by psychosis a different weight is attributed to each field and the score is not mandatory for the diagnosis[1].

(d) Prevalence

The incidence of psychosis is significant in our times; there is a reported median lifetime prevalence of 7.49 per 1000 (4.3 per 1000 over a 12-month period)[11]. Psychotic experiences have no meaningful difference in incidence between sex, with an average global peak around ages 17-19[12].

Suicide thoughts are frequent as they are present in 63% of patients[13] and the life expectancy is lowered by 10-15 years, especially in younger adults[14].

The heritability has been estimated to fall between 82% and 85% with a study conducted with 224 twin probands in 1999 following the more operational definition of the disease rather than just a clinical diagnosis[15].

(e) Etiopathogenesis and Pathophysiology

First-episode psychotic disorders have been linked to brain abnormalities. Through MRI significant alterations were observed in patients who were affected:

cross-sectional comparisons pointed out less grey matter in the right medial temporal, lateral temporal, and inferior frontal cortex, and in the cingulate cortex bilaterally, meanwhile longitudinal comparisons of re-scanned individuals who developed the disease pointed out less grey matter in the left parahippocampal, fusiform, orbitofrontal and cerebellar cortices, and the cingulate gyri. This way is possible to define some alterations of the grey matter that predates the frank symptoms and others who instead show only after the first episode[16]. Abnormalities in corpus callosum in particular, both in size and shape, seems to heavily influence the first episodes of psychosis[17].

The altered structures may be the consequences of genetic influences, with a heritability estimate of 82-85%[15]. This gives reasons to believe that the first abnormalities may be already present during the development in the utero[18].

Although the genetic factors play a central role in primary psychotic disorders, the addiction of epigenetic and environmental components are the main responsible for a full-blown illness. The exogenous factors may very well be the only cause of the illness, as psychosis it's a typical symptom of substance use, or another neurologic or medical condition[1].

Dysregulation in two main neurotransmitters' function is involved in psychosis's pathophysiology: the dopamine's and the glutamate's one.

The discovery of dopamine dysregulation's involvement in psychosis is a byproduct of the use of neuroleptics as a treatment[19], but how it happens was defined only in 1999 when Moore hypothesized that abnormal dopamine transmission in different brain regions contributes to the distinct symptoms observed in the disease. Excessive dopamine in limbic regions may cause positive symptoms like delusions and hallucinations, while inadequate dopamine in cortical regions may contribute to negative symptoms such as cognitive impairments and reduced motivation. Their proposal suggests that specific antipsychotic medications may be targeted to regulate dopamine transmission in different brain areas based on the main symptoms[20].

The glutamate neurotransmitter involvement gained more relevance thanks to discoveries about a common GRM3 haplotype strongly associated with schizophrenia. The allele is linked to a poorer performance on cognitive tests of both hippocampal and prefrontal area, where it was more heavily detected in postmortem analysis[21].

The most important findings about this excitatory neurotransmitter are about its receptors, especially the decreased function of the N-methyl-D-aspartate (NMDA) glutamate receptor[22]. The reduced function of NMDAr is the reason of the excessive release of both glutamate and acetylcholine in cortical region, thus overstimulating a downstream of excitatory neurons, while the lack of receptor excitation on interneurons is the cause of loss in overall network inhibition[23].

Section 1.02 Unitary psychosis and psychotic disorders

The Kraepelinian dichotomy[6] set a difficult framework to move within, as distinguishing between the two could be challenging, and there was a history of misdiagnosing psychotic mania as schizophrenia or other psychotic disorders[24].

Indeed, psychotic symptoms are frequently observed during both the manic and depressive phases of bipolar disorder and 58% of patients had a lifetime history of at least one psychotic symptom, usually when manic. On average, 48% of patients display at least one delusion, 15% one hallucination, and 19% display formal thought disorder[25].

While throughout the DSM editions new criteria were set to account of this manifestation of different disorders, in 2009 a study still found the existence of a significant overlap between schizophrenia and bipolar disorder, challenging the strict categories imposed by the DSM-IV[26].

In 2013 the limitations of the DSM-IV were shown again as Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP) found an overlap of psychotic symptoms in different disorders, suggesting that the traditional ways of categorizing and diagnosing certain conditions may not accurately capture distinct patterns of observable traits or features[27], while other findings revealed that when relying on traditional diagnostic categories (such as those outlined in this edition[10]), there can be significant variations or differences in the observed biomarkers (measurable indicators) across different research laboratories. This implied that using DSM-IV diagnoses as a standard reference point may not fully capture the underlying complexities and heterogeneity of the conditions[28].

Finally, in the DSM-5, a rigid categoric system was dropped in favour of the introduction of the "spectrum" and more flexible conditions for diagnosis[1].

(a) Cognitive impairment

The cognitive state of the patient can be studied through different tests, each made to identify and evaluate possible manifestation that characterize the disorder, like the Mini Mental State Examination (MMse)[29], The Montreal Cognitive Assessment (MoCA)[30] or MATRICS™ Consensus Cognitive Battery (MCCB)[31].

While cognitive dysfunction is not a symptom specific to psychotic disorders, it remains a central characteristic of conditions that encompass psychotic symptoms[32].

During an 18-year study of a cohort experiencing their first episode of psychosis, it was observed that cognitive performance gradually deteriorated in areas such as verbal memory, visual memory, attention and processing speed, as well as abstraction-executive function. These declines were consistent in magnitude across various psychotic disorders[33].

It's established that schizophrenia is associated with neuropsychological deficits[34], with patients showing generalized impairment relative to controls and a selective deficit in memory and learning compared with other functions to be linked with the disfunction of the temporal-hippocampal system[35].

Deficits are also about abstraction and executive functions, and processing speed and attention with significant heterogeneity across individual cases[36,37].

Individuals diagnosed with schizophrenia exhibit a significant decline in overall cognitive performance, typically averaging two standard deviations below that of healthy individuals[31].

The seven cognitive deficits that stand out across literature and studies on schizophrenia and thus make the criteria of the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) are: working memory, attention/vigilance, verbal learning and memory, visual learning and memory, reasoning and problem solving, speed of processing, and social cognition[38,39].

In individuals with bipolar disorder, significant effects were observed for executive functions (working memory, executive control, fluency) and verbal memory. Moderate effects were found for aspects of executive function (concept shifting, executive control), mental speed, visual memory, and sustained attention. In first-degree relatives, small effects were observed but still significantly different from healthy controls, particularly in executive function and verbal memory[40].

A deficit in response inhibition, which may indicate dysfunction in the ventral prefrontal cortex, appears to be the primary endophenotype of bipolar disorder (BD). Set shifting, along with verbal memory and sustained attention, emerged as cognitive domains that meet the criteria as potential endophenotypes of bipolar disorder. Additionally, cognitive impairments related to fronto-temporal and fronto-limbic functioning are also observed as part of the cognitive endophenotype of BD[41].

There is evidence indicating that individuals with mood disorders accompanied by psychotic symptoms exhibit similar cognitive impairments as seen in schizophrenia. These impairments affect areas such as episodic and working memory, executive functions, and attention[42].

(b) Alterations of perception

Schizophrenic patients show multiple possible alterations in perception such as deficit in early auditory processing in tone matching[auditory][43], mismatch negativity generation (a negative deflection in the ERP waveform that occurs when a deviant or unexpected auditory stimulus is presented among a sequence of standard or expected stimuli) [auditory][44], reduced pitch discrimination accuracy[auditory][45], increased intra-individual reaction time[auditory][46], reduced ability to detect phonetic boundaries[auditory][47] and substantial impairments in reading ability[visual][48].

Patients with bipolar disorders potentially display a vast array of dysfunctional perceptual mechanisms such as having difficulties recognizing objects and perceiving the spatial location of visual stimuli[visual][49], deficit in dot motion trajectory discrimination and in moving grating performance[visual][50], lower flicker fusion frequencies[visual][51] and deficits in frequency discrimination (however, less then patient with schizophrenia) [auditory][52].

Patients with psychotic disorders showed deficit while performing shine-through masking paradigm[visual][53], deficits in frequency discrimination[auditory][52] and deficits in visual motion integration[visual][54].

Hallucinations, the greatest manifestation of dysfunctional perceptual pathways, are a core component of schizophrenia and psychotic disorder according to DSM-5, described as perception-like experiences that occur in the absence of any external stimulus. They are characterized by their vivid and clear nature, resembling normal perceptions in terms of their intensity and impact[1].

When an individual experiences a hallucination and lacks insight or awareness that the hallucination is not real, it suggests impairment in their ability to accurately distinguish between their internal experiences and external reality. This lack of insight into the hallucination is considered a key feature of psychosis, indicating a significant departure from normal perception and reality testing[55].

Moreover, although hallucinations are prominently associated with psychotic disorders, they are also documented in various other significant psychiatric conditions, such as bipolar disorder and unipolar depression[56], intoxication and withdrawal from substances[57], anorexia and bulimia nervosa[58].

There are different types of hallucinations with the most common one in schizophrenia being auditory, followed by visual, tactile, olfactory and gustatory hallucinations[59]. Each of them possesses variable (mean) prevalence among psychotic disorders, such as 59% for auditory and 29% for visual hallucinations in schizophrenia and 28% for auditory and 15% for visual hallucinations in affective disorders[60].

Phenomenon	Description
Hallucination	Sensory perception in the absence of a stimulus; described according to the sensory domain in which it occurs (eg, visual, auditory, tactile, olfactory, gustatory, nociceptive, themoceptive, proprioceptive, equilibrioceptive); may be unformed (ie, nonspecific sensory perceptions within a sensory domain) or formed (ie, people, objects, voices making comments or commands)
Illusion	Misperception of a sensory stimulus; described according to the sensory domain in which it occurs (eg, visual, auditory, tactile, olfactory, gustatory, nociceptive, themoceptive, proprioceptive, equilibrioceptive)
Palinopsia	Persistent perception of a visual stimulus after that stimulus is no longer present (ie, an afterimage)
Synesthesia	Perception of a stimulus outside the sensory modality in which that stimulus is presented (eg, hearing colors, tasting sounds) or that adds perceptual features not normally perceived within a sensory modality (eg, black numbers or letters evoking the perception of color)
Derealization	Perceiving/experiencing the external world as unreal
Depersonalization	Perceiving/experiencing oneself as detached from (ie, as if an outside observer of) one's mental processes or body
Autoscopy	Seeing one's body from a position outside the body (ie, out-of-body experience)
Déjà vu	Perceiving/experiencing a novel image or scene as one previously witnessed or experienced
Déjà entendu	Perceiving/experiencing a novel sound as one previously witnessed or experienced
Jamais vu	Perceiving/experiencing a familiar image or scene as unfamiliar
Jamais entendu	Perceiving/experiencing a familiar sound as unfamiliar

[a] Adapted with permission from Arciniegas DB, Cambridge University Press.[10] © 2013 Cambridge University Press.

Figure 1 Disturbances of Perception and Experience in the Differential Diagnosis of Hallucinations[61].

The predictive coding can provide an explanation of the predominant occurrence of hallucinations in psychotic disorder: in accordance with this theory the influence of prior beliefs can alter perceptions since the very first episode of psychosis[62] and then evolve in much broader manifestations[63]. The employment of this system by the brain to make sense of reality could explain core characteristic of psychotic disorders (such as impaired reality testing[1]), as the main neural circuits used by predictive coding are usually altered in patients[64].

Perceptual alterations in psychotic disorder, especially in the visual field, find their neurobiological explanation in dysfunctional neural circuits: thanks to the binocular rivalry as a mean of study it was found significant disruption of the dopaminergic system[65],the GABAergic system[66] and the serotonergic system[67].

The DSM-5 attributes great value not only to perceptual alterations themselves but also to symptoms that provide evidence of such impairment, such as delusions[55]. Delusions are fixed beliefs that are not amenable to change in light of conflicting evidence with variable themes like persecutory, referential, grandiose, erotomaniac, nihilistic and somatic, plus the additional category “bizarre” when clearly implausible. What differentiate these from a strong idea is the degree of conviction for which the belief is held despite clear evidence of the contrary[1].

Illusions should be distinguished by hallucinations, as they are the misinterpretation of an actual, real, external stimulus[1].

(c) The link between cognition and perception: Predictive coding and the Bayesian approach

According to the theory of predictive coding, neural networks have the ability to learn and encode the statistical regularities present in the natural world. By doing so, they aim to minimize redundancy by eliminating the predictable elements of sensory input and instead they primarily transmit the information that is not easily predictable, which is referred to as the residual errors in prediction. In essence, predictive coding suggests that the brain's processing involves generating predictions about incoming sensory information and focusing on the deviations or unexpected aspects of the input[68].

The theory finds its roots in Helmholtz's work where he defines an involuntary mechanism the premise of the formation of different visual perception based on the same external stimuli[69]. This the first proposed theory about multistable perception, of which the binocular rivalry is an excellent example alongside the Necker's cube (figure 2 A) and Lissajous figures (figure 2 B)[70].

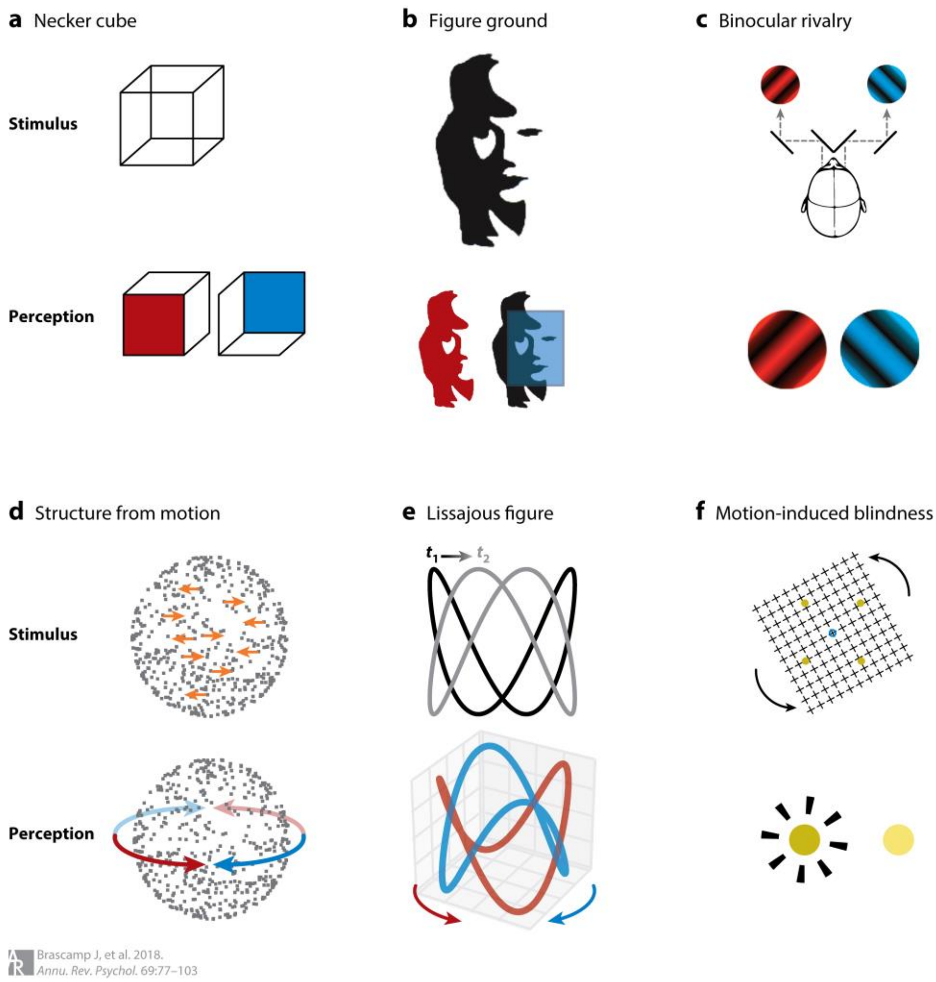

Figure 2 Examples of multistable perception: stimuli (top row) and their perception (bottom row).

It later developed in Bruner's "Value and need as organizing factors in perception" in which is demonstrated that our perception is based not only on rational and rigid determinants referred as "autochthonous", but instead a more personal and adaptive determinants, referred as "behavioural", are involved too[71].

The theory took a more modern shape with the publication of Mcalland and Rumelhart in 1981 where, on a continuum of Rechier's work in 1969[72], two different pathways are set to define the finalized perception of stimuli; the "top-down" pathway, or "conceptually driven" pathway, finds its bases in knowledge and past experiences, meanwhile the "bottom-up" pathway, or "data driven", derives directly from the senses[73].

These two pathways are not isolated and instead they work in conjunction to determine what is perceived.

In 1999 a more complex system was described by Rao and Ballard where a hierarchy of networks operate together to produce a final perception. The system takes accounts of "errors" too, "error" being described as a difference between an input signal and its statistical prediction and implements the new knowledge so to improve itself following the Bayes' theorem[74]. The bayesian approach follows Bayes' rule[75]:

$$P(A|B) = \frac{P(B|A)P(A)}{P(B)}$$

Figure 3 Bayes's theorem: A and B are events and P(B)≠0. P(A|B) is the probability of A happening if B it's true (posterior probability). P(B|A) is the probability of B happening if A it's true (likelihood). Both P(A) and P(B) are the probabilities of observing A and B respectively without any given conditions (prior probability and marginal probability).

The formula itself defines the probability of an event given no prior knowledge of conditions that may affect it and the system described by Rao and Ballard uses the same formula to constantly update the probability of the event at every level of the hierarchy as more information come from the feedforward connections. The continuous application of the rule as more variable are integrated is defined as "Bayesian inference" and it's continually and unconsciously applied by the nervous structure in a never-ending quest to predict the inputs[76]. Errors, the mismatch between predictions and inputs, and the successive integration of them in the system are the bases for learning and making knowledge and thus helping the brain to make more accurate, future predictions.

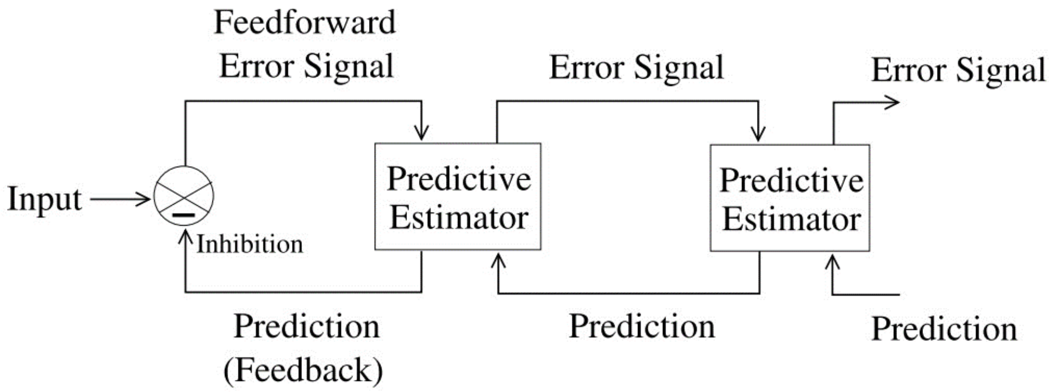

Figure 4 Feedback pathways in this neural network carry predictions or expectations of neural activity from higher-level areas to lower-level areas. Feedforward pathways transmit the residual errors, which are the differences between the predicted neural activity and the actual observed neural activity at each level. The predictive estimator at each hierarchical level utilizes these residual errors to update and refine its current estimate of the input signal. By continuously comparing predictions with actual neural activity and adjusting the estimates based on the prediction errors, the system aims to optimize its predictions and improve the accuracy of the overall representation of the input signal.

The precision of priors and sensory data determines their relative impact on the inference process and learning, with prediction errors playing a crucial role in updating the current understanding based on the balance between prior expectations and sensory information[77].

In terms of neural implementation predictive signals are sent from higher hierarchical levels predominantly via glutamatergic *N*-methyl-D-aspartate receptor (NMDAR) signalling[78,79] and an alteration in this pathway is linked with schizophrenia[80] and bipolar disorder [81].

Dysfunction in the brain’s dopamine regulation is to be linked to abnormal integration of the Bayesian inference, the premise of predictive coding, thus disrupting the balance between feedback/feedforward integrations in favour of the latter; this causes an increase in the precision of the likelihood (which is the probability of the observed effect given the particular hypothesis considered at the time[76]),resulting in the abnormally strong weighting of prediction error[64].

Predictive coding is thus capable to explain how perceptual alterations come to be in the psychotic disorders; hallucinations, for example, can happen both in healthy and psychotic individuals. To alter the healthy individual’s predictive coding we can use “sensory deprivation” for a prolonged amount of time: this way we artificially reduce the value of current sensory information and the top-down system gains more meaning. We currently have in the healthy individual the alteration we observe in the psychotic patient, where the feedforward circuit is intrinsically strengthened[64]. Now, perceptual inferences are not anymore guided by the sensory inputs and hallucinations can happen, as the brain constantly tries to make sense of the world employing top-down pathway independently of any actual stimulus is present or not[76].

Section 1.03 Multistable perception during binocular rivalry

(a) History: from Gianbattista Della Porta to our days

One way to observe the brain’s employment of predictive coding is through the sense of sight where cortico-cortical feedbacks are used with the feedforward connections to encode perceived natural images[74,82].

In order to do so binocular rivalry can be used: it was first described the Gianbattista Della Porta in his work where he noticed the need to shift focus from one to book to another one in order to read even if they were placed respectively in front of his eyes. In Porta's writings it was explained by a theory for which the sense of sight uses just one eye at the time, alternating with the other when needed or forced[83].

It was Wheatstone in 1838 who made possible through his experiments an evolution about the understanding of how vision works, demonstrating the requirement of a coordination of information between the two eyes[84]. Using the stereoscope that he himself invented Wheatstone managed to prove that stereopsis, a component of depth perception, relies on both eyes working simultaneously and described a phenomenon for which images that permitted "double interpretation" cause indetermination in perceptual judgment, famously citing the Necker's cube (figure 2 A)[84].

However, he couldn't explain the phenomenon described by Porta still, blaming it on a lack of attention of the observer's mind.

It was Breese who first made a more comprehensive approach to the case observed by Porta first and Wheatstone later, named "binocular rivalry", and set up a system that would be the base of modern experiments: in his experiment he uses two squares, one red and one green, first with diagonal lines then with vertical and horizontal lines on for each, that are placed in a stereoscope. The task of the observer was then to use two keys, respectively for one hand and color, connected to a kymograph drums, so to detect the changes of the rival stimulus[85,86]. Still, no explanation of how or why it happened was made, as only with Helmholtz later on a first possible theory (see Section 1.03 B)[69] was proposed, but Breese's work set the fundamentals of the material that is still used in the modern day to study the phenomenon. In each and every of these experiences it's imperative to understand that is not the stimulus that is changing, as the words on the books stay the same as well as the images in the stereoscope, but it's the perception of them what changes[76].

The characteristics of the stimulus itself were the focus of Meenes' work as he arranged different experiments to define not only what is the cause of the phenomenon but especially how strongly its perception could be affected. Pattern, color, dimension, movement of the stimulus and even the observers' tint of the glasses could influence the predominance (or the weakness) of perception and thus of the rivalry[87].

Important observations were made by Levelt in 1965 when he described a new fundamental characteristic of the stimulus itself as a main variable: the stimulus' strength[88]. According to Levelt the strength of the stimulus is defined by contrast, density and blur of the contours that make up an eye's stimulus itself and, during binocular rivalry, it can be assessed by the physical traits of the stimulus in one eye that suppress the stimulus presented to the other eye.

Levelt describes this mechanic working in 4 ways, to be defined as "Levelt's four propositions":

1. Increase of the stimulus strength in one eye will increase the predominance of the stimulus.

2. Increase of the stimulus strength in one eye will not affect the average dominance duration for the same eye.

3. Increase of the stimulus strength in one eye will increase the alternation frequency.

4. Increase of the stimulus strengths in both eyes will increase the alternation frequency.

These principles stood as reference points throughout every successive study about binocular rivalry and while pretty much remaining the same in concept they found some improvement so to fit more into their restrictive field of application[89]:

1. Increasing stimulus strength for one eye will increase the perceptual predominance of that eye's stimulus.

2. Increasing the difference in stimulus strength between the two eyes will primarily act to increase the average perceptual dominance duration of the stronger stimulus.

3. Increasing the difference in stimulus strength between the two eyes will reduce the perceptual alternation rate.

4. Increasing stimulus strength in both eyes while keeping it equal between eyes will generally increase the perceptual alternation rate, but this effect may reverse at near-threshold stimulus strengths.

Meenes' article in 1992 is the foundation of successive studies that tied together a single characteristic of the object to the perception of it during the rivalry; in this publication is shown that the incidence of periods of exclusive visibility of a given eye's rival target increases with decreasing target size. These results were not attributable solely to reduced peripheral acuity but instead to what was described as “spatial zone of binocular rivalry”: a set of concentrically organized zones of rivalry that do not function independently but instead exhibit a high degree of mutual excitatory cooperativity. The result is a piecemeal rivalry where is suggested that any of the “zones” of the perception correspond to hypercolumns in visual cortex[90].

Other attributes also have been studied, like the motion[91] and color[92].

Another aspect that needs to be considered is the timings of the perceptions of the stimuli: the task set out by Fox and Hermann found that not only the frequency distribution of the phases when the images are overlapped or seen independently can be mathematically described but also that the temporal lengths of rivalry phases are sequentially independent[93].

In our modern times, the multistable perception is defined as being regulated mainly by three systems:

1. Dopaminergic system (excitation)[65]
2. GABAergic system (inhibition)[66]
3. Serotonergic system (excitation)[67]

These systems, and thus their disfunction, are involved in regulating the excitatory/inhibitory balance regarding vision inputs. Disturbances in these same neural networks were found in psychotic disorders such as schizophrenia, with significant alteration especially located in the prefrontal cortex,[94] in the autistic spectrum[95] and in bipolar disorder type I and type II[96].

While how these systems are involved in such disruptions it's still unclear, it's clear the interference they cause in the timings of bistable perception, which translates to slower switching dynamics for binocular rivalry in psychotic disorders, such as bipolar disorder[97], schizophrenia[98] and the relatives of the patient with such disorder[99],maior depression[100] and autistic disorders as well[101], when compared to healthy individuals, who's rate at which perception switches is quite stable over time[102].

(b) Binocular rivalry and interocular grouping

Binocular rivalry occurs when the eyes are presented with different stimuli and subjective perception alternates between them; according to the predictive coding the fluctuation is caused by the conflict between the two images and when one stimulus becomes dominant in perception, the incoming sensory signals that support that stimulus are interpreted and explained by the brain. However, the sensory signals related to the suppressed stimulus are not fully explained and remain as prediction errors. This presence of unexplained (yet possibly explainable) prediction errors creates instability in perceptual dynamics, leading to the occurrence of perceptual transitions or alternations during rivalry[103].

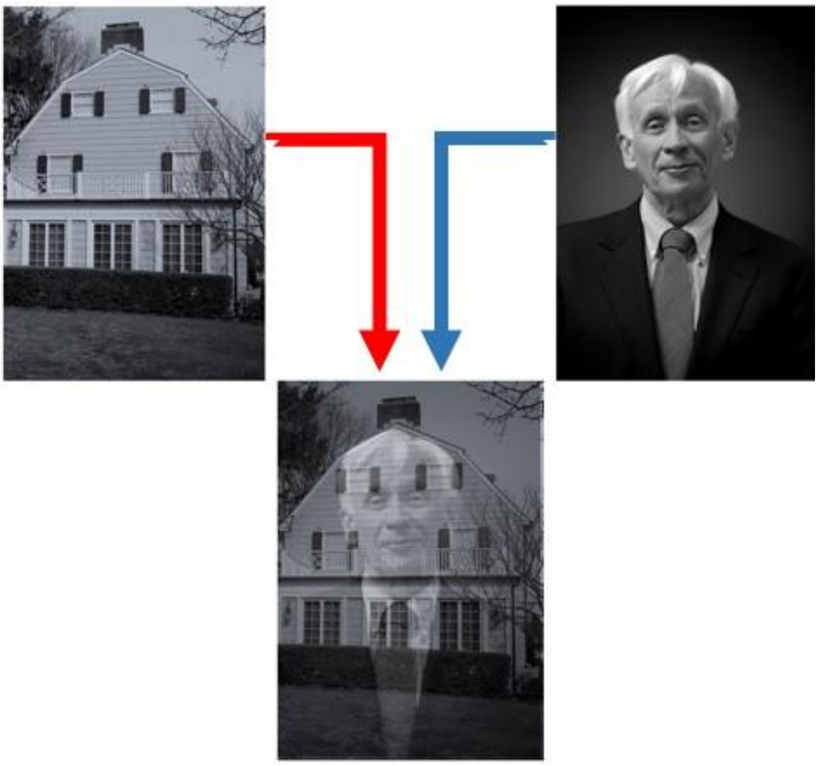

Figure 5 During binocular rivalry, dichoptically presented images like the man and the house are perceived as a mix of both, with fluctuations in the strength of the stimuli.

Key features of the phenomenon were proposed by Leopold and Logothetis in their review article in 1999 where they suggest that:

- Perceptual reversals are often initiated spontaneously or voluntarily, influenced by subjective factors such as attention and mood
- With practice, the ability to alternate perceptions becomes more efficient, indicating a learned or behavioral aspect. Lesions in non-visual cortical areas can affect this process
- The temporal dynamics of perceptual alternation are similar to those of behaviors that are spontaneously initiated

- Functional imaging studies have shown that brain areas associated with various cognitive behaviors are specifically activated when the visual perception becomes unstable during perceptual reversals[104]

Also in 1999, based upon Breese's work[85,86], Alais and Blake published a comprehensive study of the deepened knowledge gathered throughout the century and added another possible variable of the perception during rivalry: the Gestalt grouping[105].

This study stemmed directly from a first description of what is called "interocular grouping" provided by Diaz-Caneja in 1928: in his books he describes a scenario in which two different images are presented to each eye, but instead of presenting complete images to each eye, the images are cut in half and combined: for instance, one eye sees half of a house and half of a face, while the other eye sees the other halves of the house and the face. In this case, there is no rivalry between the two halves presented to each eye but instead there is rivalry between the full, uncut images of the face and the house[106].

Another milestone was provided in the 1996 publication of "when the brain changes its mind" (Kovacs et al.)[92] where grouping was shown to involve more than just eye competition, but a high-level cortex process, well above where binocular rivalry was thought to happen.

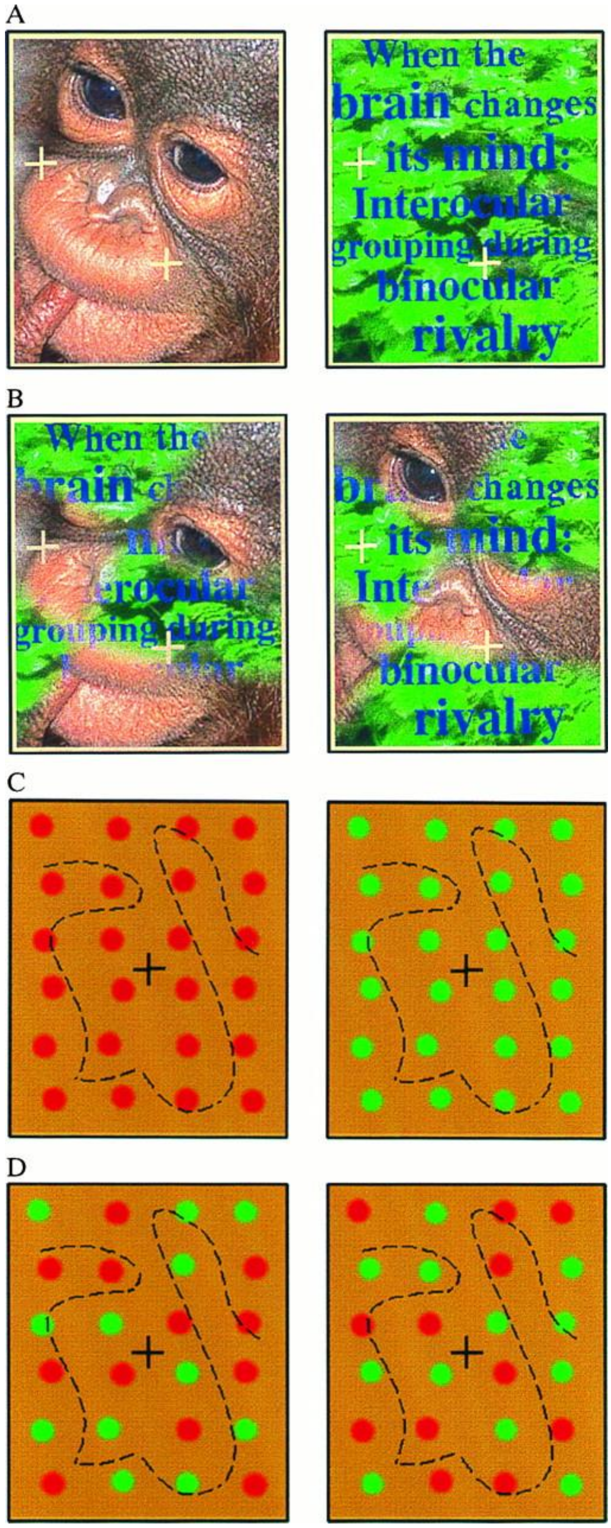

Figure 6 The dichoptic pairs shown in A–D induce binocular rivalry when brought into correspondence by means of converging (or diverging) the eyes (the black fixation marks should be fused).

Gestalt grouping finds its roots in a school of thought called Gestalt Psychology that was born in direct contrast with Helmholtz's ideas based around structuralism and behaviourism; it states that we best understand psychological phenomena when we view them as organized, structured wholes, a concept that defines how interocular grouping comes about[92]. According to this view, we cannot fully understand behaviour when we break the phenomena down into smaller parts[107].

Undoubtedly the most prominent author and founder of this school is Max Wertheimer, whose first paper published in 1913 is to be considered the fundamental of the theory itself. The experiments conducted by the czech-born psychologist were about the "Phi phenomenon", where two light lines or curves were repeatedly presented one after the other using a tachistoscope so to make the observers (in this case Wolfgang Köhler and Kurt Koffka, the other two founders of the Gestalt school) perceive an apparent motion[108]. These findings further demonstrated that the quality of the whole is different from just the sum of the parts[109].

Further development was made by Irvin Rock who managed to prove his hypothesis that the perceptual phenomenon could be explained by the involvement of high level mental system instead of a mere process of automation when tilted and not tilted observers still identified the same shape (a diamond) coming from the same object (a leaning square)[110], a theory openly in contrast with the Gestalt theory that denied the involvement of high-level processing stage in the making of perception. It's important to note that this does not mean that there isn't a low-level process stage but just that it is not the only one happening during grouping[111].

Although differences emerged between Rock and Wertheimer about “how” the perception comes to be, both found common ground in what first Wertheimer called in his book “principles of grouping”[112]: these are a set of principles used by the human mind so to seek patterns in the stimuli in order to perceive the object. Rock than expanded and more precisely defined the categories, which were even more broadened in more recent times by Professor Stephen E. Palmer, who also suggests an even higher function than the one proposed by Rock to be involved in perceptual grouping[113,114].

The categories are:

- grouping by proximity
- grouping by similarity of color
- grouping by similarity of size
- grouping by similarity of orientation
- grouping by common fate
- grouping by symmetry
- grouping by parallelism
- grouping by continuity
- grouping by closure
- grouping by common region
- grouping by synchrony

As theoretical they may appear we can see the application in everyday world, even in nature, where the camouflage, for example, relies on these principles to function. Albeit a very important one, grouping is one particular kind of organizational phenomenon such as region segmentation, parts and wholes, figure-ground organization, parsing, visual interpolation and frames of reference[111].

Interocular grouping seems to defy local competition rule of the binocular rivalry such as the stimulus strenght[88] as the perception is determined by a global stimulus structure. It also unequivocally proves that the binocular rivalry occurs at the cortex level as the stimulus' inhibitions/excitations are coherent not to the image perceived by one eye but instead to the picture as a whole generated in the cortex's higher levels[92], moving beyond a simpler model where before the signals from the left and right eyes merge, reciprocal feedback inhibition helps to regulate the visual perception[115].

Objectives of the study

A case-control pilot study aims to replicate the available literature that reported in psychotic disorder higher fusion time during binocular rivalry using more ecological methodology.

Alongside a case-control pilot study is conducted to investigate the use of interocular grouping as a method of study in psychotic disorders, capable to stimulate higher cortex involvement rather than just peripherical regulation of perception, with the same methodology.

Methods

Section 3.01 Study design

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

A Samsung A7 (10 inches) was placed on a table in front of seated subjects, at 70 cm from the eyes. The patients were then instructed to wear the anaglyph glasses and to press different areas of the screen accordingly to what was perceived.

Images used during binocular rivalry:

Images used during interocular grouping:

Other images with alternations of colours or positions of the halves were used as well.

Section 3.02 Study population

We recruited 37 participants affected by psychotic disorders (n=37) with or without treatment with antipsychotic drugs, hospitalized or in charge mental health services, of which 11 were females and 26 were males. Furthermore, a group of healthy controls (n=52) has been selected, of which 36 were females and 16 were males.

Section 3.03 Participants

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 of 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).

Section 3.04 Medical examination and evaluations

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

(a) Questionnaires and evaluations

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

(b) Binocular rivalry and interocular grouping

Alterations in perceptions core features of psychotic disorders as well as in subjects at risk of psychosis. One well-replicated paradigm able to access this alteration is known as “binocular rivalry”.

In this new approach, two different images (a face and a house), both red or cyan colour coded, are presented to each eyes using anaglyph glasses for 150 seconds each. The subject then is asked to select on the screen “face” and/or “house” according to what is perceived. During the whole task, two phases of rivalry for a total of 300 seconds were alternated with two phases of grouping (150 seconds each) for a total of 300 seconds. The whole test session took 600 seconds.

Another way to access perception's alteration is through interocular grouping. In this pilot study grouping, a subcategory of binocular rivalry, was observed using the same methodology, pictures and colour schemes used in the rivalry but in this case the images were vertically split in half: one half, alternated both in position (left/tight) and colour (red/cyan), was either half of the face or half the house, meanwhile the other half was the opposite picture but in the same colour scheme.

In both rivalry and grouping 3 measurements were made: time spent pressing one condition, two conditions and no conditions.

Section 3.05 Data management

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

Section 3.06 Data analysis

Multivariate statistical models with R SOFTWARE were employed to analyse the differences between patients (affected by schizophrenia or bipolar disorder) and healthy controls in:

- Time spent pressing both inputs (when fusion occurs)
- Time spent pressing one inputs (when fusion didn't occur)
- Time spent not pressing both inputs (when fusion didn't occur)

Differences within these three values across the two conditions (rivalry and grouping) and two groups were investigated by means of a two ways ANOVA.

Results

The analysis gave these final results:

Group	Cond	Unique	Fusion
PSI	G	25.6 ±25.8%	66.5 ±29.4%
	R	51.2 ±31.5%	43.8 ±31.9%
TD	G	29.2 ±24.2%	66.5 ±26.0%
	R	71.3 ±17.3%	25.2 ±17.0%

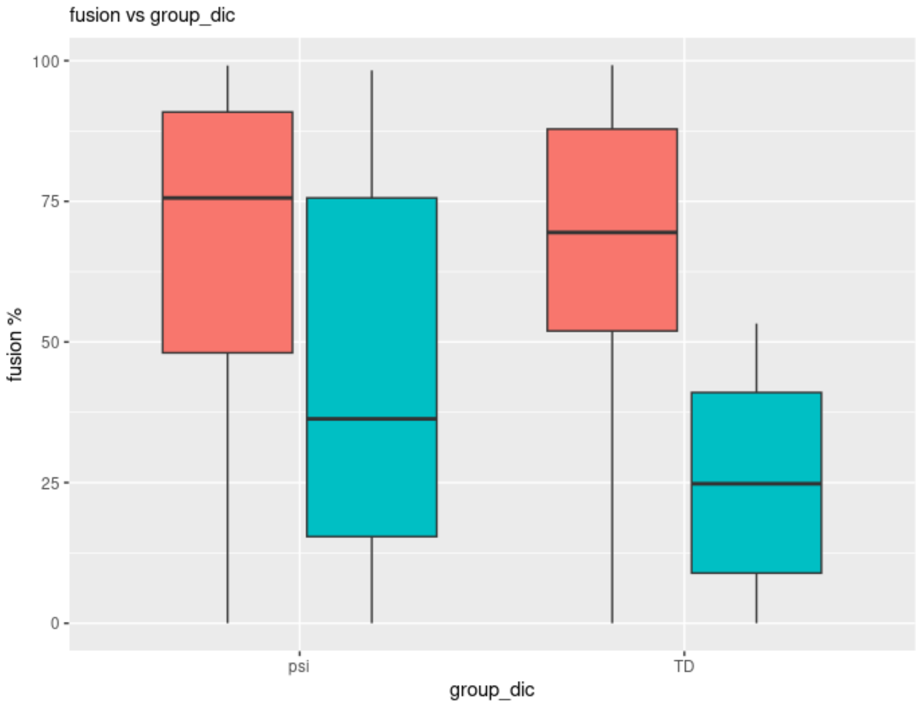

Figure 7 Higher fusion time in PSI compared to TD (red is grouping, blue is rivalry).

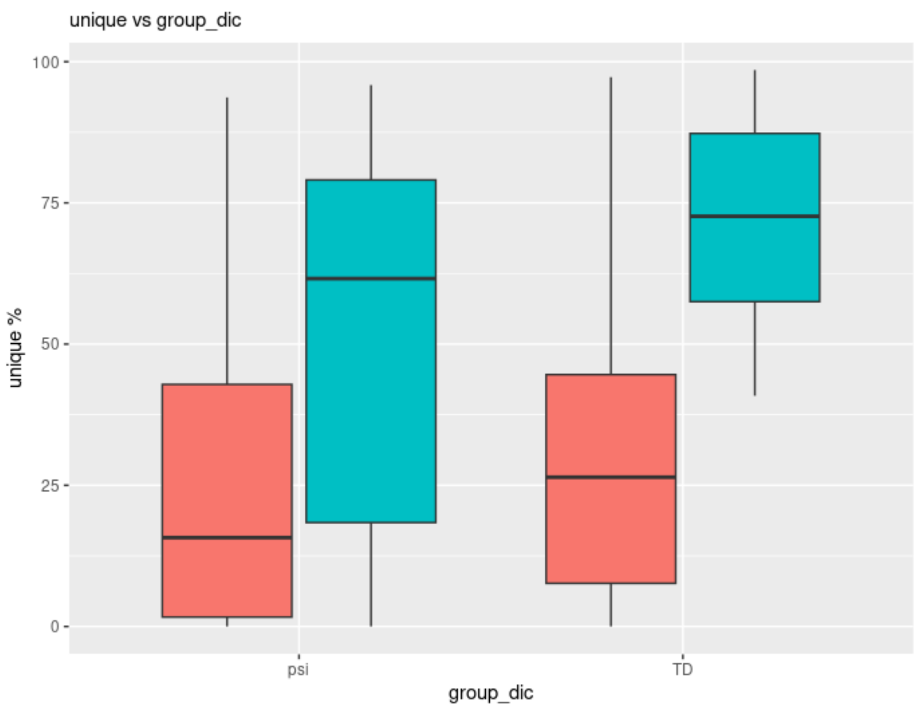

Figure 8 Lower unique time in PSI compared to TD (red is grouping, blue is rivalry).

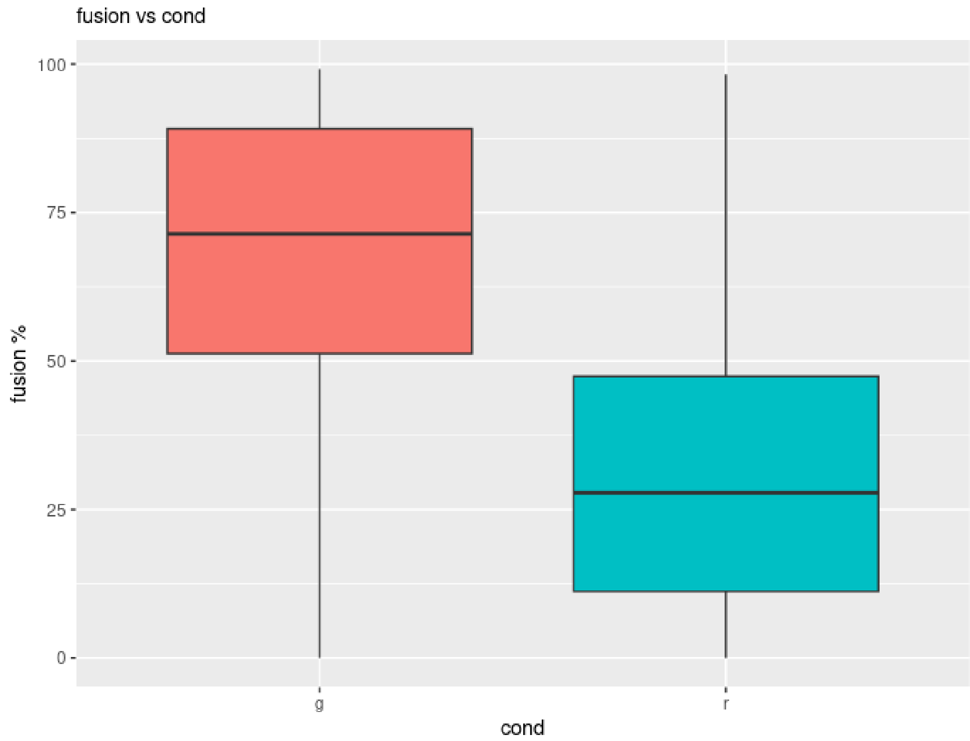

Figure 9 Fusion time in conditions.

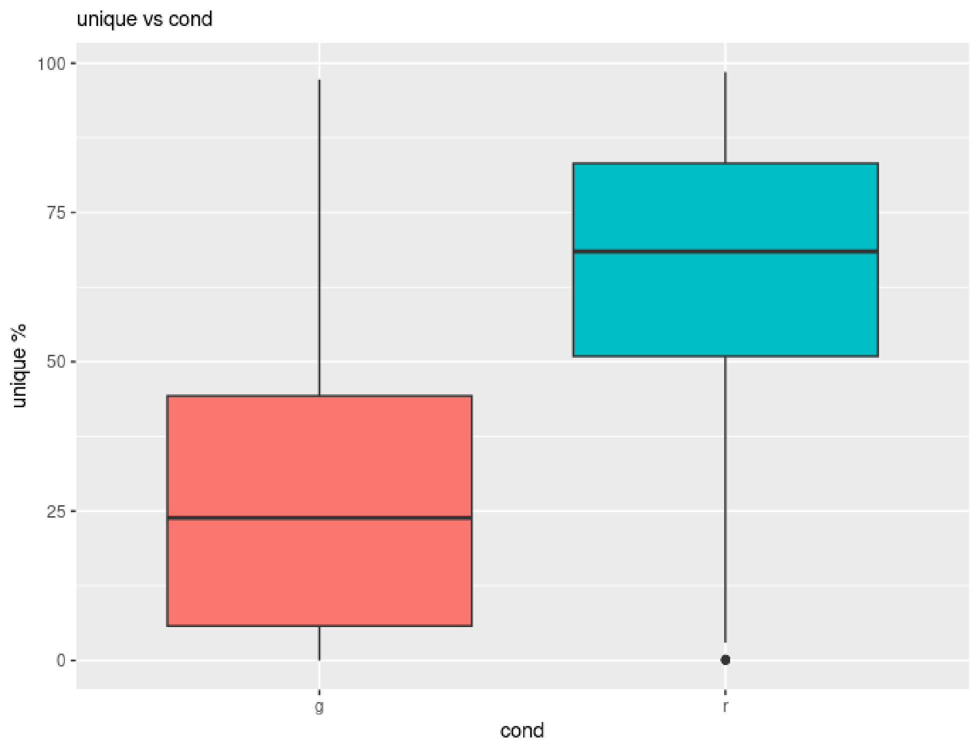

Figure 10 Unique time in conditions.

A “three X two” analysis model using two ways ANOVA provided the following results:

Factors	f	P
None		
Group	56.8115	<0.00001
Cond	0.3063	0.5802
Group X Cond	0.0948	0.7583
Unique		
Group	22.229	<0.00001
Cond	238.534	<0.00001
Group X Cond	11.816	0.0006
Fusion		
Group	11.453	0.0007
Cond	195.392	<0.00001
Group X Cond	13.417	0.0002

In condition “Rivalry” both psychotic patients had higher fusion rate than TD group.

In condition “Grouping” there are no differences between groups.

Discussion

Section 5.01 Binocular rivalry

The binocular rivalry results are coherent with the literature: patients affected by psychotic disorders score higher fusion time compared to controls, which is to be attributed to altered neural pathways leading to disruption in perception.

Section 5.02 Interocular grouping

The interocular grouping results are not aligned to the expected results: the task forces the implementation of neural circuit at higher levels than rivalry but no meaningful difference in fusion time was found between the groups of the study.

Conclusion

Section 6.01 Binocular rivalry

Using the binocular rivalry task as a mean of study of the visual multistable perception, it was analysed the average time where one or both stimuli were perceived. The results highlight that in the psychotic disorder there is a higher fusion time than healthy control group. These findings replicate previous literature, linking together psychotic disorders and perceptual alterations.

Notably this result was accomplished using more ecological methodology rather than the involvement of more invasive approach, such as TMS[70]: this promising result could lead to future application of this procedure, as an MRI study already in developing is employing such technique.

Section 6.02 Interocular grouping

Using the interocular grouping task as a mean of study of visual multistable perception, it was analysed the average time where one or both stimuli were perceived. The results found no meaningful difference between the patients and controls to be potentially attributed to multiple factors (e.g., the glasses could have been not enough to isolate each hemifield for grouping to occur, the images chosen could have been not capable to bypass peripherical stimuli regulation, the subjects could have had difficulties to define with a simple fusion/no fusion input the more complex grouping's perceptual shifts rather than rivalry's and thus a sliding input would have been more appropriate to register the subject's changing of perception).

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