NEURAL CORRELATES FOR CORRELATED PHENOMENOLOGY: A COMPARISON OF NETWORK CONNECTIVITY CHANGES IN PSYCHOSIS WITH ACUTE CHANGES FOLLOWING SEROTONERGIC PSYCHEDELICS

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ABSTRACT

Psychosis is a disordered mental state characterized by the presence of delusions and hallucinations which can be profoundly disabling and difficult to treat. Historically, psychiatric researchers observed similar mental states in subjects acutely intoxicated with the classical serotonergic psychedelics such as Psilocybin, LSD and Mescaline. Since the 70s, prohibition and Schedule 1 classification of these substances has hindered research into their mechanism of action and therapeutic potential. A resurgence of neuroimaging research with psychedelics in the past decade has shed light on the neural correlates of their hallucinogenic properties. Consistent patterns of network connectivity changes have emerged that bear a striking resemblance to changes seen across all stages in the clinical progression of psychotic disorders.

This review will summarise and evaluate the evidence that network connectivity changes in the brain following intoxication with psychedelics are comparable to those observed in subjects at multiple stages in the progression of psychosis. In addition, candidate theories that link neuronal changes to common subjective and behavioural changes will also be presented. Understanding the neurological basis of this disordered mental state by researching healthy subjects that transiently exhibit the same behaviours has the potential to inspire and inform new scientific and clinical research in psychotic disorders.

INTRODUCTION

Psychedelics as psychotomimetics

In DSM-5, psychosis is not explicitly defined, rather five 'psychotic' domains (*delusions, hallucinations, disorganized thinking, grossly disorganized or abnormal motor behavior and negative symptoms*) are necessarily present in each of the delineated disorders under the category 'Schizophrenia spectrum and other psychotic disorder' [1]. Broadly, the term psychosis refers to a disordered mental state characterized by the presence of delusions and or hallucinations with or without insight [2].

Historical literature shows that acute intoxication with psychoactive substances can produce transient phenomenological and behavioral alterations in healthy individuals that resemble the 'psychotic' state. So called 'psychotomimetics' are "*substances that produce changes in thought, perception, mood and, sometimes, in posture, occurring alone or in concert*" [3]. Some of the most important developments in our understanding of the biological basis for psychosis were inspired by research with psychotomimetics. The dopamine hypothesis of Schizophrenia (SCZ), first proposed by Van Rossum followed the discovery that dopamine mediates the behavioural changes after intoxication with psychomotor stimulants such as amphetamine [4].

Pre-prohibition in 1971, researchers using serotonergic psychedelics such as LSD, Psilocybin and Mescaline in humans frequently documented the similarities in the clinical presentation of psychosis and intoxication with psychedelics[3,5,6]. Serotonergic psychedelics induce profound but transient multisensory distortions via agonism at the serotonin type 2A receptor (5HT2AR) [7]. Clozapine, which is the most clinically effective atypical antipsychotic used to date, blocks activity at the 5HT2AR more than any other receptor with which it is known to bind [8–10]. As such there is

reason to suspect that 5HT2AR activity may underlie the shared changes in phenomenology and behaviour seen in psychosis and psychedelic intoxication.

There are unique advantages to modelling psychosis in healthy individuals using psychedelics. Measuring the acute changes in brain function, unimpaired by the impact of chronic or comorbid illness optimizes the identification of linking-variables that connect biology to clinical psychopathology [11]. Furthermore, inter-individual biological, psychological and environmental variation can be controlled. However, not all regard the psychedelic induced 'psychosis' to be an accurate model of endogenous psychoses. Among the widely reported subjective effects of psychedelics, visual hallucinations appear to be most common [12]. This contrasts with endogenous psychoses where visual hallucinations are rare and auditory hallucinations are more common. Moreover, people that have taken psychedelics usually retain insight and appreciate that the altered experience was drug related. Conversely, a loss of insight is a consistent feature of psychotic disorders.

Comparing intrinsic connectivity

The brain is organized into networks of spatially discrete but functionally connected regions called intrinsic connectivity networks (ICNs). Functional connectivity (FC) is demonstrated via time-dependent statistical relationships in the blood oxygen level-dependent (BOLD) signal between discrete brain regions, using functional magnetic resonance imaging (fMRI) [13]. In trying to understand the neurobiological basis for the intense subjective effects produced by psychedelics, fMRI data from healthy volunteers given psychedelics has revealed consistent changes to ICN activity that closely resembles the pattern of ICN activity observed in subjects with psychotic disorders. This review aims to expand on the work of Maeso and Sealfon who compared serotonin and glutamate transmission in psychedelics to psychosis[14], by reviewing and evaluating the evidence that ICN changes observed in psychosis are comparable with those following acute intoxication with psychedelics. Furthermore, theories that link network connectivity changes to phenomenological and behavioural

characteristics will be discussed.

MAIN BODY OF THE REVIEW

Loss of default mode and central executive network orthogonality

When engaged with the external world in a task directed manner, activity and FC of the ICN known as the Cognitive-Executive Network (CEN) increases. The brain region shown most consistently to activate during task is the dorsolateral prefrontal cortex (dlPFC) [15]. When externally directed attention subsides, activity in the ICN known as the task-negative or Default Mode Network (DMN) increases. Stimulus-free mental activity in the DMN is predominately internally directed, self-referential, autobiographical and concerned with predicting future outcomes [16]. It has been speculated that the DMN represents the neural correlate for a persistent self or ego [17]. The regions of the DMN that most consistently activate in the absence of task are the posterior cingulate cortex (PCC) and ventromedial prefrontal cortex (vmPFC).

Ordinarily, as attentional resources are directed to increasing demands of a task, activity in the DMN is suppressed [18]. In healthy individuals, the anticorrelated or orthogonal relationship between the DMN and CEN prevents excessive introspection from drowning out the metabolic activity required to direct resources towards an external task [19]. Therefore, absent or impaired suppression of the 'mind wandering'[20] default mode, would result in poor concentration and impaired cognitive performance during demanding, externally directed tasks. Reduced DMN-CEN orthogonality has been repeatedly observed in subjects with psychotic disorders [21] and more recently seen in the acute phase of intoxication with psychedelics.

In a within-subject placebo design, resting state BOLD fMRI signal in 15 healthy subjects demonstrated increased DMN-CEN FC following 2mg oral Psilocybin [22].

This is analogous to loss of orthogonality and a failure to suppress the DMN during externally directed task activity. The loss of orthogonality correlated with the subjective item “my thinking was muddled” although this did not stand up to a correction for multiple comparisons. Loss of DMN-CEN orthogonality was replicated in a double blind randomized controlled trial using LSD [23]. A smaller study of 10, using oral NN-Dimethyltryptamine (Ayahuasca) found no significant loss in DMN-CEN orthogonality [24].

Comparing 13 patients in the early phase of SCZ and 13 first degree relative against 13 healthy controls, Whitfield-Gabrieli and colleagues observed a statistically significant reduction in anticorrelation between the mPFC of the DMN and the dlPFC of the CEN in both patients ($p=0.02$) and relatives ($p=0.02$) [25]. Failure of task-dependent mPFC suppression was also correlated with both positive and negative symptom scoring on the scale for assessment of negative and positive symptoms (SANS/SAPS). Interestingly, this study was the first to demonstrate a potential genetic basis for impaired DMN-CEN orthogonality.

In a larger study of 28 high risk patients (HR) and 19 ultra high risk (UHR) patients with a history of brief limited psychosis, Wotruba and colleagues found less DMN-CEN anticorrelation in the UHR group than in the HR group [26]. This suggests that loss of orthogonality may worsen with disease progression and opens the possibility of using it as a marker for transition risk.

Ego dissolution or self-boundary disturbance is a hallmark of both early psychosis[27] and the psychedelic experience [28]. According to Sass, there is “profound uncertainty about the I-ness of the self” in the phenomenology of SCZ [29]. Moreover, Damiani and colleagues suggest that world/self-ambivalence may be central to the hallucinations present in both SCZ and ‘drug induced psychosis’ [30]. If the ability to discriminate between internally and externally generated stimuli is reliant on DMN-

CEN orthogonality, then loss of appropriate switching between these important ICNs may account for the self-boundary disturbance that is characteristic of a range of positive symptoms.

Loss of thalamo-cortical gating

Aberrant connectivity between the thalamus and the cortex is one of the most consistent changes observed in SCZ [31]. In one of the largest studies of its kind, 415 subjects with SCZ showed increased connectivity between the thalamus and sensorimotor regions with concurrent decreased fronto-thalamic connectivity [32]. Similarly, in a study with 20 healthy subjects, Muller and colleagues found subjects given LSD showed increased resting state connectivity of the thalamus with the right fusiform gyrus and insula compared to placebo [33]. The right fusiform gyrus has been implicated in visual hallucinations and the insula in auditory hallucinations. Muller and colleagues were able to replicate these findings in a double-blind randomized cross over study [23].

It should be noted however that BOLD measures of FC are only surrogates for the true causal influence of regions within and between ICNs. The variable perfusion across regions of ICNs limits the ability of fMRI to precisely measure this influence at the synaptic scale [34]. As a consequence, BOLD fMRI evidence alone is only circumstantial. Effective connectivity is the true measure of connectivity at the synaptic level. Using dynamic causal modelling of fMRI data, Preller and colleagues were able to demonstrate that LSD increases effective connectivity from the

thalamus to the PCC [35]. By using Ketanserin, a highly selective 5HT2AR antagonist they were also able to show that thalamo-cortical effective connectivity was dependent on 5HT2AR activation.

To understand how increased somatosensory-thalamic connectivity relates to symptomatology in psychosis and the phenomenology of psychedelics, Geyer et al suggested that the thalamus gates the neural transmission of sense data to the cortex, regulating the contents of consciousness [36]. They propose that impaired thalamo-cortical gating would lead to an overload of sensory information in the cortex and consequent hallucinations.

Disconnection of the Salience Network and dysfunctional modulation of DMN-CEN coupling

The continual stream of sensory input to the brain is filtered on the basis that it might be rewarding, surprising, pleasurable or self-relevant [37] . Resting state fMRI has identified this 'salience detection' of incoming stimuli to be strongly associated with coordinated activation of the dorsal anterior cingulate cortex (dACC) and bilateral anterior insula (AI), collectively named the salience network (SN).

Disconnection within the SN has been observed in SCZ [38] and is related to the severity of reality distortions [39]. In a task free paradigm involving 26 patients with SCZ, Orliac and colleagues found that reduced within-network connectivity of the left striatum in the SN was significant and correlated with delusion items on Positive and Negative Syndrome Scale (PANSS)[40]. Similarly, in a within-subject placebo controlled study, oral Psilocybin given to healthy subjects reduced within-network connectivity in the SN and was found to correlate with subjectivity reported 'ego dissolution' [41].

A large, authoritative systematic review found that in chronic SCZ, loss of within-network FC is an overwhelmingly consistent finding and true across different stages in the progression of the disease [42]. Acute within-network connectivity reductions are one of the most consistent findings in the growing body of fMRI research with psychedelics [24,43–45] . However, further replication of these findings in larger samples with psychedelics would be necessary to match the consistency and strength of evidence that supports these changes in SCZ. Furthermore, it might be that within-network disconnection is a secondary phenomenon that appears following widespread serotonergic activation by psychedelics. This has been observed following treatment with Sertraline [46].

The function of the SN extends beyond salience attribution to incoming stimuli. The SN also regulates and mediates activity and connectivity, within and between other networks such as the CEN and the DMN [47]. Using a resting state paradigm with 18 SCZ patients, Manoliu and colleagues found a significant loss of within-network connectivity of the right AI of the SN. The magnitude of the disconnection within the SN was correlated to between-network coupling of the DMN and CEN [48] which supports previous evidence that the SN modulates important DMN-CEN orthogonality. However, it is important to note that the majority of patients included were being treated with Olanzapine. With evidence that Olanzapine modulates the DMN it is worth considering what impact medication might have had on SN integrity in the study [49].

In UHR and HR subjects, Wotruba and colleagues found the right AI of the SN showed significantly increased coupling to the PCC of the DMN [26]. Increased between-network coupling of the SN, regions of the CEN and the anterior DMN was also observed in a double-blind randomized control trial using LSD [23]. However, it should be noted that between-network coupling to the SN following psychedelics has not been replicated elsewhere. In the absence of future contradictory findings, the pattern of within-SN disconnection and functional coupling to ordinarily anticorrelated ICNs is present following psychedelics and in psychotic disorders. In keeping with the aberrant salience hypothesis of SCZ [50], loss of functional differentiation between SN and the DMN with concurrent loss of DMN-CEN switching might account for the misattribution of salience to internally generated mentation rather than incoming sensory stimuli that is seen in both psychosis and acute psychedelic intoxication.

Loss of ICN modularity and increased global connectivity

Using graph theory, the complex topology of the brain can be partitioned in a way that facilitates within and between-network connectivity analyses. In graph theory,

brain regions are represented as *nodes*. Under normal resting state conditions, nodes within any given ICN (represented as a *group)* exhibit strong temporal coherence. Conversely, nodes within a group exhibit weak temporal coherence with nodes typically observed in other groups [51]. As such groups (ICNs) are functionally segregated, forming a highly organized modular community. Modularity is critical for the functional optimization and integrity of ICNs [52]. Compromised modularity has been implicated in a range of neuropsychiatric pathologies such as SCZ and is associated with impaired cognitive performance [53]. Cognitive impairment is well established in SCZ[54]. Intoxication with psychedelics has also been shown to produce subjective and objectively measured impairments in a host of cognitive processes in a dose dependent manner. Transient impairments in working memory, attention, problem solving and associative learning have all been observed after dosing with Psilocybin [55].

Modularity is a measure of the global segregation in the brain as opposed to global interconnectivity. In a within-subject placebo control study giving LSD to 15 healthy participants, functional connectivity density (FCD) was elevated in the frontal, parietal and inferior temporal cortices [56]. FCD is a measure of how strongly a node is connected to the rest of the brain, thereby acting as a measure of global connectivity. This study showed that the use of LSD significantly increased global connectivity and the magnitude of connectivity was correlated with the reported intensity of ego dissolution. However, this study made no adjustment for possible global signal artefacts thereby weakening the reliability of the findings. Effects such as respiratory and cardiac cycle harmonics or alterations in neurovascular coupling arising from the pharmacodynamic properties of the drug are known to elevate brain-wide relationships [57]. Psilocybin has been shown to alter neurovascular coupling in rodents [58] which would suggest that a similar effect would arise with LSD given their shared pharmacological profile. In a double blind, randomized cross over study using LSD that included global signal as a covariate, hyper connectivity was still observed

in sensory and somatoform networks but not in the insula, cingulum, temporo-parietal or prefrontal cortex [59].

Increased global connectivity and reduced within-network connectivity has been observed in childhood onset SCZ [60]. Elsewhere, Yu and colleagues measured network clustering coefficients in a group of 24 subjects with SCZ and found there to be more and smaller modules compared to the healthy control group [53]. In a similar study, infusion with Psilocybin resulted in a surge of transient modules with low stability compared to placebo in which there were a smaller number of persistent modules [63]. Taken together, there is evidence that both acute psychedelic intoxication and SCZ are characterized by attenuated network modularity.

Though not empirically verified, new idea are being developed to explain how loss of modulatory may account for the phenomenological similarities between the 'psychotic' and psychedelic state [64]. Much like the description of a potential wells in Physics, the collection of ICNs in the brain can be likened to a landscape of potential wells where the depth of each well represents the relative stability and spatiotemporal discreteness of the ICN [12]. Deep but relatively few wells are indicative of a highly segregated or modular brain topology. Loss of modularity may be considered equivalent to flattening of the 'landscape', where the functional segregation between ICNs gives way to more entropic, globally interconnected brain activity or 'free energy'. As a system, according to Karl Friston's free energy principle, the brain attempts to minimize free energy and create stable, modular organisation [65]. When confronted with the relative 'chaos' of global connectivity, delusions might be understood as the brain's compromise strategy as it attempts to minimise free energy (entropy). The formation of inappropriate but stable local minimums in the landscape of potential wells (ICNs) prevents incapacitation by widespread, disorganized brain activity [66].

INTEGRATION, SUMMARY AND FUTURE DIRECTION

The studies reviewed above largely support the general principle that excessive between-ICN coupling (SN, DMN and CEN) with concurrent loss in DMN-CEN orthogonality are consistent fMRI findings in both psychotic disorders and healthy subjects acutely intoxicated with serotonergic psychedelics. In the context of increased global connectivity, they also suggest that excessive between-ICN coupling may represent isolated instances of a more generalized picture of brain wide global connectivity present in the 'psychotic' and the psychedelic state.

SCZ is a highly heritable disorder with a mean lifetime prevalence of approximately 1% [67]. Given how disabling the symptoms can be it is surprising it has resisted the counter pressures of natural selection. One explanation for its higher than expected prevalence of SCZ is that a degree of global connectivity offers certain protective advantages. It has been suggested that whole brain network connectivity might be resilient to possible focal or multifocal lesions [68]. In addition, there is evidence that relaxed within-network connectivity may underlie the therapeutic efficacy of psychedelics in treatment resistant depression [69]. Reduced global connectivity [70] and excessive within-network coupling of the DMN[16] have been observed in depression and both are normalized following treatment [71]. Perhaps strengthened within-network connectivity may protect against the positive symptoms in psychosis while conversely, between-network connectivity may be protective against excessive rumination that is characteristic of depression.

A number of candidate theories that link the phenomenological concordance between the 'psychotic' and psychedelic state to shared aberrations in ICN activity have been suggested; [1] self-boundary disturbances arising from loss of DMN-CEN orthogonality and SN modulation [2] hallucinations arising from impaired thalamo-cortical gating of sense data [3] impaired cognition arising from diminished modularity [4] delusions arising as a byproduct of the brain's attempts to minimise

free energy in a chaotic system.

Understanding the neurological basis of profoundly disabling and potentially harmful changes in psychosis by investigating transient, reversible changes in healthy participants using psychedelics has already inspired novel pharmacological treatment targets. The observation that Ketanserin terminates the subjective effects of psychedelics inspired its later use as a treatment for intractable hallucinations in SCZ [73]. However, the strength of psychedelics as a model for psychosis must be considered in light of limitations in study design. In most of the studies fMRI scans last just 12 minutes of a total experience of several hours. This, together with abatement of the subjective effects is likely to materially impact the reliability of the recall and assessment of participants' within-scan experience. As such the reliability of correlating ICN changes to the within-scan experience is compromised. Future research might consider using micro-phenomenology [74] to improve real time precision of subjective accounts and approximation of ICN changes to phenomenological accounts. Further studies could also improve comparison of the subjective accounts in psychedelics to psychosis by using validated positive symptoms ratings for psychotic disorders such as PANSS. Perhaps the most appropriate test for the reliability of psychedelic modelling of psychosis would be to design a study that directly compares network activation and symptom rating in psychotic patients against healthy participants given psychedelics.

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