Review Article

Investigating the Role of the Endocannabinoid System in Early Psychosis

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Abstract

Accumulating evidence suggests that dysfunction within the endocannabinoid (eCB) system may play a role in psychosis. However, little is understood about how this may be related to the neurocognitive abnormalities and symptoms of psychosis. In this paper, we summarize some of the evidence supporting the role of eCB system in psychosis, as well as the current understanding of the neurocognitive underpinnings of psychosis. We particularly focus on neuroimaging evidence pertaining to alteration in the functional integration between different brain regions in patients with psychosis, and then relate this to evidence from neuroimaging studies of the effects of cannabis and its main ingredients, such as delta-9-tetrahydrocannainol and cannabidiol. Specifically, we explore this in the context of the hypothesis that psychosis is a disorder of dysconnectivity between different brain regions, focusing particularly on three large scale functional networks (the default mode, central executive, and salience networks), alterations in which have been implicated in psychosis, and we discuss the gaps in this research thus far. Finally, we propose that an approach to investigating the role of the eCB system in psychosis may be to employ a pharmacological cannabinoid challenge paradigm to examine how experimental perturbation of the eCB system may be related to abnormalities in the brain networks implicated in psychosis. We discuss challenges associated with this approach, and suggest safe and practical options to overcome the main issues involved with such an experimental approach. Studies employing such an approach have the potential of offering insight into the neurocognitive mechanisms underlying psychosis, and identifying novel therapeutic targets.

Introduction

Psychotic disorders, such as schizophrenia, are among the top ten causes of disability worldwide,[1] and are associated with a spectrum of neurocognitive deficits, which may be present from the very early stages and worsen with the onset of frank psychosis.[2] Typically, the onset of psychosis occurs in late adolescence or early adulthood,[3,4] with 70% of these individuals experiencing a second episode within 5–8 years.[3,5] Although studies have consistently identified a number of environmental as well as genetic risk factors that contribute to the risk architecture of psychosis,[4,6–8] mechanistic understanding as to how they may increase the risk of psychosis is unclear. Such understanding is critical to the identification of novel therapeutic targets as well as of biomarkers that may predict the risk of disease before the actual onset of illness, of relapse following onset, or indeed of biomarkers of response to treatment.

In this review, we explore the current understanding of the neurobiological underpinnings of psychosis, focusing on knowledge gained from one prominent risk factor in particular. Following this, we propose a novel approach that may help shed mechanistic insight on aspects of the presentation of psychosis. For the purposes of the present review, the risk factor of interest is cannabis use, and its activity within the related endocannabinoid system in man.

Cannabis, the endocannabinoid (eCB) system, and psychosis

Recreationally, cannabis is one of the most widely used illicit drugs in the world.[9] However, its use is also recognised as one of the most preventable risk factors for the onset and relapse of psychotic disorders.[10–13] A recent meta-analysis revealed that the risk of onset of psychosis amongst cannabis users is 2–4 times higher than in non-users, depending on degree of exposure.[14] A separate

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Abbreviations: eCB, endocannabinoid; Δ9-THC, delta-9-tetrahydrocannabiniol; 2-AG, 2-arachidonoylglycerol; CBD, cannabidiol; FC, functional connectivity; fMRI, functional magnetic resonance imaging; DMN, default mode network; SN, salience network; CEN, central executive network; rs-fMRI, resting-state functional MRI; MRC, Medical Research Council; NIHR, National Institute for Health Research; NHS, National Health Service.

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meta-analytic review found that the prognosis for individuals with psychosis who continued to use cannabis following onset of illness was significantly worse compared to those who discontinued use after onset, in terms of outcomes, relapse rates, hospital admissions, and positive symptoms.[15]

Of particular concern has been the heavy use of high-potency strains of cannabis, especially given evidence that the availability of high-potency cannabis has been on the rise over the last two decades.[16–18] In the context of cannabis use, potency is determined by the level of delta-9-tetrahydrocannabiniol (Δ9-THC), the main psychoactive ingredient present in the extract of the cannabis plant. Indeed, the frequent use of high-potency strains of cannabis, which contain high levels of Δ9-THC, has been associated with significantly greater risk of onset and of relapse in psychosis, compared to use of less potent forms or to less frequent use.[12,16,19]

Δ9-THC, the primary psychotropic constituent of cannabis, binds to the endogenous cannabinoid receptors, which are distributed throughout what is known as the "endocannabinoid system" (eCB system).[20,21] The eCB system mainly constitutes endogenous cannabinoid receptors (CB1 and CB2 receptors) and their ligands (including anandamide, and 2-arachidonoylglycerol, or 2-AG) distributed throughout the central and peripheral nervous systems in the mammalian brain.[22] Expression of the CB1 type endocannabinoid receptor is particularly high in the hippocampus, cerebellum, basal ganglia, and neocortex[23]—regions involved in a number of cognitive processes of particular interest in the context of psychosis, such as learning, memory, and attention processing.[24–26] Expression of the CB2 receptor is predominantly observed in immune cells, from where it is thought to exert an effect on immune functions.[21] CB2 receptor expression has also been observed in central nervous system neurons, albeit at much lower levels than the CB1 type.[21] Various animal studies have proposed links between CB2 receptor function and anxiety,[27] emesis,[28] schizophrenia-related behaviours,[29] alcohol preference,[30] and impulsive behaviours.[31] However, these functions – and the cellular mechanisms through which CB2 receptors exert these functions—are still disputed.[32]

Consistent with the known CB1 receptor distribution, acute administration of Δ9-THC in healthy individuals has been shown to induce transient psychotic symptoms,[33,34] and to cause impairments in aspects of memory and learning,[33,35] abnormalities in inhibitory control processing and attentional salience processing,[34,36,37] as well as alter the normal activity of the neural substrates underlying all of these processes.[38,39] Evidence that modulation of these brain regions and cognitive processes by acute administration of Δ9-THC resembles aspects of the neural abnormalities and psychopathology that are also observed in schizophrenia further support a role for alterations in the eCB system in the pathophysiology of the disorder, and highlight it as an important target for further research.[20]

Independent of its role in modulating the psychoactive and psychotomimetic effects of cannabis, the eCB system has also been implicated in schizophrenia in other ways.[40] One potential contributing element to the overall role of the eCB system in schizophrenia may be the relationship between eCB dysfunction and abnormal dopamine levels.[41] Normal dopamine activity is involved in a number of cognitive processes, such as motivational salience, decision making, and attention and cognitive control, which are altered in schizophrenia.[42–44] Striatal dopamine hyperactivity, in particular, is one of the most consistent findings in the pathophysiology of psychosis.[45]

Although causality is unclear, as the influence of one on the other may in fact be bidirectional, irregularities in both the availability of this neurotransmitter and in the activity of the eCB system are very likely related. This may be inferred from the dysregulated neural levels of anandamide—an endogenous cannabinoid—observed in hyperdopaminergic rat models of schizophrenia,[46] and increases in dopamine in the nucleus accumbens of healthy rats following acute administration of anandamide.[47] Additionally, an accumulating body of evidence suggests that acute and chronic cannabis use in humans may affect dopamine release and synthesis differentially, as reviewed by Sami et al.[48]

eCB system alterations have also been implicated in the pathophysiology of schizophrenia through the findings of post-mortem studies, which have identified exaggerated CB1 receptor binding in the dorsolateral prefrontal cortex as well as abnormal levels of anandamide across the brain in individuals with schizophrenia.[49,50] Indeed, dysregulated levels of anandamide have also been observed in animals following repeated Δ9-THC administration,[51] and in the cerebrospinal fluid of first-episode psychosis patients with co-morbid high frequency cannabis use, as compared to first-episode patients with low frequency cannabis use, and healthy controls,[52] further linking alterations in components of the eCB system to the psychosis-like effects of Δ9-THC.

These findings from studies of both the effects of cannabis use on behaviour and brain activity, and abnormal eCB function in psychosis warrant a systematic investigation of the eCB system in the context of psychosis, and indicate that an optimal approach would be an experimental medicine paradigm, in conjunction with cannabinoid administration. However, ethical and safety considerations preclude studies involving the administration of cannabis or Δ9-THC to individuals with psychosis.

Cannabidiol (CBD)

The use of CBD, a non-psychotropic component of the cannabis plant, is a potential approach that could overcome the ethical issues surrounding pharmacological challenge studies involving administration of cannabis or Δ9-THC in patients with psychosis. There is evidence to suggest that short-term CBD administration (4 weeks) may result in an increase in peripheral anandamide levels in patients with schizophrenia, associated with a reduction in psychotic symptoms[53]; and may also counteract the psychotic symptoms, cognitive impairments, and associated brain activation abnormalities induced by Δ9-THC administration in healthy volunteers.[54,55]

Though the mechanism of action underlying the effects of CBD is still unclear, a range of molecular mechanisms have been suggested as acting either individually or in conjunction with others to produce the aforementioned notable effects.[53,56] One theory relates to the potential action of CBD as a high-potency antagonist of CB1 receptor agonists,[57] which—in opposition to the partial agonist activity of Δ9-THC at CB1 receptors—may result in the contrasting effects induced by the two exogenous cannabinoids. Another prominent argument concerns the ability of CBD to enhance anandamide signalling via the inhibition of anandamide uptake and intracellular degradation.[56,58] As noted earlier, this increase in anandamide levels has been associated with decreases in psychotic symptoms, and though the exact nature of this relationship remains inconclusive, it is likely that this ability to increase anandamide signalling is related to the antipsychotic properties of CBD.[53]

Nonetheless, consistent with this evidence overall, in recent years there has been considerable interest in a potential role for CBD as an antipsychotic treatment.[59] Additionally, CBD has also been found to display neuroprotective properties, and has demonstrated a low side effect profile, and tolerability in doses of up to 1,500 mg.[60,61] All of these factors combine to make CBD an ideal tool for the safe perturbation of the eCB system in a pharmacologi-

cal challenge paradigm, and will allow the further investigation of abnormalities of the eCB system in clinical populations.

Psychosis as a disorder of dysconnectivity

Although abnormal patterns of brain activity in specific brain regions are well documented in psychosis and have been associated with aspects of the illness,[62] these localised abnormalities have thus far failed to provide a comprehensive account of the neurocognitive mechanisms underlying the multiple, complex phenotypic features of the disorder.[63,64] There is increasing recognition that attributing even very specific symptoms, such as auditory hallucinations, to dysfunction in just one localised area of the brain is overly simplistic, and that such an approach is far less plausible for the broad range of positive and negative psychotic symptoms and ubiquitous cognitive deficits that characterize psychotic disorders, such as schizophrenia.[64]

This is further complicated by the fact that these symptoms are not only heterogeneous in their presentation across individuals with psychosis, but can also change in prominence across time within the same individual. This limitation has prompted a more integrated approach, focusing instead on the interaction over time of brain regions that have been traditionally functionally segregated. The ensuing research drove the development of what is known as the dysconnectivity theory of schizophrenia,[65] which describes the psychopathology of the disorder as resulting from an underlying dysconnection syndrome.[65–67] The term functional connectivity (FC) describes the temporal relationship between activation measured in different brain regions, either at rest or during a task,[68] and is inferred from the correlation between regional fluctuations in the blood-oxygen-level-dependent signal of different brain regions, measured using functional magnetic resonance imaging (fMRI).

A number of studies have investigated FC alterations in the context of psychosis, which are summarized below.

Results of resting state studies

A popular approach in neuroimaging literature has been to describe brain regions as being organized into functional neural networks, three of which are of particular interest in the context of FC research across neuropsychiatric diagnoses.[64] These networks are the Default Mode Network (DMN), the Salience Network (SN), and the Central Executive Network (CEN). Resting-state functional MRI (rs-fMRI) techniques have proven particularly useful in the study of such networks in psychosis. They provide a means of representing intrinsic brain function and connectivity between brain regions under resting as opposed to activation conditions, which involve external stimuli or induced reactions.[69,70]

The DMN is largely active at rest, and as such, is engaged by a range of internally directed thought processes, including self-referential thought, aspects of autobiographical memory, and future simulations—all processes that are notably disrupted in schizophrenia.[71] Anatomically, the core nodes of the DMN include the posterior cingulate cortex and the precuneus, the medial prefrontal cortex, and the angular gyrus.[72] Additional regions involved in DMN processes include the dorsal medial subsystem, and the medial temporal subsystem.[72]

Normally, DMN and CEN activity are thought to be anti-correlated.[73] That is, DMN activity is reduced during externally oriented task states, at the same time as CEN activity is increased, and vice versa for the internally oriented/resting state. As such, the CEN is thought to be responsible for higher level cognitive functions (*e.g.* attentional control, and executive task performance), and is rooted in the dorsolateral prefrontal cortex and the posterior parietal cortices.[74]

Critical to the appropriate engagement and disengagement of CEN and DMN activity, the SN is believed to moderate this "switching" between networks through the attribution of salience to external or internal stimuli.[64] In salience literature, the attribution of salience refers to the assignment of importance to external stimuli or internal mental events, critical in the processing of an individual's experiences.[75] The anterior insula (a core region in the SN) is thought to moderate the shift between activity in the DMN (internally directed processes) and CEN (externally directed processes) by increasing cognitive and task control system activity, whilst suppressing DMN activity when a salient event is detected.[75,76] In contrast, in individuals with schizophrenia, abnormal levels of dopamine in the SN are thought to result in aberrant anterior insula activity (with a particularly high expression of dopamine D1 receptors in the anterior insula), which in turn results in the misattribution of salience to external/internal stimuli, and consequently the dysfunctional switching between DMN and CEN engagement.[64, 77–79]

The functional consequences of this sequence include greater connectivity between the DMN and CEN, greater connectivity within the DMN, and decreased anterior insula activity occurring at rest, as well as a failure to suppress DMN activity during externally driven tasks.[77,80] Decreased FC between the SN and both the DMN and CEN at rest has also been reported in patients with schizophrenia,[77,81] as well as an overall reduction in the strength of negative FC between task-positive and task-negative networks during both rest and task in patients diagnosed with schizophrenia, as well as with other psychotic disorders.[73,80]

It is thought that the potential symptomatic consequences of these connectivity abnormalities range from hallucinations and deficits in emotional processing (resulting in part from misattribution of salience) to deficits in self-referential thinking (resulting in part from the over-engagement of the DMN). As such, this triple network model is thought to provide the most unified account to date of the mechanisms underlying the spectrum of different psychosis symptom domains—from deficits of self to the classic positive, negative and cognitive domains.[82]

Apart from the anterior insula, an additional core node of the SN is the dorsal anterior cingulate cortex, though its broader functions also rely on input from the amygdala, ventral striatum, and the substantia nigra/ventral tegmental area[75]—with a high expression of both dopamine and CB1 receptors observed in the dorsal and ventral striatum, and in the substantia nigra.[21,83]

If eCB dysfunction were to have a role in the pathophysiology of psychosis, one would expect it to modulate components of the three networks described here, in a manner consistent with alterations observed in those with psychosis. However, this has yet to be examined. Indeed, few studies have investigated the effects of Δ9-THC on FC during cognitive tasks or at rest. The limited available evidence suggests that Δ9-THC can induce a reduction in connectivity between the SN and the CEN, increase connectivity between the DMN and CEN, and increase connectivity within the DMN, during salience processing in healthy individuals[37,84]—reflective of those disturbances described in the triple network model. This, coupled with the high distribution of CB1 receptors within the SN and the propensity for acute Δ9-THC to impair performance on salience processing tasks in healthy individuals,[85] would suggest a plausible if as yet undefined role for eCB dysfunction in the triple network model of schizophrenia.

Results of cognitive activation studies

In the context of characterising overall functional dysconnectivity in schizophrenia, studies that employ cognitive tasks are essential for a more complete understanding of the nature of disturbances observed during psychosis. Learning and memory impairments are particularly well-documented phenomena in the neurocognitive profile of individuals with schizophrenia, both in the context of comorbid cannabis use and its absence,[86,87] and are similarly observed in healthy individuals following both acute Δ9-THC administration and chronic cannabis use.[39,88] Across all illness stages of schizophrenia, but particularly during the first episode of psychosis, memory tasks involving verbal learning and encoding have been found to display significant impairments, compared to healthy individuals.[26] Similarly, verbal learning, memory, and attention appear to be the most consistently impaired cognitive domains in studies of acute and chronic cannabis use.[89]

Encoding refers to the mental storage of information for later retrieval or recollection from short-term or long-term memory, and is crucial for learning.[86] The brain regions largely involved in verbal learning and encoding include, but are not limited to, the medial temporal lobe (formation of new memories) and the prefrontal cortex (essential for executive control functions and salience processing).[90–92] Both regions display significant abnormalities in activation and connectivity during encoding and recall across illness stages in schizophrenia.[86, 91–96] Specifically, reports of connectivity-related abnormalities have included decreases in FC between the DMN and some regions involved in executive control, and decreased connectivity within the DMN during encoding and recall tasks.[94–96] Connectivity within the DMN and the regions involved in executive control was found to correlate positively with task performance,[93] indicating a failure to recruit crucial neural resources that is linked to level of cognitive impairment.

Neural abnormalities in corresponding regions have been observed during encoding and recall tasks in healthy individuals administered Δ9-THC, including decreases in insular activity during encoding,[97] increases in parahippocampal activity while learning during repeated trials of encoding, and a change in ventrostriatal activation during repeated trials of cued word recall condition.[98] While the effect of Δ9-THC on the FC between these regions during encoding and recall has not previously been explored, these studies do highlight the importance of such investigations, and of further research of the eCB system overall.

Effect of eCB system perturbation on neurocognitive substrates implicated in psychosis

As outlined earlier, while the justification for investigating the role of eCB dysfunction in psychosis is clearly there—focusing particularly on the relationship between experimentally induced perturbations of the eCB system and the function of neural substrates implicated in psychosis, as well as symptoms and cognitive changes characteristic of psychosis – this has yet to be carried out systematically. Additionally, as discussed previously, though its safety and pharmacological profile make CBD an ideal tool for safe perturbation of the eCB system in clinical populations, to our knowledge, no study as yet has investigated the effects of such perturbation on the neurocognitive substrates implicated in psychosis, in psychosis patients directly. However, given the clear parallels between neurocognitive abnormalities observed in psychosis and those induced by Δ9-THC, results of studies investigating the opposing effects of CBD and Δ9-THC in healthy individuals are also highly informative.

In healthy individuals, the neural effects of CBD compared to those of Δ9-THC are relatively consistent, generally showing a direct and opposite effect on brain activation and connectivity during cognitive tasks, including salience processing, emotional processing, learning, and short-term memory.[34,37,55,99,100] The results of both human and animal studies exploring the behavioural effects of CBD in comparison to Δ9-THC on these same cognitive processes that are also strongly affected in schizophrenia, specifically learning and short-term memory, have thus far been less consistent.[54,55,101,102] This variability may be related to a number of factors, such as the heterogeneity of study designs (including varying CBD dosage) and modest sample sizes, together with limited overall research on the topic. In particular, differences in cognitive activations tasks employed in previous studies may have contributed to inconsistency in results. Not only have previous studies employed cognitive tasks that engage different cognitive domains, they also commonly vary in degree of difficulty,[20] hindering cross-study comparability.

Future research directions

As outlined above, despite the importance of such investigations for understanding the neurobiological underpinnings of psychosis, there is a clear lack of studies that have investigated the relationship between dynamic perturbation of the eCB system and functional brain abnormalities, or indeed FC between the DMN, SN and CEN in patients with psychosis. We posit that the optimal approach to address this gap would be for studies to investigate the effects of acute and/or short-term perturbation of the eCB system in patients with psychosis. Exploration of the role of the eCB system in the neurobiology of psychosis is most ideal in the early stages of psychosis, as such studies will be able to overcome issues relating to the longer term effects of illness course and antipsychotic treatment on aspects of cognition.[2,103].

Indeed, previous research has also shown functional dysconnectivity to become increasingly widespread from the early to the latter stages of schizophrenia.[104]. Changes in FC have also been observed after relatively short-term antipsychotic use (12 weeks).[105] Utilising a paradigm that focuses both on resting state abnormalities as well as the cognitive domains that are notably impaired in early psychosis, such as verbal memory, will be particularly useful in informing a comprehensive understanding of the role of the eCB system in large scale network dysconnectivity in psychosis.

Conclusions

Overall, such an approach may help connect multiple theoretical strands in schizophrenia research and rationally integrate a role for the eCB system into the relatively well-established dysconnectivity theory, focusing on the dysconnectivity of large-scale networks in psychosis. This may help formulate a comprehensive framework for the neurocognitive abnormalities underlying psychosis.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Both of the authors contributed in a substantial way to the study, and approved the manuscript content. Both authors were involved in the design, analysis and interpretation of findings. O'Neill A wrote the first draft of the manuscript, and both authors contributed to its critical revision and gave final approval of the version for publication.

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