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A neural efficiency-threshold model to understand psychotic experiences

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Introduction

Psychotic experiences have been a rich area of psychiatric research for the past two decades (Johns & Van Os, 2001). These are perceptual abnormalities and unusual thought content, which, in most cases, are associated with at least a degree of intact reality testing. Much of the psychotic experiences research to date has focused on prevalence, risk factors and persistence. We believe, for the field to move forward, it is important to develop a broader understanding of psychotic experiences. This editorial proposes a framework for understanding psychotic experiences from a psychosocial and neurobiological perspective, which we term the neural efficiency threshold model.

Research to date

Early research on psychotic experiences focused on a continuum with, and prediction of, psychotic disorders (Johns & Van Os, 2001; Poulton et al., 2000; Van Os, Linscott, Myin-Germeys, Delespaul, & Krabbendam, 2009). As with a depression continuum from mild sadness to pervasively depressed mood, it was proposed that psychotic experiences could be conceptualised as existing on a continuum from minor perceptual abnormalities and overvalued unusual thought content to the fully psychotic hallucinations and delusions of schizophrenia. Meta-analyses suggested 5–7% of the general adult population experienced at least occasional psychotic experiences (Linscott & Van Os, 2013; Van Os et al., 2009) and follow-up studies showed that these individuals were at elevated risk of developing psychotic disorders (Poulton et al., 2000; Welham et al., 2009).

Research that followed highlighted that, as opposed to a homotypic relationship with psychotic disorder, psychotic experiences are predictive of a wide range of mental disorders (Fisher et al., 2013; McGrath et al., 2016; Werbeloff et al., 2012; Wigman et al., 2012). Indeed, although only a small minority of individuals with psychotic experiences go on to develop a psychotic disorder, a high proportion develop other, more common mental disorders, including depressive, anxiety, behavioural and substance use disorders (Healy & Cannon, 2020; Kelleher et al., 2012a; b; c; Rimvall et al., 2020; Scott, Chant, Andrews, & McGrath, 2006; Trotta et al., 2020; Varghese et al., 2011; Wigman et al., 2012).

A wide variety of factors have been shown to be associated with psychotic experiences, including lower IQ (Cannon et al., 2002; Johns et al., 2004), adversity (Croft et al., 2019; Crush, Arseneault, & Fisher, 2018; McGrath et al., 2017; Morgan et al., 2014; Newbury et al., 2018; Oh, Cogburn, Anglin, Lukens, & DeVylder, 2016), poorer coping skills (Lin et al., 2011; Wigman et al., 2014a), migration (Laurens, West, Murray, & Hodgins, 2008; Scott et al., 2006), ethnicity (El Bouhaddani, van Domburgh, Schaefer, Doreleijers, & Veling, 2019; Oh, Yang, Anglin, & DeVylder, 2014) and socioeconomic factors (Scott et al., 2006), as well as genetic and molecular variation (Niculescu et al., 2015; Pain et al., 2018; Ramsay et al., 2013).

Our own research has highlighted psychotic experiences as indicators of psychopathology severity, demonstrating that, compared to individuals with mental disorders without psychotic experiences, individuals with psychotic experiences have a higher psychiatric symptom burden (Kelleher, Clarke, Rawdon, Murphy, & Cannon, 2013a), greater multimorbidity (Kelleher, Cederlof, & Lichtenstein, 2014a; Kelleher et al., 2012b), more suicidal behaviour (Kelleher et al., 2014a; Kelleher et al., 2013b; Kelleher et al., 2012b), cognitive deficits (Blanchard et al., 2010; Kelleher et al., 2013a) and poorer socio-occupational functioning (Healy et al., 2018; Kelleher et al., 2015; Wigman et al., 2014a). Researchers have also demonstrated that psychotic experiences are associated with high levels of psychological distress (Armando et al., 2010), more mental health service use (Bhavsar et al., 2017) and poorer treatment responses to both pharmacotherapy (Perlis et al., 2011) and psychotherapy (Wigman et al., 2014b).

A broader biopsychosocial framework

We believe it is now timely to consider psychotic experiences in a broader framework of neurobiological and psychosocial functioning, with illness severity representing just one aspect. Specifically, we believe that psychotic experiences can be conceptualised as markers of a clinically significant mental threshold – the threshold being where mental distress transitions to dysfunction in neural systems integration and communication, which we term the neural efficiency threshold model. One of the earliest clinical signs of crossing this threshold, we believe, is the emergence of problems with sensory perception skills and, as a result, hallucinatory experiences.

Supporting evidence of neural systems dysfunction in individuals with psychotic experiences comes from a number of neurocognitive and neuromotor studies. From the perspective of neurocognition, a wide range of deficits have been demonstrated in individuals with formal psychotic disorders (Barch & Ceaser, 2012; Bowie & Harvey, 2005; Green et al., 2011; Szöke et al., 2008). Lesser degrees of cognitive impairment have also been observed in more common mental disorders – notably depression (Rock, Roiser, Riedel, & Blackwell, 2014; Service et al., 2020; Weiser et al., 2004) – which might suggest that neural systems dysfunction extends more broadly to general psychopathology. However, research on cognitive function in common mental disorders has typically failed to assess or account for co-occurring psychotic experiences. Our model suggests that common mental disorders that do not have co-occurring psychotic experiences would not be associated with significant cognitive impairment but that we would see progressive cognitive effects as psychotic experiences emerge and become more severe.

Preliminary support for this comes from Barnett et al., who looked at childhood cognitive function as it longitudinally related to psychopathology and psychotic experiences (Barnett et al., 2012). Although initial analyses suggested there may be a relationship between psychopathology and poorer cognitive performance, this relationship was, in fact, entirely accounted for by co-occurring psychotic experiences. That is, individuals with psychopathology who did not have psychotic experiences did not demonstrate poorer cognitive performance.

Similarly, in our own research, we have found that young people with psychotic experiences performed more poorly than their peers on multiple measures of cognitive processing speed, as well as in non-verbal working memory (Kelleher et al., 2013a), findings that were not accounted for by general psychopathology. Individuals with psychotic experiences have, furthermore, also been shown to score more poorly on tests of intellectual ability (Cannon et al., 2002; Johns et al., 2004).

Other evidence of neural systems dysfunction associated with psychotic experiences comes from neuromotor studies. In the Dunedin study, poorer motor skills development in infancy and early childhood was predictive of psychotic experiences at age 11 years (Cannon et al., 2002). We have also found evidence of neuromotor skills deficits in older children with psychotic experiences in terms of poorer scores on the Purdue pegboard task (Blanchard et al., 2010). What is more, we found that poorer childhood pegboard motor performance was predictive of psychotic experiences into adulthood (Carey et al., 2019).

Because of the high degree of regional specialisation within the brain, complex mental processes are dependent not just upon the efficiency of relevant brain regions but also upon high-speed communication between the different hubs that must cooperate to faithfully execute these processes. This high-speed cooperation is dependent upon the integrity and efficiency of tracts connecting diffuse neural networks, referred to as the connectome. The connectome is the matrix of neurons connecting and facilitating communication between different (specialised) brain regions.

The development of an efficient connectome allowed the evolution of a high degree of regional specialisation in the human brain because it facilitated rapid communication and coordination between the many specialised neural hubs involved in executing complex mental processes. The connectome might be likened to a complex road network, with the major white matter tracts representing the motorways, and a whole series of progressively smaller 'road networks' that connect diffuse brain regions. Each 'road network' has a limited capacity beyond which 'traffic' can no longer efficiently travel, resulting in poorer interaction and coordination between hubs.

Complex mental processes depend on rapid, coordinated transmission of information between multiple hubs. If delays arise in parts of this information transmission process then the complex mental processes carried out by these hubs will be disturbed. For example, information transmission problems in neural circuits involved in sensory perception will mean that smooth integration of sensory perceptual experiences will breakdown, leading to hallucinatory experiences. The greater the latency in information transmission, the more severe the hallucinations. This applies to many complex mental processes that require coordination between neural hubs, such as sensory-perception, motor, cognitive, social and language skills – all processes that are implicated in psychosis. Psychosis, then, might be considered the evolutionary price for developing highly specialised brains – asynchrony or poor integration of neural activity from one hub to the other may give rise to psychotic experiences.

Why are some individuals more sensitive to information transmission latencies than others? Developmental issues and individual differences

The synaptic pruning process that defines adolescent brain development leads to more efficient integration and coordination between brain hubs ('neurons that fire together, wire together'). We suggest that this is the reason why the prevalence of psychotic experiences markedly decreases over the course of adolescence (Kelleher et al., 2012a): where this maturational process proceeds smoothly, neural efficiency increases, meaning that the threshold for disordered integration and coordination (which precipitates psychotic experiences) is less likely to occur.

Individuals for whom the synaptic pruning process is less successful, however, will have lower thresholds at which their key information transmission systems break down, meaning that psychotic experiences are more likely – the more disordered the synaptic pruning process, the lower the neural efficiency threshold.

As well as between person differences, there may also be within person differences in terms of vulnerability to deficits in one domain over another. For example, an individual may have relatively poor connectivity in certain brain regions, such as in brain hubs involved in auditory sensory processing, but relatively better connectivity in other regions, such as in brain hubs involved in language or in limb movements, meaning that deficits will be more marked in terms of auditory hallucinations, with fewer problems with disorganised speech or behaviour. Individual variation in risk for psychotic experiences may be dependent upon an

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interaction between the integrity of the connectome and the levels of demand or mental stress placed upon the individual (and, therein, their available neural resources), with each individual having their own personal threshold, beyond which communication cannot continue efficiently, leading to the emergence of psychotic experiences. That is, the more efficient the connectome, the greater the demand needed to overwhelm neural resources and cause psychotic experiences.

Connectome efficiency (or the speed of transfer of information facilitated by the connectome), we believe, may also be the reason why psychotic experiences are far more prevalent in childhood than in adolescence and adulthood. Adolescence represents the key developmental stage during which consolidation of the hubs of the connectome occurs (Whitaker et al., 2016). A more efficient connectome, resulting from a healthy consolidation process, will, we suggest, result in reduced vulnerability to psychotic experiences.

We suggest that the relative hypoconnectivity of the pre-adolescent brain may be the reason that psychotic experiences are for more prevalent in children. We hypothesise that, given their stage of brain development, even relatively low levels of demand may overwhelm neural resources in otherwise healthily developing younger children and precipitate psychotic experiences.

In keeping with the above, emerging neuroimaging research in individuals with psychotic experiences has shown reduced integrity of white matter tracts that are important in coordinating high-speed information processing between distributed neural networks (Amico et al., 2017; Drakesmith et al., 2015; Drakesmith et al., 2016; Jacobson et al., 2010; Jacobson McEwen et al., 2014; O'Hanlon et al., 2015; Orr, Turner, & Mittal, 2014). Most recently, neuroimaging research has demonstrated reduced functional connectivity in young people with psychotic experiences, including relative hypoconnectivity affecting the default mode network, central executive network, salience network and motor network (O'Neill et al., 2020). Importantly, recent research suggests that hypoconnectivity associated with psychotic experiences may be dynamic and state-dependent (Mennigen et al., 2020).

Once an individual passes their neural efficiency threshold, effects on a wide range of mental processes may begin to emerge: impaired communication between hubs involved in logical thought, for example, may give rise to delusional beliefs and thought disorder. Impaired communication between hubs involved in social cognition may give rise to social skills deficits. Impaired communication between hubs involved in language may give rise to disorganised speech. Impaired communication between hubs involved in complex motor skills may give rise to disorganised behaviour. Crucially, problems integrating neural activity from hubs involved in sensory perception may give rise to hallucinations.

Although early motor, language, social or thought process problems may be subtle enough to be overlooked, unusual perceptual experiences such as perceiving one's thoughts as though they are aloud represents a qualitative difference that is difficult to ignore. Therefore, hallucinations may emerge as one of the earliest signs of neural systems dysfunction and could represent a clinical bellwether of an individual passing their neural efficiency threshold. Although problems in neurocognition, social cognition, language and motor skills might emerge at the same time, these deficits may need to be significantly more advanced before they become readily apparent.

Psychotic experiences and trauma

Beyond neurocognitive and neuromotor effects, we suggest that dysfunction associated with passing a neural efficiency threshold is also a major factor contributing to the strong relationship between psychotic experiences and trauma (Arseneault et al., 2011; Kelleher et al., 2013c; McGrath et al., 2017; Morrison, Frame, & Larkin, 2003; Schäfer & Fisher, 2011). Psychological stress, arising from exposure to adverse life events, will drive increased interaction between relevant neural hubs, including those involved in threat and stress responses. This increased neural activity ('traffic') in the connectome reduces capacity for interaction and high-speed coordination between other hubs. The greater the degree of distress, the greater the network capacity demand that is taken up responding to this stressor, which results in reduced network capacity for other interacting hubs. Therefore, coordination between neural hubs that are dependent on high-speed interaction may be delayed, including coordination between hubs involved in sensory perception, which may give rise to hallucinatory experiences.

Psychotic experiences and suicidal behaviour

We suggest that reduced efficiency of cooperation between hubs involved in complex mental processes may serve to increase the risk of suicidal behaviour at the same time as increasing risk of psychotic experiences (Bromet et al., 2017; DeVylder, Lukens, Link, & Lieberman, 2015; Fisher et al., 2013; Hielscher et al., 2019; Kelleher et al., 2014a, b; Yates et al., 2019). This includes, for example, cooperating hubs involved in the execution of complex problem-solving skills (Barzilay et al., 2019), hubs involved in language skills that allow one to verbalise one's challenges, and hubs involved in complex social skills that allow one to effectively elicit help from others. Taken together, these problems will result in difficulties generating sophisticated solutions in the face of complex problems and, as a result, may contribute to the risk of suicide.

Testable hypotheses

We propose that the neural efficiency-threshold model allows the generation and testing of many different hypotheses with regard to psychotic experiences. For example, from a cognitive perspective, the model suggests that neurocognitive deficits are a feature of the emergence of psychotic experiences rather than of the underlying mental disorder *per se*. From a developmental perspective, the model suggests that stressful situations are more likely to elicit psychotic experiences in pre-adolescent children than in adolescents and adults. From a functional perspective, the model suggests that, within individuals with mental disorders, the presence of psychotic experiences would be better predictors of functioning than information on the severity of symptoms of the underlying disorder itself.

One particular important testable hypothesis, which arises from this model, is that individuals exposed to adverse life events who develop psychotic experiences should have a higher risk of suicidal behaviour than individuals who experience the same adverse life events but who do not develop psychotic experiences. In that way, psychotic experiences might act as a measurable marker of the subjective impact of adverse life events, including in terms of suicidal behaviour risk.

We hope this neural efficiency threshold model will provide a useful framework for a broader bio-psycho-social understanding of psychotic experiences to guide and inspire future research.

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