The dysconnection hypothesis of schizophrenia: a 30-year update

We introduced the dysconnection hypothesis of schizophrenia 30 years ago[1], with the advent of human brain mapping. Actually, one could argue that the basic idea emerged even before the notion of schizophrenia itself – in Bleuler's description of psychic disintegration and Wernicke's sejunction hypothesis.

At its inception, the dysconnection hypothesis made some strong claims about the functional anatomy of schizophrenia. In the preceding decades, functional theories of the disorder had focused on notions such as abnormal hemispheric lateralization, or empirical findings such as abnormal histopathology in particular brain regions. The switch of focus – from regional abnormalities to accounts based upon brain connectivity – spoke to the broad conceptualization of functional anatomy enshrined in the principles of functional segregation and integration[2]. Early brain imaging studies quickly established evidence for functional segregation in the brain (i.e., specialization of different brain regions) and subsequently addressed the more vexed issue of how specialized brain regions were integrated through their interconnections.

On this view, it was quite natural to think about schizophrenia as resulting from dysfunctional integration or connectivity. And indeed, aberrant functional connectivity was quickly identified in people with schizophrenia. Since that time, one could argue that the notion of dysfunctional connectivity – i.e., schizophrenia as a functional dysconnection syndrome – has been one of the most enduring mechanistic frameworks within schizophrenia research. So, does the dysconnection hypothesis simply posit a disintegration of coherent brain activity?

No. It was – and remains – a specific hypothesis that distinguishes between *disconnection* and *dysconnection*. The lexical distinction may be subtle, but the conceptual distinction is fundamental. On the one hand, disconnection invokes Geschwind's notion of disconnection syndromes, reminiscent of Wernicke's sejunction hypothesis, in which there are disruptions to the organs of connection – namely, the white matter tracts that connect brain regions. For example, schizophrenia may have been a pernicious form of leukodystrophy[3]. Alternatively, *dysconnection* implies that the pathology in question is not anatomical but involves a dysfunctional integration at the synaptic level. In terms of pathophysiology, one could conceive of dysconnection as a synaptopathy[4]. But what kind of synaptopathy?

The dysconnection hypothesis commits to a particular kind of synaptopathy – namely, a failure of neuromodulation (i.e., aberrant modulation of synaptic efficacy or postsynaptic gain). This commitment is inherited from the theoretical neurobiology of value-dependent learning, in which classical neurotransmitters – such as dopamine and acetylcholine – modulate associative plasticity and experience-dependent learning at the synaptic level. This way of thinking about learning and inference in the brain came to dominate systems neuroscience in the form of reward prediction errors, with clear links to dopaminergic theories of schizophrenia, e.g., the aberrant salience hypothesis.

However, things changed after the first decade, with a shift in cognitive neuroscience to the predictive processing paradigm. This shift was important for the dysconnection hypothesis, because it brought inference and sense-making into the compass of what would be later known as computational psychiatry. In brief, hierarchical predictive processing views the brain as a constructive organ, generating explanations for the causes of its sensorium.

In this setting, neuromodulation or postsynaptic gain control plays a key role. From the computational perspective, postsynaptic gain selects the neuronal messages that are sent to higher hierarchical levels. In other words – when looked at through the lens of computational neuroscience – postsynaptic gain encodes the precision or confidence afforded by neuronal messages. Psychologically, the implicit selection can be regarded as attentional selection (and deselection or sensory attenuation). This formulation had clear implications for a computational understanding of many psychopathologies, including autism and schizophrenia[5].

Physiologically, this focused attention on the mechanisms that determine postsynaptic gain, ranging from the role of fast-spiking inhibitory neurons – through voltage dependent N-methyl-D-aspartate (NMDA) receptor function – to classical neuromodulators that are, invariably, the target of psychomimetic, psychedelic and psychotherapeutic drugs. From the perspective of the dysconnection hypothesis, this placed great emphasis on cortical or synaptic gain control and the implicit encoding of confidence or precision.

Much of the attendant theoretical neurobiology was cast in terms of the Bayesian brain hypothesis and implicit Bayesian belief updating under uncertainty. This had a fundamental implication: it meant that one could talk about psychopathology as aberrant belief updating or false inference. In other words, one could link aberrant precision or gain control to a patient's perceptual inference and sense-making. It was then a natural step to cast the symptoms and signs of schizophrenia in terms of false inference.

For example, one can classify false inference in statistical terms, where type I errors correspond to inferring that something is there when it is not – as in hallucinations and delusions. Conversely, type II errors mean inferring that something is not there when it is – as in dissociative and neglect syndromes. All these aspects of psychopathology could then be explained by a failure to implement the right kind of precision or gain control in hierarchical predictive processing. This subsequently became a compelling line of research in its own right, with precision-based accounts of schizophrenia and beyond[6,7]. But what of the underlying pathophysiology and its aetiology?

As noted above, there are a myriad of synaptic and systemic mechanisms that mediate precision or cortical gain control in the brain[8]. Many licence a focus on key receptors and attendant psychopharmacology. Obvious examples include the NMDA receptor, due to its modulatory (nonlinear) characteristics, and its deployment on inhibitory interneurons that mediate synchronous gain. Likewise, a focus on classical ascending modulatory neurotransmitter systems seems fully justified. One interesting development over the past decade is a focus on markers of aberrant precision or

gain control, such as excitation-inhibition (E/I) balance[9].

From the perspective of the dysconnection hypothesis, the question is: what are the modulatory mechanisms that lead to a failure of cortical gain control or E/I balance? The mounting empirical evidence suggests a failure to modulate the recurrent (and often synchronous) exchange between fast-spiking inhibitory interneurons and (superficial) pyramidal cells in the cortex. Interestingly, the superficial pyramidal cells are – on a canonical reading of predictive coding architectures – responsible for passing prediction errors up cortical hierarchies. This evidence rests largely upon non-invasive electrophysiological studies – in conjunction with dynamic causal modelling – which allow one to pinpoint laminar specific and, at times, receptor-specific interactions at the level of neuronal populations. So, what next?

One could argue that incredible progress has been made over the past 30 years. For example, starting with the rather broad notion of dysfunctional connectivity, people are now talking about the functional genomics and molecular biology of ontogenetically characterized inhibitory interneurons, and their role in the canonical microcircuits that underwrite predictive processing. Having said this, the primary locus of pathology has yet to be identified. Are we talking about polygenic (or delayed epigenetic) mechanisms expressed at the level of synaptic modulation in canonical microcircuits? Or, are we looking at a synaptopathy in afferents to the sources of ascending modulatory neurotransmitter systems? Or both, or neither? These are important questions, because therapeutic interventions rest on understanding the mechanisms of pathogenicity, that matter at every level and to everyone concerned.

Karl Friston
Queen Square Institute of Neurology, University College London, London, UK

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Immuno-metabolic depression: challenges ahead for identification and intervention

Major depression is associated with an increased risk of cardiometabolic disorders such as obesity, cardiovascular disease, and diabetes. Although this can be partly explained by poorer lifestyle in depressed patients, underlying shared pathophysiological and genetic mechanisms play a role as well.

Depressed persons more often have systemic low-grade inflammation, with elevated levels of C-reactive protein (CRP), cytokines and glycoprotein acetyls, and metabolic syndrome abnormalities including abdominal obesity, dyslipidaemia, and insulin and leptin resistance[1]. Immuno-metabolic processes can lead to psychiatric disease acceleration (e.g., through dysfunction of reward and emotion regulating brain circuitry, and reduced neurogenesis and monoamine signalling)[2]. The same processes play a parallel role in the genesis and progression of subclinical and clinical cardiometabolic conditions.

Genetic correlation and shared genetic variants exist between immuno-metabolic traits and depression[3,4]. Furthermore, recent Mendelian randomization studies indicate that the genetic liability for depression is associated with an increased risk for cardiometabolic conditions, whereas no strong evidence is found for the reverse direction[5].

However, depression is arguably the most heterogeneous psychiatric condition. Heterogeneity exists in the depression symptom profile experienced, the environmental risk factors encountered, and the pathophysiology observed. Only 25-30% of depressed patients present with objective signs of low-grade inflammation and metabolic syndrome abnormalities[1]. The prominent symptom profile of depressed persons with immuno-metabolic dysregulations is distinct: they report more atypical, energy-related depressive symptoms such as hypersomnia, leaden paralysis, fatigue and hyperphagia, and anhedonia and reduced motivation[1,4]. So, there is a clustering of systemic low-grade inflammation, metabolic syndrome dysregulations, and atypical energy-related depressive symptoms and anhedonia. It is this clustering of specific symptoms with specific pathophysiology that could be indicated as immune-metabolic depression.

This is a dimensional phenomenon. Atypical energy-related symptoms have dose-response associations with inflammation indicators (CRP, interleukin-6, glycoprotein acetyls) and metabolic dysregulations (waist circumference, triglycerides, cholesterol, glucose, leptin). Currently, no consensus exists on how to classify immuno-metabolic depression, although pragmatic criteria have been explored. Twenty-six percent of 1,077 patients examined in the Netherlands Study of Depression and Anxiety (NESDA) have at least moderate atypical, energy-related symptom levels *as well as* a CRP level >1 mg/L, and this is applied as inclusion criterion for an ongoing study[6].

Why is the identification of immuno-metabolic depression clinically relevant? Immune-metabolic features have been related to poorer course, and (although the evidence is still limited) to a poorer response to standard antidepressants[1]. Importantly, treatments that directly target immuno-metabolic dysregulation could be use-