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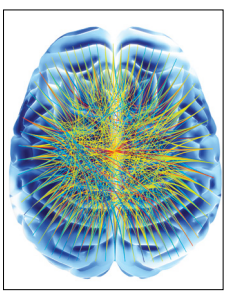
Imaging brain circuits in anxiety disorders

Despite the huge burden that anxiety disorders can impose on individuals and social systems, most people, having themselves been affected by fear at some point during their life, intuitively assume that they can empathise with anxious patients by merely extrapolating the emotion associated with such an experience. Indeed, the ease of creating models of anxiety disorders in healthy volunteers has rendered the topic approachable to researchers from a range of disciplines. A neural pathway common to physiological and pathological anxiety was suspected long before the Research Domain Criteria were announced by the National Institute of Mental Health[1] and key neurobiological correlates, such as the prevailing role of the amygdala and the importance of serotonergic modulation, were discovered early in studies of fear and anxiety. However, as Oliver Robinson and colleagues correctly state in their article in *The Lancet Psychiatry*, study of the function of the amygdala alone yields only some insight into the pathophysiology of anxiety disorders.[2] Approaches such as staging, integrating systems involved in anxiety processing,[3] together with genetic and clinical illness variables, promise to be more useful.

The development and widespread use of neuroimaging techniques has produced an increasingly diverse picture of the involvement of different brain structures and neurotransmitter systems in processing of fear. MRI allows us to study distinct brain networks. When functional connectivity is calculated, these networks emerge as regions with correlated activity, measured as a blood oxygenation level-dependent signal, over a period of time which is supposedly indicative of their involvement in processing similar information. In the context of anxiety disorders, the regulation of the amygdala by the frontal cortex has received special attention. Most studies have emphasised the disruption of the inhibition of the amygdala by the prefrontal cortex in particular anxiety disorders—eg, in social anxiety disorder, the connectivity between the orbitofrontal cortex and the amygdala is greatly impaired.[4–6] In their study, Robinson and colleagues have focused on the dorsal medial prefrontal cortex, which is distinguished from other parts of the prefrontal cortex by its increased connectivity with the amygdala, at least in generalised anxiety disorder.[7] They have shown that instead of inhibiting threatening stimuli, the dorsal medial prefrontal cortex–amygdala circuit helps their amplification. A similar mechanism was first reported in rodents[8] and translated to anxiety models in healthy people.[9,10] Now finally its role in anxious patients has been shown by Robinson and colleagues.[2] The finding affirms the view that an intrinsically self-protective circuit malfunctions in anxiety disorders.

Despite this promising result, it is premature to postulate whether or how the knowledge of this mechanism will translate into clinical practice. At this point we are presented with a finding that adds another aspect to our understanding of anxiety disorders and has the potential to become a useful biomarker. Nevertheless, the results need to be replicated before we can draw firm conclusions.[11] The reference to modification of resting-state connectivity of the dorsomedial prefrontal cortex by selective serotonin reuptake inhibitors in healthy volunteers[12] might ultimately prove to be misleading in hindsight in view of the altered neurobiology of anxious patients. We need to find out to what extent the differences shown allow for the stratification of patients to treatments. In view of the long list of statistically significant imaging results in different investigations, it seems increasingly unlikely that an isolated imaging parameter will be sufficient.[13] However, a combination of several such markers with replication across modalities might ultimately lead to a clinically useful specification of illness characteristics and tests.

The next step is to investigate pharmacological challenge of this circuit in patients, together with the long-term assessment of treatment. Sophisticated modelling should be used to assess directionality in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network processing (eg, dynamical causal modelling)[6] or more holistic network features (eg, graph theoretical approaches).[14] Combination with molecular imaging with use of PET can provide robust information about network changes in neurotransmission associated with treatment.[15] More causal approaches based on transcranial optogenetic inhibition in animal models by red light penetrating the skull might show the functions of these networks in more detail.[16] Simultaneous investigation of molecular, structural, and functional imaging changes together with illness variables is likely to increase the specificity of each and result in models with sufficient predictive values for clinical practice. Robinson and colleagues[2] present a mechanistic understanding of pathological anxiety that might contribute to this goal.

Siegfried Kasper, Gregor Gryglewski, Rupert Lanzenberger
Department of Psychiatry and Psychotherapy, Medical University of Vienna, Währinger Gürtel 18-20, A-1090 Vienna, Austria
sci-biolpsy@meduniwien.ac.at

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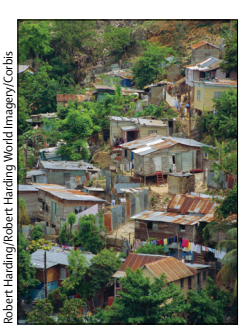
There is no wealth without mental health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Among the proposed transformative shifts in the post-2015 development agenda[1] are a focus on the most vulnerable (leave no one behind) and strengthening of economies by inclusion of all who can contribute. These issues are at the heart of global mental health, now increasingly recognised as having an essential role in the achievement of shared development objectives.[2] Mental health was a key theme in the UK International Development Parliamentary Select Committee Inquiry on Disability and Development,[3] and is part of the continuing Open Working Group consultations on the Sustainable Development Goals. Indeed, discussions at the 2014 World Economic Forum in Davos were paraphrased as "There is no wealth without mental health" on the basis that the worldwide cost of mental disorders in 2010 was estimated at US$2·5 trillion, with the cost projected to surge to $6·0 trillion by 2030.[4]

Fortunately, we now have an increased understanding of how to address these disorders in practical ways, including in low-resource settings. Over the past decade, global mental health research has clarified the effect that poor mental health has on many central issues in development,