Brief report

Evolving a new neuropsychiatry

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Clinical neuroscience struggles with poor scientific validity of neuropsychiatric diagnosis and its negative impact on management. Sydenham's ancient conformity of type approach to nosology with its assumption that the symptom cluster and course of a disorder are due to a common etiology, has proven no match for the complicated comorbidities faced in neuropsychiatry. In the absence of accurate pathological biomarkers there is a challenge in finding a solid foundation for modern neuropsychiatry. We find standard psychiatric nosology to be of limited benefit at the general hospital bedside in evaluating and treating neuropsychiatric disorders. Consequently, we have developed over the years a neurocircuitry-based training for our psychosomatic medicine fellows. In this commentary, we will introduce a strategy for understanding patients with neuropsychiatric disorders that may advance our ability to diagnose and treat them in accordance with neuroscientific evidence anchored in evolutionary neurocircuitry and attachment neurobehavior.

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"I would say that the future of psychiatry from my vantage point remains uncertain until it identifies a solid foundation."

Samuel Gershon

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An evolutionary neuropsychiatry

Academicians debate the utility of the *Diagnostic and Statistical Manual (DSM)*-5 when it comes to validly diagnosing mental disorders.[1-4] The Research Domain Criteria (RDoC) aim to develop a more valid dimensional framework.[5-7] However, questions remain.[8,9] Perhaps the biggest challenge comes when clinicians must understand and treat patients with idiosyncratic multidimensional blends of neuropsychiatric

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findings.[10-12] Psychiatric nosology is of limited benefit in evaluating and treating neuropsychiatric disorders in the general hospital. This realization led us to develop a neurocircuitry training program for fellows based on the science of brain evolution.

Tinbergen urged scientists interested in understanding any biological or psychological process to ask four questions.[13] How does the process work? How did it develop? What is it for? How did it evolve? By asking Tinbergen's four questions and combining two foundational principles that emerge in the course of answering them, we may build a neuropsychiatric nosology capable of providing greater diagnostic understanding regardless of complex comorbidities.

Evolutionary brain biology depicts life's unfolding as a sensory-motor analyzer-effecter entity.[14] Because fitness may be defined in terms of attachment solutions to separation challenges, natural selection has sculpted a specialized organ to focus functions on human life's four attachment-based objectives (metabolic energy, sexual, social, and future objects).[15] These functions are manifested through neurocircuitry allowing for discernment of brain form and function.

While wrestling with Tinbergen's questions, two foundational principles emerge. The first recognizes what the brain's workplan is and how it developed. In the brain, we see evidence of the sensory-motor analyzer-effecter bauplan (body plan) in the cortico-striato-thalamo-cortical loops that are segregated yet integrated for the purpose of deciding whether to avoid or approach, separate or attach.[16] This first foundational principle also hints at how the brain evolved its bauplan to accomplish what it is for. Indeed, the performance demands of brain function as prescribed by natural selection gave rise to brain form.

In a meta-analysis based on voxel-based morphometry (VBM) studies, six major neuropsychiatric disorders—schizophrenia, bipolar illness, depression, obsessive-compulsive disorder, anxiety and addiction—showed a common defect called the VBM psychiatric core, centered in the dorsal anterior cingulate cortex (dACC)/anterior insula network.[17] This network is central to analyzer-effecter functioning and is key to response selection. The brain actively constructs inferences based on sensory data to predict future rewards leading to approach or avoidance response selections via the dACC and other PFC zones.[18] The VBM researchers suggest that this psychiatric core "concordance provides an organizing model that emphasizes the importance of shared neural substrates across psychopathology, despite likely diverse etiologies, which is currently not an explicit component of psychiatric nosology."[17] In another recent study, conjunction analysis showed smaller VBM psychiatric core volumes in subjects with major depression and bipolar disorder, lending support to this notion.[19]

Some of the sensory-motor neural networks are confined to primary sensory and motor cortex terminal zones. Analyzer-effecter networks spread out across many brain regions, allowing for more integrative functioning. Several lines of integration are postulated. There is convergence of terminals from functionally proximate cortical areas onto increasingly more confined basal ganglia structures resulting in an interpenetration of signals.[20,21] In addition, information from the motivational system can reach the motor system through a series of interconnections. Information in the "paralimbic" and "limbic" basal ganglia-thalamo-cortical circuits and information within the "motor" basal ganglia-thalamo-cortical circuit come together to enable the organism to effect an appropriate avoidance-approach response to sensory stimulation. This occurs when the ventral striatum receives input from the paralimbic medial prefrontal cortex (mPFC) and in turn projects to a midbrain region that feedforwards to the central associative striatum. The central striatum then projects in part to a section of the substantia nigra, which connects with the dorsolateral motor striatum.[20,22] Haber and Calzavara[20] conclude that cortex "exploits" basal ganglia as an additional processor forming a central selection-effecter mechanism that enhances decision-making in the service of attachment goal-directed behaviors and habits.

One important integrative neural network is the *default-mode network (DMN)*.[23,24] It has nodes in mPFC, posterior cingulate cortex (PCC), precuneus, and lateral parietal cortex. The DMN mediates self-focused introspective and prospective thinking. Another network looks outward and is known as the *task-positive network* and includes the *frontoparietal central executive sub-network (CEN)*, which is important for working memory and attention. Another task-positive subnetwork is the *anterior cingulo-insular network (aCIN)* or *salience network*, which overlaps with the *VBM psychiatric core (left and right insular cortex* and *dACC* also known as the *midcingulate [MCC])*.[25] Much of neuropsychopathology emerges from dissolution of

aCIN (implicit) and CEN (explicit) emotion regulation pathways, which emanate from the ventral ACC and medial orbital frontal ventromedial PFC in the former case and from the dACC/MCC and the dorsolateral PFC (dlPFC) in the latter case, to provide circuit-based control of the amygdalar fear conditioning separation stress pathway. This dissolution may come from disruptions in point-to-point channel connectome functions leading to neurological defects in informational content flow and/or from state shifting modulatory system psychiatric dysfunctions leading to deficits in the state of information processing. Modulatory systems include neurotransmitter, neurohormone, and neuroimmune cytokine impacts on these neural node terminals via the brain reward and motivation circuitries in the medial forebrain bundle (MFB) as well as frontocerebellar and dorsal diencephalic habenular tract influences.[26-28] A strategy for assessing loop channel and state functioning at the bedside or in the clinic becomes an integral part of the neuropsychiatric exam. For example, interrogating MFB dopamine tracts entails monitoring eye blink rate and speech latency.

The second foundational principle defines the relationship between separation challenge and attachment solution. Because fitness can be defined in these terms, the brain has been sculpted to focus its form and structure on the four attachment-based objectives of life mentioned above. This understanding helps us assess how individuals perform when experiencing amygdalar stress.

Bowlby contended that human evolutionary adaptedness was sourced in an environment of secure base attachment.[29,30] Recently a transdiagnostic model of psychopathology based on Bowlby's attachment behavioral system has emerged.[31] There are mechanisms through which epigenetically developed attachment dispositions serve as transdiagnostic risk factors when insecure attachment, be it attachment anxiety or avoidance, becomes the residual internal working model for self and the world perhaps reflecting DMN and aCIN disconnection. MacLean cited the ACC as the hub for what he called the mammalian behavioral triad comprised of key attachment sustaining behaviors—the separation cry, maternal nurturance, and play.[32] This may tie in the VBM psychiatric core in the first foundational principle with the second foundational principle. Thus, attachment-based transdiagnostic risk factors may mediate pathways that set the stage for so-called "multifinality" in which the attachment risk factor leads to multiple disorders.[33]

Analyzing separation stress and implementing attachment solutions is integral to caregiving. If we examine anxiety based in separation threat and depression based in attachment loss according to these principles, we discover particular subset neural network dysfunctions.[34] The DMN may contribute to maladaptive rumination and negative thinking as an endophenotype; the aCIN salience circuit may produce social anxiety and panic as well as depression; the cingulo-opercular sub circuit may play a role in anxious avoidance; the negative affect circuit (mPFC, ACC, vmPFC, hippocampus, insula, and amygdala) may mediate negative bias and implicit separation threat dysregulation; the positive affect circuit (mPFC, mOFC, nucleus accumbens, ventral striatum, VTA) may mediate an anhedonia endophenotype when dysfunctional; the attention circuit (medial superior frontal cortices, anterior insula, anterior inferior parietal lobe, and precuneus) may contribute to inattentiveness; and a disordered cognitive control circuit (dlPFC, dACC, dorsal parietal cortex, and precentral gyrus), may lead to an explicit inability to dampen default mode rumination. A similar analysis can be made for a wide variety of neuropsychiatric diseases.[35,36]

These sensory-motor analyzer-effector malfunctions disturb a patient's ability to separate or attach expeditiously, efficiently, and effectively. In this dysfunctional matrix, we can begin to see analyzable biological markings that correlate with the dimensions of neuropsychiatric disorders.

By using our own segregated yet integrated analyzer-effecter capacity, we neuropsychiatrists can endeavor, with our patients, to effect an attachment solution to their illness separation challenge.[15]

Conclusion

Embedding neuropsychiatry in the dual principles of evolutionary neuroanatomy and attachment theory should be a priority. Our diagnostic tasks require attention to two foundational principles, ie, neurology anchored in an understanding of brain evolution and psychiatry based on the concept of separation challenge and attachment solution decision-making. Building the capacity of neuropsychiatrists to ask the Tinbergen questions and to link up foundational principles with the mechanisms on which they are based can create brain doctors capable of

anchoring their diagnoses in a scientific safe harbor and of providing healing care. It is the evolution of the brain's neurocircuitry that has led to the meaningful experience of separation stress and attachment loss that fuels neuropsychiatric dysfunction and distress.

After decades studying brain evolution, MacLean concluded in an inscription in his magnum opus, *The Triune Brain*, that separation is "the most painful mammalian condition." We would do well to take heed in developing a solid foundation for neuropsychiatry. ❑

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