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A proposed solution to integrating cognitive-affective neuroscience and neuropsychiatry in psychiatry residency training: The time is now

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ABSTRACT

Despite increasing recognition of the importance of a strong neuroscience and neuropsychiatry education in the training of psychiatry residents, achieving this competency has proven challenging. In this perspective article, we selectively discuss the current state of these educational efforts and outline how using brain-symptom relationships from a systems-level neural circuit approach in clinical formulations may help residents value, understand, and apply cognitive-affective neuroscience based principles towards the care of psychiatric patients. To demonstrate the utility of this model, we present a case of major depressive disorder and discuss suspected abnormal neural circuits and therapeutic implications. A clinical neural systems-level, symptom-based approach to conceptualize mental illness can complement and expand residents' existing psychiatric knowledge.

1. Introduction

Modern day psychiatry and neurology have shared origins. Among the most impactful examples of this shared history are the clinical efforts performed at the La Salpêtrière Hospital in France in the late 19th century, where visionaries including Jean-Martin Charcot, Sigmund Freud, Gilles de la Tourette, and Pierre Janet all worked collaboratively in their care and study of patients with conditions at the interface of brain and mind (Bogousslavsky, 2014). In a unifying statement Charcot wrote "the neurological tree has its branches; neurasthenia, hysteria, epilepsy, all the types of mental conditions, progressive paralysis, gait ataxia (Charcot, 1887)." Unfortunately, despite this shared history, a "great divide" emerged throughout the 20th century with psychiatric mental disorders being largely defined by the presence of symptoms in the absence of any grossly visible pathology and neurological disorders based in the clinical-pathologic correlate (Price et al., 2000; Martin, 2002). Significant advances in cellular-molecular and systems-level cognitive-affective neuroscience and *in vivo* neuroimaging research across psychiatric disorders have now proven this distinction to be misleading. As examples, post-mortem pathological changes in the hippocampus in schizophrenia (Harrison, 2004) and in the anterior cingulate cortex in major depressive disorder (MDD) (Ongur et al., 1998; Cotter et al., 2001) have been well characterized. Yet, despite significant advances in our knowledge of the biological basis of psychiatric disorders and calls from international leaders such as the Nobel Laureate Eric Kandel (Cowan and Kandel, 2001) for increased neuroscience and clinically-relevant neurology education in psychiatry residency, cognitive-affective neuroscience and neuropsychiatry remain a challenge to integrate into clinical practice and psychiatric training experiences.

While there has been increasing recognition for the need to better incorporate neuroscience and psychiatrically relevant neurology into the education and training of psychiatry residents (Benjamin, 2013), successfully implementing such efforts and

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achieving tangible results has remained elusive. A recent study, for example, noted that while 94% of surveyed academic chairs, practicing psychiatrists, and residents agreed on the need to further promote neuroscience education, only 13% of trainees considered themselves to have a strong neuroscience knowledge base (Fung et al., 2015). In this article, we present the integrated perspectives of a current psychiatry resident in training (JT), a neuropsychiatry fellow with a background in neuroimaging research (JLP), an early career academic faculty psychiatrist with a background in neuromodulation (APS), a researcher in psychiatric neuroscience (MSK), and a dual trained early career neurologist-psychiatrist and cognitive-affective neuroscientist (DLP) to explore how trainees can bridge in real-time brain-symptom relationships in psychiatry. This article outlines how psychiatry residents can integrate systems-level neuroscience into their training to conceptualize psychiatric symptom-complexes and advance translational therapeutic efforts. An illustrative case example is presented to model this approach.

2. Current challenge

Many psychiatry residents may not be aware of their potential interest in a clinical psychiatric neuroscience approach to patient care due to a lack of clinical exposure. While any patient presentation can, and should, inspire a comprehensive, neuroscientifically and neurologically informed approach, trainees need clinical exposure to cases with salient neuropsychiatric elements to develop relevant conceptual and technical skills. High yield neuropsychiatric cases may include patients with prominent emotional, perceptual and/or behavioral symptoms in the context of neurodegenerative disease, epilepsy, cerebrovascular disease, traumatic brain injury, movement disorders and autoimmune disorders with neuropsychiatric features such as anti-NMDA encephalitis. However, depending on the training environment, some residents may be rarely exposed to such patients, as they are instead treated in sub-specialty clinics or other departments.

A related challenge for residents in developing a strong neuroscience and neuropsychiatric foundation may be the nature of the didactics available within many training programs. A recent study of 226 adult and child/adolescent psychiatry program directors noted that 39% felt that a lack of neuropsychiatry faculty, and 36% a lack of neuroscience faculty, were perceived barriers to appropriately offering increased training in neuropsychiatry and the neurosciences respectively (Benjamin et al., 2014). Other barriers also included the lack of relevant curriculums and faculty availability.

While a long-term solution to both these issues could be to establish neuropsychiatry divisions within academic psychiatry departments, in which psychiatry residents readily care for patients with psychiatric symptoms secondary to neurological illnesses, an equally important solution as discussed below is for academic psychiatry departments to place greater emphasis on a brain-symptom based approach in the formulation and treatment of patients experiencing idiopathic (primary) psychiatric symptoms.

3. Evolving large-scale solutions

Recognizing the challenges likely experienced by most residents in United States training programs and globally, several solutions have been proposed and developed at the national level. The National Institute of Mental Health (NIMH) has taken a dual approach to specifically support trainees who will define psychiatry as a field of "clinical neurosciences" and encourages neuroscience literacy through development of online modules and teaching based on the Research Domain Criteria (RDoC) project (Chung and Insel, 2014). RDoC is essentially a systems-level, dimensional research approach that conceptualizes psychiatric illness in part as disorders of neural circuitry (Insel et al., 2010). It emphasizes the association between broadly defined emotional and cognitive domains (e.g., negative and positive emotional valence systems) and neurobiological measures, ranging from genetics to physiology, in a manner agnostic to traditional diagnostic categories. The National Neuroscience Curriculum Initiative (NNCI) (http://www.nncionline.org/) has also been recently established to create, pilot, and disseminate a comprehensive set of shared resources for psychiatry residents and already features online educational modules, resources, and videos. Also, the Accreditation Council for Graduate Medical Education (ACGME) in the United States recently implemented a novel framework for evaluating resident performance and one of the these evaluation metrics is that all residents must show competency in clinical neuroscience. However, the specifics behind how individual residency programs implement and meet this clinical neuroscience requirement are less well defined. Beyond the evolving resources and changes discussed in this section, the time is now for residents, educators and like-minded academic psychiatrists to develop a culture of embracing cognitive-affective neuroscience and neuropsychiatry to expedite the "bench-to-bedside" translation of brain-symptom relationships to help guide clinical thinking and future innovative therapeutic interventions.

4. Proposed solution

We suggest that one potentially immediate and impactful method of increasing psychiatry residents' awareness, interest, expertise and clinical appreciation of clinical psychiatric neuroscience and neuropsychiatry is to encourage real-time circuit-specific discussions of brain-symptom relationships across the care of psychiatric patients. Akin to daily discussions occurring in neurology wards and outpatient clinics related to localizing the structural lesion, we specifically propose that psychiatry residents should be taught and encouraged to engage in discussions around *identifying suspected abnormally functioning brain circuits* (and particular nodes within a broadly distributed network that may be linked to a patient's particular symptoms). Given that the bio-psycho-social model is an integral part of psychiatric formulation (Engel, 1977) and residency educational experience, encouraging residents to use clinically-oriented neuroscience and neuropsychiatric principles to discuss the likely affected brain circuits as part of their overall case formulation offers an inexpensive and readily available translational neuroscience paradigm.

While identifying a discrete lesion remains important in making a neurological diagnosis, specific focal lesion localization in psychiatry has proven more difficult. Rather than there being a specific lesion or neuroanatomical site of damage that we can localize through examination or neuroimaging, psychiatric diseases may be better framed as disorders of distributed, interconnected brain networks. To use a metaphor, these diseases can be considered like the abnormal traffic flow patterns in a congested city where old and narrow roads, inefficient traffic lights, and bottlenecks at bridges create in combination a horrible traffic jam of the city's network of streets. While no one traffic light, single narrow road, or individual bridge may in itself be typically sufficient to cause a traffic jam, their effects combine to bring the city's traffic to a halt. Furthermore, at times there is one specific bridge or intersection that receives traffic from many distinct parts of the city and its disruption by itself can cause significant delays. Likewise, psychiatric symptoms can be conceptualized as brain network problems where often times no single isolated region, or lesion, of the brain is responsible for a psychiatric illness but rather

multiple disrupted brain regions within a network or across several networks function abnormally to produce particular symptom complexes. Furthermore, there may be a critical region or "hub" within a group of interconnected regions that if disrupted may have particularly adverse effects of brain function and symptom expression (Bullmore and Sporns, 2009). This perspective of brain circuits, particularly at the level of prefrontal cortex-subcortical circuits was emphasized by Alexander and colleagues in the mid 1980s following their detailed descriptions of five discrete prefrontal-subcortical brain circuits (Alexander et al., 1986). Prefrontal regions including the dorsolateral prefrontal cortex, anterior cingulate cortex and orbitofrontal cortex each were shown to have discrete basal ganglia and thalamic connections and primarily involved in higher-order cognitive or affective functions. Didactic efforts by Cummings and others demonstrated the utility of these circuits to explain psychiatric symptoms including linking impairments of the anterior cingulate cortex-subcortical circuit to motivational deficits, the orbitofrontal cortex-subcortical circuit to disinhibited behavior, and the dorsolateral prefrontal cortex-subcortical circuit to dysexecutive symptoms (Bonelli and Cummings, 2007; Mega and Cummings, 1994). Over the past two decades, these brain-symptom relationships have been refined and these neural network connections have been implicated in the real-world clinical practice of psychiatrists. For example, it was shown that treatments targeting specific neuroanatomical locations such as repetitive transcranial magnetic stimulation (rTMS) to the dorsolateral prefrontal cortex in depression displayed treatment efficacy (Pascual-Leone et al., 1996). While a more detailed up-to-date discussion of the default mode (Zhang and Raichle, 2010), salience (Seeley et al., 2007), attention (Corbetta et al., 2008), emotional processing (Etkin, 2010; LeDoux, 2007; Etkin et al., 2011), cognitive control (Badre and Wagner, 2007; Ridderinkhof et al., 2004), social cognitive (Lieberman, 2007; Adolphs, 2003; Bickart et al., 2012), memory (Eichenbaum, 2000) and visceral-somatic processing (Perez et al., 2015a) networks among others is beyond the scope of this perspective article, they have been reviewed elsewhere (Perez et al., 2015b,c,d). From an educational perspective, systems-level brain-symptom discussions offer a useful mechanism to transform more abstract neuroscience concepts into clinically useful tools for patient care. Integrating regular brain circuit discussions into diagnostic and therapeutic discussions may foster active learning and facilitates the translational process of bringing neuroscience advancements to the clinic.

5. Therapeutic implications of a brain-based approach to psychiatric symptoms

A brain-based, neuroscientifically informed understanding of psychiatric illness is of more than academic interest to future psychiatrists. It will be increasingly relevant in understanding, selecting and administering psychological and biologically-informed treatments. While expert clinicians and the clinical interview are likely to remain the gold standard for clinical diagnosis, clinicians often lack clear guidance around which particular treatment is most likely to be beneficial for a given patient. Adjunct structural and functional neuroimaging biomarkers may serve as clinically useful biomarkers of psychopharmacology and psychotherapy treatment selection (Gabrieli et al., 2015; Pizzagalli, 2011). Neuroimaging studies investigating neural mechanisms of selective serotonin re-uptake inhibitor (SSRI) administration have shown decreased amygdala-hippocampal reactivity following drug administration, while norepinephrine reuptake inhibitors have been demonstrated to increase dorsolateral prefrontal cortex and cingulate gyrus activations (Outhred et al., 2013). Studies evaluating associations between treatment response and baseline neuroimaging patterns have also shown, for example, that pretreatment subgenual anterior cingulate cortex hypermetabolism in patients with major depressive disorder is potentially linked to failure to achieve remission following SSRI medication or cognitive behavioral therapy (either alone or in combination) (McGrath et al., 2014). Preliminary evidence also suggests that baseline insula metabolic profiles may serve as a treatment selection biomarker to guide treatment initiation of SSRI versus cognitive behavioral therapy in untreated individuals with major depression (McGrath et al., 2013). A meta-analysis of neuroimaging studies in depression probing functional and structural neural biomarkers of treatment response across pharmacologic and psychological interventions showed that positive treatment response was linked to baseline increased perigenual anterior cingulate cortex activations; poor treatment response was predicted by decreased striatal and anterior insula activations and regional atrophy in the dorsolateral prefrontal cortex and hippocampus (Fu et al., 2013). While further prospective and multi-site research studies are necessary to validate these structural and functional profiles as possible treatment related biomarkers, an equally important obstacle to incorporating these and other brain science advances is the lack of clinical proficiency and comfort psychiatrists have in using and integrating brain circuit discussions in the care of patients. Our proposal to encourage all psychiatrists and psychiatry residents to engage in discussions around *localizing suspected abnormally functioning brain circuits* provides a necessary bridge to allow promising advances to be actually adopted once well-validated.

Interventional neurotherapeutics, which seek to optimize functional activations and connectivity patterns, are an increasingly widespread treatment modality in which brain circuit expertise is critical for the clinician. TMS was first approved by the Food and Drug Administration (FDA) for use in treatment-resistant depression in 2008 (Stern and Cohen, 2013). While this device specifically targets the dorsolateral prefrontal cortex to modulate baseline lateral prefrontal hypoactivation in depression, a newer device capable of targeting deeper structures such as the anterior cingulate and the orbitofrontal cortex was approved in 2013 (Stern and Cohen, 2013). In addition, recent resting state analyses have linked anti-correlated dorsolateral prefrontal cortex - subgenual anterior cingulate cortex functional connectivity to TMS therapeutic efficacy (Fox et al., 2012), which connects the non-invasive and invasive neuromodulation literature in MDD.

Deep brain stimulation (DBS), which involves implantation of electrodes in strategic brain regions, is an emerging neurotherapeutic approach which has displayed promising results in clinical research studies of treatment-resistant depression (Blomstedt et al., 2013; Mayberg et al., 2005; Kisely et al., 2014). Thus far, DBS of the subgenual anterior cingulate cortex (Brodmann area 25), ventral striatum, and nucleus accumbens have shown potential efficacy in alleviating treatment-resistant depression (Malone et al., 2009; Bewernick et al., 2010; Holtzheimer et al., 2012). These targeted brain regions are particularly notable since each is a component of the anterior cingulate-subcortical circuit. An understanding of the neural circuits underlying these disorders is essential to the successful application of these emerging treatments. Given the continued momentum of neurotherapeutic investigations in psychiatric research to modulate brain networks, it is increasingly necessary for psychiatric trainees to understand interventional neurotherapeutic approaches, including their anatomical basis, and gain mastery of their use as part of their training. If psychiatrists do not embrace opportunities to become specialists in neuromodulation, the void could be filled by other clinical experts in brain functioning.

6. Model case illustrating a brain-symptom, systems-level formulation

A 28 year-old single, employed woman with a family history of mood and anxiety disorders presented with 6 months of depressed and mildly anxious mood, negatively themed rumination, decreased interest in previously enjoyed activities, low-self worth, impaired concentration with reported forgetfulness at work, delayed sleep onset, preserved appetite and no suicidal ideation. Psychiatric review of symptoms was otherwise negative. Symptoms began following a romantic breakup, and psychosocial history was notable for early-life maternal emotional abuse and parental divorce during her teenage years. Mental status evaluation revealed poor eye contact, mildly labile affect, depressed mood and multiple negatively themed self-referential comments. Cognitive Assessment showed slowed processing speed on abbreviated Trails B and serial 7s, impaired executive function (increased perseverative errors on the Wisconsin Card Sort Test) and spontaneous word recall at 5 minutes of 4/5 improving to 5/5 with categorical cues. Elemental neurological examination and medical work-up for reversible causes of depression were within normal limits. She previously failed to achieve benefit from an adequate trial of an SSRI medication.

A clinical psychiatric neuroscience-based formulation for this patient's symptom complex would be as follows. The patient's depressive symptoms appear to at least partially localize to the anterior cingulate cortex and related striatal-thalamic subcortical components. This individual exhibits ruminative negatively valenced thinking which is suggestive of impaired modulation of negative mood states, which has been linked to functional abnormalities of the subgenual anterior cingulate cortex (Hamani et al., 2011; Holtzheimer and Mayberg, 2011) and the amygdala (Belzung et al., 2015). The patient reports anhedonia which has been observed to also localize to the anterior cingulate cortex-subcortical circuit, particularly the ventral striatum/nucleus accumbens (Epstein et al., 2006; Epstein et al., 2011; Pizzagalli et al., 2009). The patient's concentration deficits and mild dysexecutive syndrome is suggestive of lateral prefrontal dysfunction including the dorsolateral prefrontal cortex (Grimm et al., 2008). Of note, the dorsolateral and anterior cingulate cortices are reciprocally connected through cortico-cortical connections (Hamani et al., 2011). Also, the patient's mixed depressed-anxious mood, a commonly encountered clinical presentation, highlights that depression and anxiety have overlapping frontolimbic neural substrates (Ionescu et al., 2013). From a developmental neuroscience perspective, the patient's emotion regulation and expression circuits (including the medial prefrontal cortex and amygdala) may have been sensitized by childhood emotional abuse leading to aberrant (maladaptive) neuroplastic changes (Leuner and Shors, 2013; Dannlowski et al., 2012). These neuroplastic changes may have led to heightened reactivity (in-part from impaired top-down prefrontal cortex regulation of limbic activity) following recent relational stress, triggering negative ruminations and a dysphoric-anxious mood.

From a brain-based therapeutic perspective, given that several aspects of the patient's symptom complex (such as emotional dysregulation and impaired executive function) localize to medial and lateral regulatory prefrontal and amygdalar circuits, consideration was given to a possible trial of a serotonin-norepinephrine reuptake inhibitor. Alternatively or in combination, cognitive behavioral therapy may be beneficial to treat the patient's self-referential, negatively valenced rumination which localizes to the subgenual anterior cingulate cortex and related frontolimbic connections (Holtzheimer and Mayberg, 2011), and cognitive behavioral therapy may improve depression symptoms by modulating medial prefrontal circuits (Yoshimura et al., 2014). Another possibility includes rTMS to the dorsolateral prefrontal cortex which can modulate medial prefrontal regions through afferent connections. Lastly, consideration could be given to a referral to a clinical trial such as for cognitive bias modification (CBM; Almeida et al., 2014); the patient's dysphoric-anxious mood suggests increased amygdala activation, and a positive response to attention bias modification is associated with increased pre-treatment amygdala activation (Britton et al., 2014). In part due to patient preference and resource availability, a therapeutic course of cognitive behavioral therapy, using CBM principles, was pursued.

7. Conclusions

In this article, we highlighted several important barriers to the incorporation of clinical psychiatric neuroscience and neuropsychiatry in general psychiatry residency training. Our proposed approach integrates cognitive-affective neuroscience and neuropsychiatry into the real-time training experiences of residents in a clinically relevant way (Fig. 1). Several counterarguments may be raised against our proposal. One, is the evidence for the aforementioned brain-behavior relationships substantial and consistent enough to introduce into a general psychiatry curriculum? The answer at this point is an unequivocal yes. Even if some of the specific details change, it is clear that the fundamental paradigm of psychiatric illness as neural circuit based disorders is here to stay. Second, would training programs without trained neuropsychiatrists and neuropsychiatry divisions (or similar biologically-oriented divisions such as consultation-liaison psychiatry) have the resources to educate their residents in this approach? This is a potentially more difficult challenge, but we would suggest that with some creative problem-solving, most programs would find it feasible to at least introduce a deeper focus on neuroscience and neuropsychiatry into the curriculum and daily training experience. The national efforts noted earlier in this

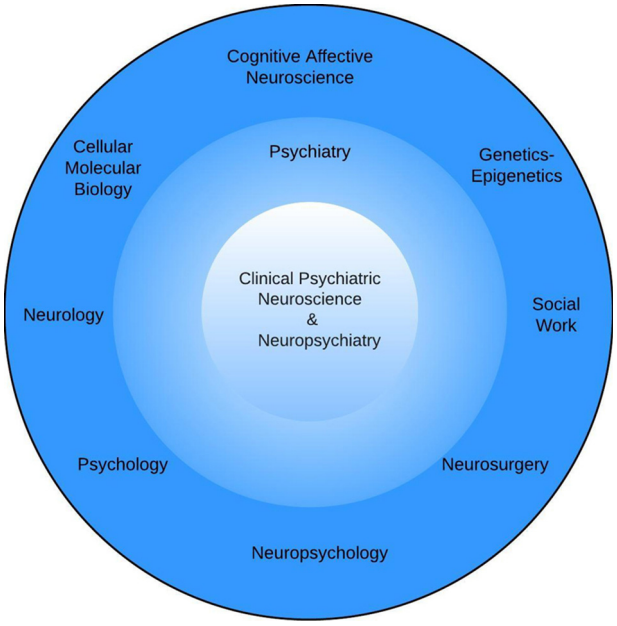

Fig. 1. A conceptual framework of the suggested central role of clinical psychiatric neuroscience and neuropsychiatry in academic psychiatry and closely related fields. In part, these core (inter-related) disciplines can help bridge the rapidly evolving field of systems-level, cognitive affective neuroscience to enable brain-symptom relationship discussions to more comprehensively formulate psychiatric symptom complexes and foster the development of validated biologically informed therapeutic interventions.

paper also suggest a potential solution, with the promise of many online educational resources.

The past several decades have witnessed the impressive progress of neuroscientific research in elucidating the relationships between brain function and mental states. It is more important than ever for the next generation of psychiatrists to be educated in a brain-based approach to psychiatric illness. Although the examples in this article have focused on depression, the education model presented is applicable to any psychiatric illness including bipolar disorder (Brady et al., 2014), schizophrenia (Keshavan et al., 2008), post-traumatic stress disorder (Pitman et al., 2012), and functional neurological symptom disorder (Perez et al., 2012, 2015e) among others. Parallel translational efforts will also look to integrate cellular-molecular biology, neurochemistry, and epigenetic-genetic influences on brain-symptom relationships. Such education will ensure that psychiatrists remain at the forefront, rather than the periphery, of advances in the diagnosis and treatment of mental illness in the 21st century and beyond.

Authorship contributions

Drs. Torous and Perez participated in the conception and design of this manuscript, and Drs. Torous, Perez, Stern, Padmanabhan, and Keshavan participated in the drafting and critical review of the manuscript. All authors approved the final version for publication.

Disclosures/conflicts of interest

The authors have no disclosures or conflicts of interest to report.

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