Circuitry-Based Human Neuroanatomy for the Next Generation in Psychiatry and Neuroscience

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We are experiencing a very exciting time in neuroscience. Imaging studies through functional measurements such as fMRI have pointed to activities in brain regions in humans that are linked to behavioral outcomes [e.g., 1], far better and more precisely than Broca did in identifying the brain region responsible for language [2]. Several seminal papers have emerged as a result of large collaborative studies that establish the fine details of structures in the human brain [3], more detailed than Brodmann did in his classic work [4], and the current brain initiatives in the USA, Japan, and other countries are attempting to obtain comprehensive connectome maps of the human and nonhuman primate brain [5]. Gene expression profiles for each brain area, as well as individual cell populations, are being annotated, information that can be utilized to understand brain connectivity even at the cellular level in a developmental trajectory (allenbrainatlas.com [6]). Human genetic and genomic analyses have identified vast numbers of genes that are implicated in psychiatric disorders in humans, many of which overlap with genes expressed in certain cortical layers and are important for brain development [7, 8]. This wave of new information and technology offers great hope that we may at last be able to treat patients who suffer from devastating neurological and psychiatric disorders by understanding

the underlying neurosciences in the very near future. In psychiatry, interest in brain functions and the underlying neurosciences is growing among clinicians, and some of the training programs in psychiatry have integrated learning modules for most current neurosciences into their components [e.g., 9–11; for model curricula with an evaluation system, see 12]. Some of them of course include human neuroanatomy, a structural framework for the nervous system of humans [12–14].

Psychiatry, traditionally and to this day, uses subjective observational diagnoses of symptoms to categorize people who suffer from a psychiatric illness into a particular disorder entity (e.g., the DSM-5 [15]). In these situations, it is not necessarily crucial to identify perturbations or to localize them to specific anatomical locations in the brain in order to explain their illness, behavioral phenotypes, and possible therapeutic strategies. However, today, more and more imaging studies focus on functional aspects and attempt to link the brain circuitry with functional changes and psychiatric disorders, introducing more circuitry-based approaches and linking psychiatry with the underlying neurocircuitry [16–18] (Fig. 1). Recently, a dimensional approach (e.g., RDoC) has been introduced into psychiatry, in which several behavioral domains that are associated with specific circuitries have

Fig. 1. Currently available technique to identify the brain circuitry in humans and animal models and an example of neural correlates associated with psychiatric disorders. The upper panel is a list of methods for identifying neural correlates/circuitries associated with particular behaviors in humans and animal models. The lower panel is an example of neural correlates associated with mood and anxiety disorders. Both the subgenual cingulate gyrus and the amygdala have been shown to be associated with mood and anxiety disorders in humans by imaging studies [40]. These areas are also demonstrated to be important for control of mood and anxiety in animal models, using the imaging as well as circuitry modulation methods listed above [e.g., 18]. DTI, diffusion tensor imaging; DBS, deep brain stimulation; TMS, transcranial magnetic stimulation; mPFC, medial prefrontal cortex.

been used to reclassify psychiatric disorders across the disorder “entity,” with the hope of accelerating translational research (e.g., facilitating the application of findings from animal models to clinical research in humans under the assumption that a circuit activated in a particular behavior is somewhat conserved among species) [19, 20]. An anatomical understanding of functional circuitry is a prerequisite for this approach. A molecular/genetic understanding of disorders also requires knowledge of anatomical and functional connections and circuitry, linking altered molecules to behavioral phenotypes by precisely localizing molecular changes to the particular locations in the circuitry of the brain [8, 21, 22] (Fig. 2). Once functional connectomes are mapped, they may provide some ways toward fixing altered circuitry, which would in turn ameliorate behavioral symptoms [23, 24]. In fact, this is the strategy/translational roadmap pro-

Fig. 2. An example of studies in which gene expression profiles combined with human genetics lead to localization of affected cell populations in psychiatric disorders. Mid-fetal deep cortical long projecting neurons may be affected in brains with autism based on gene expression profiles combined with genome analysis of humans [see 8 for details].

posed by Dr. Joshua Gordon, the head of the NIMH [25]. Dr. Gordon, a self-proclaimed circuit psychiatrist, emphasizes collaboration between clinicians working on humans and basic neuroscientists working on model systems in order to link genes, circuits, and behaviors [25], activities leading to new and more specific therapeutic approaches to psychiatric disorders. One good example of linking behaviors, circuits, and genes is recent work from the Deisseroth laboratory [26], in which after behavioral characterization, the authors identified connectomes of different cell populations in the medial prefrontal cortex of mice activated during a certain behavior in a brain-wide manner and characterized differences in gene expression patterns in these cells. As for leading to therapeutics, the fear circuitry, for example, has been studied extensively both in animal models and in humans [27–29] (Fig. 3). This knowledge is now applied to potential therapeutic approaches to posttraumatic stress disorder, an aberrant behavioral response associated with fear memory [30]. Recent techniques such as optogenetics, deep brain stimulation, and transcranial magnetic stimulation have great potential for circuitry-based interventions in psychiatric disorders [23, 24]. In fact, deep brain stimulation and transcranial magnetic stimulation have been approved for use in treatment-resistant depression, and other disorders including drug addiction may be in

Fig. 3. Comparison of circuitries between humans and animal models. The upper panel is an example of the neurocircuitry for drug addiction, and this circuitry may be modulated by methods such as optogenetics and TMS [23]. The lower panel is an example of the neurocircuitry for anxiety [27, 28]. PFC, prefrontal cortex; DS, dorsal septum; NAc, nucleus accumbens; VTA, ventral tegmental area; Amy, amygdala; Hypo, hypothalamus; Hipp, hippocampus; TMS, transcranial magnetic stimulation. Modified from the figure in Ferenczi and Deisseroth [23].

sight for clinical application (Fig. 3). In addition, approaches including neurofeedback using fMRI combined with coding/decoding systems, as well as extensive cognitive training focusing on circuitry, are also promising methods [31, 32]. More potential targets for these manipulations have been identified through imaging studies; these targets may be shared by many psychiatric illnesses [33, 34]. The key to success of these trials depends on a precise understanding of the detailed human neuroanatomy of circuitries.

Human neuroanatomy is based on a huge amount of descriptive data on locations of cells and tracts within a framework of various cross sections obtained by many imaging modalities routinely used in clinical settings, which are crucial for understanding signs and symptoms when certain areas of the nervous system are affected or lesioned. Students are inclined to memorize names of structures and their locations. This has been especially

useful for neurology and neurosurgery, but the emphasis is on locations rather than on circuitries. In some instances, a circuitry-based understanding is appreciated even in the traditional neuroanatomy course, namely, in the case of the visual system containing the retina, optic nerve, optic chiasm, optic tract, lateral geniculate nucleus, optic radiation, and visual cortex. Understanding the visual pathway enables us to explain what kind of functional defects, namely, loss in the visual field, can be observed when a particular position in the pathway is affected. However, when we pick any neuroanatomy textbook widely used in medical schools and graduate courses, such as those by Martin [35], Waxman [36], and Bear et al. [37], we realize that this has hardly been extended to other brain functions such as fear, emotion, attention, and cognition as yet (perhaps with the exception of learning and memory). Moreover, if searching PubMed for terms like neuroanatomy, teaching, and circuitry, very few papers would show up. When we turn to cognitive psychology and cognitive neuroscience, they have integrated human neuroanatomy into their subfields, and through functional imaging studies they try to correlate the information flow of cognition with brain activities. However, sometimes correlations are not linked to detailed neuroanatomical structures and their wiring in the brain. Moreover, the technical terms utilized for describing anatomical structures in the imaging fields are not exactly the same as the ones taught in traditional human neuroanatomy courses in medical schools, sometime causing confusion and miscommunication among researchers. For example, networks important for cognitive function, such as default mode and cingulo-opercular networks, include many brain regions that are not traditionally emphasized in neuroscience courses in medical schools (e.g., in the textbooks listed above). Nevertheless, cognitive functions are supported by connections among many different brain areas, many of which are between cortical areas, as well as between subcortical and cortical areas. Incorporating the existing, detailed information on human neuroanatomy should be a foundation for understanding human cognitive function, both in normal and disease situations.

As we move forward to a new era, I believe that medical education and training in circuitry-based human neuroanatomy to acquire the skills to relate circuitries to cognitive functions and psychiatric/behavioral phenotypes – instead of traditional human neuroanatomy emphasizing memorization of locations of cells/nuclei and tracts – is crucial for the next generation of psychiatrists and researchers in psychiatry to make headway in re-

search on neuropsychiatric disorders. This knowledge is important for understanding not only symptomatology and imaging data but also the pathogenesis and pathophysiology of disorders [14]. As for psychiatry residency programs, a psychiatry milestone project developed a matrix to evaluate trainees' achievements during the program (www.acgme.org). At this point, however, it does not lay much emphasis on a circuitry-based understanding of human neuroanatomy. Recently, online material called NNCI has been developed that is intended for use for clinical trainees to self-study most current neurosciences (www.nncionline.org), and there are several circuitry-based neuroanatomy components such as those for addiction and fear. Some of the proposed psychiatry model training programs that integrate neuroscience modules do have functional systems too [see Table 2 in 12]. Nevertheless, they are not sufficient to make people imagine a particular circuitry when they observe behavioral phenotypes. This kind of neuroanatomical understanding is beneficial not only in medical training but also to trainees in other neuroscientific areas such as systems neuroscience, human and animal brain imaging, animal studies of cognitive function, and computational neuroscience, whose contribution is crucial to the success of the next generation of neurosciences [38, 39]. Currently, these young, talented people are either still taught in traditional human neuroanatomy courses or studying on their own, which sometimes is difficult and makes them lose sight of the big picture of the human brain.

To this end, I would like to propose developing a circuitry-based human neuroanatomy course including suitable training material/textbooks. For a start, we may use the circuitries for the domains defined in RDoC (www.nimh.nih.gov), such as negative valence (fear, anxiety), positive valence (reward, motivation), cognitive functions (attention, perception, declarative memory, working memory), and social behavior (communication, perception of others, attachment, social memory), but we are open to discussion, i.e., where to start and what to teach. This should be considered both in medical schools and in graduate schools related to neuroscience. It should also eventually be incorporated into training programs during residency and postgraduate programs for psychiatry, programs that try to incorporate neuroscientific components. Experts in brain imaging such as fMRI and classic neuroanatomy would contribute to such courses. For the training material, we could start compiling a series of review articles on circuitry-based human neuroanatomy, each focusing on a selected functional circuitry, eventually transforming them into forms readily accessible on-

line (perhaps into interactive online material that can be used for self-learning). With this material readily available, both younger and more senior-level investigators in clinical and basic science will become knowledgeable in circuitry-based human neuroanatomy, facilitating discussions among these groups and enhancing translational and clinical research [11, 14]. It is my hope that such interaction between clinicians and basic scientists will accelerate the development of new therapeutic approaches for psychiatric disorders by which many people are affected.

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Statement of Ethics

The work in the author's laboratory has been conducted using procedures approved by the institutional review board. However, there is no need for an ethics statement for this article.

Disclosure Statement

There is no conflict of interest to declare.

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