Chapter 42

Applying a neural circuit taxonomy in depression and anxiety for personalized psychiatry

Leanne M. Williams[a,b] and Andrea N. Goldstein-Piekarski[a,b]

[a]*Department of Psychiatry and Behavioral Sciences, Stanford University, Stanford, CA, United States;* [b]*Sierra-Pacific Mental Illness Research, Education, and Clinical Center (MIRECC), Veterans Affairs Palo Alto Health Care System, Palo Alto, CA, United States*

1 Getting a handle on our terminology for precision psychiatry

The concept of "precision psychiatry" can be considered aligned with the overall move toward measurement-based care and precision medicine. Three aspects of precision medicine have been described by at least three other interchangeably used terms: *stratified medicine*, *personalized medicine,* and *precision health*, respectively (Coalition PM, 2014; Fernandes, Williams, Steiner, et al., 2017; Sciences AoM, 2015). Stratified medicine focuses on identifying subgroups of patients who will benefit from treatments as a step toward a fully personalized approach that tailors treatments to individual people. Personalized medicine has focused on harnessing new advances in genomics to select treatment options with the greatest likelihood of success. Precision health can be thought of as a major new frontier, expanding our breakthroughs in precision medicine to a wider concept of health and prevention that goes beyond a focus on disease.

In 2015, the Obama Administration launched a major research effort aimed at improving health and changing the way we treat disease (Secretary OotP, 2015a). In this initiative, precision medicine is described as "an innovative approach that takes into account individual differences in people's genes, environments, and lifestyles," thereby allowing doctors to tailor treatment to individual patients (Secretary OotP, 2015a). When launching the Precision Medicine Initiative, President Obama said: "Precision medicine—in some cases, people call it personalized medicine – gives us one of the greatest opportunities for new medical breakthroughs that we have ever seen" (Secretary OotP, 2015b).

This federal Precision Medicine Initiative is paralleled by two federal research efforts focused specifically on psychiatry and neurosciences. First, the "BRAIN Initiative" is aimed at developing neuro-technologies for demystifying brain disorders, including psychiatric disorders (Markoff, 2013). This depth of understanding of the brain will only strengthen our ability to precisely identify dysfunction at the level of a single patient. Second, the U.S. National Institute of Mental Health (NIMH) is pioneering the Research Domain Criteria (RDoC) project (Insel, 2010), which has initiated a research approach to generating a neurobiologically valid framework for classifying psychiatric disorders, and for generating novel interventions related to neurobiological underpinnings. Together, the Precision Medicine, BRAIN, and RDoC initiatives will support and promote great advances in precision psychiatry.

A major challenge for precision medicine in psychiatry is that psychiatry does not yet use measurement to track the equivalent of vitals (Harding, Rush, Arbuckle, Trivedi, & Pincus, 2011), or image the organ of interest (the brain). Although modern neuroimaging techniques have generated many insights about types of brain circuit dysfunction that underlie psychiatric disorders, these insights have not been systematically linked to prediction of clinical outcomes, and have not been delivered into the hands of clinicians as an actionable system for improving people's lives. That precision psychiatry is new to the game in precision medicine is not surprising given the complexity of the organ and behavior of interest. However, psychiatry can benefit tremendously by including advanced diagnostic and therapeutic technologies that form an integral part of other clinical specialties.

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2 Foundations for a precision psychiatry taxonomy for depression and anxiety based on neural circuits

With advances in brain imaging techniques with sufficient spatial and temporal resolution to quantify neural connections in vivo, we have the foundations for formulating an understanding of mental illness as disorders of brain functioning (Williams, 2016, 2017). Here, the focus is on depression and anxiety as an illustration of such a formulation.

.The term "neural circuit" has typically referred to how one neuron communicates with another through synaptic connections and transmission (Yuste, 2015). Here, the term "large-scale neural circuit" is used to refer to the macroscale neural organization. In brain imaging studies, these macroscale circuits have commonly been referred to as "networks" (e.g., the "default mode network") (Greicius, Krasnow, Reiss, & Menon, 2003; Raichle, 2015).

Neural circuits can be considered a pertinent scale of measurement from which to delineate a neurobiology of human mental disorder. Circuits integrate across different levels and measures of brain function, but still reflect the complexity of the brain. Circuits are engaged by specific human cognitive, emotional, and self-reflective functions, and offer promise for defining appropriate animal homologues. It is likely that most of the human brain involves multiple parallel circuits that are interdigitated such that each cortical lobe contains components of multiple circuits (Felleman & Van Essen, 1991; Mesulam, 1998). This organization may have occurred with the expansion of the association cortex in humans relative to non-human primates (Mesulam, 1998). Mood and anxiety disorders may be possible maladaptive consequences of this expansion.

Researchers have identified intrinsic neural circuits that support domain-general processes of self-reflection, salience perception, and alertness (Fig. 1; Buckner, Krienen, & Yeo, 2013), as well as conflict monitoring, attention, sensori-motor, visual, and auditory processes (Fox, Snyder, Vincent, et al., 2005; Gordon, Laumann, Adeyemo, et al., 2014; Lindquist & Barrett, 2012; Oosterwijk, Lindquist, Anderson, et al., 2012; Power, Cohen, Nelson, et al., 2011; Seeley, Menon, Schatzberg, et al., 2007; Sheline, Price, Yan, & Mintun, 2010; Spreng, Sepulcre, Turner, Stevens, & Schacter, 2013; Yeo, Krienen, Sepulcre, et al., 2011). The intrinsic architecture has been demonstrated using large-scale functional connectivity analysis of hundreds of brain regions that have been identified using parcelation and meta-analysis, and that define major brain systems at rest and across many task-evoked states (e.g., Cole, Bassett, Power, Braver, & Petersen, 2014). These circuits may be observed in the task-free state and during task-evoked conditions. During rest, the default mode circuit tends to upregulated, and other circuits, downregulated (Cole et al., 2014; Fox et al., 2005). Specific task states (such as those designed to probe reactivity to potential threat or reward) engage more specialized functional components of these circuits (e.g., Castelli, Happe, Frith, & Frith, 2000; Haber & Knutson, 2010; Rushworth, Mars, & Sallet, 2013; Touroutoglou, Andreano, Barrett, & Dickerson, 2015; White, Coniston, Rogers, & Frith, 2011; Williams, Das, Liddell, et al., 2006) (Fig. 1).

In the illustrative formulation, dysfunctions are considered in relation to six circuits: default mode, salience, negative affect, positive affect, attention, and cognitive control.

Research to date has understandably focused on case:control comparisons of diagnostic groups of mood and anxiety disorder defined by traditional symptom criteria. These previous studies have also focused on activation within specific brain regions of interest, and typically on one imaging modality at a time. While the emphasis has been on regional activation, there has been a noticeable expansion of functional connectivity studies of depression. Findings from case:control studies tend to be inconsistent. This inconsistency is not surprising, given the heterogeneity of depression and anxiety. It is feasible that the heterogeneity reflects the contributions, depending on each sample, of different profiles of neural hypor-eactivity and hyper-reactivity, along with hypoconnectivity and hyper-connectivity, compared with healthy peers.

3 "Default Mode" circuit

The default mode circuit (usually referred to as the "default mode network") encompasses the anterior medial prefrontal cortex (amPFC), posterior cingulate cortex (PCC), and angular gyrus (AG) (Greicius et al., 2003; Greicius, Supekar, Menon, & Dougherty, 2009) (Fig. 1; Table 1). This circuit is probed under task-free conditions, and typically when participants are instructed to reflect on their freely generated thoughts (Seeley et al., 2007; Shulman et al., 1997). Anterior and posterior regions may represent sub-networks of the default mode circuit (for review, Mulders, van Eijndhoven, Schene, Beckmann, & Tendolkar, 2015). The default mode circuit is engaged, even during "rest" periods that occur between task stimuli (Korgaonkar, Ram, Williams, Gatt, & Grieve, 2014). By extent of default, more network functioning may also be quantified as a summary composite, and used to locate an individual, relative to a normative distribution (Ball, Goldstein-Piekarski, Gatt, & Williams, 2017).

TABLE 1 A summary of the current state of knowledge for macroscale circuits involved in core human functions, the functional role of these circuits, the nature of their functional disruptions in mood and anxiety disorders, corresponding structural alterations and the contribution of these circuits to understanding treatment outcomes

Circuit	Role	Functional alterations in depression and anxiety	Structural alterations in depression and anxiety	Treatment outcomes
Default mode: Anterior middle frontal cortex (amPFC), posterior cingulate cortex (PCC), and angular gyrus (AG) (Greicius et al., 2003, 2009)	Self-referential thinking at rest (Greicius, Flores, Menon, et al., 2007; Shulman, Fiez, Corbetta, et al., 1997)	*Hypoconnectivity:* Posterior hypoconnectivity correlated with over-general memory (Zhu, Wang, Xiao, et al., 2012) and treatment sensitivity in MDD (for review, Dichter, Gibbs, & Smoski, 2014). mPFC-AG hypo-connectivity in SAD (Qiu, Liao, Ding, et al., 2011) *Hyper-connectivity:* Anterior medial hyper-connectivity in MDD (Greicius et al., 2007; Kaiser, Andrews-Hanna, Wager, & Pizzagalli, 2015; Sheline et al., 2010), correlated with rumination in MDD (Hamilton, Furman, Chang, et al., 2011; Zhu et al., 2012) and treatment resistance in MDD (de Kwaasteniet, Rive, Ruhe, et al., 2015; Dichter et al., 2014; Wu, Andreescu, Butters, et al., 2011) Hyper-connectivity of the default mode with the attention circuit in MDD for meta-analysis (Kaiser et al., 2015)	*Gray matter:* Reductions in MDD (Grieve, Korgaonkar, Koslow, Gordon, & Williams, 2013; Singh, Kesler, Hadi Hosseini, et al., 2013) *White matter:* Hypoconnectivity in MDD (Korgaonkar, Fornito, Williams, & Grieve, 2014; Qin, Wei, Liu, et al., 2014)	*Hypoconnectivity:* Hypoconnectivity predicts nonremission to common antidepressants in older adults with depression (Andreescu, Tudorascu, Butters, et al., 2013) *Intact connectivity:* Patients with depression correlated with remittance with antidepressants (Liston, Chen, Zebley, et al., 2014) Functional connectivity between subgenual ACC and default mode posterior cingulate predictive of response to TMS (Philip, Barredo, van't Wout-Frank, et al., 2018)
Salience: Dorsal anterior cingulate cortex (dACC), anterior insula (aI), Temporal Pole (TP), and sublenticular extended amygdala (SLEA) (Seeley et al., 2007; Oosterwijk et al., 2012)	Detecting salient changes (Seeley et al., 2007)	*Hypoconnectivity:* Amygdala-insula hypoconnectivity in MDD (Veer, Beckmann, van Tol, et al., 2010) Insula hypoconnectivity in MDD correlated with overall symptom severity (Manoliu, Meng, Brandl, et al., 2014) Amygdala—ACC hypoconnectivity in SAD (Arnold Anteraper, Triantafyllou, Sawyer, et al., 2014) Amygdala hypoconnectivity correlated with avoidance symptoms (Liao, Qiu, Gentili, et al., 2010) *Hyper-connectivity:* Hyper-connectivity of the salience with the default mode circuit in MDD (Manoliu et al., 2014), correlated with severity of depressive rumination (Hamilton et al., 2011)		*Right anterior insula metabolism:* Greater resting state metabolism associated with better response to escitalopram, poor response to CBT (Dunlop, Kelley, McGrath, Craighead, & Mayberg, 2015; McGrath, Kelley, Dunlop, et al., 2014) *Insula hyporeactivity:* Hyporeactivity to IAPS stimuli associated with response to fluoxetine/olanzapine (Rizvi, Salomons, Konarski, et al., 2013) *Hyper-connectivity:* Rostral ACC hyper-connectivity predicts response to placebo (Sikora, Heffernan, Avery, et al., 2016) *Intrinsic functional connectivity:* Insula and dorsal ACC connectivity changes correlated with response to rTMS (Philip et al., 2018)

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Circuit	Role	Functional alterations in depression and anxiety	Structural alterations in depression and anxiety	Treatment outcomes
Threat: Amygdala, dorsal, rostral, and subgenual ACC, mPFC and insula (Seeley et al., 2007; Oosterwijk et al., 2012)	Threat reactivity and regulation (Williams et al., 2006)	*Altered activation for threat:* Amygdala hyper-activation for threat faces in MDD, GAD, SAD (Blair, Shaywitz, Smith, et al., 2008; Prater, Hosanagar, Klumpp, Angstadt, & Phan, 2013) and anxiety traits (Clauss, Avery, VanDerKlok, et al., 2014; Etkin, Klemenhagen, Dudman, et al., 2004) ACC hypoactivation to threat faces in GAD and SAD (Blair, Geraci, Smith, et al., 2012; Etkin, Prater, Hoeft, Menon, & Schatzberg, 2010; Palm, Elliott, McKie, Deakin, & Anderson, 2011) and amygdala hypoactivation to threat faces in MDD (Lawrence, Williams, Surguladze, et al., 2004; Matthews, Strigo, Simmons, Yang, & Paulus, 2008; Thomas, Drevets, Dahl, et al., 2001; Williams, Korgaonkar, Song, et al., 2015) *Hypoconnectivity for threat:* Amygdala-ACC hypoconnectivity to fear in MDD (Matthews et al., 2008; Musgrove, Eberly, Klimes-Dougan, et al., 2015), SAD (Prater et al., 2013), and GAD (Etkin et al., 2010; Etkin, Prater, Schatzberg, Menon, & Greicius, 2009) Amygdala hypoactivation to fear/anger is a general predictor of response to antidepressants, and amygdala hyper-activation to sad is a differential predictor of nonresponse to SNRI antidepressants (Williams et al., 2015)	*Gray matter:* Reduced hippocampal gray matter in MDD and GAD (Bossini, Tavanti, Calossi, et al., 2008; Kempton, Salvador, Munafo, et al., 2011; Moon, Kim, & Jeong, 2014; Mueller, Aouidad, Gorodetsky, et al., 2013; Zhao, Du, Huang, et al., 2014) *White matter connectivity:* Reduced uncinate fasciculus white matter connections in MDD (Steffens, Taylor, Denny, Bergman, & Wang, 2011)	*Hyporeactivity:* Amygdala hypo-reactivity and smaller amygdala volume associated with response to escitalopram, sertraline, and paroxetine (Li, Lin, Chou, et al., 2010; Ruhe, Booij, Veltman, Michel, & Schene, 2012; Williams et al., 2015) *Hyper-connectivity:* Hyper-connectivity between amygdala and ACC distinguishes nonremitters to SSRI escitalopram (Fu, Williams, Cleare, et al., 2004) *Functional connectivity:* Subgenual ACC functional connectivity attenuated by rTMS (Taylor, Ho, Abagis, et al., 2018)

Reward: Ventral striatum, orbitofrontal cortex (OFC), dACC, and mPFC regions (Berridge & Kringelbach, 2008; Haber & Knutson, 2010)	Sensitivity to and anticipation of reward stimuli	*Striatal hypoactivation:* Anhedonic MDD: Striatal hypo-activation for happy faces (Keedwell, Andrew, Williams, Brammer, & Phillips, 2005a) (for review, Treadway & Zald, 2011; for meta-analysis, Zhang, Chang, Guo, Zhang, & Wang, 2013) and monetary tasks (Treadway & Zald, 2011) (for meta-analysis, Hamilton, Etkin, Furman, et al., 2012); mPFC hypoactivation for positively valenced stimuli (Mitterschiffthaler, Kumari, Malhi, et al., 2003) *Altered frontal activation:* ACC/ MPFC/OFC/ hyper-activation for happy faces (Keedwell et al., 2005a; Keedwell, Andrew, Williams, Brammer, & Phillips, 2005b; Mitterschiffthaler et al., 2003; Zhang et al., 2013), reward anticipation and reward outcomes (Dichter, Kozink, McClernon, & Smoski, 2012) in MDD	*Gray matter:* Reduced striatal volume in MDD (Kim, Hamilton, & Gotlib, 2008; Pizzagalli, Holmes, Dillon, et al., 2009) *White matter:* Reduced white matter connectivity in MDD (Sacchet, Prasad, Foland-Ross, et al., 2014)	*Increased activation:* Higher activation of ACC associated with greater symptom reduction with behavioral activation therapy for depression (Carl, Walsh, Eisenlohr-Moul, et al., 2016) Increased nucleus accumbens activation associated with response to venlafaxine and fluoxetine (Heller, Johnstone, Light, et al., 2013) *Hyper-connectivity:* Hyper-connectivity between the striatum and the ventral medial region of the orbitofrontal cortex associated with response to rTMS (Downar, Geraci, Salomons, et al., 2014)
Attention: Medial superior frontal cortices (msPFC), aI, anterior inferior parietal lobule (aIPL), and precuneus (PCu) (Gordon et al., 2014)	Alertness and sustained attention (Fornito, Harrison, Zalesky, & Simons, 2012)	*Hypoconnectivity:* Hypoconnectivity in MDD (Liao et al., 2010; Qiu et al., 2011; Veer et al., 2010) *Hyper-connectivity:* Frontoparietal hyper- connectivity with the striatal node of the reward circuit in SAD (Arnold Anteraper et al., 2014)	*White matter:* Reduced frontoparietal diffusion centrality in MDD (Qin et al., 2014)	*Intrinsic functional connectivity:* Connectivity between intraparietal sulcus and orbital frontal cortex predicts somatic symptom improvement with behavioral activation therapy for depression (Crowther, Smoski, Minkel, et al., 2015) Increased perfusion and connectivity between attention circuit and amygdala associated with response to CBT (Shou, Yang, Satterthwaite, et al., 2017; Sosic-Vasic, Abler, Gron, Plener, & Straub, 2017)

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TABLE 1 A summary of the current state of knowledge for macroscale circuits involved in core human functions, the functional role of these circuits, the nature of their functional disruptions in mood and anxiety disorders, corresponding structural alterations and the contribution of these circuits to understanding treatment outcomes—cont'd

Circuit	Role	Functional alterations in depression and anxiety	Structural alterations in depression and anxiety	Treatment outcomes
Cognitive control: Dorsolateral prefrontal cortex (DLPFC), ACC, precentral gyrus (PCG), dorsal parietal cortex (DPC) (Niendam, Laird, Ray, et al., 2012)	Working memory and selective attention (Chen, Oathes, Chang, et al., 2013; Niendam et al., 2012)	*Hypoactivation:* DLPFC/ACC hypoactivation in MDD (Elliott, Baker, Rogers, et al., 1997; Elliott, Sahakian, Herrod, Robbins, & Paykel, 1997; Holmes & Pizzagalli, 2008; Korgaonkar, Grieve, Etkin, Koslow, & Williams, 2013; Siegle, Thompson, Carter, Steinhauer, & Thase, 2007; Vasic, Walter, Sambataro, & Wolf, 2009; Vilgis, Chen, Silk, Cunnington, & Vance, 2014) and in social anxiety (Koric, Volle, Seassau, et al., 2012) and induced anxious mood (Fales, Barch, Burgess, et al., 2008) *Hypoconnectivity:* DLPFC-ACC hypoconnectivity in MDD (Holmes & Pizzagalli, 2008; Vasic et al., 2009) *Hyper-activation:* Hyper-activation in MDD, suggesting compensation to achieve normal cognitive performance (Fitzgerald, Srithiran, Benitez, et al., 2008; Harvey, Fossati, Pochon, et al., 2005; Matsuo, Glahn, Peluso, et al., 2007; Walter, Wolf, Spitzer, & Vasic, 2007)	*Gray matter:* Reduced DLPFC and ACC gray matter in adult MDD (Grieve et al., 2013) and late-life MDD (Chang, Yu, McQuoid, et al., 2011)	*Activation:* Go-NoGo activation of middle and inferior gyrus within the DLPFC associated with depression symptom improvement with SSRIs (Langenecker, Kennedy, Guidotti, et al., 2007). For the DLFPC, greater Go-NoGo inhibition predicts worse outcomes for escitalopram and sertraline (Gyurak, Patenaude, Korgaonkar, et al., 2016), and less inhibition predicts remission on the SNRI venlafaxine-XR (Gyurak et al., 2016) GoNoGo-elicited dACC hyper-activation associated with poorer response to escitalopram and duloxetine (Crane, Jenkins, Bhaumik, et al., 2017) *Intrinsic functional connectivity:* Increased DLPFC-amygdala connectivity associated with group CBT treatment of depression in adolescents (Straub, Metzger, Plener, et al., 2017)

3.1 Default mode circuit disruptions in depression and anxiety

Most commonly, depression has been associated with over-activation and hyper-connectivity relative to controls within the default mode network (Greicius et al., 2007; Kaiser et al., 2015; Sheline et al., 2010). Hyper-connectivity of the default mode circuit with subgenual ACC in MDD has been associated with higher levels of maladaptive rumination about depressive thoughts (Hamilton et al., 2011; Zhu et al., 2012). There is also evidence for *hypo*connectivity of the default mode circuit, particularly in posterior medial cortex regions, in MDD relative to controls that are correlated with clinical indicators of over-general autobiographical memory (Zhu et al., 2012). Within those with depression, a data-driven approach using community detection algorithms has identified two unique subtypes of depression, differentiated by the presence or absence of PCC-anterior cingulate cortex (ACC)/mPFC connectivity (Price, Gates, Kraynak, Thase, & Siegle, 2017).

Anatomical abnormalities might contribute to default mode circuit hyper- and hypofunction. Structurally, MDD has been associated with decreased regional gray matter connectivity (Singh et al., 2013) and loss of white matter connectivity (Korgaonkar, Fornito, et al., 2014) within the default mode circuit, particularly within the posterior sub-network. Widespread reductions in gray matter have also been observed across regions of the default mode circuit and in nodes within interacting circuits (Grieve et al., 2013). Specifically, MDD patients show reduced gray matter volume in ACC and anterior medial regions of the prefrontal cortex, and in parietooccpital regions, consistent with components of the default mode circuit, as well as in striatal and limbic components of the affective circuits (Grieve et al., 2013).

3.2 Default mode circuit and treatment implications

The observations of multiple default mode network connectivity profiles in depression suggest distinct implications for treatment.

One promising line of treatment research indicates that knowing about the type of default mode circuit dysfunction at a pretreatment baseline is important for predicting which patients are likely or not to be responsive to a specific type of treatment. This knowledge is important for ultimately adding objective measures to the armamentarium of clinicians, and getting people to the right treatment early. Default mode circuit hypoconnectivity between anterior and posterior nodes relative to controls at baseline appears to characterize a form of depression that is resistant to typical first-line medications (Goldstein-Piekarski, Staveland, Ball, et al., 2018). Pretreatment hypoconnectivity of the default mode also predicts non-remission to commonly prescribed antidepressants in older adults with depression (Andreescu et al., 2013). By contrast, relatively intact default mode connectivity, indistinguishable from healthy controls, characterizes patients with depression who go on to remit to antidepressant treatment. These findings suggest that a certain degree of intact connectivity may be necessary for antidepressant action. Complementing these findings, distinct profiles of functional connectivity between the subgenual ACC and default mode posterior cingulate may be predictive of treatment response to the newly FDA approved technique, transcranial magnetic stimulation (TMS) (Liston et al., 2014; Philip et al., 2018). TMS may act to improve depression symptomology in this subtype by normalizing hyper-connectivity within the default mode network (Liston et al., 2014). Together, these findings lend support to a circuit-guided approach to helping tailor choice of intervention.

4 "Salience" circuit

The "salience" circuit is defined by core nodes in the ACC, anterior insula (aI), and sublenticular extended amygdala (Oosterwijk et al., 2012; Seeley et al., 2007) (Fig. 1). This circuit is implicated in the detection of salient interoceptive and exteroceptive stimuli (Seeley et al., 2007).

4.1 Salience circuit disruptions in depression and anxiety

Within the salience circuit, insula hyper-reactivity has been observed in MDD when evoked by sadness and disgust (Sprengelmeyer, Steele, Mwangi, et al., 2011; Suslow, Konrad, Kugel, et al., 2010) (for review, Stuhrmann, Suslow, & Dannlowski, 2011) (Table 1). Heightened insula reactivity is positively correlated with severity of depressive symptoms (Lee, Seong Whi, Hyung Soo, et al., 2007), suggesting a bias toward salient and mood-congruent stimuli. Individuals with generalized social anxiety disorder also show exaggerated insula reactivity when attending to salient emotional faces (Klumpp, Post, Angstadt, Fitzgerald, & Phan, 2013). These functional activation differences might be due, in part, to structural deficits. For example, MDD patients show a loss of insula gray matter, which is negatively correlated with symptom severity (Sprengelmeyer et al., 2011).

In regard to functional connectivity, profiles of both hyper- and hypoconnectivity have been observed in depression and anxiety. Insula hypoconnectivity within the salience circuit has been observed in depression, social anxiety disorder, and in panic disorder (for review, Mulders et al., 2015; Peterson, Thome, Frewen, & Lanius, 2014). Insula hypoconnectivity has been inversely associated with symptom severity (Mulders et al., 2015). In generalized anxiety, a weakening of the normal connectivity between the insula and the ACC has been observed, specifically when the patient is required to focus attention on salient emotional faces presented among neutral stimuli (such as shapes) (Klumpp et al., 2013).

Hypoconnectivity between the insula and amygdala has also been reported in MDD (Veer et al., 2010) and correlated with overall symptom severity (Manoliu et al., 2014) (for review, Mulders et al., 2015). Amygdala hypoconnectivity has been more specifically correlated with avoidance symptoms in social anxiety disorder (Liao et al., 2010). Correspondingly, hypoconnectivity between the amygdala and ACC has also been observed in social anxiety disorder (Arnold Anteraper et al., 2014).

Hyper-connectivity between the insula and anterior nodes of the default mode circuit has been positively correlated with symptoms of nervous apprehension, and reported in both depression (for review, Mulders et al., 2015) and social anxiety disorder (for review, Peterson et al., 2014).

Dorsal nodes of the salience circuit show both hyper- and hypoconnectivity with the posterior precuneus node of the attention circuit (for meta-analysis, Kaiser et al., 2015). The direction of altered connectivity between salience and other circuits may fluctuate with the nature of interoceptive or exteroceptive stimuli.

4.2 Salience circuit and treatment implications

Relatively few studies have focused on the salience circuit with respect to treatment outcome. Nonetheless, the small number of studies already indicates promise in utilizing profiles of salience circuit dysfunction to guide differential treatment choices to a broad array of depression treatment modalities, including psychotherapy, SSRIs, and TMS. For example, greater right anterior insula resting state metabolism as measured by positron emotion tomography (PET) imaging has been associated with a better response to escitalopram, but a poor response to CBT (Dunlop et al., 2015; McGrath et al., 2014; McGrath, Kelley, Holtzheimer, et al., 2013). Response to fluoxetine/olanzapine has also been associated with a pre-treatment hyporeactivity of the insula elicited by IAPS stimuli (Rizvi et al., 2013). Salience circuit function may also help differentiate patients for whom harnessing the value of placebo conditions can be clinically beneficial. Hyper-connectivity of the salience circuit, specifically with the rostral ACC (rACC), has been found to predict symptom alleviation in response to a placebo condition (Sikora et al., 2016).

Salience circuit connectivity may be changed by interventions designed to noninvasively target neural modulation. Changes in intrinsic functional connectivity in components of the salience network, including the insula and dorsal ACC (dACC), identified by a whole-brain multivoxel pattern activation (MVPA) analysis were correlated with response to rTMS (Philip et al., 2018). These findings involve changes in connectivity between the salience circuit and other circuits, consistent with the role of the salience circuit role in orienting attention toward meaningful stimuli, and in attentional biases in depression. As an example, rTMS has been found to decrease functional connectivity between the salience circuit and the hippocampus, and this decrease is correlated with depressive symptom improvement (Philip et al., 2018). Relatively greater resting state functional connectivity between the insula and middle temporal gyrus has also been found to predict response to psychotherapy when regions of interest are defined by those that differ in connectivity between depressed patients and healthy controls (Crowther et al., 2015).

5 Affective circuits

Affective circuits are commonly probed by biologically relevant stimuli such as facial expressions of potential threat (fear, anger) and social reward (happy).

6 Negative Affect

The circuit engaged by negative affect comprises subcortical nodes in the amygdala, brainstem regions, hippocampus, and insula, and both dorsal and ventral prefrontal nodes—dorsal medial prefrontal cortex (dmPFC) and dACC connections as well as ventral mPFC (vMPFC) and ventral (subgenual and pregenual)-rACC connections (Kober, Barrett, Joseph, et al., 2008; Robinson, Krimsky, Lieberman, et al., 2014; Fig. 1; Table 1). In light of their commonly observed co-activation (Kober et al., 2008), the negative affect circuit might subserve the perception of negative emotion cues and the salience circuit, the arousal aspects of feeling these emotions.

In the task-free state, hyper-connectivity between the anterior (subgenual ACC and dMPFC) nodes of the negative affect circuit and the default mode has been observed in depression (Hamilton, Farmer, Fogelman, & Gotlib, 2015; Sheline et al., 2010). This state of intrinsic hyper-connectivity is thought to drive rumination and the negative attributions that underlie negative biases and negative mood.

Threat-evoked components of the negative affective circuits comprise the amygdala, hippocampus, insula, and both dorsal and ventral portions of the prefrontal cortex, including the dorsal medial prefrontal cortex (dmPFC) and its dorsal ACC connections, and the ventral mPFC (vMPFC) and its ventral (subgenual and pregenual)-rostral ACC connections (Kober et al., 2008; Robinson et al., 2014; Fig. 1; Table 1). The dorsal prefrontal sub-circuit has been preferentially implicated in appraisal and expression of emotion, and may be considered an "aversive amplification" sub-network (Robinson et al., 2014) that serves to boost the processing of signals of potential threat (Robinson et al., 2014). Complementing this function, the ventral sub-circuit has been implicated in automatic regulation of negative emotion (Etkin et al., 2010; Kober et al., 2008) (for review, Phillips, Drevets, Rauch, & Lane, 2003; for meta-analysis, Kober et al., 2008). These components overlap with components of the salience circuit, and they may both be engaged by the arousal and valence properties of threat stimuli, respectively. These sub-networks may be engaged, even in the absence of conscious sensory awareness (Williams et al., 2006) (for meta-analysis, Kober et al., 2008). In light of their commonly observed co-activation (Kober et al., 2008), the negative affect circuit might subserve the perception of negative emotion cues and the salience circuit, the arousal aspects of feeling these emotions.

6.1 Negative affective circuit disruptions in depression and anxiety

Altered threat processing, involving amygdala-ACC activation and connectivity, have been observed across multiple diagnostic categories (for review, Kim, Loucks, Palmer, et al., 2011; Phillips et al., 2003; Price & Drevets, 2010). Amygdala over-reactivity elicited by implicit or non-conscious processing of threat-related stimuli has been reported in current depressive disorder (Peluso, Glahn, Matsuo, et al., 2009; Sheline, Barch, Donnelly, et al., 2001; Surguladze, Brammer, Keedwell, et al., 2005; Williams et al., 2015; Yang, Simmons, Matthews, et al., 2010) (for review, Jaworska, Yang, Knott, & Macqueen, 2014), generalized anxiety disorder (Fonzo, Ramsawh, Flagan, et al., 2015), generalized social phobia/anxiety disorder (Fonzo et al., 2015; Phan, Fitzgerald, Nathan, & Tancer, 2006; Stein, Goldin, Sareen, Zorrilla, & Brown, 2002), specific phobia (Killgore, Britton, Schwab, et al., 2014), and panic disorder (Fonzo et al., 2015; Killgore et al., 2014). Excessive amygdala activity elicited by masked threat faces has also been associated with a dimension of trait anxiety, and with neuroticism in otherwise healthy people (Etkin et al., 2004), consistent with a trait-like phenotype of hyper-reactivity to sources of threat. Hypo-activation of the ACC has been observed in generalized anxiety disorder (Blair et al., 2012; Etkin et al., 2010; Palm et al., 2011) and generalized social anxiety (Blair et al., 2012). The amygdala is also more generally engaged by biologically significant emotion. In addition to the findings for threat, MDD has also been associated with mood-congruent hyper-reactivity of the amygdala evoked by sad faces (Arnone, McKie, Elliott, et al., 2012; Fu et al., 2004; Victor, Furey, Fromm, Ohman, & Drevets, 2010).

Alterations in amydala activation may also reflect a reduction in connectivity between the amygdala and subgenual/ventral ACC, observed during implicit processing of threat-related faces in unmedicated MDD (Matthews et al., 2008; Musgrove et al., 2015), generalized social anxiety disorder (Prater et al., 2013) and generalized anxiety disorder (Etkin et al., 2010). A lack of connectivity elicited during the conscious evaluation of threat has also been observed between the amygdala and prefrontal regions, including the ACC (Clauss et al., 2014), OFC (Sladky, Hoflich, Kublbock, et al., 2013), mPFC (Hahn, Stein, Windischberger, et al., 2011; Prater et al., 2013) for social anxiety disorder. Disruptions in amygdala-ACC functional connectivity might also have a basis in disruptions to white matter connectivity. For example, MDD has been associated with reduction in the uncinate fasciculus white matter connections that support functional communication between the amygdala and ACC (Steffens et al., 2011).

6.2 Negative affective circuit and treatment implications

Pretreatment hyporeactivity of the amygdala during implicit processing of threat-related faces has been found to predict subsequent response to escitalopram and sertraline, with around 75% cross-validated accuracy (Williams, Korgaonkar, Song, et al., 2015b). Amygdala hypoactivation to negative emotional faces has also been associated with treatment response to another SSRI, paroxetine (Ruhe et al., 2012). By contrast, nonresponders had relative hyper-reactivity of the amygdala at the pretreatment baseline (Williams et al., 2015). Complementing these findings, smaller amygdala volume at pretreatment baseline has also been associated with remission of depressive symptoms following pharmacotherapy (Li et al., 2010). Response to the SSRI escitalopram after 6 weeks has also been associated with decreases in amygdala activation early

in treatment (7 days) (Godlewska, Browning, Norbury, Cowen, & Harmer, 2016). Relatedly, functional hyper- (rather than hypo-) connectivity between the amygdala and ACC during the processing of fearful faces has also been found to distinguish non-remitters to the SSRI escitalopram (Matthews et al., 2008), whereas remitters have not been found to differ from healthy controls on amygdala connectivity (Vai, Bulgarelli, Godlewska, et al., 2016).

Supplementing these findings for prediction based on baseline affective circuit function, a third line of mechanistically oriented research has demonstrated changes in circuit function post-pharmacotherapy. These findings suggest that circuit function is a viable target endpoint for intervention studies. For studies showing hypoactivation or hypoconnectivity at baseline, both SSRIs (escitalopram and sertraline), and the SNRI venlafaxine-xr have been found to increase amygdala activation to implicit threat stimuli (Williams et al., 2015). Moreover, the SSRI fluoxetine increased amygdala-ACC connectivity elicited by such stimuli (Chen, Suckling, Ooi, et al., 2008). Other studies report that, following treatment with SSRIs (sertraline, escitalopram, citalopram, fluoxetine, or paroxetine), there is attenuation of baseline amygdala hyperactivation elicited by negative valence emotional faces (Arnone et al., 2012; Fu et al., 2004; Victor et al., 2010), particularly for responders (Godlewska, Norbury, Selvaraj, Cowen, & Harmer, 2012; Ruhe et al., 2012). Together, both studies of both prediction and pre-post treatment change suggest that the direction of disruption (hypo- or hyper-) may depend on the task used to probe the affective circuit, such that both directions of disruption are relevant for future study. In one illustrative rTMS study to date, stimulation (relative to sham) in patients with major depression was found to attenuate subgenual ACC (sgACC) resting state functional connectivity with the negative affective network, most apparent in responders to stimulation (Taylor et al., 2018).

7 Positive affect circuit: "Reward"

Reward processing components of the affective circuits are defined by the striatal nucleus accumbens, and ventral tegmental areas (collectively referred to as "the striatum") and their projections to the orbitofrontal cortex (OFC) and mPFC (Berridge & Kringelbach, 2008). These regional components are preferentially engaged by different types of reward processing, including sensitivity to the presence of salient reward stimuli and the anticipation of these stimuli. There are also connections between the striatum and the amygdala, consistent with interactions between the processing of threat and reward and of significant stimuli that encompass multiple valences (Haber & Knutson, 2010).

7.1 Reward circuit disruptions in depression and anxiety

Across studies, hypoactivation of the striatum has been identified as a robust characteristic of at least some patients with depression, especially those who report experiences of anhedonia (for meta-analysis, Hamilton et al., 2012; for review, Treadway & Zald, 2011). Such hypoactivation in depression is elicited not only by primary signals of social reward (such as happy faces), but also by tasks that rely on reward-motivated decision-making (Treadway & Zald, 2011). Striatal hypoactivation also characterizes adolescents at risk of depression (Gotlib, Hamilton, Cooney, et al., 2010), suggesting that a trait-like disruption to reward circuits may contribute to the development of mood disorder. Consistent with the possibility of a trait-like biotype for altered reward circuitry and anhedonia, depression has also been associated with gray matter loss in the striatum (Kim et al., 2008; Pizzagalli et al., 2009). In addition, depression has been associated with increased white matter connectivity in bilateral corticospinal tracts, a structural alteration that might underlie some aspects of the striatal and motor functional disruptions in this disorder (Sacchet et al., 2014).

For socially rewarding facial expressions of happiness, hypoactivation of the amygdala has also been observed in unmedicated MDD (Williams et al., 2015), generalized anxiety disorder (Blair et al., 2008), panic disorder (Ottaviani, Cevolani, Nucifora, et al., 2012), and obsessive compulsive disorder (OCD) (Cannistraro, Wright, Wedig, et al., 2004), and may reflect a further neural characteristic of transdiagnostic anhedonia. Frontally, in remitted depression, *hyper*-activation of the OFC, medial prefrontal/midfrontal regions and ACC has also been observed in response to happy faces (Keedwell et al., 2005a; Mitterschiffthaler et al., 2003), reward outcomes (Dichter et al., 2012), and reward anticipation (for meta-analysis) (Zhang et al., 2013). Frontal hyper-activation might reflect an adaption accompanying striatal hypoactivation. However, the opposing finding of medial frontal hypoactivation for positive valence processing in anhedonic female patients has also been observed (Keedwell et al., 2005a; Mitterschiffthaler et al., 2003).

7.2 Reward circuit and treatment implications

Arguably, because reward circuit dysfunction does not appear to be modulated by typical SSRIs (Dunlop & Nemeroff, 2007), to our knowledge there have been no studies to date assessing whether baseline reward circuit dysfunction in

MDD predicts antidepressant outcomes. There have been studies of behavioral therapy and of rTMS. When probed at baseline by a reward task, lower relative to higher sustained activation of the ACC has been associated with greater symptom reduction in response to behavioral activation therapy for depression (Carl et al., 2016). For rTMS, responders to stimulation are characterized by relative hyper-connectivity between the striatum and the ventral medial region of the broader orbitofrontal cortex, as well as other regions related to reward function (Downar et al., 2014). Other mechanistically oriented studies have investigated antidepressants in regard to their impact on modulating reward circuits. The antidepressants venlafaxine and fluoxetine have been associated with an increase in nucleus accumbens activation that also track increases in experienced positive emotion (Heller et al., 2013). Corresponding increases in accumbens-middle prefrontal connectivity have similarly been associated with increases in self-reported positive emotion (Heller et al., 2013).

Notably, treatment-resistant patients experiencing characteristics of anhedonia do not tend to benefit from antidepressants that act on serotonin (Dunlop & Nemeroff, 2007). In cases in which there is an underlying disruption to reward circuits, a rationale alternative to consider would be antidepressants that facilitate plasticity in striatal dopamine pathways. In animal models, PET shows that pramipexole binds to extrastriatal dopamine receptors, and modulates striatal function when probed by a reward task (Dunlop & Nemeroff, 2007). Bupropion is also thought to act on dopamine and modulate striatal function (Dunlop & Nemeroff, 2007). Positive affect (reward) circuit function is a promising probe for target-driven, mechanistically focused, intervention studies that test whether there is a relationship among positive affect circuit dysfunction, dopamine-related plasticity, and phenotypes characterized by anhedonia features.

8 Attention circuit

The frontoparietal "attention" circuit is defined by the medial superior frontal cortices, lateral prefrontal cortex, anterior inferior parietal lobule, and precuneus (Fornito et al., 2012; Gordon et al., 2014). The anterior insula is also involved in the integration of dorsal and ventral components of frontoparietal attention circuits. This circuit is implicated in alertness, sustained attention, and the support of recollection (Fornito et al., 2012; Gordon et al., 2014). It interacts closely with the default mode circuit to configure the switching from resting to task-context processing (Fornito et al., 2012; Vincent, Kahn, Snyder, Raichle, & Buckner, 2008).

8.1 Attention circuit disruptions in depression and anxiety

There has also been relatively little work done on disruptions to the frontoparietal attention circuit in depression and anxiety. However, several studies have observed hypoconnectivity within the attention circuit in MDD and in social anxiety (Liao et al., 2010; Qiu et al., 2011; Veer et al., 2010). Such hypoconnectivity within the attention circuit has been correlated with a specific behavioral profile of false alarm errors (e.g., responding to "no go" stimuli as if they are "go" stimuli) in anxiety disorder, suggesting a biotype of inattention and impairments in vigilance.

8.2 Attention circuit and treatment implications

Response to psychotherapy may be linked to attention network function. Intrinsic functional connectivity between the left intraparietal sulcus and orbital frontal cortex has been found to predict somatic symptom improvement following behavioral activation treatment for depression (Crowther et al., 2015). It is possible that psychotherapy action may be, in part, mediated by changes in attention circuit function. Increases in perfusion (as measured by arterial spin labeling MRI), as well as connectivity between the attention circuit and the amygdala, have been observed in response to CBT (Shou et al., 2017; Sosic-Vasic et al., 2017).

9 Cognitive control circuit

The "cognitive control" circuit comprises the DLPFC, ACC, dorsal parietal cortex (DPC), and precentral gyrus (Table 1). Together, these regions and their interconnectivity are implicated in the support of higher cognitive functions such as working memory and selective attention (for meta-analysis, Niendam et al., 2012; evidence from convergent neuroimaging methods, Cole & Schneider, 2007). Under task-specific demands, the cognitive control circuit is implicated in cognitive flexibility (Roalf, Ruparel, Gur, et al., 2014).

9.1 Cognitive control circuit disruptions in depression and anxiety

Dysfunction of the cognitive control circuit may be elicited by tasks that require effortful selective processing of relevant stimuli and inhibition of irrelevant stimuli, such as in a working memory task. Hypo-activation of the DLPFC and dorsal anterior cingulate cortex (dACC) during cognitive tasks, and in stress-induced situations, has been found in depressed patients and in social anxiety (Elliott, Baker, et al., 1997; Elliott, Sahakian, et al., 1997; Korgaonkar et al., 2013; Siegle et al., 2007). Induced anxiety has also been related to persistent DLPFC hypo-activation during working memory performance (Fales et al., 2008). Hypoactivity in defining nodes of the cognitive control circuit has been observed in adolescents with depression, and found to persist after recovery in adult and later-life depression (Aizenstein, Butters, Wu, et al., 2009; Elliott, Baker, et al., 1997; Halari, Simic, Pariante, et al., 2009; Harvey et al., 2005), suggesting that this type of dysfunction may have a trait-like status. This trait-like status is also suggested by the presence of reductions in gray matter volume of the same DLPFC and ACC regions in younger and older adults with MDD (Chang et al., 2011; Grieve et al., 2013).

Cognitive control problems in depression may also involve problems suppressing default circuit function, reflected in positive correlations (rather than anticorrelation) between DLFPC cognitive control regions and posterior cingulate default mode regions (Bartova, Meyer, Diers, et al., 2015; Sheline et al., 2010). Suggesting a second type of cognitive control circuit dysfunction, some depressed patients show *hyper*- (rather than hypo-) activation of the DLPFC during working memory and executive function tasks. DLPFC hyper-activation has been observed in depression during tasks with an increasing cognitive demand, but in the absence of behavioral deficits in performing the task (Fitzgerald et al., 2008; Harvey et al., 2005; Holmes, MacDonald 3rd, Carter, et al., 2005; Hugdahl, Rund, Lund, et al., 2004; Matsuo et al., 2007; Wagner, Sinsel, Sobanski, et al., 2006; Walter et al., 2007). In this context, hyper-activation may reflect an attempt at compensation to retain normal cognitive behavior (Fitzgerald et al., 2008; Harvey et al., 2005). Over-activity in both the rostral and dorsal portions of the ACC (Harvey et al., 2005; Rose, Simonotto, & Ebmeier, 2006; Wagner et al., 2006), as well as DLPFC-ACC hyper-connectivity, has also been observed in MDD when performance is similar to that of controls. Hyper-activation in regions of the cognitive control circuitry has been observed in adolescents with depression (Harvey et al., 2005) and in medicated (Harvey et al., 2005; Rose et al., 2006; Walter et al., 2007) and unmedicated (Matsuo et al., 2007) individuals with MDD, and it persists in the ACC after remission (Schoning, Zwitserlood, Engelien, et al., 2009). *Hyper*-connectivity of the DLPFC and cingulate has also been observed in MDD during working memory tasks (Holmes & Pizzagalli, 2008; Vasic et al., 2009).

9.2 Cognitive control circuit and treatment implications

Two studies have found that activation of attention circuit regions elicited by a Go-NoGo task is associated with pharmacotherapy treatment response. Depression symptom improvement following an SSRI was associated with pretreatment activation of the bilateral insula, middle frontal gyrus, and inferior frontal gyrus to successful rejections (Langenecker et al., 2007). Go-NoGo activation in attention regions may also help distinguish those who would respond to different classes of pharmacotherapy. Remission on SSRIs has been associated with relatively greater inhibitory response in the inferior parietal cortex, and SNRI remission with relatively lower inhibitory response (Gyurak et al., 2016).

Comparative hypoactivation of the DLPFC region of the cognitive control circuit, elicited during the inhibition condition of a Go-NoGo task, has been found to predict worse outcomes for SSRIs (escitalopram and sertraline) (Gyurak et al., 2016), as well as for behavioral therapy for PTSD (Falconer, Allen, Felmingham, Williams, & Bryant, 2013). There is also evidence that DLPFC hypoactivation pretreatment predicts poorer outcomes for the SNRI venlafaxine-XR in treating depression (Gyurak et al., 2016), although there is also evidence that patients with poor cognitive control function benefit from venlafaxine-XR (Tian, Du, Spagna, et al., 2016). In the task-free state, relatively lower functional connectivity within the cognitive control circuit has been found to predict poor response to the SSRI escitalopram in an older adult population (Alexopoulos, Hoptman, Kanellopoulos, et al., 2012). Additionally, depression symptom improvement following an SSRI has been associated with pretreatment activation of the bilateral insula, middle frontal gyrus, and inferior frontal gyrus to successful rejections during a Go-NoGo task (Langenecker et al., 2007). Greater dACC activation to commission errors during a parametric version of the Go-NoGo task also was associated with poorer treatment outcome to escitalopram and duloxetine (Crane et al., 2017). Greater engagement of the DLPFC during an emotional face task, both before and after paroxetine, was also associated with better treatment response (Ruhe et al., 2012). Go-NoGo activation in overlapping attention regions may also help distinguish those who would respond to different classes of pharmacotherapy. Remission on SSRIs has been associated with relatively greater inhibitory response in the inferior parietal cortex, and SNRI remission

with relatively lower inhibitory response (Gyurak et al., 2016). Structurally, nonremission has been associated with reduced volume in the DLPFC compared with controls (Li et al., 2010).

Psychotherapy and pharmacotherapy both have been shown to alter these cognitive control profiles, and in some cases, the degree of change has been associated with improved outcome. For example, increased intrinsic DLPFC—amygdala functional connectivity (Straub et al., 2017) was observed following group CBT treatment in depressed adolescents. Moreover, the degree of change in DLPFC—amygdala connectivity was positively correlated with the degree of depression symptom improvement, possibly suggesting that these changes in connectivity may be mediating treatment effects. CBT has also been shown to increase DLPFC perfusion as measured by continuous arterial spin labeling independent of symptom improvement (Sosic-Vasic et al., 2017). With respect to pharmacotherapy, treatment with SSRIs, including escitalopram and paroxetine, has been found to increase DLPFC activation during a cognitive (Fales, Barch, Rundle, et al., 2009) and emotional task (Ruhe et al., 2012). However, the extent of the degree of change in DLPFC engagement has not been associated with the extent of symptom improvement.

10 Future directions to close the clinical translational gap

To accelerate progress toward a clinically applicable precision psychiatry model of depression and anxiety, that builds on circuit findings to date, there is a need for standardized protocols, normative data, multimodal data integration, new computational models, and expansion to prospective intervention studies.

10.1 Standardized protocols

Currently, our understanding of the role that brain circuits and their activation play in clinical dysfunction is limited, in part, by inconsistent findings stemming from a lack of standardization across research protocols. To advance the field of precision psychiatry, it will be necessary to undertake larger, multi-site investigations made possible by the use of standardized protocols, integrative analytic models, and databases (Korgaonkar et al., 2013; Siegle, 2011). This approach has been implemented with success in several imaging studies to date (Korgaonkar et al., 2013; Trivedi, McGrath, Fava, et al., 2016). While novel imaging protocols are important for new scientific discoveries, standardized protocols will be essential for the future viability of routine scans for mental health assessment.

10.2 Normative data

In order to incorporate neural circuit taxonomies into practice, we need to establish thresholds for normative vs abnormal function that apply to an individual patient. It will be important to define the normative distribution of neural circuit function in healthy individuals (e.g., Ball et al., 2017), and identify thresholds for overt disorder and failures of function. Methods for establishing the reproducibility of imaging data across people, sites, and time will also be needed (Biswal, Mennes, Zuo, et al., 2010).

10.3 Integration across modalities within the same patients

To further refine circuit taxonomies, it will be essential to integrate imaging data with other modalities. We could consider imaging as just one starting point for directing such effort. To refine classifications based on neural circuits, there is a need to consider the relations among activation, connectivity, and structure within a circuit, as well as the more nuanced interactions between circuits. In parallel, there is a need to dive in depth into understanding the precise ways that brain circuits relate to behavior and symptoms: which specific symptoms reflect the activation of particular circuits, are there symptoms that reflect a "final common pathway" as the outcome of multiple different types of circuit disruptions, does a change in a brain circuits predict a change in symptoms, and so on. An integrated understanding of how neural circuit dysfunctions are modulated by more distal factors, such as genetic variation, genetic expression, life events, and their interaction will also be paramount. These multi-modal efforts will necessarily accumulate increasingly "big data." In turn, big data requires computational innovation.

10.4 Computational innovation

Integrating imaging datasets with other rich data in a manner that translates insights into clinically meaningful outcomes requires special attention to computational approaches. Broadly speaking, there are two complementary approaches: data-

driven and theory-driven (for review and synthesis see Huys, Maia, & Frank, 2016; Redish & Gordon, 2016). Regardless of the exact approach, it is increasingly recognized (as it is in other areas of medicine), that demonstration of the reproducibility of findings is key to ultimately having sufficient confidence to warrant clinical translational.

10.5 Prospective, circuit-guided interventions

Short-term progress can be made using precision psychiatry to better match patients to existing treatments and/or prevention strategies. Prospective trials, guided by circuit targets, will be important for accelerating progress. Longer-term progress in precision psychiatry will come not only from prospectively improving existing interventions, but also generating new ones. As neurobiologically based subtypes of psychiatric disorders are refined, new medications can be developed to target specific deficits. As one illustration of circuit-based approaches, neurostimulation technologies, such as repetitive transcranial magnetic stimulation (rTMS), allow for intervention strategies that can capitalize on emerging circuit models. rTMS, a non-invasive high-frequency stimulation of the cortex, was initially conceptualized as an intervention for treatment-resistant depression due to the low response and remission rates for rTMS in early trials. However, applications of rTMS are rapidly expanding to allow precise tailoring based on individual patients' circuit-level dysfunction, with corresponding increases in response and remission rates (e.g., Downar & Daskalakis, 2013).

11 Conclusions

Advances in human neuroimaging of circuits involved in self-reflective, affective, and cognitive functions provide the foundations for formulating a neural circuit understanding of depression and anxiety. Such an approach offers a tangible means to advance precision tools and taxonomies for classification of subtypes, and for tailoring inventions, according to underlying neurobiological dysfunctions. Circuit subtypes also provide objective targets from which to guide prospective, personalized intervention studies, and to inform an understanding of underlying mechanisms. Ultimately, these approaches will accelerate the translation of knowledge into the routine practice of neural circuit-informed precision psychiatry. To close the translational gap between current knowledge and translation into the clinic, important future directions for our field are a focus on building circuit-based norms and standardized protocols, accelerating computational approaches that can fuse imaging and phenotype data in a manner that is clinically interpretable, and establishing collaborative efforts to launch prospective circuit-guided trials that move us into the realm of actionable outcomes.

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Psychiatry has not yet been in the game for precision medicine, in contrast to cardiovascular disease and other chronic diseases. Cardiovascular care is further ahead in linking precise insights about the organs of interest to treatment indications. For example, the EKG can be used to identify types of arrhythmia (too fast, too slow, irregular) and to indicate specific treatments (pacemaker), and the angiogram to confirm the presence of blockage (emboli, stroke, myocardial infarction) and to indicate other treatments (lifestyle changes, medications, surgery).

This situation is now changing rapidly as we witness the emergence of precision psychiatry informed by neuroscience. With advances in technologies for imaging the human brain in action, and for integrating other biomarkers, we are now identifying types of brain circuit dysfunction that underlie depression and anxiety, analogous to types of heart dysfunction that underlie phenotypes of cardiovascular disease. An important next step is to accelerate translational research addressed at the question of how we apply these new insights within an actionable system for improving people's lives.

The goals of precision psychiatry are three-fold: precise classification (i.e., a specific understanding of the pathophysiology of each individual patient—what has gone wrong), precise treatment planning (i.e., tailoring treatment plans in a personalized manner—how can we fix what has gone wrong), and precise prevention (i.e., targeted and tailored prevention strategies—how can we keep things from going wrong).

The first of these three goals, precise classification, hinges on the identification of subtype profiles (or "biotypes") that coherently map neurobiological disruptions onto symptoms and behaviors, take into account life experience and context, and are relevant to guiding treatment choices (Williams, 2016, 2017). These profiles and biotypes may, in some instances, align with our rich symptom classifications currently defined by the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (Publishing D-APAJAAP, 2013), and in other cases, may cut across diagnostic classifications and, in others, may reflect unforeseen, novel subtypes. Precision psychiatry, a rapidly emerging field, encompasses the discovery of these types, as well as their application to treatment and prevention. Although the scientific insights and treatment models on which precision psychiatry is based are well-established, the integration across science and practice, and the dissemination of scientific insights into clinical practice, is at the forefront of our field.

Here, the primary focus is on the organ of dysfunction in psychiatry: the brain. In particular, the focus is on large-scale neural circuits probed by functional neuroimaging. Necessarily, there is also a need to incorporate other biomarker domains, such as genetics, life history, and cognition. Genetic variants and life experience have an important role in modulating neural circuit function. In turn, neural circuit functions are expressed in

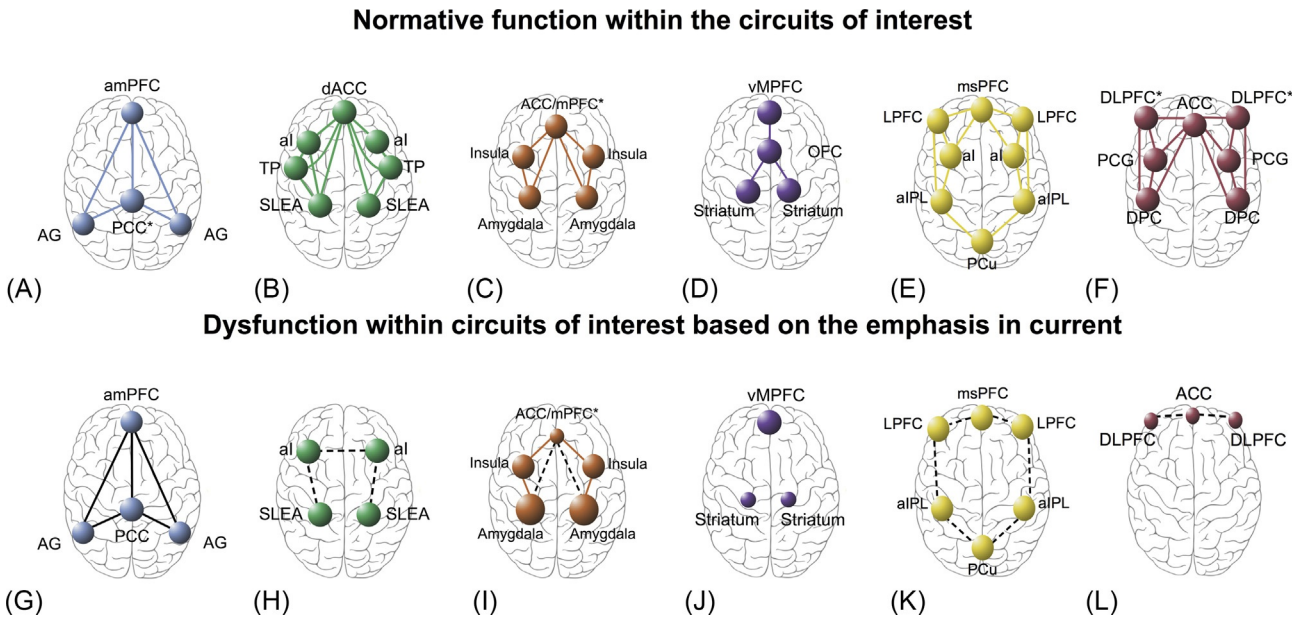

FIG. 1 An illustration of our circuits and circuit dysfunction of interest. Panels A–F show normative function within the default mode node network (A) defined by the anterior medial prefrontal cortex (amPFC), the posterior cingulate cortex (PCC), and the angular gyrus (AG), salience circuit (B) defined by the anterior insula (aI), dorsal ACC (dACC), sublenticular extended amygdala (SLEA) and temporal parietal junction (TP), the negative affect circuit (C) defined by the amygdala, insula and ACC/medial prefrontal cortex* (encompassing the dACC, subgenual ACC, and medial PFC), the positive affect circuit (D) comprising the ventral and dorsal striatum, orbitofrontal cortex (OFC) and ventromedial PFC (vmPFC), the attention circuit (E) defined by the middle superior. PFC (msPFC), lateral prefrontal cortex (LPFC), anterior inferior parietal lobule (aIPL) and precuneus (PCu) and cognitive control circuit (F), defined by the DLPFC* (encompassing the dorsolateral prefrontal cortex, anterior prefrontal cortex, and inferior frontal cortex), ACC, precentral gyrus (PCG), and dorsal parietal cortex (DPC). Panels G through L illustrate dysfunctions of these circuits observed in mood disorders, focusing on the findings emphasized by our current accumulated knowledge. Not shown is the distinct dysfunction of the negative affect circuit associated with hyporeactivity to sad-related negative stimuli. The size of the regions illustrated here represents the direction of dysfunction in activation (smaller = hypoactivation, larger = hyper-activation). The style of the connections between regions represents the direction of dysfunction in functional connectivity (thick lines = hyper-connectivity, dashed lines = hypoconnectivity).

how individuals perform on tests of general and emotional cognition. The synthesis of evidence presented here focuses on depression and anxiety. A unifying premise is that we have sufficient evidence to develop a new taxonomy for depression and anxiety that considers these disorders as types of disruptions in underlying neural circuits (Fig. 1). It is proposed that, through quantification of neural circuits, we can start laying the foundations of a neural-circuit guided precision psychiatry that informs classification and treatment planning.

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