Title: Toward an Integrative Perspective on the Neural Mechanisms Underlying Persistent Maladaptive Behaviors.

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Running Title: Mechanisms of Persistent Maladaptive Behaviors

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Introduction

A host of public health problems—from drug addiction to obesity—are associated with persistent, maladaptive behaviors. The underlying causes of such behaviors have received considerable attention from psychologists, clinicians, computational theorists, and neuroscientists. These diverse perspectives were showcased in a symposium at the University of Rochester entitled *Persistent, Maladaptive Behaviors: Why We Make Bad Choices*. Here, we synthesize novel findings and perspectives arising from the symposium and integrate those findings within the broader literature. We begin by reviewing theoretical models of maladaptive behaviors and their underlying neural circuitry. We then discuss the behavioral and clinical manifestations of maladaptive behaviors. Given the multifaceted nature of maladaptive behavior, we argue that a dimensional approach may help inform theoretical models and clinical interventions, particularly those that rely on brain stimulation to induce neuro-plastic changes that rescue and remediate aberrant neural responses. We conclude that an interdisciplinary approach to studying maladaptive behavior will help advance the field toward improved prevention, diagnosis, and treatment.

Many societal and psychiatric issues result from persistent, maladaptive behaviors. On the surface, these behaviors span a wide range of outward manifestations, but often share underlying mechanisms. Consider individuals with substance dependence, who compulsively use drugs despite debilitating negative consequences. Likewise, patients with obsessive-compulsive disorder (OCD) feel compelled to perform rituals that interfere with daily functioning. These issues are often regarded in society as purely voluntary “disorders of choice,” and are rarely understood within the context of their neurobiological mechanisms (Epstein et al., 2010, Volkow et al., 2016, Stojek and MacKillop, 2017). Understanding the neurobiological mechanisms is necessary to prevent, treat, and eventually change the public perception surrounding these “disorders of choice.” To achieve this, there is merit in taking an

interdisciplinary approach. At the symposium on *Persistent, Maladaptive Behaviors: Why we make bad choices*, neuroscientists, computational theorists, and clinicians gathered to discuss the latest advancements on behavioral and neural mechanisms, clinical abnormalities, and therapeutic approaches related to maladaptive behaviors.

An important goal is to develop testable theories about *why* maladaptive behaviors emerge (see section on *Models of Maladaptive Behavior*). Some explanations involve the possibility that mechanisms are more or less adaptive as a function of context. Developing theories of optimal decision making will guide future research in both animal and clinical models of mental health. A second goal is to *identify* specific dimensions of behavior that are disturbed in disorders marked by maladaptive decisions (see section on *Clinical Syndromes: Toward a Transdiagnostic Approach*). Rather than focusing on distinct psychiatric illnesses, the National Institute of Mental Health (NIMH) launched its Research Domain Criteria (RDoC; Insel et al., 2010) initiative to promote research on the dimensions of behavior and their underlying biology. These dimensions may be present in multiple disorders with different symptom profiles. The dimensional approach is especially beneficial in identifying specific behaviors and neural circuits that can be studied with greater precision in animal models (see section on *Using Animal Models to Probe the Neural Circuits of Persistent Maladaptive Behavior*).

With such a multi-level approach, biological markers identified in clinical and pre-clinical (i.e., animal) models can guide individualized medicine, neuro-prediction models, and the development of targets for effective interventions, such as non-invasive brain stimulation (see section on *New frontiers in therapeutic interventions for maladaptive decision making*). Taken together, the symposium highlighted recent progress in translating between species, and from bench to bedside to enhance our understanding of persistent, maladaptive behaviors.

Models of maladaptive behavior

69 In order to determine the neural mechanisms of persistent maladaptive behaviors,
70 researchers must first carefully define and quantify natural behaviors (Krakauer et al., 2017).
71 One approach for defining and quantifying behaviors relies on computational models that
72 characterize trial-to-trial changes in beliefs and expectations. These types of models can serve
73 as powerful tools for identifying novel causes of maladaptive decision making that may cut
74 across traditional diagnostic boundaries. For example, recently developed models suggest that
75 maladaptive decision processes may be better characterized as maladaptive learning processes
76 (Maia and Frank, 2011). This framework posits that biases in decision making arise from a
77 learned representation of the environment that was previously useful but is no longer
78 appropriate (Huys et al., 2016). Several sessions at the symposium discussed these
79 computational and theoretical models of maladaptive behavior including: “Human studies and
80 clinical abnormalities”, “Common circuits and traits in disease”, and “Why we make bad
81 decisions”, which included Daniela Schiller, Claire Gillan, Timothy Behrens, Joseph Kable, and
82 Peter Dayan.

83 Classic features of maladaptive decisions can be considered rational, but over-
84 generalized behaviors, as discussed in Peter Dayan’s presentation. Impulsivity - the tendency to
85 select immediate rewards at one’s long-term expense - is typically considered a maladaptive
86 bias and is a common dimension of neuropsychiatric disorders (see *Clinical syndromes: toward*
87 *a transdiagnostic approach*). However, it is rational to be impulsive in volatile environments. If
88 experience has taught an individual that their environment is unstable, then plans for achieving
89 future rewards become less attractive because the environment might change before the reward
90 can be acquired (Williams and Dayan, 2005). Therefore, choosing smaller immediate rewards
91 over larger delayed rewards may reflect beliefs about the stability of the environment.

92 Another related form of impulsivity is the choice to quit pursuing long-term rewards after
93 expressing a preference for them, which was the key theme in Joseph Kable’s presentation.

This choice may reflect expectations about the uncertainty of the timing of those long-term rewards. For example, drug users may experience relapse if they have uncertainty about when and whether they can achieve the goal of staying sober. In a series of experiments discussed at the symposium, McGuire and Kable (2012, 2013, 2015) showed that individuals can calibrate how long they wait for delayed rewards based on previous experience. Specifically, people wait longer when rewards are certain to arrive within a predictable time period but wait less when delays are more variable. Future work should test how perceptions of environmental uncertainty and stability can lead to impulsivity, and how this might manifest in psychiatric disorders. Moreover, this work has implications for clinical treatments because it shows that encouraging persistence for long-term rewards may depend on changing expectations about the environment, rather than directly changing choice.

In another classic example of maladaptive behavior, fear associations that are no longer relevant often continue to influence behavior, as is the case with Post Traumatic Stress Disorder (PTSD). Recent theoretical and experimental work suggests that this phenomenon arises from a learning strategy for relating causes to effects based on animal studies, as mentioned by Yael Niv (Gershman and Niv, 2012). According to this model, animals infer underlying causes about environmental stimuli based on statistical co-occurrence. For example, during auditory fear conditioning, the co-occurring tone and shock are generated by the same latent, or unobservable, cause. During fear extinction, aspects of the environment have changed sufficiently such that the theoretical model infers a new latent cause. Rather than unlearning the original association, the animal learns two independent, latent causes: one that causes only tones and one that causes tones as well as shocks. If the animal is not expecting a tone or a shock, because time has passed or the animal's environment has changed, then the fear response rapidly recovers. Therefore, statistically optimal learning can result in a maladaptive maintenance of fear associations that are no longer relevant (Dunsmoor et al., 2015). This type

of maladaptive learning could underlie the disordered neural response to rewards observed in many neuropsychiatric disorders.

These theoretical approaches suggest that deficits in decision making arise from representations of the environment that were previously accurate but are now inappropriate in novel contexts. This allows for more precise hypotheses about the etiology of maladaptive decisions in clinical populations (Huys et al., 2016). Further, this approach generates novel avenues for therapeutic approaches (Montague et al., 2012). For instance, the latent cause theory predicts that extinction learning will be more effective if it is made to be more similar to the learning context. This prediction has been borne out in rodents: gradually weakening the contingency between tone and shock, rather than abruptly eliminating it, reduces spontaneous recovery of fear behavior (Gershman and Niv, 2012). Finally, these models allow for a more precise characterization of the computations performed by different neural circuits and how they may be disrupted in disease (Laurent et al., 2016).

Recent work has made substantial progress towards such a characterization. Timothy Behrens presented experimental data suggesting that the neural representation of concepts is organized in a similar manner to the neural representation of space (Constantinescu et al., 2016). These conceptual representations reside in a region of medial prefrontal cortex (mPFC) associated with valuation and decision making. Daeyeol Lee presented recording data from nonhuman primates suggesting that neurons in the dorsolateral prefrontal cortex (dlPFC) integrate decision-relevant information at the time of decision making (Donahue and Lee, 2015). These are the same areas that are disrupted or atrophied in compulsive behavioral disorders (see *Clinical syndromes: toward a transdiagnostic approach*). Exciting work presented by Hesheng Liu suggested that even more precise functional characterization of cortex can be determined by examining different functional parcels using resting state data (Yeo et al., 2011). These characterizations of where and how the brain represents information and makes

decisions are critical for bridging theoretical conceptions of maladaptive decision making with clinical care.

Clinical syndromes: toward a transdiagnostic approach

The symposium's sessions on "Human studies and clinical abnormalities" included presentations by Diego Pizzagalli, Rita Goldstein, Hugh Garavan, Mary Phillips, and John O'Doherty as well as keynote speaker Trevor Robbins, who discussed clinical syndromes and psychopathologies within the context of maladaptive behavior. Persistent maladaptive behaviors characterize a number of clinical diagnoses, including addiction, OCD, bipolar disorder, and Major Depressive Disorder (MDD). Commonalities in symptomatology, and implicated neuronal circuitry, across these disorders present the opportunity to identify functional constructs associated with maladaptive behavior transdiagnostically. This is in line with the initiatives outlined by the NIMH's RDoC initiative (Cuthbert and Kozak, 2013, Kozak and Cuthbert, 2016). The global aim of RDoC is to advance our understanding of "basic dimensions of functioning underlying the full range of human behavior from normal to abnormal" (Morris and Cuthbert, 2012, Cuthbert and Kozak, 2013). In doing so, it seeks to provide a structured framework for investigating psychiatric disorders across multiple approaches, ranging from genomics to neuroimaging biomarkers. In contrast to the categorical approach currently embodied in the Diagnostic and Statistical Manual (DSM; American Psychiatric Association, 2013), the RDoC dimensional approach incorporates etiological factors and novel scientific knowledge into the understanding and diagnosis of psychiatric conditions (Schutz and Christian, 2012). Indeed, several speakers throughout the symposium—including Diego Pizzagalli and Claire Gillan—stressed the importance of implementing an RDoC approach to understanding maladaptive behaviors in psychiatric disease.

Adopting RDoC to identify pathological mechanisms common to multiple psychiatric disorders will aid in breaking down arbitrary distinctions between categorically defined disorders

and may assist in understanding comorbidity among current diagnostic categories (Nusslock and Alloy, 2017). As discussed at the symposium, deficits in threat and reward processing as well as goal-directed control are observed across multiple psychiatric disorders, including MDD (Wagner et al., 2006, Satterthwaite et al., 2015), bipolar disorder (Phillips and Vieta, 2007, Almeida et al., 2010), schizophrenia (Barch and Ceaser, 2012, Barch et al., 2016), anxiety disorders (Etkin and Wager, 2007, Pacheco-Unguetti et al., 2011, Apergis-Schoute et al., 2017), and addiction (Volkow et al., 2016, Steele et al., 2018). Therefore, problems in any of these domains might be risk factors for symptoms that occur transdiagnostically. Uncovering deficits that cut across multiple diagnostic categories can now be done in single studies with the proper assessment tools and large sample sizes (e.g., large-scale web-based studies collecting a wide range of behavioral variables from thousands of participants; Gillan and Daw, 2016). Computational models can further specify the underlying processes that give rise to transdiagnostic behavioral and neural abnormalities. Claire Gillan presented recent work using this approach, showing that compromised goal-directed behavior is associated with the symptom of compulsivity, which is common to several disorders (e.g., OCD, substance dependence, and eating disorders; Goldstein and Volkow, 2011, Gillan et al., 2016).

Keynote speaker Trevor Robbins presented complementary work, proposing that compulsivity could be understood in terms of imbalanced cortico-striatal networks. His group has recently sought to identify common impairments in discrimination learning, action-outcome knowledge, and habitual responding across both OCD and substance use disorder (Vaghi et al., 2017b). Robbins framed addiction as a “devolution of striatal control” paired with progressive loss of top-down, frontal control over behavior. This was evidenced by studies showing both dorsal striatal involvement in drug seeking habits (Everitt and Robbins, 2005), as well as decreases in prefrontal activity and white matter tract integrity in drug users and siblings of drug users (Vaghi et al., 2017a). Highlighting the commonality with OCD, Robbins suggested that

compulsivity is the trait underlying the progression of substance use from its initial (impulsive) stages to chronic stages (Figue et al., 2016). Future work should investigate the extent to which these neural changes are related to beliefs about the future that could contribute to impulsive behavior.

Dimensional approaches used in neuroimaging work have the potential to result in brain-based transdiagnostic biomarkers capable of informing therapeutic interventions (Goodkind et al., 2015, Clementz et al., 2016, Drysdale et al., 2017). For instance, Diego Pizzagalli presented work suggesting that reduced ventral striatal activity in response to reward prediction errors (RPE) might be a biomarker for anhedonia, a transdiagnostic symptom that is common in MDD (Pizzagalli et al., 2009). He also presented new work showing that individual differences in expression of the cytokine interleukin-6 following stress can predict whether stress will decrease RPE signaling in ventral striatum (Treadway et al., 2017). Given the vast individual differences in responsiveness to stress, discovering these biomarkers will have important implications for diagnosis and treatment.

Complementarily, identifying mechanisms *unique* to specific symptoms that reflect markers of differential risk will not only advance our understanding of distinct pathological processes, but will allow for development of targeted therapeutics. For example, MDD and bipolar disorder are marked by reward processing deficits, but these deficits are quite dissimilar in nature. MDD has been associated with abnormally *reduced* positive emotionality, reward processing, and approach motivation (Pizzagalli et al., 2008, Treadway and Zald, 2011, Treadway, 2016), whereas bipolar disorders are associated with abnormally *elevated* reward processing and approach motivation (Alloy and Abramson, 2010, Nusslock et al., 2014), as noted by Mary Phillips. Understanding the distinct neurobiological biomarkers associated with MDD and bipolar disorder would have diagnostic value for distinguishing between these two disorders during the initial presentation of a depressive episode, as well as for developing

targeted treatment protocols (Manelis et al., 2016). Therefore, future studies are needed to disentangle neural subcomponents of reward processing and learning in order to predict differential symptom profiles (Wang et al., 2016, Zald and Treadway, 2017).

The *same* symptoms can also emerge through multiple mechanisms. For example, research using an RDoc approach has begun to shed light on personality traits, genetic factors, and endophenotypes that lead to differences in reward sensitivity, and therefore vulnerabilities to addiction (Belcher et al., 2014). Continuing to adopt this approach that does not limit hypotheses to diagnostic categories, but instead characterizes variation in genetic, biological, and behavioral symptoms (Sanislow et al., 2010, Cuthbert and Kozak, 2013, Kozak and Cuthbert, 2016) will clarify inconsistent data. Such efforts may be facilitated by large-scale or multi-site studies (Nees et al., 2013, Gillan and Daw, 2016). In fact, Hugh Garavan described a longitudinal study emerging from the IMAGEN project (a large, longitudinal dataset of adolescents Nees et al., 2013) suggesting that in adolescents, blunted ventral striatal signaling to anticipated rewards predicted later problematic drug use (Büchel et al., 2017). These findings dovetailed nicely with Rita Goldstein's work, which identified grey matter reductions in prefrontal networks of cocaine users, including the inferior frontal gyrus (Parvaz et al., 2017), and ventromedial prefrontal cortex (vmPFC; Konova et al., 2017), providing potential biomarkers for decision-making deficits in substance abuse.

Implementing an RDoC approach to study the pathophysiological mechanisms underlying drug initiation, its transition to dependence, and relapse, may also advance research efforts to develop novel treatments. Indeed, a strategic planning workgroup at NIDA has set in motion an initiative to prioritize the identification of genetic, environmental, and developmental factors leading to substance use disorders (Polluck et al., 2015, NIDA, 2015). The goal of this initiative is to understand the factors underlying vulnerability to addiction, and how they interact across the lifespan, ultimately leading to the development of "effective and personalized

prevention and treatment interventions for substance use disorders” (Polluck et al., 2015, NIDA, 2015). However, as cautioned by Schutz and Christian (2012), in order for the value of the RDoC approach to be realized by service providers, scientific findings must be integrated within the current diagnostic system (DSM) to provide a “diagnostic system that is stable, reliable, easy to apply, and informative for treatment” (Schutz and Christian, 2012). Linking the two systems represents a challenge within the field, but provides a promising avenue for the advancement of diagnosing and treating mental health disorders and addiction.

Using animal models to probe the neural circuits of persistent maladaptive behavior

The symposium’s sessions on “Reward, fear, and value,” “Common circuits and traits in disease,” and “Why we make bad decisions” included Benjamin Hayden, Masamichi Sakagami, Catharine Winstanley, Jeansok Kim, Gregory Quirk, Yael Niv, Suzanne Haber, Elisabeth Murray, and Daeyol Lee, all of whom covered various aspects of using animal models to understand the neural underpinnings of persistent maladaptive behavior. Animal models are integral to probe the neural circuits of decision making and to understand the mechanisms underlying persistent maladaptive behaviors at the cellular level.

One unsolved puzzle that remains in addiction research is: what makes some individuals exposed to drugs develop substance dependence, whereas others do not? Here, animal studies can help uncover mechanisms and individual differences in susceptibility through which drug initiation transitions to drug dependence. This was showcased in Catherine Winstanley’s presentation. Winstanley and colleagues have developed a rat gambling task (rGT) which models human gambling, particularly slot machines (for task details, see Zeeb and Winstanley, 2011). Rodents that were more risk-seeking at baseline were more drug-seeking for cocaine and showed an increase in risk-seeking behavior following cocaine exposure in the rGT (Ferland and Winstanley, 2017). In contrast, rodents that were relatively less risk-seeking at baseline did not show these vulnerabilities. Such animal models provide a valuable avenue for

identifying biomarkers for susceptibility to addiction, and importantly, identifies risk-seeking as a common underlying trait for vulnerability to addiction.

Rodent studies can also be useful in elucidating the mechanisms underlying other compulsive behaviors. In a modified version of the rGT, rats made more disadvantageous choices when audiovisual cues were added to mimic the context of a casino (Barrus and Winstanley, 2016). As rats' risky behavior increased, dopamine D3 receptors modulated this 'cue reactivity' – representing yet another important aspect of reward processing that may be a vulnerability factor for addictive disorders (Barrus et al., 2016). Moreover, pharmacological inactivation of the mPFC during uncued rGT resulted in overall increased risky behavior (Zeeb et al., 2015), whereas contralateral disconnection lesions between the orbitofrontal cortex (OFC) and the basolateral amygdala (BLA) impaired rats' cost-benefit decision making (Zeeb and Winstanley, 2013). These findings suggest that prefrontal-amygdala circuits guide optimal decision making under conditions of risk.

Non-human primate (NHP) studies have also investigated the function of OFC-amygdala connectivity in other forms of decision making. Devaluation tasks can be used to assess whether choices are habitual or directed toward a reinforcement goal by altering the value of the reward. If reducing the value of the reward changes the motivation to seek that reward, then the choice is goal-directed, but if it does not, then the individual's choice is habitual. Elisabeth Murray described studies in rhesus macaques demonstrating that OFC-amygdala connections are necessary to choose optimal rewards after reward devaluation (Murray et al., 2015, Fiuzat et al., 2017). Using a crossed-lesion approach, monkeys with surgical disconnections between OFC and amygdala were unable to update their decision to choose a higher value food reward after devaluation (Fiuzat et al., 2017), suggesting a role for the OFC-amygdala circuit in goal-directed behavior. Moreover, distinct subregions within OFC were necessary for either updating information about value (area 13) or were necessary for selecting actions on the basis of value

(area 11; Murray et al., 2015). Interestingly, Benjamin Hayden's presentation also emphasized the OFC's role in information updating; his group found that single unit activity in the OFC correlated with task-switching events (Sleezer et al., 2017). These findings suggest an executive role for the OFC by updating information about stimulus value or rules of a task. In addition, monkey studies of decision making that combine opto- and pharmaco-genetics to understand prefrontal-striatal circuits (Oguchi et al., 2015) have suggested that lateral PFC projections to the striatum are necessary for deciding between large and small rewards, as detailed in Masamichi Sakagami's presentation. Taken together, these findings from NHPs and the previously mentioned rodent studies highlight the necessity of OFC-amygdala as well as PFC-striatal connectivity for optimal decision making about rewards.

Evaluating danger also requires adaptive decision making, and maladaptive behaviors such as persistent avoidance can be detrimental to daily functioning. Just as updating information about a reward is important, updating the information about a neutral stimulus after it no longer occurs with an aversive stimulus is also crucial. For example, patients with PTSD and other anxiety disorders often exhibit excessive avoidance behaviors, in which reminders of the traumatic experience prevent a person from engaging in everyday activities that are safe. This avoidance might be due to excessive anxiety behaviors (Teng et al., 2016) and deficits in extinction learning (Dunsmoor et al., 2015). Most of the literature on fear learning and avoidance has employed unnatural cues paired with an aversive event (e.g., a pure tone paired with a mild footshock). More recently, researchers have begun to probe fear circuits under more naturalistic and dynamic conditions, as described by Jeansok Kim. In one study, predatory threats altered rats' decision making during foraging in a dynamic fear environment (for task details, see Choi and Kim, 2010). Unlike classical fear conditioning studies in which fear is assessed by animals' physiological reactions to a learned association, this task effectively simulated a naturalistic environment under controlled laboratory settings. Both lesions and pharmacological

inactivations (GABA-A agonist) in the amygdala resulted in increased foraging, whereas pharmacological disinhibition of the amygdala (GABA-A antagonist) decreased foraging in this task (Choi and Kim, 2010). Moreover, both the amygdala and dorsal periaqueductal grey (dPAG) were recruited during fleeing responses (Kim et al., 2013), which facilitated the rats' decision to freeze or flee the dangerous encounter. More recently, synchronous spiking between the lateral amygdala and prelimbic cortex correlated with approach or avoidance of a direct threat during foraging (Kim et al., 2018). Future studies should examine how prefrontal-amygdala circuits work in concert with the dPAG to modulate rats' behavior during fear assessment to dynamic predatory threats.

At the symposium, Gregory Quirk discussed active avoidance, an adaptive behavior learned in the presence of danger. Avoidance can be beneficial if it facilitates avoiding danger but maladaptive if the organism excessively avoids at the cost of missed opportunities. In a task developed to probe this phenomenon, rats learn to avoid a shock by stepping onto a platform (for task details, see Bravo-Rivera et al., 2014), and it has recently been shown that inhibition in the rostral prelimbic prefrontal cortex is required for avoidance behavior (Diehl et al., 2018). Using avoidance extinction with response prevention (modeled after exposure therapy in OCD patients), most rats learned that they no longer need to avoid the shock (Rodriguez-Romaguera et al., 2016). However, approximately 25% of rats exhibited persistent avoidance and failed to extinguish their avoidance response during the tone in the absence of the shock (Bravo-Rivera et al., 2015, Rodriguez-Romaguera et al., 2016). Interestingly, inactivation of the lateral OFC "rescued" these persistent avoiders, by eliminating persistent avoidance responses (Rodriguez-Romaguera et al., 2016). This finding further demonstrates a role for the OFC in modulating persistent, maladaptive behaviors and is consistent with other rodent paradigms assessing maladaptive behaviors, such as risky gambling (Ferland and Winstanley, 2017). Future studies on avoidance behavior are needed to assess which OFC projections are necessary for

avoidance extinction. It is possible that OFC projections to the amygdala may play a role in avoidance extinction, similar to how OFC-amygdala connectivity is necessary for assessing risk and reward (Zeeb and Winstanley, 2013), but this remains unclear.

One can view active avoidance as the animal modifying its evaluation of the tone from an aversive stimulus to a safety stimulus. This is akin to devaluation of a conditioned response. An interesting idea highlighted by John O'Doherty compared devaluation in Pavlovian learning (e.g. tone predicts shock) with instrumental learning (e.g., tone signals animal to avoid shock). Devaluation may only occur during instrumental learning where actions were knowingly performed, rather than reflexively, to increase the probability of reward or avoid punishment. Sub-regions of the striatum played a role in both Pavlovian (ventral striatum) and instrumental (dorsal striatum) learning (Liljeholm and O'Doherty, 2012), suggesting a potential differentiation in the devaluation process. In a similar vein, Daniela Schiller focused on how threat learning and the updating of fear memories can occur in the absence of conscious awareness (LeDoux and Pine, 2016). This mechanism could be used to develop potential treatments for patients with PTSD or other anxiety disorders (Kroes et al., 2016).

How relevant are these findings for the treatment of human diseases that lead to maladaptive decision making? A plethora of studies have demonstrated anatomical homologies between rodents, human, and NHPs (Preuss, 1995, Phillips et al., 2014, Bolkan et al., 2016, Sigurdsson and Duvarci, 2015, Leonard, 2016). For example, anatomical studies have shown similar patterns of connectivity between distinct regions of PFC with the amygdala, subiculum, entorhinal and perirhinal cortices in rodents and NHPs (Ongur and Price, 2000). Single unit electrophysiology data correlating neuronal activity during decision making have demonstrated that the rat PFC shares similar functional properties with NHP anterior cingulate cortex (ACC) and dIPFC (for review, see Seamans et al., 2008). This suggests that the rat PFC contains the rudimentary elements found in NHP ACC and dIPFC needed for decision making, which later

evolved into larger dedicated regions in primates in order to encode abstract rules. Suzanne Haber presented work in which the ACC and OFC in rats and NHPs were anatomically analyzed based on their corticostriatal terminals, and it was found that the topography of the OFC was more conserved across rats and NHPs, as compared to the ACC (Heilbronner et al., 2016). Moreover, Haber presented ongoing work that dissected corticostriatal circuits further by identifying functional hubs where specific types of information are integrated (Choi et al., 2017). For example, the anterior limb of the internal capsule, which connects the striatum with the PFC, can be segmented according to the same functional parcellation (Safadi et al., 2018, Coizet et al., 2017). Such cross-species studies can help us determine which animal circuits to probe for studying specific clinical populations (e.g., using deep brain stimulation in OCD patients based on animal and human circuitry; Rodriguez-Romaguera et al., 2015). Overall, anatomical and behavioral studies of animal models of decision making can be used to develop theoretical and computational models to help us better understand decision making in the healthy versus diseased brain.

New frontiers in therapeutic interventions for maladaptive decision making

The symposium's final session on "New therapeutic approaches" included presentations by Cameron McIntyre, Michael Fox, Ben Greenberg, and Alvaro Pascual-Leone, who discussed novel therapies for persistent maladaptive decision making. Neuroscience has made significant strides toward understanding how neuropsychiatric disorders are linked to specific behavioral deficits and neural circuits (Montague et al., 2012, Lee, 2013, Huys et al., 2016). Although these efforts provide improved targets for interventions, many patients do not respond to traditional pharmacological or behavioral therapies (Fava, 2003, Castle et al., 2015, Harvey and Rosenthal, 2016). This observation has sparked considerable interest in how therapeutic benefits can be derived from brain stimulation approaches (Haber and Greenberg, 2012). Brain stimulation has a long history within psychiatry, with early practitioners passing large, seizure-

inducing electrical currents through the skull in an approach known as electroconvulsive therapy (ECT; Endler, 1988). While the use of ECT has been refined over the years (Loo et al., 2011, Pinna et al., 2016), recent work has focused on the therapeutic potential of alternative stimulation approaches. For example, deep-brain stimulation (DBS)—an invasive approach requiring surgical implantation of either unilateral or bilateral electrodes—has been used to remediate treatment-resistant symptoms associated with OCD (Goodman et al., 2010, Rodriguez-Romaguera et al., 2015) and mood disorders (Holtzheimer et al., 2012). Similar therapeutic benefits have been observed with non-invasive brain stimulation approaches such as transcranial magnetic stimulation (TMS) and transcranial current stimulation (TCS). For example, TMS applied to the dlPFC reliably improved symptoms associated with major depression (Chen et al., 2013) and when applied to the supplementary motor area, it can remediate symptoms associated with OCD, as highlighted in Ben Greenberg’s presentation. In addition, depression and other neuropsychiatric disorders can also be remediated by passing small electrical currents (0.5 to 2mA) through the skull with TCS approaches (Shiozawa et al., 2014, Tortella et al., 2015). Taken together, these observations suggest that brain stimulation can be used as a therapeutic intervention.

The promise of brain stimulation as a potential therapeutic intervention has motivated efforts to understand its effects on behavior, many of which were highlighted at the symposium. One area of particular focus has been the relationship between brain stimulation and brain connectivity (Fox et al., 2012b, Anderson et al., 2016, Dunlop et al., 2016, Wang et al., 2016). Indeed, stimulation applied to a single region propagates to other regions via structural connections, making it imperative to characterize how stimulation affects interconnected brain regions (Driver et al., 2009). Both Cameron McIntyre and Michael Fox presented evidence suggesting that the intertwined nature of brain connectivity and brain stimulation may contribute to inconsistencies in therapeutic benefits conferred by stimulation. For example, in both

depression and OCD, the efficacy of DBS depends critically on how specific white matter tracts are activated by stimulation (Riva-Posse et al., 2014, Hartmann et al., 2015), a point emphasized in Cameron McIntyre's presentation. Brain connectivity also contributes to the therapeutic effects of noninvasive brain stimulation approaches such as TMS and TCS, as detailed in Fox's presentation. For instance, the antidepressant effects of TMS depend on whether the targeted portions of the dlPFC are functionally connected to the subgenual cingulate, a popular target of DBS treatment for major depression (Fox et al., 2012a). Other recent work has extended these observations by demonstrating that effective subcortical sites for DBS are functionally connected to effective cortical sites for noninvasive approaches, which was highlighted in Pascual-Leone's presentation (Fox et al., 2014). Strikingly, this relationship was observed for a wide range of diseases—including depression, Parkinson's disease, OCD, and addiction (Fox et al., 2014). Collectively, these findings highlight how brain connectivity can be used to optimize therapeutic interventions employing brain stimulation. In addition, we believe these findings also raise the tantalizing possibility that cortical areas could be used as targets for noninvasive brain stimulation interventions seeking to remediate aberrant subcortical responses, such as blunted striatal responses to reward in major depressive disorder (Pizzagalli et al., 2009, Treadway and Zald, 2013, Whitton et al., 2015, Ng et al., 2018) and addiction (Volkow et al., 2010, Koob and Volkow, 2010, Hanlon et al., 2015, Luijten et al., 2017).

Although knowledge of brain connectivity can help optimize the beneficial effects of brain stimulation, it is important to recognize that this new frontier in therapeutic interventions still faces several key challenges. For example, the wide array of brain stimulation approaches (e.g., DBS, TMS, TCS) and the massive variability of stimulation parameters (e.g., frequency, intensity, duration, anatomical location) can make it difficult to draw meaningful conclusions across studies (Dedoncker et al., 2016). Yet, after controlling for stimulation technique and parameters, other factors can contribute to whether a stimulation protocol confers therapeutic

benefits. For instance, recent studies have shown that the efficacy of stimulation depends critically on inter-individual differences in endogenous oscillations (Frohlich, 2015) and head morphometry (Datta et al., 2012). Hesheng Liu described efforts required to overcome these challenges using careful quantification of head models (e.g., gyral folding patterns and scalp conductivity patterns) and individualized electroencephalographic signatures from each patient (Wang et al., 2015). Finally, it is important to note that the effects of brain stimulation are highly state dependent, making it necessary to investigate the effects of stimulation across diverse tasks and contexts (Silvanto et al., 2007, Dayan et al., 2013, Kar and Krekelberg, 2014). These challenges present several opportunities for future studies that aim to hone our understanding of the therapeutic effects of brain stimulation.

Conclusions and Future Directions

The symposium highlighted key advances in our understanding of the neural circuits that shape persistent maladaptive decisions. These circuits are composed of, but not limited to, the ACC, striatum, amygdala, and various regions within the PFC. In addition, evidence from a wide range of studies—including neuroimaging, single-unit recordings, and brain stimulation—indicates that responses within these regions are correlated with multiple psychopathologies. These advances underscore recent progress and supply a rich foundation for future studies.

Future work will benefit from investigating how adaptive and maladaptive behaviors are influenced by social factors. Recent work has shown that the presence of a close friend enhances responses within the vmPFC to positive social feedback (Sip et al., 2015) and also striatal responses to monetary reward (Fareri et al., 2012). Yet, the reward-enhancing effects of a friend can also be maladaptive, particularly within adolescents, who exhibit increased impulsivity (O'Brien et al., 2011) and increased risk taking (Chein et al., 2011) in the presence of peers. Overall, these observations suggest that social context could be a fruitful dimension to explore in the future.

Beyond examining the influence of social context on maladaptive decisions, future work should also capitalize on state-of-the-art technological and analytical advances. For example, recent advances in neuroimaging data acquisition and analysis (Glasser et al., 2016b) have advanced our understanding of cortical organization (Glasser et al., 2016a) and patterns of brain connectivity (Park and Friston, 2013, Smith et al., 2016). In addition, we believe that continued efforts to promote open science (McKiernan et al., 2016, Wiener et al., 2016) and collect larger sample sizes will enhance rigor and reproducibility within the neuroimaging community (Yarkoni et al., 2010, Gorgolewski and Poldrack, 2016, Poldrack et al., 2017). In addition, analytical advances within neuroimaging also have a bright future in predicting a range of individual differences that may modernize prognosis and diagnosis of persistent maladaptive behaviors (Calhoun et al., 2014, Arbabshirani et al., 2016, Calhoun and Sui, 2016, Woo et al., 2017). Previous efforts have successfully differentiated clinical groups with neural structure (Cope et al., 2014, Steele et al., 2017) and function (Aharoni et al., 2013, Arbabshirani et al., 2013, Steele et al., 2014, Steele et al., 2015, Fink et al., 2016).

The symposium at the University of Rochester reflected a consistent trend that an interdisciplinary approach is the most efficient way toward understanding persistent maladaptive behaviors. Theoretical models, combined with well-designed behavioral studies, will identify specific mechanisms that go awry in psychiatric disorders, which will then improve treatment. For example, theoretical work on latent causes in fear and extinction learning has pointed to a novel strategy for improving the efficacy of extinction-based therapy. It remains to be seen, however, whether this can translate to clinical settings. Complementarily, psychiatric research has moved toward identifying dimensions of maladaptive behaviors in psychopathologies that are often transdiagnostic. This enhances the contribution of animal research, since researchers then do not have to create all-encompassing models of a given psychiatric disorder in the lab. As the field moves forward to better map our understanding of maladaptive behaviors, many

exciting avenues of research are apparent. Translating findings between pre-clinical and clinical models is essential to generate positive outcomes in patients. Adopting the RDoC application of symptomatology would prove beneficial in mapping circuits with behavior. Knowing these circuits and how the spectrum of symptoms map onto one another would facilitate individualized medicine and effective treatments. A larger effort (e.g. large-scale collaborations) is needed to integrate the different levels of science with treatment to rapidly augment our understanding of how best to treat maladaptive behaviors. This will ultimately enable us to fully understand neural predictors for effective treatment and neural changes related to treatment. We are 18 years past the *end* of the Decade of the Brain, and it is time for researchers and clinicians to work together to develop efficacious treatments for maladaptive behaviors using all possible models and techniques available.

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