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Computational Psychiatry

Quentin Huys*
Translational Neuromodeling Unit, Institute of Biomedical Engineering, ETH and University of Zurich, and Department of Psychiatry, Psychosomatics and Psychotherapy, Hospital of Psychiatry, University of Zurich, Zurich, Switzerland

Definition

Computational psychiatry is a heterogeneous field at the intersection of computational neuroscience and psychiatry. Incorporating methods from psychiatry, psychology, neuroscience, behavioral economics, and machine learning, computational psychiatry focuses on building mathematical models of neural or cognitive phenomena relevant to psychiatric diseases. The models span a wide range – from biologically detailed models of neurons or networks to abstract models describing high-level cognitive abilities of an organism. Psychiatric diseases are conceptualized either as an extreme of normal function or as a consequence of alterations in parts of the model.

As in computational neuroscience more generally, the building of models forces key concepts to be made concrete and hidden assumptions to be made explicit. One critical function of these models in the setting of psychiatry is their ability to bridge between low-level biological and high-level cognitive features. While many neurobiological alterations are known, the exclusively atheoretical focus of standard psychiatric nosology on high-level symptoms has as yet prevented an integration of these bodies of knowledge. David Marr pointed out that models at different levels of description may be independent (Marr 1982). Nevertheless, algorithmic details may constrain functions at the computational level. The models used in computational psychiatry make these constraints explicit and thereby aim to provide normative conduits between the different levels at which neural systems are analyzed (Stephan et al. 2006; Huys et al. 2011; Hasler 2012; Montague et al. 2012). This in turn allows for a principled approach to study dysfunctions and indeed may allow the dysfunctions observed in psychiatry to inform neuroscience in general.

Practically, it underpins hopes that computational techniques may facilitate the development of a psychiatric nomenclature based on an understanding of the underlying neuroscience. Computational models enhance experimental designs by allowing more intricate neural and/or cognitive processes to be inferred from complex features of the data, often via Bayesian inference. These aspects motivate hopes that it may facilitate the development of clinical treatment and decision tools informed by advances in neuroscience.

Detailed Description

This entry describes four types of models applied to psychiatric diseases. The earliest models were connectionist (McClelland et al. 1986) or dynamical (King et al. 1984) and emphasized properties of the brain as a neural network. The second, and now most common, class is models of reinforcement learning (Montague et al. 1996; Schultz et al. 1997; Sutton and Barto 1998). The third and fourth classes emphasize explicit model-based planning or social cognitive processes, respectively.

*Email: qhuys@cantab.net

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Connectionist and Neural Network Models

Connectionist approaches model psychological functions using a neural network in which particular neurons take on specific computational roles, for instance, representing a sensory input. Key aspects of the neural networks are based on particular features derived from biology (or known to be involved in psychopathology). This allows the consequences of these features for complex computation to be probed and hence is one direct approach to examining the link between Marr's levels. In psychiatry, connectionist models have been prominently applied to schizophrenia.

Patients with schizophrenia or mania can characteristically display rapidly changing, loose associations in their speech. Early work examined how parameters governing the dynamics of associative networks might reproduce this. An increase in noise, corresponding to a decrease in the dynamic gain, led to less specific memories, mirroring a broadening of associations in schizophrenia, and less stable, constantly altering memories, possibly mirroring the pressure of speech observed in mania. Spurious memories reminiscent of hallucinations arose when overloading the network with memories beyond its capacity (Grossberg and Pepe 1970; Hoffman 1987).

Patients with schizophrenia also show impairments in cognitive flexibility and control tasks that require the inhibition of a prepotent response. Cohen et al. (1996) used a connectionist network partitioned into four modules to model this. One module represented stimuli, another other responses, and a third the prefrontal cortex. A fourth module integrated the inputs from all modules. The prefrontal cortex had a critical function in maintaining representations of task-relevant variables. When this memory function was impaired by a reduction in its gain, the network could accurately capture the impairments in performance seen in schizophrenia. As the gain was thought to depend on dopaminergic input, this work correctly predicted a prefrontal reduction of dopamine in schizophrenia. Later work further refined the role of dopamine in gating of information into the prefrontal cortex (Braver et al. 1999; Frank 2005).

Many psychiatric disorders are relapsing-remitting, with periods of well-being punctuated by times of illness. This is prominent in bipolar disorder, which can cycle rapidly between phases of depression and mania. Conversely, loss of diurnal sleep-wake rhythms is also common. These phenomena can be described by dynamical systems models of neural networks with feedback loops and delays interacting to produce oscillatory phenomena at various timescales (Mackey and Milton 1987; Milton 2010). The complexities of the local circuit, with synthesis, breakdown, and reuptake, can add substantial further complexity and facilitate the emergence of highly variable, chaotic solutions potentially relevant to multiple disorders (King et al. 1984).

Reinforcement Learning Models

Reinforcement learning (RL; Sutton and Barto 1998) describes a set of techniques aimed at choosing that action which maximizes the long-term expected reward. In terms of applications to psychiatric diseases, it is useful to differentiate between two approaches to solving this problem (Daw et al. 2005): a model-based and a model-free one. In the *model-based* approaches, the agent has a model $\mathcal{M}$ of the world that describes the consequences of actions and the desirability of the consequences. For instance, a player may know the rules of chess. The best move can then be inferred by considering all moves, their consequences, and the subsequent moves iteratively. For most problems of interest, this model-based decision procedure is computationally unachievable. *Model-free* approaches replace computation by experience, maintaining a lookup table $\mathcal{Q}(s,a)$ of the expected reward (and hence goodness) of each behavior a in situation s. This can be iteratively updated online with new experience by computing a prediction error (PE) δ which compares the obtained with the expected future reward $\mathcal{Q}(s,a)$. This expectation $\mathcal{Q}(s,a)$ can then be updated by letting $\mathcal{Q}(s,a) \leftarrow \mathcal{Q}(s,a) + \epsilon\delta$, where $0 \leq \epsilon \leq 1$ is a learning rate that determines how rapidly the

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qualities are allowed to change over time. That is, rather than inferring decisions from an understanding of the world, model-free choices are the result of repeated trial-and-error learning. This motivates the characterization of habits as model-free (Daw et al. 2005). Seminal work has shown that phasic signals by dopaminergic neurons are proportional to this PE δ (Montague et al. 1996; Schultz et al. 1997).

The application of reinforcement learning models to psychiatric diseases is motivated by a trio of facts. First, decisions are central to psychiatric disorders, and reinforcement learning techniques allow for a principled approach to decision-making. Decisions are the final common pathway preceding many aberrant behaviors, and poor decisions can have profound consequences for affected individuals. For instance, around a third of the life stress associated with major depressive disorder is due to poor decisions by individuals (Kendler et al. 1999). Second, many psychoactive substances and clinically useful medications influence neuromodulators: dopamine (antipsychotics such as haloperidol or clozapine and stimulants such as methylphenidate), serotonin (selective serotonin reuptake inhibitors, tricyclic antidepressants), noradrenaline (tricyclic antidepressants, serotonin-noradrenaline reuptake inhibitors), or acetylcholine (certain antipsychotics, cholinesterase inhibitors). Third, and unifying the first two, these same neuromodulators are central to computational models of decision-making. This is particularly clear for phasic dopamine, which appears to report a signal akin to the PE δ used for learning in model-free RL (Montague et al. 1996; Schultz et al. 1997; Sutton and Barto 1998).

Predominantly Model-Free RL Accounts of Psychiatric Diseases

The simplest application of reinforcement learning models is in examining anhedonia, a central component of *depression*. Anhedonia describes a reduced ability to experience pleasure and is usually measured by verbal reports. People who report such a lack of pleasure are less likely to choose the more rewarding stimulus in a variety of standard learning (Costello 1972; Henriques et al. 1994; Pizzagalli et al. 2005) and stimulus reactivity (Bylsma et al. 2008) tasks. Decisions in some of these tasks can be captured by simple model-free reinforcement learning. Depression interferes with this learning by reducing the PE signal δ (Steele et al. 2007; Kumar et al. 2008; Chase et al. 2010a, b; Gradin et al. 2011), leading to reduced expectations of rewards over time. The PE δ is composed of the difference between expected reward and obtained reward, and anhedonia appears to reduce the former, while alterations of tonic dopamine affect the latter (Chowdhury et al. 2013; Huys et al. 2013).

Addictive substances release dopamine either directly or indirectly and modify dopamine receptors chronically (Volkow et al. 2009). This might simply suggest that addictive substances thereby result in overly large values of the drug-taking action by adding an irreducible floor to the PE signal δ. This would result in a persistent signal for learning, increasing the value of drug-taking actions without bound (Redish 2004; Dayan 2009). Other reinforcement learning models address the transformation from hedonic to compulsive drug taking (Everitt and Robbins 2005) by emphasizing the difference between model-free and model-based reinforcement learning (Redish et al. 2008). Drugs of abuse are known to lead to a shift toward habitual behavior (Dickinson et al. 2000; Nelson and Killcross 2006), which can be captured by a shift from model-based to model-free decision-making (Daw et al. 2005). Neurobiologically, this shift might be accompanied by a progressive engraining of drug-taking actions through progressively more dorsal corticostriatal loops (Belin and Everitt 2008) and impairments of orbitofrontal function (Lucantonio et al. 2012).

Parkinson's disease is characterized by a progressive reduction of dopamine-producing cells in the midbrain and treated with dopamine precursors or agonists. Clinically, it results in a pronounced slowing (bradykinesia) and experimentally in facilitated learning of action omission compared to

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action production (no-go rather than go learning) that is normalized by dopaminergic medication. The effects of dopamine on *go and no-go* learning are accounted for by biologically detailed computational models of the basal ganglia (Frank 2005). Two critical structural aspects of the basal ganglia inform these models: (a) the presence of parallel corticobasal ganglia-thalamocortical loops for go and no-go learning and (b) the prevalence of activating D_1-type dopamine receptors on the go and inhibiting D_2-type receptors on the no-go loop (Maia and Frank 2011). Positive prediction errors are thus linked with go and negative prediction errors with no-go learning (Frank et al. 2007; Guitart-Masip et al. 2012). Such considerations are also relevant for *schizophrenia*, *Tourette's syndrome*, and *attention-deficit hyperactivity disorder* (Maia and Frank 2011). The work on Parkinson's disease is remarkable in that it has informed understanding of the function of the basal ganglia and dopamine in the healthy brain.

Finally, dopamine also plays a particular role in *schizophrenia* research because (a) the positive symptoms of psychosis respond to dopaminergic D_2 antagonists such as haloperidol (Seeman et al. 1976; Kapur et al. 2000; Laruelle et al. 2003) and because of (b) findings of increased dopamine synthesis, release, and synaptic levels in psychotic states (Heinz 2002; Kapur 2003) from the first episode onward (Egerton et al. 2013). Model-free reinforcement learning models that link phasic dopamine to prediction error signals have been instrumental in relating the dopaminergic dysfunctions to cognitive phenomena. They have provided detailed accounts of the effects of dopamine manipulations on both learning and expression of learned contingencies in preclinical animal models such as the conditioned avoidance response and latent inhibition (Smith et al. 2004, 2005, 2007; Moutoussis et al. 2008). In humans, reinforcement learning models of decision-making have been combined with fMRI to examine the correlates of putatively dopaminergic PEs. Schizophrenia patients have a reduced response to prediction errors in striatal and midbrain regions (Juckel et al. 2006; Corlett et al. 2007; Jensen et al. 2008; Murray et al. 2008) that is normalized by treatment with second-generation antipsychotic medications (Juckel et al. 2006).

Passivity phenomena are another important characteristic feature of schizophrenia, where movements or sensations are experienced as not originating from oneself. Incorrect expectations about the consequences of one's own actions may lead to the assignment of the sensory consequences of one's own actions to external sources (Gray et al. 1991; Fletcher and Frith 2009). This may arise from an impaired connectivity between areas generating the predictions and those assessing the input (Ford et al. 2007), speaking to a generalized notion of PEs that is less directly related to phasic dopaminergic prediction errors (Rao and Ballard 1999) but rather to the consequences of dopamine in modulating synaptic plasticity (Friston and Frith 1995; Stephan et al. 2006; Friston 2008; Stephan et al. 2009).

Predominantly Model-Based Accounts of Psychiatric Diseases

Higher-level cognitive aspects of psychiatric diseases are captured by reinforcement learning models in which decisions are the product of searching an explicit model of the task at hand. These have been applied to the concept of helplessness in depression, to the role of serotonin, and to delusional belief formation in schizophrenia.

In depression research, the concept of *helplessness* – a perception of lack of control – arose from animal behavior and describes animals who fail to escape from shocks after experiencing other stressors that were not under their control (Seligman and Maier 1967). Similar findings exist in humans (e.g., Miller and Seligman 1975). The simplest mathematical formulation of controllability is as a low action-outcome contingency $p(o|a)$ (Maier and Seligman 1976). More detailed accounts view controllability as relating not to individual available actions but to the average achievability of different outcomes by different choices of actions (Dayan and Huys 2009). This definition is close to

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the definition of control in control systems theory. The psychological construct whereby controllability is related to particular desirable outcomes can be captured by defining controllability as the fraction of rewards reliably achievable through appropriate action selection (Dayan and Huys 2009). These definitions of controllability can be used as prior beliefs and thereby account qualitatively for learned helplessness and chronic mild stress (Willner 1997) effects (Dayan and Huys 2009). Further refinements accounting specifically for generalization issues and for the computational costs of goal-directed decisions allow for more quantitatively detailed accounts (Lieder et al. 2013).

Serotonin plays an important role in research on depression because selective serotonin inhibitors (SSRIs) are first-line pharmacotherapeutic agents (Gelder et al. 2006) and because dietary manipulations that are thought to acutely reduce serotonin (acute tryptophan depletion) can lead to a rapid recurrence of symptoms in formerly depressed patients (Smith et al. 1997). However, animal work has related increased serotonin to behavioral inhibition, aversive expectations, and expression of helplessness (Soubrié 1986; Maier and Watkins 2005), suggesting that a reduction in serotonin should improve depressive symptoms. Reinforcement learning models have linked the inefficient avoidance of negative events due to serotonin in a model-free system with an increased exposure to more negative events. These experiences might in turn underlie more negative moods due to serotonin reductions (Dayan and Huys 2008; Boureau and Dayan 2011; Dayan 2012). Further work has characterized the interaction of this model-free behavioral inhibition with internal cognitive planning models and has suggested that serotonin might also inhibit internal thought processes. This would be instrumental in facilitating planning by pruning overly large decision trees to a computationally manageable size (Huys et al. 2012). While serotonin is also central to helplessness, this computational relationship has not yet been examined.

"Jumping to conclusions" is a phenomenon that aims to capture *delusional belief formation*. It describes a tendency for patients with *paranoid ideation* to declare a strongly held belief based on data that should not be sufficient to warrant such strong beliefs (Garety et al. 2005). However, a model-based reinforcement learning model of the standard task used to measure jumping to conclusions (the "beads-in-a-jar" task) suggested that the reason patients with schizophrenia jumped to conclusions was not due to aberrantly strong beliefs but due to taking into account their future inability to exploit further data (Moutoussis et al. 2011).

Game-Theoretical Approaches to Social Dysfunction

Psychiatric disorders have a profoundly detrimental effect on social function. Social interactions are extremely complex and therefore difficult to investigate directly. Game-theoretical approaches allow interpersonal cognition to be probed parametrically because the social communication channel is highly restricted yet functional. Economic games benefit from having been extensively examined both theoretically and experimentally in economics (Camerer 2003).

Borderline personality disorder (*BPD*), which is characterized by unstable personal relationships and inappropriate emotional responses, leads to a breakdown of cooperation in *trust tasks*. In this task, the first participant (the investor) chooses which fraction of an endowment to invest. The investment is multiplied, and the trustee chooses what fraction of the multiplied amount to return to the investor. When played over multiple rounds, both players are best off when they cooperate (i.e., when the investor invests and the trustee faithfully returns a substantial fraction). However, this cooperation is easily broken. Healthy participants maintain cooperation by repairing lost trust through signals (e.g., by investing a large fraction to signal willingness to cooperate; King-Casas et al. 2005). Patients with BPD fail to recognize social signals used to repair social bonds after temporary ruptures, potentially due to a failure of the insula to respond (King-Casas et al. 2008). *Autistic spectrum disorder* (*ASD*) on the other hand does not affect the maintenance of cooperation

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in the trust task, but the cingulate cortex does not tag "self"-responses accurately (Tomlin et al. 2006; Chiu et al. 2008). In related cooperative games (e.g., the "stag hunt" game), ASD patients have a less rich representation of the other's strategic abilities (Yoshida et al. 2008, 2010a, b). Responses of healthy volunteers to patients with a variety of psychiatric disorders in the trust task fall into distinguishable classes (Koshelev et al. 2010). This might allow the use of healthy volunteers as "biosensors" and formalizes one important aspect and use of empathy or even countertransference in psychiatric clinical practice. Formally, these tasks are partially observable Markov decision problems and can be modeled as such (Yoshida et al. 2008; Ray et al. 2009).

Limitations

Computational approaches to psychiatric disorders focus on decision-making, valuation, and cognition. While this is critical to many psychiatric disorders, immunological, endocrine, or vegetative dysfunctions are so far largely beyond these accounts.

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