Developmental Computational Psychiatry

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Abstract

Most psychiatric disorders emerge during childhood and adolescence. This is also a period that coincides with the brain undergoing substantial growth and reorganisation. However, it remains unclear how a heightened vulnerability to psychiatric disorder relates to this brain maturation. Here, we propose 'developmental computational psychiatry' as a framework for linking brain maturation to cognitive development. We argue that through modelling some of the brain's fundamental cognitive computations, and relating them to brain development, we can bridge the gap between brain and cognitive development. This in turn can lead to a richer understanding of the ontogeny of psychiatric disorders. We illustrate this perspective with examples from reinforcement learning and dopamine function. Specifically, we show how computational modelling deepens an understanding of how cognitive processes, such as reward learning, effort learning, and social learning might go awry in psychiatric disorders. Finally, we sketch the promises and limitations of a developmental computational psychiatry.

The importance of development in psychiatry

Psychiatric disorders are strongly rooted in development, with most mental health problems emerging during childhood and adolescence (Kessler et al., 2005; Paus, Keshavan, & Giedd, 2008). This holds for classic developmental psychiatric disorders, such as dyslexia or attention-deficit/hyperactivity disorder (ADHD), but also for disorders that are typically associated with adulthood, such as obsessive-compulsive disorder (OCD), depression or personality disorders. While developmental disorders are typically being diagnosed around school entry, OCD rises during early adolescence, and depression and psychosis during late teenage years (Box 1; Kessler et al., 2005). These well-described temporal patterns underpin the notion that development plays a crucial role in the emergence of psychiatric disorders. Ignoring these sensitive developmental periods for the emergence of psychiatric disorders risks a neglect of critical mechanisms that cause psychiatric disorder (Frankenhuis & Fraley, 2017).

Despite the relevance of development for psychiatry, the bulk of research is focused on adult disorders such that developmental issues are still left in the shadows. Here, we advocate that characterising developmental trajectories of psychiatric disorders is of utmost importance for understanding the core mechanisms that lead to psychiatric disorders. We start by outlining why an understanding of brain computations is likely to be pivotal for understanding typical and atypical brain development. We then highlight the importance of computational modelling for understanding cognitive development and its relation to brain maturation. We discuss this in the context of reinforcement learning and the developmental trajectory of brain dopamine function. Finally, we consider the promises and challenges of developmental computational psychiatry.

The importance of computations in developmental psychiatry

For decades, neuroscientists have investigated the functional anatomy of cognition, i.e. finding out where in the brain a process takes place. This endeavour has been incredibly successful, showing among a range of key findings that faces consistently activate the fusiform face area (Kanwisher, McDermott, & Chun, 1997), that working memory maintenance involves dorsolateral prefrontal cortex (Curtis & D'Esposito, 2003), and that parts of the medial prefrontal cortex responds to errors (Iannaccone et al., 2015). Although such approaches have widely been applied to psychiatry (e.g., Schumann et al., 2010), they only had modest success when it comes to understanding psychiatric disorders. In our view this might be related to the issue of asking the wrong question. We suggest that rather than asking *where* something is impaired in the brain we need instead to ask *how* it goes awry. In other words we need to understand the computations performed by the brain, and how these computations go wrong in order to fully understand the mechanisms that underlie psychiatric disorders.

Computations in the brain

Fundamental for understanding brain function is to determine what computations are performed in neuronal populations that support a particular cognitive process. Although cognitive constructs, such as learning, cognitive flexibility or decision making, allow us to understand behaviour at a psychological level, it is unlikely that the brain adheres to this notional taxonomy. Equally, it is unlikely that a single brain region is responsible for a construct such as cognitive flexibility. Instead it is likely that most expressions of cognition are the product of multiple distinct processes that necessitate different computations, in turn executed by separate neural populations. A disordered cognitive flexibility can thus arise from multiple distinct impairments, which may share little more than them contributing to what we call cognitive flexibility. We thus need to try to understand how neuronal populations integrate

information to compute what we conceptualise as a cognitive process. Only by parcellating the computational mechanisms underlying cognition can we truly understand which processes go awry in pathology.

A promising way to bridge the gap between neural activity and cognition builds on the idea that the brain is a sophisticated information-processing machine. How can we understand such a complex device? One approach is to exploit working principles of artificial intelligence and relate these to brain processes. The goal of artificial intelligence is to create machines capable of learning and reasoning with minimal instruction (e.g., Dayan, Hinton, Neal, & Zemel, 1995). This has enabled the creation of powerful algorithms that solve complex tasks, such as playing Chess or Go (Silver et al., 2016) without a necessity to provide detailed prior instruction. We as investigators can take a lead from the algorithms used in artificial intelligence and assess how an artificial agent might solve a task faced by human agents. The predictions from such models can then be used to analyse whether cognitive processes approximate similar principles, and if so, which neural systems support these.

Computational modelling from neurons to cognition

Computational models for understanding the workings of the brain can broadly be divided into two types of models. One class describes *what* these neural populations are computing (i.e. the algorithm), and the other explain *how* such an algorithm is implemented at a neural level (Hauser, Fiore, Moutoussis, & Dolan, 2016). We can label these classes as algorithmic and implementation models as per the nomenclature proposed by Marr (1982) (Fig. 1).

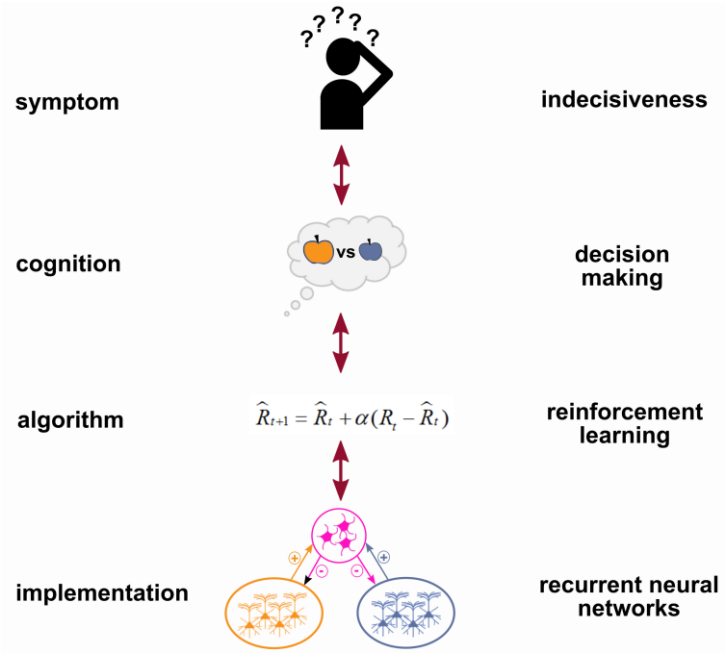


Figure 1. Understanding the neurocomputational mechanisms driving developmental psychiatric symptoms. Computational modelling in developmental psychiatry allows us to understand how the emergence of psychiatric symptoms during development is linked to atypical brain maturation. To bridge the gap between brain (e.g. disrupted dopamine signalling) and symptoms (e.g. indecisiveness or apathy), we can employ computational models. Implementation models simulate neural population activity and make predictions about how aberrant neural function might cause cognitive deficits. Alternatively, we can use algorithmic models that describe the computations underlying cognitive processes. These models allow us to parse a behaviour (e.g. decision making) into its component computations (here: reinforcement learning, detailed in Fig. 2), which allows us to relate them to neural substrates that perform these computations. By connecting brain maturation to the development of specific computational processes, we can understand how aberrant developmental trajectories might lead to psychiatric disorder.

Implementation models describe how (populations of) neurons process information and how they interact in order to solve a task. These models can capture how computations unfold in the brain (e.g., Hunt et al., 2012), but their complexity render it difficult to model more sophisticated aspects of cognition. Although these models have substantial potential for developmental computational psychiatry (e.g., Krystal et al., 2017), in the interest of brevity we focus on algorithmic models alone in the remainder of this article.

Algorithmic models come in various flavours, such as reinforcement learning (Sutton & Barto, 1998), Bayesian models (Friston et al., 2014), but also deep neural networks (Yamins et al., 2014; Zipser & Andersen, 1988). An advantage of these models is that they provide a

principled understanding of the computational mechanisms that underlie cognitive processes, and thus allow to link cognitive mechanisms to symptoms. However, linking these computational principles to their neuronal implementation is not always trivial (cf. Hauser, Fiore, et al., 2016).

It is worth noting that both types of models are 'generative' rather than 'descriptive' models. This means they make mechanistic predictions how a behaviour (or neural activity) is generated. A key advantage of generative models is that they can be used to make (probabilistic) predictions about how an agent would perform and through simulation can be assessed how well the model describes actual human behaviour (cf. Maia & Frank, 2011). In what follows, we focus on algorithmic models describing the role of dopamine in learning and we explain why these mechanisms are of interest to developmental psychiatry.

Algorithmic models: dopamine and reinforcement learning

Reinforcement learning (RL) comprises a multitude of models, which adhere to a core principle that agents seek to maximise reward over time (Sutton & Barto, 1998). RL allows an agent to learn about its environment through a process of trial and error and by so doing the agent can learn to maximise its future reward.

A key aspect of RL (Fig. 2) is the idea that the agent forms predictions about what is going to happen conditional on performing a certain action in a specific environment (state). These predictions are continuously evaluated and refined. To perform this refinement, the agent compares what happened following an action (outcome, R) with what it had predicted would happen prior to taking the action (expectation, $\bar{R}$). The difference between an experienced outcome and a predicted outcome forms a quantity referred to as a prediction error (PE). The PE indicates whether an outcome is better or worse than expected (positive or negative PE respectively), and how much the expectation deviated from the outcome (magnitude of PE).

This PE is then used to update future predictions leading to a refinement of the agent's model of the environment.

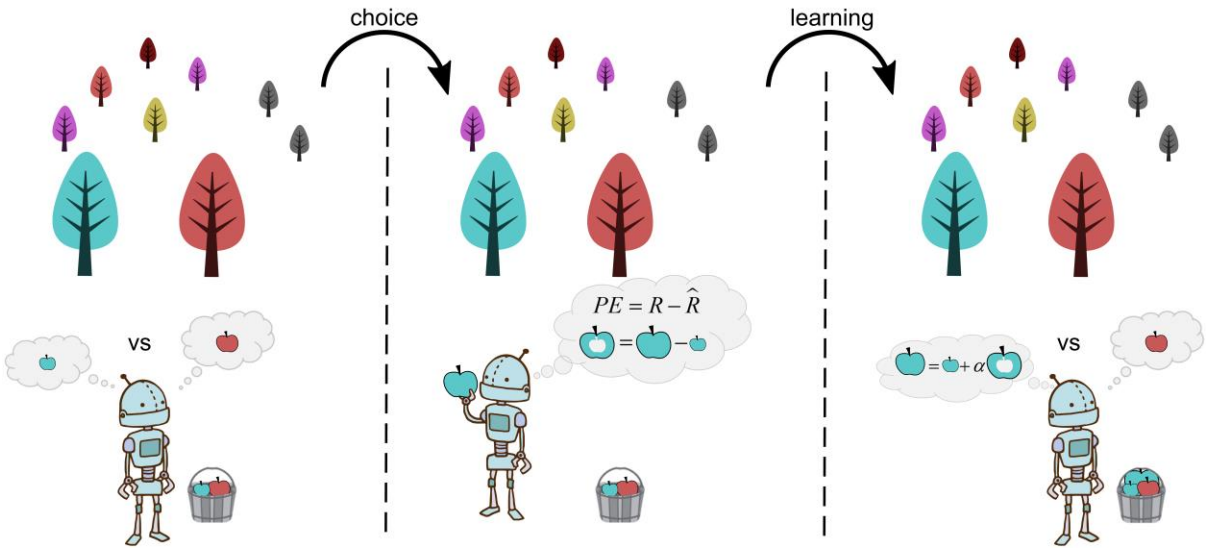


Figure 2. Understanding the neural mechanisms of reinforcement learning. One of the most successfully used algorithms for computational neuroscience is prediction error-based reinforcement learning. To make decisions that lead to a rich harvest, our robot Joko has to try to pick the best (in this case largest) apples. To decide which tree to choose from, he forms an expectation about how good each tree is, based on what he has collected so far (left panel). After he has made a choice (middle), he re-evaluates how good the tree is, based on the size of the currently harvested apple. To do this he computes a prediction error (*PE*), the difference between what he expected ($\hat{R}$) and what he actually got (*R*). Here, the apple was much larger than expected, which elicited a positive PE. For his subsequent decision (right), he updates his expectation for the blue tree using the PE. In the example, his expectation increased because he experienced a positive PE. The influence of this PE on his expectation is moderated by a learning rate α, which determines how much weight to ascribe to current over previous experiences. Through iterative interactions with the environment, PE-based learning allows Joko to converge on the most accurate belief regarding which tree produces the biggest apples (cf. Rescorla & Wagner, 1972). Some of the subfigures are used from freepik.com.

RL is a method used in artificial intelligence (Sutton & Barto, 1998), but what does the brain have to do with it? In the mid to late 1990s it was discovered that PE signals had a direct correlate in the brain, where phasic release of dopamine during reward learning accorded with predictions of so-called temporal-difference RL models (Montague, Dayan, & Sejnowski, 1996; Schultz, Dayan, & Montague, 1997). Neurons in dopaminergic midbrain (Fig. 3a), located in the substantia nigra and the ventral tegmental area, fired when an outcome was more rewarding than expected (positive PE), but decreased their firing rate when an outcome was worse than expected (negative PE).

Since then, PEs have been found not only in the dopaminergic midbrain, but also in dopamine target regions, such as the ventral striatum (O'Doherty et al., 2004; O'Doherty, Dayan, Friston, Critchley, & Dolan, 2003), which belongs to the mesolimbic dopamine pathway (Fig. 3). Activation in this area increases with a positive reward PE, i.e. if an outcome is more rewarding than anticipated, and decreases when the outcome is less rewarding (i.e. negative PE) (e.g., Rutledge, Dean, Caplin, & Glimcher, 2010; Hauser, Eldar, & Dolan, 2017; O'Doherty et al., 2003). Although human studies use methods (such as functional MRI) which cannot directly measure neurochemicals, such as dopamine, pharmacological manipulations have shown that the PE signal in humans most likely reflects phasic dopamine activity (Pessiglione, Seymour, Flandin, Dolan, & Frith, 2006), and that dopamine-boosting drugs restore blunted reward PEs seen in older adults (Chowdhury et al., 2013). In what follows, we discuss how the concept of prediction errors provides a fundamental understanding of how the brain is able to learn in various contexts.

Prediction errors beyond reward

PEs have mainly been investigated in the context of reward learning. More recently, it was discovered that PE-based learning is a more general motif for learning, and is exploited in other domains. Besides reward learning, PE signals are important for learning about pain (Seymour et al., 2004, 2005; Eldar, Hauser, Dayan, & Dolan, 2016), effort (Hauser, Eldar, et al., 2017), and social evaluation (Will, Rutledge, Moutoussis, & Dolan, 2017). Importantly, these PEs appear to be encoded in dopaminergic target regions.

The ventral striatum is a key region for the expression of PEs not only for learning about food or monetary rewards, but also about social rewards such as approval (Jones et al., 2011, 2014). Recently, we showed that such striatal PEs not only drive learning about social approval, but also the subjective value people attribute to themselves (i.e., self-esteem) based

on learning how much others value them (Fig. 3b; Will et al., 2017). We used a social evaluation task wherein subjects repeatedly reported on their self-esteem after receiving approval and disapproval feedback from strangers (Fig. 3b). We found that subjects' self-esteem was strongly influenced by PEs that capture the difference between expected and received social feedback, such that self-esteem depends both on being liked and on being liked more than expected. These social approval PEs were encoded in ventral striatum and feedback induced updates in self-esteem updates were reflected in ventromedial prefrontal cortex (vmPFC) activity. Together, these results show that learning how much others value us, and updating of self-esteem, rely on mechanisms akin to those used in non-social reward learning at both an algorithmic (i.e., prediction error driven) and neural (i.e., shared neural circuitry) level.

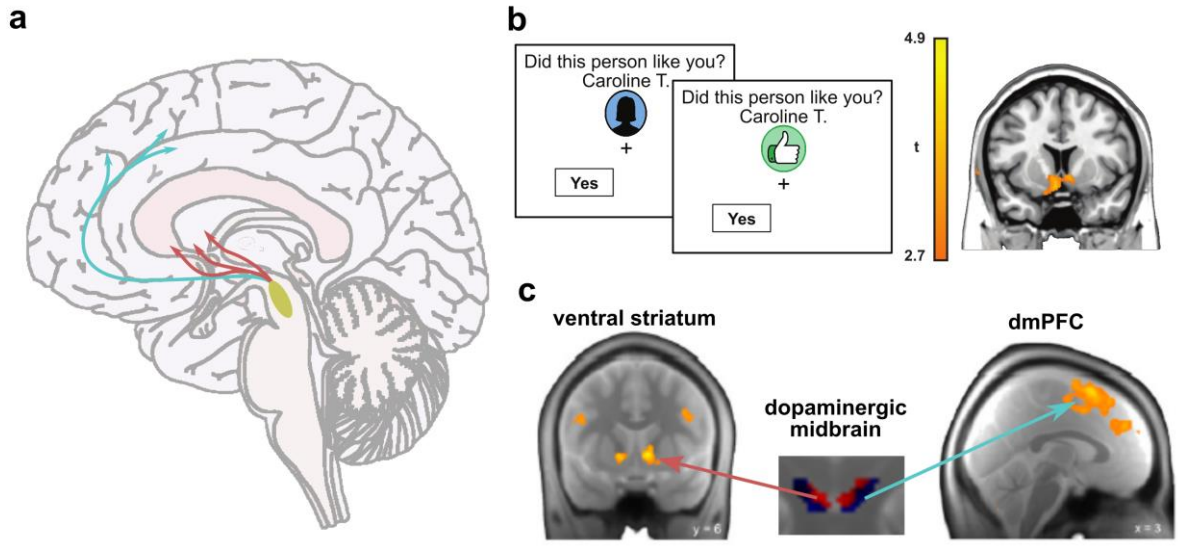


Figure 3. Dopamine pathways in learning. **(a)** The majority of dopamine neurons are located in dopaminergic midbrain nuclei of ventral tegmental area and the substantia nigra (yellow). Dopamine is then released through several ascending projections. The two main pathways are mesolimbic projections (red) and mesocortical projections (blue). The mesolimbic projections target areas such as the ventral striatum and mature in early adolescence. The mesocortical pathway targets areas of the prefrontal cortex, such as dorsomedial prefrontal cortex (dmPFC), and does not mature until late adolescence. **(b)** Using a computational model inspired by models of value-based decision-making, we showed that the ventral striatum responds to prediction errors that represent the difference between a received and expected social reward in the form of social approval. People used such social approval prediction errors to learn how much others value them and to update the value they attribute to the self, i.e., their self-esteem. **(c)** Mesolimbic and mesocortical pathways have different functions in learning.

While the former is critical for learning about rewards, the latter is implicated in processes such as effort learning. Both learning signals are simultaneously encoded in the dopaminergic midbrain (middle), but show a spatial segregation, where reward PEs are primarily encoded in dorsomedial areas (red) and effort PEs in ventrolateral areas of the midbrain. The distinct developmental trajectories of these pathways (Box 1) pose critical questions about the development of the functions they subserve and how they are related to the emergence of psychiatric symptoms, such as apathy. Figures in panel (b) are in part taken from Will et al. (2017) and (c) from Hauser et al. (2017).

The dopamine system not only consists mesolimbic pathways that project to ventral striatum, but also a mesocortical pathway that projects to several prefrontal regions, including dorsomedial prefrontal cortex (dmPFC; Paus, 2001). Given that dmPFC has been found to encode effort associated with a choice option (Croxson, Walton, O'Reilly, Behrens, & Rushworth, 2009; Kurniawan, Guitart-Masip, Dayan, & Dolan, 2013; Walton, Bannerman, Alterescu, & Rushworth, 2003), we speculated that it may also encode an effort PE signal. To formally test this we tasked subjects to learn about the reward and effort associated with a stimulus (Hauser, Eldar, et al., 2017). Subjects had to simultaneously learn both features in order to make good decisions. We found that subjects used PE-like learning mechanisms during reward and effort learning. Using functional MRI, we also found that both types of PEs were encoded in the dopaminergic midbrain (Fig. 3c). However, these PEs seemed to be processed along different pathways, with reward PEs expressed in ventral striatum and effort PEs expressed in dmPFC. Moreover, we found that the encoding of these PEs in the latter region was related to subjects' apathy, a trait characterised by a loss of motivation to exert effort for rewarding outcomes (Marin, 1991).

Computations beyond prediction errors

Besides simple PE-based learning, other RL-related mechanisms have been discovered in the brain during more complex tasks. For example, when an unobservable model of task structure is guiding behaviour, in alignment with 'model-based' planning (Daw, Gershman, Seymour, Dayan, & Dolan, 2011; Keramati, Smittenaar, Dolan, & Dayan, 2016; Wunderlich,

Smittenaar, & Dolan, 2012). Moreover, evidence for forward and backward planning in both spatial and non-spatial tasks suggests that the brain might solve complex, hierarchical planning by exploiting core RL principles (Johnson & Redish, 2007; Kurth-Nelson, Economides, Dolan, & Dayan, 2016; Wunderlich, Dayan, & Dolan, 2012). These more complex computations are still very much subject to ongoing investigations to the extent that there is current discussion about the computational framework within which PE and dopamine should be considered in general (Friston et al., 2014; Gershman & Schoenbaum, 2017; Wang et al., 2018) and the role of other neurotransmitters in computing such signals (e.g. Iglesias et al., 2013). A close exchange between basic cognitive neuroscience and developmental psychiatry is thus critical.

Importantly, if we want to understand why these computations may change with development, and how this could be relevant for the emergence of psychiatric disorder, we need to understand how neural systems that support these computations, such as dopamine, develop and mature.

From brain anatomy to cognition: tracing developmental trajectories

The brain undergoes fundamental structural change throughout childhood and adolescence, and the developmental trajectories extend into the third and fourth decades of life (Foulkes & Blakemore, 2018; Giedd et al., 1999, 2015). After an initial increase in gray matter size there is then a relative decrease during adolescence (cf Box 1; Paus, 2010). This decline is thought to be driven by a pruning of cortical connections, meaning that neural connections become more selective, possibly supporting a more efficient information-processing capability. In white matter, there is a monotonic increase throughout development, probably driven by axonal myelination (Ziegler et al., 2018). Myelination provides insulation for connections between neural populations (Virchow, 1854) and supports fast and reliable information transmission.

Importantly, this structural development is not homogeneous across the entire brain, but rather has specific trajectories in different regions (Gogtay et al., 2004). While primary sensory and motor areas show early maturation, higher cognitive areas of the prefrontal cortex are among the last to fully develop. These distinct developmental trajectories are likely to drive – at least in part – the maturation of distinct computational mechanisms. It is thus of little surprise that motor skills ripen prior to complex reasoning skills.

Dopamine development

Although we have a good understanding of how cortical regions mature, we know much less about developmental trajectories of neurotransmitter function, such as dopamine. Given the importance of dopamine in signalling PEs, its role in reinforcement learning, and its supposed involvement in many development-related psychiatric disorders (e.g., Denys, Zohar, & Westenberg, 2004; Hauser et al., 2014; Hauser, Iannaccone, et al., 2017; Tripp & Wickens, 2012), it is critical to understand its ontogeny. A key challenge in tracing dopamine development is that neural populations that release dopamine – and neurotransmitters in general – are located in small structures in the midbrain. These areas present a challenge for traditional neuroimaging methods (Hämmerer et al., 2018) as they are among the most susceptible to movement and other development-related artefacts (Kasper et al., 2017). A second challenge is that structural integrity of these brainstem nuclei carries little information about the maturity of a system as a whole. The effectiveness of a neurotransmitter system depends on multiple factors, such as the pattern of its branching projections and the configuration of receptors in its target regions.

To obtain a proxy for dopamine development in humans, scientists have turned to its development in rodents (cf. Ernst & Luciana, 2015). Research here has focused on the development of three aspects of the dopamine system: Development of dopamine neurons,

growth of dopamine projections, and density of dopamine receptors (Box 1). Dopamine neurons emerge relatively early in brain development. At 6-8 weeks after conception, the foetal human brain possesses functioning dopamine neurons (Sundström et al., 1993). With dopamine neurons in place at birth, the system still needs at least another two decades to fully mature. For dopamine to be effective, dopamine-sensitive receptors must be available at target sites. The availability of dopamine receptors, such as D1- and D2-receptors, differs substantially between brain regions as a function of maturation stage. In the ventral parts of striatum, dopamine receptor density increases during childhood and peaks around onset of puberty (Caballero, Granberg, & Tseng, 2016). During adolescence, receptor density in the striatum shrinks again with an overall loss of approximately 25% of its receptor population (Caballero et al., 2016).

Dopamine receptors in prefrontal cortex show a later maturation than in the striatum. Prefrontal receptor expression does not peak until late adolescence, and then continues to prune well into adulthood (Naneix, Marchand, Di Scala, Pape, & Coutureau, 2012). These findings highlight that dopamine in limbic areas including ventral striatum have a different developmental trajectory compared to prefrontal cortex. The distinction between striatal and prefrontal dopamine development is particularly pronounced when investigating the maturation of dopamine projections. Dopamine projections to the striatum develop during childhood, suggesting that most of the mesolimbic pathway is in place in early adolescence (Coyle & Campochiaro, 1976). The mesocortical pathway, however, shows protracted development. Most dopamine projections only reach prefrontal cortex during late adolescence, a process that continues into adulthood (Caballero et al., 2016; Naneix et al., 2012). Some of the projections are connections that originally terminated in the striatum and that during adolescence expand into prefrontal areas, leading to a relative decrease of mesolimbic connections (Reynolds et al., 2018). This makes mesocortical projections the only known long-

range connections in the brain that continue their growth throughout adolescence (Hoops & Flores, 2017). Interestingly, dopamine maturation is also mirrored in structural maturation of the target brain regions, where striatum appears to mature before prefrontal cortex (Giedd et al., 2015).

A caveat to the above concerns extrapolating these dopamine findings to humans. Development is much faster in rodents than in humans (weeks vs. decades), while the mature rodent brain is less complex than the human brain, especially in prefrontal cortex. It thus remains challenging to fully understand dopamine development in humans (cf. Box 2).

Computational mechanisms in development and psychiatry

So far, we have discussed why computational modelling is important for understanding how the brain processes information. Moreover, we have seen that the anatomical bases on which these computations build upon change fundamentally, often continuing into adulthood. In what follows, we will highlight why it is critical to bring these two perspectives together to understand how psychiatric disorders might emerge from atypical brain development.

Development of computational abilities

Despite the importance of computational mechanisms in development, there is surprisingly little, and in addition purely cross-sectional, research on how these mechanisms change with age. Decision making and learning are relatively complex cognitive processes and it is reasonable to assume these processes have protracted developmental trajectories (Palminteri, Kilford, Coricelli, & Blakemore, 2016).

A small number of studies have investigated the development of PE-based learning in the context of reward processing. Using a reward learning task in children, adolescents and

adults, Cohen et al. (2010) investigated how reward PEs differ in various phases of development. Interestingly, the authors found a quadratic relationship between age and PE encoding activity in the striatum. This means that adolescents showed the strongest responses for positive reward PEs, stronger than both children and adults (Cohen et al., 2010). This striatal hyper-responsiveness could be modulated by activity in the network wherein it is embedded, such as the connectivity between striatum and vmPFC which appears to strengthen with age (van den Bos, Cohen, Kahnt, & Crone, 2012). This suggests that striatal hyper-responsivity is downregulated in adulthood via prefrontal control, in line with the general notion that prefrontal cortex acts to balance a mesolimbic dopamine system (Galvan, 2010). Adolescent hypersensitivity not only relates to rewarding stimuli, but also to losses, where enhanced PEs in the insula are associated with increased learning for these stimuli (Hauser, Iannaccone, Walitza, Brandeis, & Brem, 2015; also cf. Davidow, Foerde, Galván, & Shohamy, 2016). Next to nothing is known about the development of other forms of PE learning, such as learning about social evaluation or effort. We highlight below why it is essential to characterise the development of these PEs (longitudinally) to understand how psychiatric symptoms emerge.

For more complex aspects of decision making, such as model-based reasoning, some first developmental studies have started to surface (Hartley & Somerville, 2015; van den Bos, Bruckner, Nassar, Mata, & Eppinger, 2017). An important aspect of reinforcement learning algorithms is knowing that one's environment has hidden, unobservable connections and inferring these is at the core of 'model-based' reasoning. Studies of model-based decision making indicate this form of reasoning only comes online during adolescence, and does not reach full maturity until early adulthood (Decker, Otto, Daw, & Hartley, 2016; Potter, Bryce, & Hartley, 2017).

Another challenging decision making process is to arbitrate between choice options, especially if one has to arbitrate between exploring a novel option and exploiting a well-known

option. Humans solve this exploration-exploitation trade-off using different strategies, such information-directed or random exploration (Gershman, 2018; Kidd & Hayden, 2015; Wilson, Geana, White, Ludvig, & Cohen, 2014). These exploration strategies show distinct developmental patterns, with younger children using simpler, random exploration while adolescents start using complex information-directed exploration (Somerville et al., 2017).

These findings underline that the development of neuro-computational mechanisms is not a unitary process, but rather the result of multiple developmental trajectories that are at work (cf. Box 1). These trajectories are hypothesised to determine how decisions are made at each specific developmental stage. In order to fully understand how these different computational strategies emerge, we need more sophisticated longitudinal investigations of decision making and relate these to structural and functional brain development.

Computational deficits in psychiatric disorders

Decision making and learning deficits are common across psychiatric disorders (Montague, Dolan, Friston, & Dayan, 2012). A putative dopamine deficit in several disorders has led to a growing literature on aberrant RL-related computations in psychiatry. However, almost no studies have investigated how psychiatric disorders are related to developmental aspects of these deficits. Here, we briefly summarise some key results that are related to PE processing and reinforcement learning to subsequently sketch out how a developmental perspective can change the way we understand how these impairments arise.

Impaired reward PE learning has been observed in a number of psychiatric disorders. These include psychosis (Gradin et al., 2011; Murray et al., 2007), alcohol abuse (Reiter et al., 2016), OCD (Hauser, Iannaccone, et al., 2017; Hauser, Eldar, & Dolan, 2016), ADHD (Hauser et al., 2014), and depression (Gradin et al., 2011; Kumar et al., 2008; though see Rutledge et al., 2017 for contrary findings). However, a relative heterogeneity of where in the brain these

impairments were found renders it difficult to understand whether impaired PE-learning forms a general, transdiagnostic feature of psychopathology, or whether there are distinct impairments in specific disorders. Unified approaches and comparable settings across disorders would therefore be desirable.

The development of such deficits has hardly been studied. In a study of ADHD patients, PE impairments seem to be present already during adolescence, and these deficient learning signals render patients to manifest more exploratory decision making using random exploration (Hauser et al., 2014). Based on knowledge that different forms of exploration have distinct developmental trajectories (Somerville et al., 2017) a critical question arises as to when during development these impairments emerge, and whether ADHD patients show distinct developmental trajectories in their exploration strategies compared to typically developing children. This would allow to trace when the developmental trajectories of exploration and PE learning deviate from normal development and how such impaired maturation drives ADHD symptoms.

While PEs involved in reward learning exemplify a relatively basic computation with an early development, it is likely that other computational aspects of decision making lead to deficits only at a later stage. For example, OCD has been associated with deficits in model-based reasoning in the reward domain (Gillan et al., 2011, 2015; Gillan, Kosinski, Whelan, Phelps, & Daw, 2016; Voon et al., 2015). Knowing this model-based reasoning does not fully develop until adolescence (Decker et al., 2016) renders critical the question as to when this deficit emerges in OCD patients.

The importance of a developmental computational psychiatry

So far we have highlighted several contexts where mechanistic understanding of aberrant developmental trajectories could provide insight into psychiatric disorders (cf. Box 3). However, we also believe that developmental computational psychiatry is likely to be even more fundamental for some psychiatric deficits, where aberrant developmental trajectories are likely to be the driving causative factor. We highlight this in two examples, apathy and self-esteem.

Apathy as aberrant maturational separation of dopamine pathways?

Apathy is characterised by a lack of motivation and an inability to expend effort to realise goal-directed actions (Chong, 2018; Marin, 1991). It is a transdiagnostic feature present in several neurological and psychiatric disorders (Pessiglione, Vinckier, Bouret, Daunizeau, & Le Bouc, 2017) and may arise from a similarly impaired mechanism in all these disorders (Chong, 2018). We also know that many apathy-related disorders, such as depression or schizophrenia, emerge during adolescence (Kessler et al., 2005; Paus et al., 2008) and that reinforcement learning is already altered in youth at risk for psychosis (Waltz et al., 2015). As a fundamental component of negative symptoms, apathy is a key determinant of long-term disability in schizophrenia (Green, Horan, Barch, & Gold, 2015). Recent computational theories have characterised apathy as an imbalanced trade-off between reward and effort (Chong, 2018; Green et al., 2015; Pessiglione et al., 2017). An inflated representation of effort or a diminished expectation of reward can lead to a belief that an action is not worth carrying out, which in turn leads to apathetic behaviour. We recently showed that apathy is related to how subjects learn about the effort and reward associated with a stimulus. More specifically, we showed that effort and reward PEs overlap in dmPFC to a greater degree in non-clinical adults with increased apathy (Hauser, Eldar, et al., 2017). This suggests that the mesolimbic

and the mesocortical pathways might be less well differentiated in such subjects and this overlap might bias the reward and effort representations.

As seen above, mesocortical projections are among the last brain pathways to mature (Hoops & Flores, 2017). Only during adolescence do these projections extend from ventral striatum to prefrontal target areas. This suggests that a spatial separation of effort and reward PEs as seen in adults might not be present before the mesocortical pathway is fully matured. This also hints that apathy (as part of a disorder or as an independent symptom) might arise if mesocortical growth and signalling goes awry during adolescence, where for example projections meant to target striatum extend into prefrontal areas. Such aberrant growth during adolescence might lead to a failure of segregation of learning signals and lead to an imbalance between striatal and prefrontal dopamine (Elert, 2014).

To test this hypothesis, we need to employ a fully developmental computational psychiatric approach, where we trace learning of reward and effort in a longitudinal fashion using computational neuroimaging. Having characterised a canonical developmental trajectory, we should then assess development in individuals at risk for apathy and ask whether a misguided unfolding in dopaminergic pathways leads to symptoms such as apathy. Although such endeavours are complex and resource-intense, without a developmental perspective such putative maladaptive developmental patterns will remain undetected.

Self-esteem instability as vulnerability for adolescent-onset psychiatric disorders

Low or fragile self-esteem is present in almost every psychiatric disorder. It is a core characteristic of depression (Orth & Robins, 2013), anxiety (Sowislo & Orth, 2013), and eating disorders (O'Dea & Abraham, 2000), all conditions that commonly have their onset in

adolescence (Kessler et al., 2005). Adolescence is also the period where we are particularly sensitive to what peers think of us and it is a period when we are more likely to internalize social rejection in our self-view (Rodman, Powers, & Somerville, 2017). This greater propensity to internalize rejection may be a key driver for the elevated risk of developing mood or anxiety disorders during adolescence (Davey, Yücel, & Allen, 2008; Sowislo & Orth, 2013). However, the precise mechanisms that underlie this vulnerability remain to be investigated.

A good example of how computational psychiatry may help us uncover such mechanisms is our study where we showed that healthy adults use social PEs to update their self-esteem based on how much others value them (Will et al., 2017). Crucially, adults who give more weight to social PEs when updating their self-esteem report more mental health symptoms than those who give less weight to social PEs. Individual variation in such vulnerability to mental health problems was associated with distinct neural processing of social PEs and self-esteem updates. Together, these findings provide mechanistic insight into how social feedback is internalized into self-views at both an algorithmic and neural level, which cannot be observed from subjective reports or behaviour alone.

Given that PEs during non-social learning seem overexpressed during adolescence (Cohen et al., 2010; Hauser et al., 2015), we hypothesize that a similar overexpression in social PEs may drive adolescents' greater propensity to internalize rejection. As such an increased tendency to give more weight to social PEs when updating self-evaluative beliefs may represent a mechanistic explanation for adolescence as a period of increased vulnerability to depression when faced with repeated social rejection.

Such insights not only inform our understanding of how psychiatric disorders arise, but can also inform treatment. Depressed adults with unstable self-esteem are more responsive to certain treatments than those with a stable low self-esteem (Roberts, Shapiro, & Gamble, 1999). However, self-esteem instability may stem from a range of different sources, including greater

sensitivity to social feedback. A computational modelling approach allows for a neurobiologically plausible parameterization of such vulnerabilities (e.g., greater self-esteem instability as a result of giving more weight to social PEs when updating self-esteem). By phenotyping individuals along such newly defined computational dimensions, this type of approach could help identify subgroups of depressed adolescents with unstable self-esteem who might benefit more from therapies targeting self-esteem reactivity than patients whose self-esteem is less open to change.

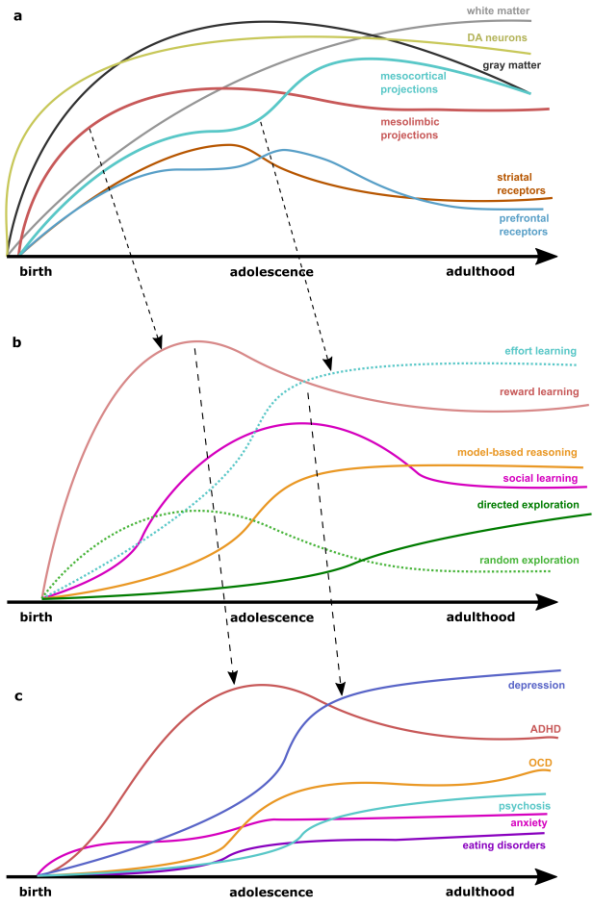
Multiple disorders that first emerge in adolescence (e.g. depression, anxiety disorders, eating disorders) share similar vulnerability, including declines in self-esteem preceded by adversity in the interpersonal domain (e.g. peer rejection, romantic breakup) (Allen & Badcock, 2003; Davey, Yücel, & Allen, 2008; Sowislo & Orth, 2013). A computational psychiatry approach has the potential to uncover whether the onset of these different disorders during adolescence stems from similar or distinct mechanisms, with important ramifications for treatment. Computational models can also aid in determining how existing treatments (e.g. cognitive behavioural therapies or drugs) impact on psychosocial functioning through quantifying how they modulate parameters in our models (e.g. decreases in self-esteem instability through a decrease in weight given to social PEs). Such endeavours have the potential to provide mechanistic insights into the efficacy of treatments that exceed the limits of purely descriptive observations of self-esteem instability.

Conclusions

In this article, we advocate a consilience between the fields of computational psychiatry and developmental neuroscience to establish a field of developmental computational psychiatry. We highlight why such a computationally inspired framework is likely to be critical

for understanding how the brain processes information, and how this might go awry during sensitive periods in development. We illustrate how computational mechanisms are likely to follow specific developmental pathways, because the anatomical substrates upon which they are grounded continue to develop throughout the second and early third decade of life. We highlight the potential insights that a developmental perspective on computational psychiatry can provide and how key questions related to psychopathology are only addressable by employing a developmental perspective. We believe that developmental computational psychiatry can allow us to begin to unravel why so many psychiatric disorders emerge during this period of development.

Box 1: Trajectories in cognition, brain and psychiatry



A key challenge in developmental computational psychiatry is to determine how developmental trajectories across multiple systems interact. We need to understand how the development of a neurotransmitter system influences the emergence of a specific cognitive skill, and how an impaired unfolding of this trajectory might promote the emergence of a psychiatric disorder (even decades later in life). A striking feature of brain development **(a)** is a heterogeneity in developmental trajectories. Although many prefrontal brain areas follow a general pattern of gray and white matter maturation, there is considerable variability both between areas and between individuals. Even within a single neuromodulatory system, such as the dopaminergic system, there are likely to be strikingly different trajectories. For example, dopamine receptors in ventral striatum increase in number mainly during childhood, while cortical receptors show a much later maturation (cf. main text). **(b)** Cognitive functions also show a relative heterogeneity in terms of development. Interestingly, these cognitive trajectories parallel the developmental trajectories of the brain systems with which they are associated (e.g. mesolimbic connections and reward learning). **(c)** To establish a link between brain, computation and the emergence of psychiatric disorders we need to establish normative developmental trajectories and assess when and how they deviate in psychiatric patients. It is thereby critical to note that these trajectories themselves are likely to be highly malleable, so that events taking place in a

child's environment can alter a developmental trajectory. A prime example is early life stress and adverse childhood experiences (Sheridan & McLaughlin, 2014), where such experiences can have a profound impact on brain structure, function and reward learning (Dennison et al., 2017; Hanson et al., 2017; Kamkar, Lewis, van den Bos, & Morton, 2017; Will, Crone, van Lier, & Güroğlu, 2016; Will, van Lier, Crone, & Güroğlu, 2016). A further challenge is that developmental trajectories are unlikely to obey chronological age, but instead are influenced by factors known to modulate brain maturation, such as puberty (Blakemore, Burnett, & Dahl, 2010; Giedd et al., 2006; Herting et al., 2014, 2017), where hormones impact on behaviour and brain development (Peper & Dahl, 2013), with known effects of testosterone on reward and social status processing (Cardoos et al., 2017). All trajectories in this Figure are speculative illustrations with dashed lines indicating trajectories that are based little or no empirical data.

Box 2: Challenges for Developmental Computational Psychiatry

Developmental computational psychiatry faces several challenges, some of which fundamentally limit our abilities to generate novel insight. Here, we provide an incomplete list of what we consider key challenges:

- Understanding the development of neurotransmitters (e.g. dopamine). Understanding this in humans is inherently limited because imaging techniques, such as positron-emission-tomography (PET) are not practical for developmental neuroimaging.
- Sensitive tasks for development. A key to understanding the development of computational mechanisms is to use tasks that measure computations reliably and objectively, and at the same time are viable for research with younger children. To date, most computational tasks have not been systematically evaluated in terms of reliability and other key psychometric criteria, as well as in terms of their sensitivity to computational modelling.
- Longitudinal developmental studies of computational tasks are sparse. We need to rigorously examine how computational mechanisms develop, and overcome limitations in tasks, such as accounting for practice effects, the limitations to use deception in social tasks, or the low reliability of some computational tasks.
- For understanding a cognitive process, we need to have adequate computational models that describe the computations that are carried out by the brain. To overcome these challenges, the field needs a close collaboration between experts in computational modelling, computational neuroscience, developmental scientists and experts in psychiatry.
- The understanding of a neurocognitive process is limited by the quality of the computational model that was used. If we our model is insufficient because (i) it captures the data only partially, (ii) it is not generalizable to other tasks/data, (iii) it is too complex

(i.e. overfitting), then insight will be limited. Additional practical challenges, such as uncertainty about the model parameters, accounting for decision noise, or how to define a model space need careful consideration. A detailed discussion of the challenges in computational psychiatry and computational modelling in general can be found elsewhere (e.g., Dayan, Dolan, Friston, & Montague, 2015; Nassar & Frank, 2016; van den Bos et al., 2017).

Box 3: What can we learn from Developmental Computational Psychiatry?

We should hail scientific endeavours (and most other endeavours too) based on their outcomes, not their promises. Nevertheless it is of importance to sketch out what developmental computational psychiatry can offer to improve patients' lives.

Psychiatric disorders are enigmatic and psychiatry as a field lags behind many areas of medicine in terms of mechanistic understanding. A key aim of developmental computational psychiatry is to address the neurobiological mechanisms that underlie psychiatric disorders, particularly with respect to how deficits arise during childhood and adolescence. The reality is that we are still operating with purely descriptive classifications, with only limited biological validity. More challenging is the likelihood that a single diagnosis lumps together several neurobiological disorders that may be entirely distinct in their pathomechanisms (Stephan et al., 2016). A computational perspective could help tease apart different underlying neurobiological disorders. In addition, a developmental perspective can help address when in development an impairment arises, and how external influences such as adverse events, chronic stress or poor parenting lead to a derailing of neurocognitive developmental trajectories. We suggest developmental computational psychiatry offers a unique toolset to unravel mechanisms that underlie interactions between these complex features of a person's biography, environment and brain development.

Understanding the developmental mechanisms also holds promises for intervention. If we are able to align diagnosis better with a neurobiological deficit, then we can use interventions that directly target that specific deficit, for example modulating a specific component of the dopamine system. Finding new mechanisms might even lead to the development of novel treatments that target these causative mechanisms.

Establishing new markers does not have to involve expensive neuroimaging, an unrealistic avenue at a time where budgets of health care services are overstretched. A more

promising avenue is to develop tasks and computational models that act as a proxy for detecting aberrant brain functioning. Neuroimaging thereby would only come into play when investigating these aberrant mechanisms and to evaluate the potential of such behavioural markers, rather than being necessary for actual clinical diagnoses. Developmental computational psychiatry by identifying computational principles arising from task analysis has the potential to improve pharmacological interventions, but equally interventions that target psychological processes (cf. Moutoussis, Shahar, Hauser, & Dolan, 2017).

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