

A Dimensional Approach to Modeling Symptoms of Neuropsychiatric Disorders in the Marmoset Monkey

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ABSTRACT: Some patients suffering from the same neuropsychiatric disorder may have no overlapping symptoms whilst others may share symptoms common to other distinct disorders. Therefore, the Research Domain Criteria initiative recognises the need for better characterisation of the individual symptoms on which to focus symptom-based treatment strategies. Many of the disorders involve dysfunction within the prefrontal cortex (PFC) and so the marmoset, due to their highly developed PFC and small size, is an ideal species for studying the neurobiological basis of the behavioural dimensions that underlie these symptoms. Here we focus on a battery of tests that address dysfunction spanning the cognitive (cognitive inflexibility and working memory), negative valence (fear generalisation and negative bias) and positive valence (anhedonia) systems pertinent for understanding disorders such as ADHD, Schizophrenia, Anxiety, Depression and OCD. Parsing the separable prefrontal and striatal circuits and identifying the selective neurochemical modulation (serotonin vs dopamine)

that underlie cognitive dysfunction have revealed counterparts in the clinical domain. Aspects of the negative valence system have been explored both at individual- (trait anxiety and genetic variation in serotonin transporter) and circuit-based levels enabling the understanding of generalisation processes, negative biases and differential responsiveness to SSRIs. Within the positive valence system, the combination of cardiovascular and behavioural measures provides a framework for understanding motivational, anticipatory and consummatory aspects of anhedonia and their neurobiological mechanisms. Together, the direct comparison of experimental findings in marmosets with clinical studies is proving an excellent translational model to address the behavioural dimensions and neurobiology of neuropsychiatric symptoms. © 2016 The Authors. *Developmental Neurobiology* Published by Wiley Periodicals, Inc. *Develop Neurobiol* 77: 328–353, 2016

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INTRODUCTION

One in five people will suffer from a neuropsychiatric disorder at some point in their life (Kessler et al., 2009), yet the prognosis for successful treatment is still only about 40%. Currently, a handful of pharmacological and psychological therapies are used to

treat multiple psychiatric disorders, with the former mostly targeting the widespread monoamine systems in the forebrain (Arroll et al., 2005; Miyamoto et al., 2005). Why is this? First, disorders such as depression and schizophrenia are broadly defined and two individuals may be diagnosed with the same disorder but have no overlapping symptoms, making it unlikely that they will be treated successfully by the same therapeutic strategy. Second, patients diagnosed with different psychiatric disorders may share the same symptom, which could explain why specific pharmacological therapies can be used successfully across multiple disorders. For example, selective serotonin reuptake blockers can be effective in treating patients with general anxiety disorder and depression (Reinhold et al., 2011; Gorman et al., 2014), probably because they target a shared symptom, such as enhanced negative emotion or negative bias. Third, the clinical symptoms are often poorly characterized so two patients may exhibit similar symptoms that actually have different underlying psychological and neurobiological causes. For instance, anxiety may be the result of poor learning of predictive cues signaling negative consequences, causing uncertainty, a known contributor to anxious behavior. Alternatively, impaired attentional flexibility may promote anxiety by making it more likely that subjects stay focused on salient negative stimuli, unable to switch their attention toward more positive events in the environment (Clarke et al., 2015; Shiba et al., 2016). Fourth, even when treatments are successful there is poor understanding of the underlying psychological and neurobiological mechanisms, making it difficult to match specific treatments to specific symptoms in individual patients.

For all these reasons there is growing emphasis in clinical and preclinical studies of therapeutic strategies to target common symptoms regardless of the disorder with which they are associated. Moreover, improved characterization of these symptoms requires a fundamental understanding of the psychological and neurobiological mechanisms that cause them, as recognized by the Research Domain Criteria [RDdoc; National Institute of Mental Health, (Insel et al., 2010)]. Although imaging studies of patients suffering from neuropsychiatric disorders have revealed much, both in terms of the neural circuits that appear dysregulated in untreated patients and reversal of this dysregulation following successful treatment, it cannot be ascertained whether this dysregulation is causal or compensatory. Vital for achieving this understanding is animal-based research, in which experimental manipulations can

establish causal relationships and identify the complex interactions between, and within, neural circuits that underlie adaptive and maladaptive behavior. Such research can also identify the neural circuits upon which current therapies act in order to optimize therapeutic targets, eliminate undesirable side effects, and identify new therapeutic targets.

A key brain structure showing altered activity across the range of neuropsychiatric disorders is the prefrontal cortex (PFC) (Strakowski et al., 2005; Shin et al., 2006; Etkin and Wager, 2007; Milad and Rauch, 2007; Koenigs and Grafman, 2009), a multimodal cortical association region with the most extensive reciprocal connections with the rest of the forebrain of all cortical regions (Carmichael and Price, 1996; Ongur and Price, 2000; Petrides and Pandya, 2002; Petrides, 2005; Petrides and Pandya, 2007; Petrides et al., 2012; Yeterian et al., 2012). It is also the only neocortical region that has regulatory control over the brainstem and forebrain chemically specific arousal pathways (Arnsten and Goldman-Rakic, 1984) which, along with its direct reciprocal connections, gives this region a pervasive influence on perceptual, motoric, attentional, mnemonic, language and emotional systems of the forebrain, both directly and indirectly. Its anatomical and functional organization is relatively preserved across primate species (Ongur and Price, 2000; Burman et al., 2006; Burman and Rosa, 2009; Petrides et al., 2012) making Old World and New World, non-human primates particularly valuable for translational studies of the prefrontal circuits that underlie the regulation of behavior.

The marmoset, a New World monkey, is ideal for studying the effects of interventions within prefrontal circuits, including their modulation by the monoamine systems. Their brains are relatively small, compared with the much larger brained Old World monkeys, and their cortex, lissencephalic, making it easier to target localized regions of interest cortically and subcortically, either permanently, via fiber-sparing excitotoxins (e.g., quinolinic acid) and neurochemically specific toxins (e.g., 5,7 dihydroxytryptamine), or temporarily, by infusions of drugs through indwelling cannulae. This will also prove an advantage when applying state-of-the-art molecular and imaging techniques to neural circuit analysis of cognition and emotion, including optogenetics (MacDougall et al., 2016) and pharmacogenetics. Like humans, vision and audition are dominant senses in monkeys, including the marmoset, (in contrast to rodents in which the dominant sense is olfaction), and the expansion of cortical processing of these senses in humans is also seen in non-human primates (Orban et al., 2004; Rauschecker and Scott, 2009). In addition, compared with rodents,

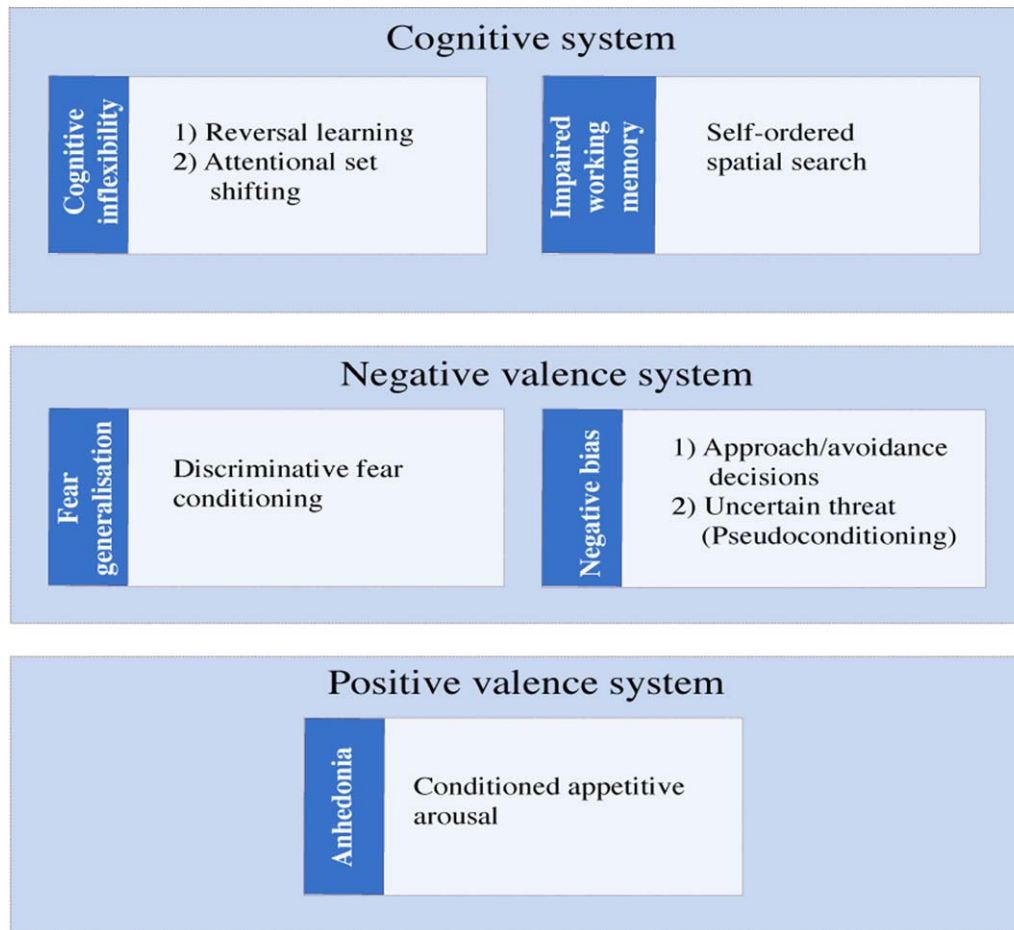


Figure 1 RDoC in the marmoset. Tasks developed in the marmoset are represented in white, linked to the relevant behavioral dimension that is impaired across disorders (blue) and placed within the appropriate system (Cognitive, Negative Valence, and Positive Valence, light blue). [Color figure can be viewed at wileyonlinelibrary.com]

marmosets show distinct gene expression patterns in the visual and prefrontal cortex despite similarities in genetic markers in many other areas (Mashiko et al., 2012). This makes primates ideal for translational studies of higher-order cognitive and affective processes using behavioral tests that rely on these dominant senses. An additional advantage of marmosets is that it is possible to maintain purpose bred colonies within spacious accommodation at local institutions as a consequence of their small size and their ease of breeding in captivity. This allows for the necessary large scale studies of neural circuits. Maintaining a large breeding colony allows the investigation of the interaction between genetic and behavioral traits that are known risk factors for neuropsychiatric disorders, for instance, the serotonin transporter polymorphism and high trait anxiety. The onset of many neuropsychiatric disorders occurs during childhood and adolescence (Jones, 2013) and 75% of adults suffering from

a mental disorder have an onset before the age of 25 (Kessler et al., 2005). Thus, the short 5 month gestation period of marmosets and the fact that they reach adulthood by 2 years (Abbott and Hearn, 1978; Abbott et al., 2003; Schultz-Darken et al., 2016) makes them the ideal primate species in which to study the normal and abnormal development of prefrontal circuits related to these genetic and behavioral risk factors.

In this review we will focus on a number of behavioral dimensions common to a variety of neuropsychiatric disorders and describe the range of cognitive and affective tests that have been developed to study their psychological and neurobiological bases in the marmoset. We will include dimensions associated with dysfunction in the cognitive (cognitive inflexibility and working memory), negative valence (fear generalization and negative bias) and positive valence (anhedonia) systems, as defined by RDoC (Fig. 1). Since symptoms are core to neuropsychiatric diagnoses and

are often the trigger for individuals to seek help and advice from a clinic, knowledge of the relationship between behavioral dimensions and symptomatology is critical for progress in our understanding of the etiology and treatment of these disorders.

COGNITIVE SYSTEM DYSFUNCTION, COGNITIVE INFLEXIBILITY, AND IMPAIRED WORKING MEMORY

Impairments within the cognitive systems are prominent in disorders such as schizophrenia, obsessive-compulsive disorder (OCD) and attention deficit hyperactivity disorder (ADHD). These disorders may share a range of cognitive impairments including deficits in cognitive flexibility and inhibitory response control and aspects of working memory (Morice, 1990; Chamberlain et al., 2005; Castellanos et al., 2006). Such deficits may also be present in affective disorders, including anxiety and mood disorders (Airaksinen et al., 2005; Mantella et al., 2007; Rock et al., 2014). Numerous behavioral tasks have been developed to study cognitive flexibility and working memory abilities in marmosets. Here we focus on those tests that have been successfully translated into clinical and pre-clinical studies in humans, and back translated into rodents. Specifically, cognitive flexibility has been measured using discrimination reversal-learning and attentional set shifting tasks, whilst working memory and its underlying mechanisms have been studied using a spatial self-ordered sequencing task (Fig. 1). The translational success of these tasks for modeling the overlapping deficits in behavioral dimensions and symptoms across disorders has already provided enormous insight into the separable prefrontal circuits and neurochemically specific modulation that underlie such dimensions.

Cognitive flexibility is the ability to adapt mental strategies and actions to the changing contingencies and conditions of the environment (Cañas et al., 2003). It has been suggested that cognitive inflexibility underlies the compulsions present in OCD patients as they shift from flexible, goal directed actions to persistent maladaptive habitual behaviors (Graybiel and Rauch, 2000; Gillan et al., 2011). Although cognitive inflexibility has also been linked to perseverative thinking and the inability to perform mental shifts in schizophrenia (Delahunty et al., 1993; Elliott et al., 1995; Pantelis et al., 1999), it is unclear whether it underpins these symptoms or is simply a by-product of the prefrontal dysfunction associated with the disorder (Orfei et al., 2013; Weinberger and Berman, 1996). Using the Wisconsin Card Sorting task

(WCST, Berg, 1948; Milner, 1963) a commonly used clinical test to evaluate set-shifting ability in patients with frontal lobe damage, some studies have shown that OCD patients display marked impairments in shifting attentional sets (Okasha et al., 2000; Fontenelle et al., 2001; Veale et al., 2009); but see (Abbruzzese et al., 1995, 1997; Purcell et al., 1998; Simpson et al., 2006). In one such study the level of the impairment correlated with the severity of the symmetry/ordering obsessions (Lawrence et al., 2006) suggesting that difficulties in shifting attention may contribute to the development of these obsessions. Similar difficulties have also been reported not only in patients suffering from schizophrenia (Canavan et al., 1989; Beatty and Monson, 1990) but also Huntington's disease (Malmo, 1974; Lysaker et al., 1995; Everett et al., 2001).

In order to dissect out the underlying cognitive deficits that may contribute to impaired WCST performance, which may include disrupted motivation, attention, learning and memory, a multidimensional discrimination task was developed for use in both humans and marmosets (Roberts et al., 1989). The task was based on intra-dimensional (ID) and extra-dimensional (ED) shift studies of animal learning (Mackintosh and Little, 1969). It required subjects to attend to the different aspects of multidimensional stimuli (varying in shape and lines for instance) and either attend to the same dimension across discriminations (intra-dimensional shift) or shift attention from one dimension to another [extra-dimensional shifts; Dias et al., 1996a, b; Fig. 2a]; the latter is a direct parallel of the switch from sorting cards according to one category, to sorting them according to another, that is at the core of the WCST. The test also enabled direct comparison with another type of cognitive flexibility that had commonly been studied in primate neuropsychological studies (Jones and Mishkin, 1972), namely reversal learning. Here, having learned to respond to one of two stimuli in order to receive reward, subjects had to reverse their responding to the other, previously unrewarded stimulus in order to gain reward.

By directly comparing the effects of excitotoxic lesions of two distinct PFC regions, namely the orbitofrontal cortex (OFC) and ventrolateral prefrontal cortex (vlPFC), studies in marmosets revealed their differential contribution to these two forms of cognitive flexibility (Dias et al., 1996a,b). While OFC lesions disrupted reversal learning but not attentional set-shifting, vlPFC lesions disrupted attentional set-shifting but not reversal learning [Fig. 2(b)], implicating the former in monitoring the changing affective value of stimuli in the environment and the latter in

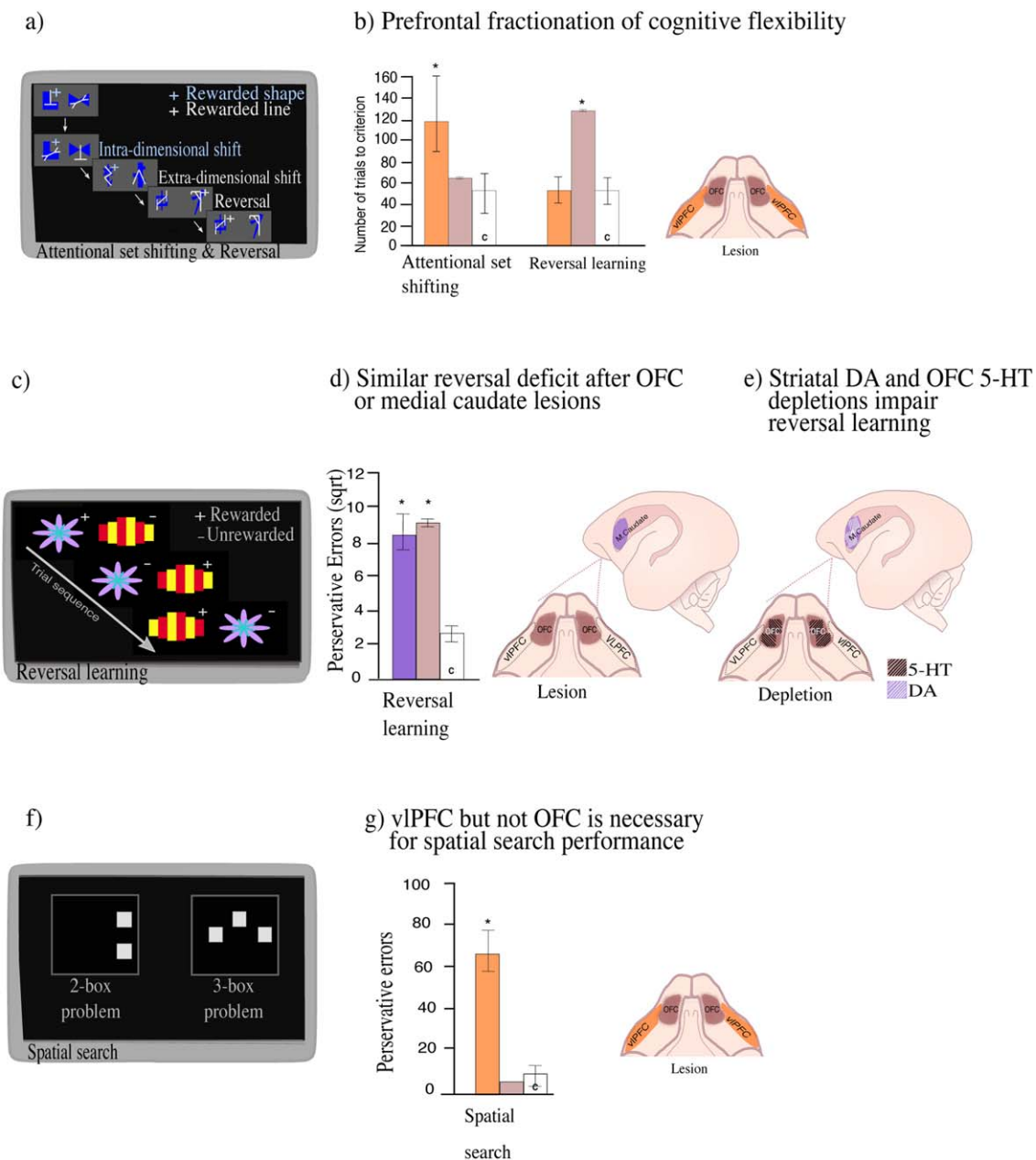


Figure 2 Studying cognitive system dysfunction in the marmoset. (a) Schematic of the attentional set shifting and reversal learning paradigm. In Intra-dimensional shifts, new exemplars, still varying along the same two perceptual dimensions of shapes and lines are presented and the previously relevant dimension for example, shape, remains relevant and animals must learn which of the two new exemplars from that dimension is rewarded. In extra-dimensional shifts the relevant dimension is changed (e.g., shape to line) and an exemplar from the new relevant dimension is now rewarded. In contrast, in reversal, the exemplars and dimensions remain the same but the rewarding contingency is reversed (e.g., shape A to shape B). (b) Number of trials required to reach criterion performance during an extra-dimensional shift (attentional set shifting) and reversal after antOFC or vIPFC excitotoxic lesions. Bars represent the range of scores in each group (Dias et al., 1996a, b). (c) Schematic of the serial reversal learning paradigm, showing an example set of three trials. (d) Perseverative errors (consecutive responses to the unrewarded exemplar, square-root transformed) made across four reversals after excitotoxic lesions of antOFC or the medial caudate nucleus (Clarke et al., 2008). Error bars represent SEM. (e) Depletions of 5-HT in the OFC and DA in the medial caudate selectively impair reversal learning. (f) Schematic of the self-ordered spatial search task with 2-box and 3-box examples. The locations of the boxes change across trials. (g) Number of perseverative errors (consecutive responses to the same spatial location) made after antOFC or vIPFC excitotoxic lesions (Walker et al., 2009). Error bars represent SEM. In all figures the location of the excitotoxic lesions are shown on the diagram of the orbital (antOFC, vIPFC) or sagittal (medial caudate) view of the brain. White bars (C) represent control group and stars (*) represent $p < 0.05$.

attentional control. This double dissociation was subsequently replicated in human functional neuroimaging studies (Hampshire and Owen, 2006) as well as in rats (Birrell and Brown, 2000) and mice (Bissonette et al., 2008), highlighting the forward and back translatability of these findings. Further studies in the marmoset have implicated the medial caudate nucleus in reversal learning (Clarke et al., 2008) with the pattern of impairment similar to that seen following OFC lesions. In both cases, animals displayed perseverative responding, whereby the previously rewarded option is chosen repeatedly, despite the lack of reward.

Marked differences in the underlying monoaminergic modulation of these circuits have also been revealed. Reductions in dopamine, but not serotonin affect higher-order attentional selection in the vIPFC (Roberts et al., 1994; Clarke et al., 2005). In contrast, reductions of serotonin, but not dopamine, within the OFC mimic the perseverative effects of excitotoxic OFC lesions on reversal learning (Clarke et al., 2004, 2005, 2007). The converse, however, is the case at the level of the caudate nucleus where reversal learning is impaired following reductions in dopamine but not serotonin (Clarke et al., 2011). Thus, distinct neurochemical systems at the level of the striatum and OFC regulate reversal learning, and although both serotonin and dopamine pathways richly innervate the PFC, their contributions differ with respect to the different forms of cognitive flexibility [Clarke et al., 2008; Fig. 2(e)].

Together these findings provide considerable insight into the specific fronto-striatal circuitry subserving cognitive flexibility and are beginning to reveal how these different forms of cognitive flexibility contribute to disorders such as schizophrenia and OCD. For example, ED shifting, as assessed in the CANTAB (Cambridge Neuropsychological Test Automated Battery), generally shows a significant impairment in OCD patients (Watkins et al., 2005; Chamberlain et al., 2006). This deficit appears to be pre-symptomatic as it is also present in their healthy, first degree relatives (Chamberlain et al., 2007). This may implicate altered functioning in vIPFC in OCD patients and a recent report specifically links attentional set-shifting performance and vIPFC function. Specifically, decreased functional connectivity between vIPFC and caudate at resting state was linked to impairments in attentional set-shifting performance and predicted greater number of errors during ED shifts (Vaghi et al., 2016). In contrast, OCD patients display mild or no detectable impairment in reversal learning. However, they do show a speed-for-accuracy trade off that has been correlated to the

severity of compulsions (Chamberlain et al., 2007, 2008; Valerius et al., 2008). Moreover, at the level of underlying brain circuitry, OCD patients and their unaffected first-degree relatives display decreased recruitment of the OFC during reversal learning (Chamberlain et al., 2007; Remijne et al., 2013) and symptom provocation (Morgiève et al., 2014) and abnormalities in resting state activity in this region (Menzies et al., 2008). A meta-analysis of imaging studies highlights not only the OFC but also vIPFC regions as areas with increased likelihood of activation in response to symptom provocation (Rotge et al., 2008). Thus, altered activity in both OFC and vIPFC circuitry involved in response reversal and rule shifting, respectively, may underlie the impairments in cognitive flexibility in OCD and contribute to the compulsions and obsessions, respectively.

Similarly, patients with schizophrenia also show marked deficits in shifting attentional sets (Elliott et al., 1995; Morris et al., 1999; Pantelis et al., 1999; McKirdy et al., 2009) and in reversal learning (Thoma et al., 2007; Waltz and Gold, 2007; Leeson et al., 2009). Performance on the latter is related to the severity of the negative symptoms (Pantelis et al., 1999; Leeson et al., 2009), which if they persisted were linked to greater impairment in set shifting at follow-up (Leeson et al., 2009). This pattern of impairments also implicates dysfunctional OFC and vIPFC circuits in the cognitive inflexibility associated with schizophrenia, similar to that proposed for OCD. However, the specific neural basis of these deficits across the disorders remains to be determined, given that, for example, similar perseverative responding in reversal learning is associated with disrupted OFC or medial striatal activity (Dias et al., 1996a; Clarke et al., 2008).

In schizophrenia, support for dysfunction within the medial striatum is provided by evidence for disturbances in activation and connectivity within this region (Vink et al., 2006; Rolland et al., 2015) and the finding that reduced functional activity within the ventral striatum is associated specifically with impaired reversal performance in unmedicated patients compared with controls (Schlagenhauf et al., 2014). This can be contrasted with the decreased recruitment of the OFC during reversal learning in OCD patients described above. It can be argued that given vIPFC and OFC form part of a neural network to control attentional set-shifting and reversal learning respectively, dysregulation at any node within the network will disrupt its overall functioning. However, identifying the underlying cause of that disruption has important implications for the development of therapeutic strategies for the two disorders. For

example, studies in the marmoset have revealed that the OFC and striatal mechanisms that underlie reversal learning in the marmoset are differentially modulated by serotonin and dopamine, respectively. Thus, the improvement in OFC function and symptoms in OCD patients following administration of selective serotonin reuptake inhibitors (SSRIs) (Nakao et al., 2005; Saxena et al., 2009) would be predicted by the selective actions of serotonin on reversal learning within the marmoset OFC. It may also explain why medicated OCD patients do not show errors in reversal performance as the boosting of serotonin with SSRI treatment may alleviate their reversal performance deficits. In contrast, pharmacotherapies targeting the dopamine system (rather than SSRIs) would be predicted to alleviate the striatal-related reversal deficits in schizophrenia. Although both typical (Michara and Goldberg, 2004) and atypical (Keefe et al., 1999) antipsychotics primarily targeting dopaminergic function have been linked to general improvements in cognitive function, whether schizophrenia patients specifically benefit from antipsychotic medication in terms of improvements in striatal based cognitive flexibility remains to be determined.

Within the domain of cognitive symptoms, schizophrenia patients also display impairments in working memory (Green, 1996), which are also a core symptom of attention deficit/hyperactivity disorder (ADHD) (Westerberg et al., 2004; Lee and Park, 2005; Martinussen et al., 2005). Working memory is the ability to hold information “on-line” in memory, to update that information across time and to use that information to guide responding. A variety of tests has been used to study working memory including delayed response tasks (Pontecorvo et al., 1996), multi-arm mazes (commonly used in rodents; Dudchenko et al., 2013) and self-ordered search tasks (Petrides, 1995a,b). An example of the latter developed in the marmoset is conceptually very similar to the CANTAB self-ordered spatial search task used to study working memory in patients (Owen et al., 1990; Manes et al., 2002; Luciana, 2003; Chase et al., 2008). It requires a combination of working memory, response inhibition and strategy implementation abilities [Fig. 2(f)]. Marmosets are presented with squares simultaneously placed in two, three, or four spatial locations (out of eight possible combinations) on a touch-sensitive computer screen. On all trials, marmosets are required to respond once only to each square in a self-ordered sequence in order to receive reward (Collins et al., 1998; Walker et al., 2009). In the marmoset, excitotoxic lesions of the vIPFC, but not OFC, dramatically impair performance [Walker et al., 2009; Fig. 2(g)]. Marmosets are unable to attain

pre-lesion levels of performance and exhibit high numbers of perseverative responses, as they touch the same square repeatedly, failing to move on to the next, previously untouched square. However, performance can be rescued by removing the previously touched square from the touchscreen until another response has been made, thereby preventing perseveration of the immediately preceding response. This suggests that the inability to solve this task stems from a tendency to repeat previous responses.

In the human version of the task, patients with schizophrenia and ADHD patients exhibit similar impairments. Both adults (Dowson et al., 2004) and children (Fried et al., 2015) with ADHD exhibit a profound impairment in this task. Moreover, schizophrenia patients in particular fail to adopt a systematic strategy and make numerous between-search errors, performing worse than frontal lobe patients (Pantelis et al., 1999; Badcock et al., 2005) and being impaired even at first-episode psychosis (Joyce, 2002; Joyce et al., 2005). This was evident even when controlling for low visuo-spatial memory span, suggesting that impaired executive function and strategy implementation are at the core of the working memory problem. Deficits in spatial working memory extend to the healthy monozygotic twins of patients (Pirkola et al., 2005) or first degree relatives (Wood et al., 2003). This would suggest that the working memory impairment is an endophenotype of schizophrenia.

Whilst evidence from the clinical literature supports global prefrontal impairment in ADHD (Lenartowicz et al., 2014; Arai et al., 2015; Mattfeld et al., 2015) and schizophrenia patients (Manoach, 2003; Orfei et al., 2013; Pu et al., 2013; Marumo et al., 2014; Buchy et al., 2015), the identification of the vIPFC as critical for self-ordered spatial memory in marmosets specifically implicates vIPFC impairment in this working memory deficit in patients. This is supported by the accompanying profound dysfunction in attentional set shifting, which also is associated with vIPFC dysfunction. Similarly, children (Kempton et al., 1999) and adult (Clark et al., 2007) ADHD patients that exhibit marked impairment in the self-ordered spatial search task also show impaired response inhibition. Such deficits in working memory can be ameliorated by either domain specific cognitive training or psychostimulant medication (Kempton et al., 1999; Bedard et al., 2004; Mehta et al., 2004; Klingberg et al., 2002, 2005; see Del Campo et al., 2011), the latter implicating the dopamine or noradrenaline systems. In support of the dopamine system, administration of a D1 agonist improves a ketamine-induced deficit on the spatial-order search task in marmosets (Nakako et al., 2013) suggesting that the working memory processes in this task are under

dopaminergic modulation. However, given that striatal dysfunction is also implicated in these disorders (Durstion et al., 2003; Cubillo et al., 2012 for a review) it remains to be determined whether the improvements are due to the actions of drugs at the level of the PFC or striatum (see, e.g., Clatworthy et al., 2009).

In summary, the marmoset is proving an excellent model in which to parse the neural circuitry and neurochemical pathways that underlie the cognitive symptomatology associated with a range of neuropsychiatric disorders including OCD, schizophrenia, and ADHD. This is an important first step toward stratification of specific symptoms both within, as well as between, disorders. Moreover, identification of the level within a particular circuit from which a cognitive impairment may arise, for example, PFC or striatum, and the specificity of the neurochemical modulation of that level within the circuit, for example, dopamine or serotonin, has important implications for targeting current therapies more effectively. Future studies employing viral mediated vectors to target specific pathways using optogenetics or pharmacogenetics can further delineate the circuit and the marmoset is an ideal model for such studies with a highly differentiated prefrontal cortex but a relatively small and lissencephalic brain.

DYSREGULATION OF NEGATIVE VALENCE SYSTEMS, ATTENTIONAL BIASES, AND FEAR GENERALIZATION

Although there are evolutionary advantages to fear and anxiety (they can act as a protective defense mechanism in dangerous situations), they can easily become maladaptive and deleterious once left unregulated. Pathological anxiety, affecting more than 28% of the general population (Kessler et al., 2009), specific phobias, PTSD, abnormally low mood in depression and disturbances of emotion in schizophrenia (Staring et al., 2009) are all a result of a dysregulated negative valence system. In generalized anxiety disorder, patients exhibit pathological worry and apprehension over long periods of time about situations that are normally causing no distress to the healthy population (Tyrer and Baldwin, 2006; Craske et al., 2009). In specific phobias and PTSD the worry and distress are focused on, and triggered by, a single event, situation or stimulus (Kessler et al., 2009; Pacella et al., 2013).

A particularly prominent symptom in patients suffering from all types of anxiety and depression is fear over-generalization, whereby they indiscriminately develop fearful responses to threatening and non-threatening stimuli alike (Lissek et al., 2008; Craske

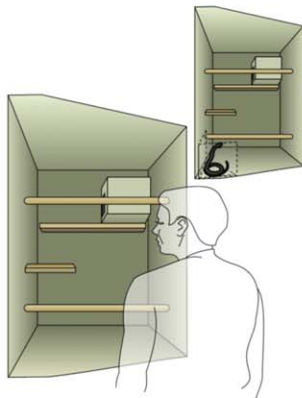
et al., 2009; Lissek et al., 2014). They also tend to develop negative biases, not only within the affective domain but also extending into the cognitive domain, and influencing attention and memory (Murphy et al., 1999; Gotlib et al., 2004; Mogg and Bradley, 2005; Bar-Haim et al., 2007). It is still unclear whether fear generalization and negative biases are causal to the development of the disorder, or constitute underlying symptoms that appear in its presence and contribute to its maintenance. Evidence for the former comes from the study of individuals within the healthy population who display quite dramatic differences in anxiety. This variation in anxiety is recognized as a stable personality trait. Individuals at the extreme high end of this trait can be more at risk of developing pathological anxiety and, like individuals suffering from clinical anxiety, have a tendency to over-generalize in fear provoking situations and display mild negative biases (Sexton et al., 2010; Arnaudova et al., 2013). Such behavioral traits are the product of interactions between genes and early life experiences (Nugent et al., 2011). Life experiences that may trigger the development of these traits include physical and psychological stressors, which impact on the development of brain circuits underlying emotion. Indeed, affective disorders commonly emerge during childhood and adolescence (Jones, 2013), making the study of gene–environmental interactions and brain development important for our understanding of emotion dysregulation.

The common marmoset, like humans, displays marked individual responsivity to anxiety provoking situations that appears stable across time and thus trait-like in character. This makes the marmoset an ideal species for studying emotion regulation and dysregulation. Consequently, a range of specific tasks have been developed to formally characterize their anxious temperament and to measure fear over-generalization and negative biases (Fig. 1). An important aim in developing these tasks has been to bridge the gap between existing studies of negative emotion in rodents, monkeys and humans. The neural mechanisms underlying fear and anxiety have been extensively studied in rodents (LeDoux, 2000; Maren, 2001; Davis et al., 2010; Tovote et al., 2015), primarily using Pavlovian fear conditioning paradigms (acute and sustained fear) and tests of innate anxiety, such as the open field and elevated plus maze (Belzung and Griebel, 2001). In contrast, specific tests of innate fear (responsivity to snakes) and anxiety (responsivity to unknown humans) have been more commonly used in non-human primates (Izquierdo et al., 2005; Rudebeck et al., 2006; Kalin et al., 2007; Machado and Bachevalier, 2008) making

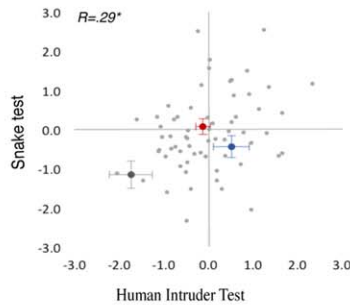
cross-species comparison and translation difficult. Moreover, although fear conditioning has been used to test both humans and rodents alike, the metric of emotion differs between the two species; a behavioral freezing response is commonly measured in rodents

contrasted to an autonomic and/or self-reported state used in humans. Since an emotional state is the product of changes across the range of outputs, both behavioral and physiological, it is important to measure multiple aspects of the response in order to

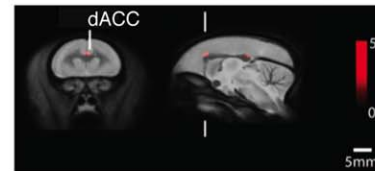
a) Testing innate fear and anxiety in the marmoset using a human intruder or snake



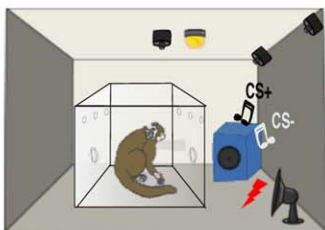
b) Innate fear-anxiety relationship and the effects of antOFC and vIPFC lesions



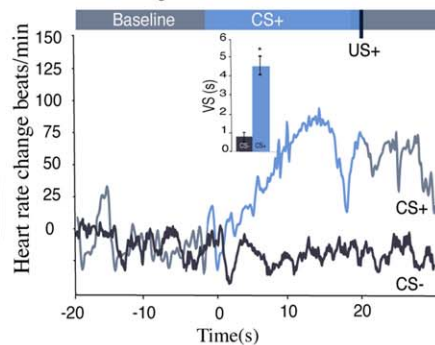
c) High anxiety phenotype is linked to reduced volume of dACC



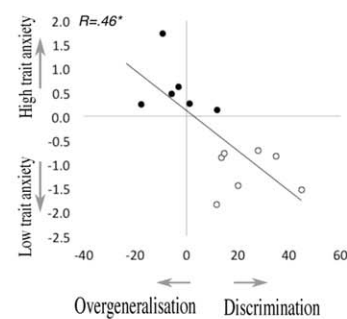
d) Discriminative fear conditioning in the marmoset



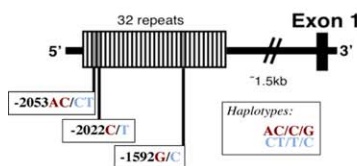
e) Conditioned heart rate and vigilant scanning response during discriminative fear conditioning



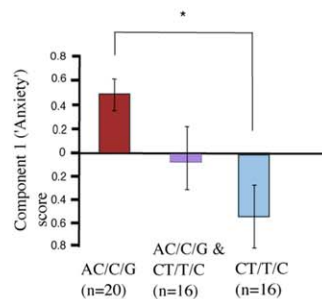
f) High trait anxiety correlates with fear generalisation



g) Marmoset SLC6A4 promoter region



h) Individual differences in anxiety linked to SLC6A4 polymorphism



i) Opposing effects to acute SSRI treatment linked to SLC6A4 polymorphism

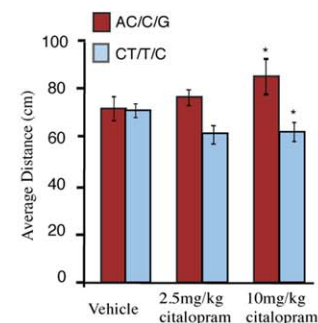


Figure 3.

determine the neural circuits that regulate emotional states. This is particularly important since there are strong brain-body-brain pathways resulting in patients with anxiety and mood disorders being more likely to suffer cardiovascular disease and vice versa (Khawaja et al., 2009; Stapelberg et al., 2012).

A test commonly used to measure an anxious temperament in macaque monkeys is the human intruder test, whereby the experimental animal encounters an unfamiliar human (Kalin and Shelton, 1989). The unfamiliar intruder could be a potential “friend,” for instance bringing food, or they could be a threat. Hence, the ambiguity of the situation creates a state of anxiety, with subjects varying in the extent to which they approach the intruder. In the marmoset version of the task, the level of anxiety is measured based upon a component score that includes the distance the animal chooses to maintain between themselves and the intruder, their behavioral reactivity in the form of calls made, and other attentive behaviors such as body and head bobbing. This test is relatively quick to perform, as it is based in the home cage, requires no training and thus is ideal for screening large numbers of animals. Another paradigm to assess emotional reactivity in marmosets is based on the response to a snake, which is a stimulus that primates find inherently fearful [Shiba et al., 2014a, b; Fig. 3(a)]. Although the human intruder and snake test measures are somewhat independent of one

another [see significant but weak correlation in Fig. 3(b)] and may measure overlapping but also distinct aspects of negative emotion, for example, innate fear versus uncertainty, they both reflect the general anxious temperament of the animal. High scores in both tests on repeated occasions indicate a high-anxious phenotype in the marmoset. They have been linked to structural alterations in the dorsal Anterior Cingulate Cortex (dACC) [Fig. 3(c)] as measured by MRI and reductions in serotonin release in the amygdala in response to an acute dose of an SSRI, as measured by *in vivo* microdialysis (Mikheenko et al., 2015). In addition, microPET analysis of the 5-HTT has also revealed lowered binding in the dACC related to social anxiety in marmosets (Yokoyama et al., 2013).

The translational potential of this anxiety phenotype has been determined by studying an individual marmoset’s ability to display discriminative fear conditioning, and their responsiveness to an uncertain or ambiguous stimulus. The tendency to generalize between threatening and non-threatening cues and contexts, and the negative appraisal of neutral or ambiguous cues (Hirsch and Mathews, 1997; Constans et al., 1999), is characteristic of high trait-anxious humans (Craske et al., 2009; Lissek, 2012; Dymond et al., 2015) and rats (Duvarci et al., 2009). Thus, it would be predicted that high anxious marmosets would show a similar phenotype. Consequently, Pavlovian discriminative fear conditioning has been

Figure 3 Dysregulation of negative valence systems. (a) Human intruder and snake tests are conducted in the home-cage, with the animal separated from their cage mate in one quadrant of the cage for a brief period. (b) The negative emotional response to the snake, as measured by the component 1 (“Anxiety”) score in the Principal Component Analysis (PCA), is positively correlated with the negative emotional response to the human intruder. AntOFC (red) and vIPFC (blue) excitotoxic lesions increase negative emotion relative to controls (gray) but the lesioned animals remain within the normal variation of trait anxiety within the colony (Agustín-Pavón et al., 2012). (c) Two clusters (dACC, labeled, and posterior cingulate cortex) identified by tensor based morphometry analysis were negatively correlated with high anxiety in the human intruder test. (d) Schematic of discriminative fear conditioning apparatus. The CS+ is paired with an aversive loud noise (300–600 ms car siren at 118 dB), whereas the CS– is paired with a neutral event (0.5 s of darkness). (e) Example of conditioned behavioral (vigilant scanning, time in seconds) and cardiovascular (heart rate, beats/min) responses. “Vigilant scanning” includes attentive visual search of surroundings in combination with forward extension of body/head and rearing. A conditioned heart rate rise is observed for the CS+ (blue) but not for the CS– (gray) indicating successful discrimination between the two stimuli. (f) Correlation between component 1 score (“Anxiety”) and performance in discriminative fear conditioning. High scoring in component 1 was associated with failure to achieve discriminative conditioned cardiovascular responses to CS+ and CS–. (g) Schematic representation of the marmoset *SLC6A4* promoter region showing 32 repeats. Third, fourth, and 23rd repeats containing the double and the two single-nucleotide polymorphisms, respectively, are shaded in gray. (h) Comparison of component 1 (“Anxiety”) behavioral scores derived from the PCA of the HIT performance. Error bars represent SEM. (i) The human intruder test was used to assess anxiety levels in response to vehicle and to a single dose of 2.5 mg/kg or 10 mg/kg citalopram, 25 min prior to the intruder phase. Effects on average distance (cm) are shown (Santangelo et al., 2016). Error bars represent SEM, stars (*) represent $p < 0.05$.

developed for marmosets based on paradigms used effectively in humans (Lau et al., 2008; Lissek et al., 2008) and rodents (Herry et al., 2008). It involves the presentation of two distinct auditory cues, one of which is paired with a mildly aversive loud noise [300–600 ms car siren at 118 dB; the specific parameters are adjusted for each individual animal based on their performance; Fig. 3(d)]. Successful discriminative conditioning is demonstrated by the development of conditioned attentional orienting/vigilant scanning responses and heightened heart rate [Fig. 3(e)] in response to the stimulus paired with the loud noise but not the alternative stimulus paired with a neutral event, (0.5 s period of darkness). Animals that had shown higher anxiety and avoidance of the rubber snake were unable to successfully learn such a discrimination and their conditioned autonomic and behavioral responses generalized to the safety cue or to the context [Shiba et al., 2014b; Fig. 3(f)], much like high trait anxious humans who tend to generalize from threatening, aversive, and negative stimuli to neutral ones. Importantly, marmosets that failed to learn discriminative fear conditioning were perfectly successful in learning an appetitive Pavlovian discrimination paradigm by discriminating the same auditory cues when they were predictive of reward. High anxious marmosets also displayed high levels of behavioral vigilance when presented with a novel, neutral cue in a threatening context (Mikheenko et al., 2015). This is a form of pseudo-conditioning as the aversive loud noise and a neutral stimulus were presented within the same test session but were not correlated with one another, yet high anxious marmosets still developed conditioned responses to the neutral stimulus.

High anxious marmosets and humans not only display a similar behavioral phenotype but that phenotype may also share common genetic influences. In humans, variation within the serotonin transporter gene (*SLC6A4*) that results in reduced gene expression has been linked to a high trait anxiety phenotype (Lesch et al., 1996; Canli and Lesch, 2007; Caspi et al., 2010) and marked changes in the activity of emotion circuits in the brain (Brown and Hariri, 2006; Murphy et al., 2013); although meta-analyses have called into question the gene-behavior association (Munafò et al., 2009; Risch et al., 2009). Recently, genetic variation in the *SLC6A4* upstream repeat region of the marmoset has also been linked to differential *SLC6A4* gene expression, with lower gene expression being associated with heightened anxiety on the human intruder test [Santangelo et al., 2016; Fig. 3(g,h)]. This gene-behavioral association in the marmoset highlights the potential advantage to

studying such relationships in a purpose-bred primate colony. The relatively controlled environment dramatically reduces the impact of variation in life experiences on an individual's behavior, allowing gene-behavior relationships to be more easily revealed compared with that of humans.

Further exploration of the phenotype has revealed that genetic variation in the *SLC6A4* gene is related to opposing effects of an acute dose of a selective serotonin reuptake inhibitor (SSRI) on anxious behavior. The low gene expressing, high trait anxious marmosets displayed an anxiogenic response in contrast to the anxiolytic response of the high gene expressing, low trait anxious marmosets [Santangelo et al., 2016; Fig. 3(i)]. These results bridge the gap between the findings in humans that report reduced responsivity to the therapeutic effects of chronic SSRI treatment in low expressing carriers with anxiety disorders (Perna et al., 2005) and depression (Keers et al., 2011; Porcelli et al., 2012), and the individual differences in sensitivity to the anxiogenic effect of acute SSRIs (Harmer and Cowen, 2013). This finding implicates *SCL6A4* genetic variation in the latter (Harmer et al., 2006; Murphy et al., 2009) which may provide insight into the underlying brain mechanisms that account for the later improvement of the clinical symptoms observed in high expressing carriers. The marmoset model therefore has enormous potential for revealing the interactions between the *SCL6A4* gene and functional activity in the serotonin system in the control of behavior.

Changes in activity of brain networks that are associated with heightened anxiety and dysregulated negative emotion, upon which serotonin may act, have been reported by functional neuroimaging studies of high trait anxious individuals in the healthy population (Killgore and Yurgelun-Todd, 2005; Bishop, 2007) as well as in adults (Etkin and Wager, 2007; Milad and Rauch, 2007; Price & Drevets, 2010), children and adolescents (Monk et al., 2006; Guyer et al., 2008; Strawn et al., 2012) with specific anxiety disorders. These implicate a number of prefrontal subregions including the OFC and vIPFC. However, whether those changes are causal to the phenotype or merely compensatory cannot be determined in humans.

Such cause and effect has been established in marmosets, by studying the effects of selective excitotoxic lesions of the anterior OFC (antOFC) and vIPFC on fear and anxiety. At face value, the effects of both lesions seemed almost identical, increasing anxiety as measured by the human intruder test, increasing innate fear in response to a snake stimulus [Fig. 3(b)] and inducing inflexible conditioned

cardiovascular and behavioral fear responses following acute alterations in the pairing of a stimulus with aversive loud noise (Agustín-Pavón et al., 2012; Shiba et al., 2014a). This resembles the robust pattern of conditioned fear found in anxiety patients who display stronger responses to conditioned cues during extinction and are delayed in extinguishing responses compared with controls (Wessa and Flor, 2007; Duits et al., 2015). Whilst the effects of OFC lesions on tests of anxiety and innate fear have been somewhat variable in macaque monkeys (Izquierdo et al., 2005; Rudebeck et al., 2006; Kalin et al., 2007; Machado and Bachevalier, 2008) the reasons for these discrepancies have been attributed mostly to differences in lesion methodology, lesion extent and task sensitivity (for a thorough discussion on the issue see Shiba et al., 2016). The anxiety phenotype induced by antOFC and vIPFC lesions in marmosets altered the entire repertoire of behaviors that contributed to the high anxiety trait, including all aspects of behavior, coping strategy and emotionality. The finding that the lesion-induced heightened anxiety remained within the “normal” range of such behavior displayed by marmosets within the colony [Fig. 3(b)] highlights the important role that both regions play in determining levels of trait anxiety. Moreover, the apparently similar symptomatology associated with lesions to two distinct regions of PFC illustrates the multivariate nature of anxiety.

The question remains as to what is the distinct contribution of these two prefrontal regions to the anxiety phenotype, the answer of which will help to stratify anxiety disorders and develop targeted treatments. Besides the failure to regulate negative emotions, patients with anxiety and depression often make poor decisions. Because they are particularly sensitive to negative information, they tend to perceive threat with increased intensity and are more risk averse (Murphy et al., 2003; Dickson, 2006; Smoski et al., 2008; Mueller et al., 2010) and thus display negative biases when making decisions (Bradley et al., 1998; Murphy et al., 1999; Mogg et al., 2000; Williams et al., 2007; Peckham et al., 2010). Indeed, reductions in serotonin within the OFC of marmosets have been implicated in such negative biases (Rygula et al., 2015) as identified in a probabilistic discrimination task similar to that used to reveal altered activity in prefronto-amygdala circuitry related to negative biases in depressed patients (Taylor Tavares et al., 2008).

To compare the impact of antOFC and vIPFC inactivation in marmosets on decision making we developed an approach-avoidance instrumental decision-making task. In this task, animals optimize their

reward by responding equally to two, equivalently rewarded left and right locations on a touch-sensitive computer screen. In occasional probe sessions, superimposed over the reward schedule, an aversive loud noise, a form of punishment, is associated with responding at one of the two locations. This results in a conflict at that location between responding to gain reward, and avoiding responding due to the punishment. However, animals normally maintain responding to both stimuli, choosing to optimize reward, despite the occasional punishment. However, transient pharmacological inactivation of the antOFC and vIPFC alters performance in distinct ways. Inactivation of the vIPFC has no impact on overall levels of responding but causes the animal to avoid making the punished response, resulting in many more responses being made to the side on which responding only receives reward. Hence, the cost-benefit balance of responding for reward in the face of punishment is switched from a positive approach response to a negative avoidance response. In contrast, inactivation of antOFC has no effect on the day of receiving punishment, but it acts to bias responding away from the punished side the following day, presumably as a consequence of its effects on memory consolidation (Clarke et al., 2015).

The vIPFC has been implicated in attentional processing and specifically the shifting of higher-order attentional sets as described in the cognitive section above. Thus, a parsimonious account of the on-line negative bias induced by inactivation of the vIPFC is that the marmoset is unable to shift attention away from the intrinsically salient aversive loud noise and toward the rewarding aspects of the context in order to perform a cost-benefit analysis. Consequently, this prolonged attention to the aversive stimulus leads to the negative bias. This hypothesis is also consistent with the contribution of the vIPFC to cognitive reappraisal, whereby individuals explicitly shift their attention from a salient negative interpretation of a context to a more positive interpretation (Buhle et al., 2014), and down-regulation of emotion during conflict and acceptance of unfair outcomes (Tabibnia et al., 2008; Feng et al., 2015). Consequently, it is proposed that a compromised vIPFC induces anxiety because subjects fail to switch their attention away from negative events.

On the other hand, the antOFC inactivation-induced negative bias is not linked to the online appraisal and processing of the negative stimulus but rather to its memory. The OFC has been linked to the development of stimulus-reward associations and the ability to predict outcomes, particularly within probabilistic contexts (Schoenbaum and Roesch, 2005;

Schoenbaum et al., 2007; Balleine et al., 2011; Walton et al., 2011; Rudebeck and Murray, 2014). Therefore, it can be argued that a compromised OFC makes the punishment no longer predictable. This learned state of uncertainty leads to establishment of a stronger punishment memory that underlies the negative bias and avoidance behavior upon its retrieval the next day. This is consistent with the role of uncertain environments in the development of anxious responses (Grupe and Nitschke, 2013). The negative bias is abolished by inactivation of either the amygdala or the hippocampus on the day of retrieval, or disconnection of the two, implicating an OFC-amygdala-hippocampal network that drives the expression of such negative biases. This account of the symptoms of anxiety and depression induced by compromised OFC function differs from that proposed above for vIPFC dysfunction. Instead of an inability to down-regulate responses on-line, a dysfunctional OFC may leave the system unregulated and result in the learning of maladaptive negative associations due to a failure to predict aversive outcomes, supporting the negative cognitions prevalent in anxiety and depression.

In summary, the marmoset model has allowed the investigation of regulation and dysregulation within the negative valence system (Fig. 1) at both the individual- (trait anxiety and genetic variation in the serotonin transporter gene) and circuit-based levels (prefronto-amygdala-hippocampal manipulations). The finding of an interaction between the serotonin transporter gene and the effects of acute SSRI treatment on anxious behavior has implications for the individual targeting of treatments. On the other hand, the proposed roles of vIPFC and antOFC, respectively, in attentional processing and in the prediction of negative outcomes, provide an important framework for the stratification of anxiety disorders. Future studies will focus on the contributions of other regions of PFC that have been implicated in the regulation of negative emotion, including primate dorsolateral PFC (Buhle et al., 2014) and peri- and sub-genual anterior cingulate cortex (Drevets et al., 2008; Etkin et al., 2011). While numerous studies have implicated the prelimbic and infralimbic regions of ACC in rodents, respectively, in the expression and extinction of freezing to a conditioned fear stimulus, their putative homology to primate peri- and subgenual ACC remains unclear (for a critical review see Myers-Schulz and Koenigs, 2012). This further emphasizes the importance of the marmoset primate model in parsing out the distinct cognitive functions of, and interactions between, these prefrontal brain regions and their downstream targets, in the control of

negative emotion. It will also provide the basis by which we can determine the neurobiological and psychological mechanisms underlying the action of current pharmacotherapies that target the serotonin (e.g., SSRIs), noradrenaline (selective noradrenergic reuptake inhibitors) and glutamatergic (e.g., ketamine) systems in the treatment of dysregulated emotions. Only then can these treatments be targeted appropriately to the individual.

IMPAIRED POSITIVE VALENCE: MODELING ANHEDONIA

Positive valence systems, as defined by the RDoC framework, are responsible for responding to positive situations and contexts, including reward seeking, consummatory behaviors and reward/habit learning. Dysfunction within these systems occurs in a number of major psychiatric disorders. One specific example of a clinical symptom involving disturbed positive valence is anhedonia (Fig. 1). Anhedonia is defined according to the DSM (I–V) as “decreased interest or pleasure in most activities, most of each day” and is prevalent in about 37% of depressed patients (Kessler et al., 2009). Indeed, for a patient to be diagnosed with depression they must suffer from one or other form of anhedonia or depressed mood (DSM V). Besides depression, anhedonia constitutes one of the primary negative symptoms of schizophrenia, being present in half of the patients (Pelizza and Ferrari, 2009), is present in eating disorders (Davis and Woodside, 2002) and is associated with withdrawal in drug abuse (Markou and Koob, 1991). It has also been reported in a number of neurodegenerative disorders, including Parkinson’s Disease (Isella et al., 2003) and Alzheimer’s disease (Starkstein et al., 2005).

Clinically, it has been identified by self-report measures of hedonic experiences using a variety of questionnaires, such as the Snaith Hamilton (Snaith et al., 1995) and Fawcett–Clark Pleasure scales (Fawcett et al., 1983). The majority of the questions on these scales focus on the consummatory aspects of positive experiences such as “one food tastes as good as another to me.” As a consequence, pre-clinical models of depression have tended to use the sucrose consumption test as the primary measure of anhedonia (Slattery et al., 2007) when investigating novel pharmacotherapies. However, preclinical neurobiological studies of positive valence systems have recognized motivational, reinforcing, decision making and consummatory components [see Treadway and Zald (2011) for a comprehensive review], all of

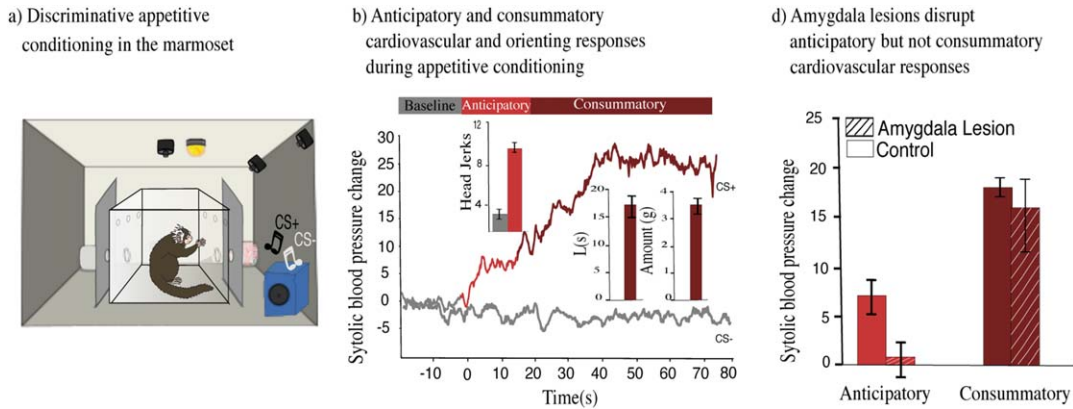


Figure 4 Parsing consummatory and anticipatory aspects of positive valence in the marmoset. (a) Schematic of discriminative appetitive conditioning apparatus. CS+ resulted in opening of the door revealing food box with reward (e.g., right), whereas CS- resulted in presentation of empty food box (e.g., left). The anticipatory period entails viewing the full food box and is followed by the consummatory period, when marmosets are allowed access to the reward. (b) Conditioned behavioral response during the anticipatory phase is measured by the number of orienting head movements (head jerks) toward the food box. Consummatory behavior is measured by the latency to eat the reward (“L”, seconds) and the amount of reward eaten (grams). A conditioned systolic blood pressure rise is observed for the CS+ (Light red for anticipatory period, dark red for consummatory period) but not for the CS- (gray). (c) Systolic blood pressure response during the CS+ after excitotoxic lesions of the amygdala (lined bars) presented for the anticipatory (Light red) and the consummatory (Dark red) periods compared with controls (empty bars) (Braesicke et al., 2005). Error bars represent SEM, stars (*) represent $p < 0.05$.

which can be parsed at the level of neural circuits and neurochemistry. Thus, anhedonia could arise from a lack of the ability not only to experience pleasure (consummatory anhedonia) but also to anticipate pleasure (anticipatory anhedonia). Indeed, a failure to anticipate pleasure has a major impact on an individual’s motivation to seek out pleasure (motivational anhedonia). Treadway and Zald (2011) further proposed the concept of decisional anhedonia to include the effects of anhedonia on decision making in the context of reward.

Recently, distinctions between these different types of anhedonia have begun to emerge in clinical research. For example, patients with depression show anticipatory (McFarland and Klein, 2009) as opposed to consummatory anhedonia (Dichter et al., 2010). On the other hand, schizophrenia patients show intact anticipation of reward but deficits in motivational/effortful responding for reward, a form of apathy (Gard et al., 2009, 2014). Another distinction to have arisen is that between self-report measures of pleasurable experiences retrospectively and experiencing pleasure per se. In particular, patients with schizophrenia and depression do not show reductions in their hedonic response to different sucrose solutions compared with controls, despite scoring high on the Chapman and Fawcett anhedonia questionnaires (Amsterdam et al., 1987; Berlin et al., 1998).

Moreover, self-reported affective flattening and anhedonia in schizophrenia, as measured by questionnaires, is actually associated with an almost normal experience of emotion as measured by hedonic ratings during the experience of pleasant stimuli, including pictures, films, words, or faces (Burbridge and Barch, 2007; Heerey and Gold, 2007; Trémeau et al., 2010). This inconsistency between retrospective self-reports of anhedonia and the actual on-line experience may well be a consequence of the reliance of clinical questionnaires on the ability of patients to “represent” hedonic experience, as opposed to the hedonic experience per se. This ability to “represent” consummatory pleasure is also a major component of anticipatory and motivational hedonic processes and thus illustrates the difficulty in interpreting self-report questionnaires in the clinical population.

Considerable insight into the distinct consummatory, anticipatory and motivational components of reward processing has been gained from neurobiological and neurochemical studies at the level of the striatum and amygdala of both rodents (Cardinal et al., 2002; Wassum and Izquierdo, 2015) and monkeys (Schultz et al., 2000; Schultz, 2004; Murray, 2007; Bermudez and Schultz, 2010). The anhedonia associated with depression, however, is linked to altered activity within the ventromedial PFC (Keedwell et al., 2005). This is a complex region in humans

composed of a number of discrete cytoarchitectonic areas, including Brodmann's areas 10, 14, 25, and 32, and their contribution to the regulation of reward processing and their interaction with striatal and amygdala reward systems is unknown. This again highlights the need for studies in a primate in which the organization of ventromedial PFC appears far similar to humans than that of rodents (Myers-Schulz and Koenigs, 2012).

We have developed a paradigm in the marmoset that distinguishes between the consummatory and anticipatory aspects of pleasure and uses independent measures of the behavioral and autonomic arousal (cardiovascular) components. The latter is seldom measured in studies of reward processing in animals (but see Rudebeck et al., 2014) but can be an important component of positive emotional responses, as it is for negative emotions, and is often the metric used in humans, alongside self-report questionnaires. Using a Pavlovian procedure [Fig. 4(a)], one version of the paradigm used the "sight of the food" viewed through a transparent door of a food box as the conditioned stimulus. This constitutes the anticipatory period and was followed by the consummatory period when the door opened, resulting in access to the reward. With training, a conditioned rise in systolic blood pressure accompanied by approach behavior toward the food box developed during the anticipatory period, as the animals learned that the presentation of the food box was predictive of subsequent reward [Fig. 4(b)]. In contrast, the rise in blood pressure that accompanied the consummatory period was present from the beginning. The consummatory arousal was, nevertheless, motivational in nature since it was only seen in the context of the marmosets gaining access to their preferred, high incentive reward and not the food pellets that they received daily (Braesicke et al., 2005). Consistent with the role of the amygdala in appetitive conditioning, excitotoxic lesions of the amygdala in the marmoset reduced anticipatory behavioral responses directed toward the conditioned stimulus, as shown previously in rodents (Holland, 1999) and also reduced the conditioned cardiovascular arousal. In contrast there was no effect on the food box approach response or the cardiovascular arousal during the consummatory period. Thus, damage to the amygdala induced anticipatory but not consummatory anhedonia [Fig. 4(c)].

A revised version of the Pavlovian paradigm has since been developed to identify the brain mechanisms underlying the ability of marmosets to adapt their anticipatory hedonic responses to changes in environmental contingencies. Animals were conditioned to discriminate between two auditory stimuli,

either predicting reward (CS+) or an empty food box (CS-). Changes in behavioral and cardiovascular arousal during the CSs were assessed both after a single extinction session, in which the decline in conditioned cardiovascular arousal was measured following omission of the expected reward and after reversal of the reinforcing contingencies, in which the previous CS- became the CS+, and vice versa. So far this revised version has been used to study the contribution of the antOFC to the regulation of appetitive Pavlovian conditioning. Marmosets with excitotoxic lesions of the antOFC failed to show the normal decline in the conditioned systolic blood pressure response after reward omission, instead showing a prolonged arousal response. Moreover, upon reversal, antOFC lesioned animals were much slower to reverse their blood pressure response. Significantly, even when the cardiovascular response was successfully reversed, conditioned behavior was not (Reekie et al., 2008). This was in marked contrast to controls in which there was strong coupling between the rate of reversal learning of the conditioned behavioral and cardiovascular responses. Thus, antOFC lesions caused uncoupling of cardiovascular and behavioral responses. This is particularly relevant for the motivational-anticipatory distinction in anhedonia, as a patient may display cardiovascular anticipatory arousal, but due to uncoupling this may fail to result in motivated behavior.

Future studies in marmosets are ideally placed to focus on the contribution of the distinct regions of the ventromedial PFC in the regulation of striatal and amygdala reward processing, including their modulation of the monoamine systems. Downregulation of striatal activity (Heller et al., 2009; Robinson et al., 2012) and of striatal dopamine receptors in particular (Cannon et al., 2009), has been reported in depressed subjects, along with reductions in amygdala responsiveness to happy faces (Beesdo et al., 2009), the latter being correlated with symptoms of anhedonia (Stuhrmann et al., 2013). An understanding of the relationship between these cortical and subcortical changes and their causal role in the anhedonic symptoms will inform treatment strategies since the symptom of anhedonia appears particularly resistant to current pharmacotherapies. It is largely unresponsive to SSRI based treatments of depression (Shelton and Tomarken, 2001; Dunlop and Nemeroff, 2007) and similarly fails to improve when SSRI administration is used as an add-on therapy in schizophrenia (Sepehry et al., 2007). Whilst drugs that target the dopamine system are successful in alleviating many symptoms of depression and schizophrenia, reports of the direct effects of such drugs on anhedonic symptoms are

mixed (Nutt et al., 2007). This may not be surprising since evidence from psychopharmacological experiments in animals implicates dopamine primarily in motivational and reward prediction processes rather than pleasure per se (Robbins and Everitt, 1992; Salamone, 1997; Berridge and Robinson, 1998; Denk et al., 2005; Schultz et al., 2015). Thus, depending upon what type of anhedonia a patient is displaying, for example, consummatory, anticipatory, or motivational, the neurochemical target for alleviating anhedonia may differ.

UTILITY OF THE MARMOSET IN FUTURE INVESTIGATIONS OF NEURAL AND COGNITIVE DEVELOPMENT RELEVANT TO MENTAL HEALTH

Seventy five per cent of patients with a mental disorder will have shown neuropsychiatric symptoms by age 25 (Kessler et al., 2005), making the first years of life extremely important for understanding the development of neuropsychiatric disorders and their behavioral dimensions. The marmoset has distinct but, relatively, short duration developmental stages, compared with old world monkeys, lasting just a few months each, until they reach adulthood and sexual maturity at approximately 18-20 months (Abbott et al., 2003; see Schultz-Darken et al., 2016 for a comprehensive review). These developmental stages have been well characterized in terms of typical behaviors observed, including social interactions (Chalmers and Locke-Haydon, 1984), vocalizations (Pistorio et al., 2006; Braun et al., 2015), and sensorimotor abilities (Piper et al., 1992; Kaplan and Rogers, 2006; Izumi et al., 2012). Moreover, the impact of early life experiences, such as maternal deprivation and infant isolation, on some of these behavioral outcomes, as well as on levels of cortisol, adrenaline and noradrenaline are already known (Dettling et al., 2002; Pryce et al., 2004; Dettling et al., 2007). This research provides the community with a useful toolbox to study gene-environment interactions and the effects of early life experiences on cognitive and affective development and pinpoints the different milestones of physical ability according to age. As Schultz-Darken et al. (2016) highlight, marmosets pose the great advantage of primarily breeding twins, which allows the direct comparison of subjects with the same genetic background after being placed in different experimental conditions. What remains to be studied is how cognitive functions are acquired in the marmoset in relation to brain development in

order to inform our understanding of the emergence of neuropsychiatric disorders.

In humans, the development of cognitive functions, including reversal learning and attentional set-shifting occur at different ages (Luciana, 2003; Davidson et al., 2006) and are affected by early life experiences and the home environment (Sarsour et al., 2011). Unraveling the genetic and environmental contribution to this development is difficult in humans because of the complexity of, and the lack of experimental control over, their environment. In the marmoset, the relationship between the development of these cognitive processes and their underlying neural circuit can be determined in a highly controlled environment. Taking advantage of their quick progression from infancy to adulthood, the common problem of high attrition rates in human studies of development (Barnett, 1995) and the impossibility of following subjects over a period of twenty years can be overcome. Young marmosets can be assessed with CANTAB tasks using a home-cage apparatus that allows testing in a relaxed environment (Crofts et al., 1999; Takemoto et al., 2011) while neuroimaging will be used to determine brain alterations across the different developmental stages. These aspects of development can also be studied as predictors of anxious phenotypes in adulthood in conjunction with genetic variations, which would provide a rich dataset for studying the development of neuropsychiatric disorders.

CONCLUSIONS

In conclusion, the marmoset is proving a valuable species in which to study many of the symptoms of neuropsychiatric disorders associated with dysfunction within cognitive, negative and positive valence systems (Fig. 1). In the marmoset, a range of tests have been developed which are designed to dissect out the behavioral dimensions that underlie these symptoms. Some of these dimensions are already being successfully mapped on to specific prefrontal circuits and neurochemical pathways within the marmoset using a range of neurobiological techniques including temporary or permanent brain manipulations, microdialysis, microPET, and structural MRI. The new generation of viral mediated tools for targeting chemically specific neural pathways, including opto- and pharmacogenetics, in combination with fluoro-deoxyglucose and receptor ligand based microPET and high field MRI for measuring functional and resting state activity will reveal interactions between and within cognitive and emotional circuits. While

marmosets may not replace Old World macaques for studying certain aspects of higher-order executive functioning, their compact, but highly developed primate brains, small body size and thus ease of keeping large groups of marmosets in spacious accommodation make them the ideal primate for large scale research programs investigating cortical–subcortical circuit interactions. Moreover, their relatively short 5 month gestation and 2 year period of development provides a major opportunity to determine the effects of genetic and behavioral risk factors for neuropsychiatric disorders on the development of these neurocognitive circuits and neurochemical modulatory pathways across childhood and adolescence, in order to understand their impact on complex cognitive and emotional behaviors.

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