The Common Marmoset in Captivity and Biomedical Research

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CHAPTER

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The Marmoset as a Model in Behavioral Neuroscience and Psychiatric Research

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INTRODUCTION

In its mission statement, the US National Institutes of Health provides a clear statement of its focus: "… to seek fundamental knowledge about the nature and *behavior* of living systems and the application of that knowledge to enhance health, lengthen life, and reduce illness and disability" [*emphasis added*, www.nih.gov/about-nih/what-we-do/mission-goals, 2015). Disorders associated with brain or behavioral dysfunction represent the leading disease burden and highest source of lifetime years living with disability on a global basis (YLD: [1]) and together these disorders represent one of the leading contributors to disease-associated mortality worldwide [2]. Clearly, then, there is a premium on understanding both normative behavioral states and their relationship to brain function and the nature of brain dysfunction as is relates to pathological behavioral states.

As in all fields of biomedical science, animal models play an important role in characterizing the basic biology of brain–behavior relationships, in exploring the potential etiology of disorders (genetics, development, environmental perturbations), and in developing and refining treatments in a number of modalities that target dysfunction on brain processing. Nonhuman primates (NHPs) constitute an attractive animal model for behavioral and psychological states for a variety of important reasons. Given the relatively recent common evolutionary origin of primates [3], NHPs share commonalities in complex brain structure and function (homologies), most importantly represented by an increase in brain size and elaboration of the neocortex, especially the prefrontal cortex (PFC) [4]. As a consequence of these morphological adaptations, NHPs are capable of complex cognitions that involve multisensory integration, complex and conditional decision-making, and top-down as well as bottom-up regulation of affect and emotion. Finally, the changes in NHP brain structure and function can facilitate the mediation of challenges associated with group living, including aggression, affiliation, and the establishment and maintenance of long-term complex social relationships that distinguish these species from nonprimate animals [5].

The Utility of Marmosets in Behavioral Models in Neuroscience and Psychiatric Research

From the perspective of a biomedically oriented focus, research on behavioral states (both normative and atypical) is of interest to the extent that it can provide useful information regarding the developmental factors that lead to normative neuropsychological function, as well as the underlying neurobiological properties that contribute to atypical or pathological states. Animal models, primarily rodents, have been widely used in exploring both developmental and neurobiological functions in the behavioral realm [6,7], but progress has been limited with rodent models, relative to primate models, for multiple reasons. First, the complexity of the central nervous system, primarily in cortical regions important for complex thought, cognition, affect, sociality, and decision-making, is not as elaborate in rodents as it is in primates, including humans [8]. The 80 million years since the last common ancestor between rodents and primates has led to divergence in the relative functional morphology and connectivity of the brain, in particular the expansion of the PFC in the primate lineage [9]. Second, the cognitive, social, and behavioral phenotypes of primates are much richer and more complex than those of rodents [10], presumably a result of the elaboration and patterns of connectivity among

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cortical regions of the primate brain. As a consequence, there is a premium in developing suitable NHP models from the perspective of face validity (behavioral phenotypes in primates are more likely to be similar to humans) and construct validity (the genetics, ontogeny, and neural architecture are likely to be homologous in primates and humans).

The common marmoset (*Callithrix jacchus*) represents an NHP species of growing interest in biomedical and behavioral research. Among the reasons for the increased use of this species are both practical and management issues. These include their small size (350–500 g), thereby reducing the need for large enclosures and animal facilities. Marmosets are also highly fecund, capable of producing two twin (or larger) litters per year. Relative to cercopithecine models (e.g., rhesus macaques) or hominoid primates (e.g., chimpanzees), the zoonotic risk posed by marmosets is low.

A more compelling case for the marmoset as a model in biobehavioral and neuroscience research derives from the scientific relevance of a host of features associated with the natural history and associated phenotypes of the species. Marmosets (and most other callitrichinae primates) are obligate twinning species, producing dizygotic twins. Twins are dizygotic or fraternal, and because of unique features of the development of placental and shared embryonic vasculature, twin fetuses exchange embryonic stem cells and multiple signaling molecules across these vascular anastomoses. As a consequence, marmoset twins are chimeric in hematopoietically derived tissues [11] and perhaps in other tissues as well [12]. Twinning is thus potentially important from the perspective of experimental design (e.g., differential twin phenotypes that develop in spite of a shared intrauterine environment [13] and in the exploration of immune–brain interactions [14–16]). From a developmental perspective, marmoset life span trajectories are considerably accelerated relative to other NHP models and humans, passing through the infant stage in several months, reaching sexual and social maturity by 18 months of age, and displaying morphological and behavioral signs of senescence within 6–8 years [17,18]. From the perspective of social neuroscience, the marmoset represents an exceptional model for human sociality [19]. The marmoset shares many features in the realm of social phenotypes with humans, including the fundamental social unit (small nuclear or extended family social groups [20]), offspring rearing dynamics (cooperative breeding, which entails shared infant care by mothers, fathers, and older offspring within the family group [21]), and the nature of adult heterosexual social relationships (consisting of many features associated with social monogamy [22]).

From the perspective of biobehavioral model development, there is a wealth of normative information on marmoset brain anatomy and function, including a well-annotated brain atlas that is continuously updated [23], critical information regarding the structure and connectivity of frontal cortices [24,25], a growing knowledge of sensory processing in a number of modalities [26–29], and details on motor control circuitry [30]. In addition, in the past 5 years a remarkable suite of tools in the neurosciences have been developed with and/or applied to the marmoset central nervous system. Silva [31] recently reviewed advances in imaging of the marmoset brain, and the methodologies include high-resolution structural MRI, functional connectivity among multiple brain regions during processing in a host of sensory modalities, and two-photon laser capture microscopy for monitoring neural activity at the level of individual neuronal cells. A host of techniques have been utilized to alter gene function in the marmoset brain (see review in Ref. [32]), including the production of transgenic marmosets relevant for a number of pathologies associated with the brain, lentiviral retrograde vectors for tract tracing in the brain, and shRNA silencing of gene expression in targeted regions of the brain. Finally, the "proof of concept" for an optogenetic preparation in the marmoset, via the induction of channelrhodopsin into multiple cortical regions of the brain [33], anticipates the potential to manipulate neuronal function in the marmoset brain within tight spatial and temporal boundaries. Thus, within the neurosciences the marmoset may well deserve its recent designation as a "*supermodel*" in the biomedical sense of the word [34].

Organization of this Review

This review of marmosets as behavioral models in biomedical and behavioral research is organized in line with the Research Domain Criteria (RDoC) taxonomy. The RDoC movement at the NIH began in light of decreasing rates of morbidity and mortality from a host of disease states (e.g., cardiovascular disease, cancer) as a consequence of investments in and knowledge gained in basic and clinical science, but mortality rates have remained unchanged for mental illness, and depending on the disorder, prevalence rates across recent decades have remained stable or have increased [35]. The RDoC as a research tool represents a move away from the standard clinical diagnostic protocols for psychological disorders [the American Psychiatric Association's DSM-V (www.dsm5.org) and the World Health Organization's ICD-10, www.who.int/whosis/icd10]. These protocols dictate the diagnosis of mental disorders based on clusters of behavioral symptoms, a procedure that likely poses a potential problem for fundamental research and translational insights into the underlying mechanisms of these disorders.

Two major problems have been identified with these approaches [35–38]. First, the breadth of the diagnostic criteria for any given disorder is wide, and any given diagnostic classification includes multiple symptoms, not all of which need be presented by a patient for a diagnostic decision. It is possible therefore that two individuals diagnosed with the same "mental" disorder would share no symptomology in common, and treating the underlying cause therefore becomes problematic. As an analogy to this issue from a nonpsychiatric context, a patient that presents at the clinic with the symptom "shortness of breath" would not be provided with a single treatment regimen without further diagnostic evaluation. A physician would need to identify the underlying cause of dyspnea. Once diagnosed, differential therapeutic treatments would be created, depending on the cause: heart failure, myocardial infarction, lung congestion, a broken rib, or a state of anxiousness. Second, there are multiple symptoms that are common in dramatically different diagnostic states. For instance, dysfunction in social communication constitutes one of the DSM-V diagnostic criteria for schizophrenia spectrum and other psychotic disorders, social anxiety disorder, and autism spectrum disorder. Given that the brain regions and the perceptual and motor circuitry underlying communication in humans is fairly well established, it would seem logical to look across diagnoses for the underlying etiology of the symptom(s) that are common across psychiatric diagnoses.

The RDoC construct is premised on the notion that looking for underlying pathology as a function of the broad DSM and ICD classifications has not proven to be useful. Instead, an inversion of the process may be more fruitful, that is, utilize the knowledge about normative brain function derived from the breadth of modern neuroscience (from genetics to cognition) and identify the degree to which these multiple mechanisms are disrupted in individuals suffering from "brain illness" [37]. While the utility of the RDoC in a diagnostic context remains unresolved and is a matter of considerable debate (e.g., Ref. [39]), there is a clear heuristic value of the RDoC approach in the context of basic research into the neural mechanisms underlying the symptoms associated with psychopathology. Beginning in 2009, the US National Institutes of Mental Health, under the guidance of the director of the institute, Thomas Insel, has developed and elaborated the RDoC construct to guide basic and clinical research in this area. The outline of the RDoC construct is shown in Table 26.1. The five major research "Domains," identified by multiple experts over several years, constitute important, broad areas of psychological and behavioral processes. Within each Domain are multiple constructs that nest within each Domain. What is critical from the RDoC perspective is that each of the constructs can be operationally defined in multiple model systems, can be measured in normative or in perturbed conditions, and can lead to testable, hypothesis-driven science regarding the brain circuitry underlying each construct and can be revised and validated according to standard scientific methods.

The literature review that follows will highlight significant or innovative behavioral protocols that have been developed or modified for use in marmosets and their relevance for RDoC domains. An exhaustive review of the all of the findings in each of the RDoC Domains is beyond the scope of this contribution, and the examples provided within each Domain are meant

TABLE 26.1 RDoC (Research Domain Criteria), NIMH[a]

Negative Valence Domain	Positive Valence Systems	Cognitive Systems	Systems for Social Processes	Arousal/Modulatory Systems
Acute threat ("fear")	Approach motivation	Attention	Affiliation and attachment	Arousal
Potential threat ("anxiety")	Initial responsiveness to reward	Perception	Social communication	Biological rhythms
Sustained threat	Sustained responsiveness to reward	Working memory	Perception and understanding of self	Sleep–wake
Frustrative nonreward	Reward learning	Declarative memory	Perception and understanding of others	
	Habit	Language behavior		
		Cognitive control		

Major domains (neurobehavioral systems) are listed in **bold**, and constructs (potentially operationalized and measured features of domains) are listed underneath each domain.
[a]*Cuthbert and Insel [35]; Insel [36]; Insel and Cuthbert [37].*

to highlight the ways in which the unique attributes of the marmoset model can be utilized to explore the neurobiological mechanisms underlying the constructs within each Domain. The RDoC approach is inspired by a recent review by Oikonomidis et al. [38], who applied the RDoC organization to marmoset models in a few of the RDoC Domains (especially Valence and Cognition Domain). This chapter will cover Negative Valence, Social Processes, and Arousal in some detail, and readers interested in a fuller discussion of Positive Valence and Cognitive Systems are referred to Oikonomidis et al. [38], for a more complete review. One final comment: considerable information on normative function in marmosets within each Domain is accessible from observations of routine behavior in undisturbed conditions. However, experimental manipulations in the realm of learning, motivation, cognition, sociality, and arousal and other aspects of marmoset behavioral biology yield greater confidence in the inference of causality, and hence the focus in this review will be primarily on experimental models.

MARMOSET BEHAVIORAL MODELS WITHIN THE CONTEXT OF RDOC

Negative Valence Systems

This domain is characterized by the processing of stimuli and generating responses to aversive stimuli and events, and the antecedents (anticipation) and consequences (long-term function) of these stimuli and events. The constructs within this domain include the activation of *fear* circuits associated with adaptive defensiveness from real or perceived danger and can be elicited by both interoceptive and exteroceptive stimuli. Furthermore, constructs also entail the psychological and physiological processing associated with potential aversive events in which the events are distant, ambiguous, or have a low or uncertain probability of occurring (*anxiety*). Further constructs focus on emotional states that result from a sustained or uninterrupted exposure to contexts or stimuli that are normally avoided (*sustained threat*), situations involving deprivation or separation from a significant physical or social resource (loss), and responses to the lack of positive outcomes in the face of efforts to produce them (*frustrative nonreward*).

Two common behavioral models are utilized in the exploration of the responses of marmosets to fear- and anxiety-inducing stimuli. The first involves exposure of marmosets to actual or simulated models of predators, hereafter referred to as the Marmoset Predator Confrontation Test (MPCT) [40,41]. In the northeastern Brazilian coastal forests, marmosets of the genus *Callithrix* are at predation risk from multiple predators, including aerial raptors, terrestrial felines, and terrestrial and tree-climbing snakes [42]. As such, these classes of predators constitute significant naturalistic threats and reliably elicit a cluster of responses even in captive-house marmosets, including modification in locomotory patterns like movement along substrate or jumps from location to location, piloerection, movement of the upper body back-and-forth on a stable substrate, and spatial proximity to the predator stimulus. A prominent feature of predator exposure is the production of species-specific vocalizations that are observed in wild marmosets [43]. Among those typically elicited by predatory stimuli are vocalizations labeled tsik, egg, peep, and twitter, all of which are carefully characterized and rigorously quantified by Pistorio et al. [44]. The second widely used model for fear and anxiety also involves confronting marmosets with an actual or potential stimulus, in this case a human standing in close proximity to the marmosets' cage (HIT—Human Intruder Test). While less ecologically relevant than the MPCT, this assessment tool relies on the notion that marmosets show fear to the presence of humans, either innately or as a consequence of routine captive husbandry or testing. Similar behavioral measures are employed in the HIT as in the MPCT.

From the perspective of test validation of these common methods, an explicit comparison of the responsivity of marmosets to the HIT and MPCT revealed that the two tests induce similar behavioral responses [45]. This investigation demonstrated a strong, positive correlation between the two methodologies. Furthermore, individual variability among marmosets in their response profiles remained highly stable in independent assessments separated by as much as 3.5 years. Neural and neurochemical correlates of high-responsive (low proximity to stimulus, high rates of tsik and tsik-egg calls) versus low-responsive marmosets were documented. High-responsive marmosets had lower levels of serotonin (5-HT) in the amygdala as measured by microdialysis and smaller structural volume of the anterior cingulate cortex (ACC), an important region for the integration of cognitive and emotional information. While the two methodologies are correlated, another side-by-side comparison of the two protocols revealed greater behavioral responsiveness of marmosets to the HIT than to MPCT [46].

The MPCT has provided insight into both the behavioral components associated with exposure to fear- and anxiety-inducing stimuli and further details on the neural mechanisms that underlie these behavioral elements. A multivariate principal component analysis (PCA) of differential behavioral responding by marmosets when confronted with predator stimuli or human intruders [47] revealed two significant components that account for significant variance: **emotionality**, a PCA dimension

that loads heavily on visual avoidance of the threatening stimulus, reduced locomotion, and greater distance from the stimulus, and **coping**, which loads primarily on tsik and tsik-egg vocalizations. Support for the role of predator-induced vocalizations as a coping mechanism for marmoset derives from two findings. First, high rates of tsik vocalizations during predator exposure are associated with low baseline cortisol (as measured by hair cortisol [48]). Second, playback of recorded tsik calls to marmosets during social isolation (a procedure that typically elevates cortisol [49–51]) eliminates separation-induced cortisol responses [52]. A third potential behavioral component relevant to RDoC constructs (**anxiety**) derives from the consequences of repeated exposure to predatory stimuli, which reliably elicits elevated rates, relative to baseline or acute exposure to predatory stimuli, of scratching, self-grooming, and scent-marking behavior [53].

A third paradigm common in this arena is traditional aversive Pavlovian (classical) conditioning, in which an initially neutral conditioned stimulus (CS, e.g., a light, a soft tone, or an environmental context) is paired with an aversive unconditioned stimulus (US, e.g., a loud noise, an exteroceptive shock, a predatory stimulus), and with sufficient associative pairings, the CS acquires the ability to elicit conditioned fear or anxiety response. Marmosets easily acquire conditioned responses under these contexts, as measured by increased autonomic output (heart rate and blood pressure) and enhanced vigilance elicited by the previously neutral or irrelevant CS [54–57].

Additional behavioral models in the marmoset relative to the Negative Valence Domain have not received as much attention as the HIT and MPCT but have the potential to contribute to the development of unique measures of behavioral phenotypes and their underlying neurobiology. Among these methods are open-field testing, a modification of the rodent model in which behavioral indices of fear/anxiety as well as spatial navigation within the open field are assessed [58]. In another modification of a standard rodent model for fear/anxiety (the elevated plus maze), Wang et al. [59] tested location preferences of marmosets in a multiple-chambered testing box, in which some compartments had opaque walls and others had transparent walls. In general, marmosets showed a preference for the transparent chambers, and this technique may prove useful in protocols that induce anxiety-like states, either behaviorally or pharmacologically.

Most of these behavioral protocols have yielded significant insights into the basic neuroscience of Negative Valence constructs in the marmoset, including structural regions of the brain that are important regulators of responsiveness and in the neurotransmitter systems that modulate these brain circuits. Structurally, the orbitofrontal cortex (OFC) and PFC in marmosets appear to independently play an important role in modulating responses to threatening stimuli because bilateral lesions of either area enhanced emotional components and reduced coping components in an MPCT [47]. In the context of aversive Pavlovian conditioning, marmosets with lesions of the OFC and PFC maintain elevated conditioned HR responses during extinction trials (CS only, no US), especially in PFC-lesioned marmosets [54]. In the same study, animals lesioned in either OFC or PFC exhibited elevated emotional responses in the HIT, but reduced coping responses were noted only in the marmosets with PFC lesions, suggesting a structural separation of function for these components of emotional responding. Marmosets that are highly responsive in either HIT or MPCT have reduced volume of the ACC, an important region for the integration of cognitive and emotional information [45]. Finally, localized pharmacological manipulations in restricted brain regions highlight important regulatory circuit nodes. Local deactivation via a GABA agonist of Area 25 in the PFC reduced the strength of aversive Pavlovian conditioning, whereas deactivation of Area 32 enhanced some autonomic measures of conditioned responding [57].

Pharmacological manipulations or measurements in the context of this Domain have also produced findings of basic and potentially therapeutic importance. The $GABA_A$ agonist diazepam, a widely used anxiolytic treatment, clearly impacts behavioral and physiological measures in these paradigms and reveals the importance of the GABA system in regulating fear/anxiety. Marmosets given anxiolytic diazepam in the HIT exhibit reduced threat postures toward the intruder and increased proximity to the intruder, but administration of anxiogenics ($GABA_A$ inverse agonist or amphetamine) does not produce augmented behavioral reactivity in the HIT [60]. Diazepam also reduces behavioral indices of anxiety (phee calls, vigilance) and eliminates the normal preference for spending time in the periphery in the open-field test [58]. Simultaneous testing of marmosets in multiple behavioral paradigms has revealed a differential sensitivity of response characteristics to varying doses of diazepam. High doses of diazepam reduce responsiveness of marmosets in both the HIT and MPCT tests, whereas lower doses of diazepam are effective only in the MPCT model [46]. Treatment of marmosets with the inverse $GABA_A$ agonist FG-7142 increases tsik and tsik-egg vocalizations to comparable levels as those noted in novelty exposure and MPCT [61]. Other neurotransmitters no doubt play a role in the manifestation of fear/anxiety phenotypes in marmosets, including CRH [62], dopamine (DA) [63], and 5-HT [64].

A recent study has provided evidence of a genetic substrate for variation in responding in the behavioral protocols that tap into constructs within the Negative Valence RDoC domain. Santangelo and colleagues [64]

genotyped marmosets from three sources—the Cambridge University colony, the NIH colony, and a wild population in Brazil. They documented variable number tandem repeat polymorphisms in several loci of the promoter region of the 5-HT transport allele, *SLC6A4*. On a population basis, a dinucleotide polymorphism in the third repeat and two single nucleotide substitutions in the fourth and 23rd repeat yield the haplotypes AC/C/G in 49.6% of the target colony and CT/C/C in 42.4% of a colony, with roughly similar proportions in the second colony and in wild marmosets. These polymorphisms have meaningful consequences, as qPCR revealed the highest SLC6A4 expression in the CT/C/C haplotype, the lowest in AC/C/G, and intermediate expression in heterozygotes for this polymorphism. Responses in the HIT revealed behavioral consequences of these polymorphisms as well, with AC/C/G marmosets displaying the highest anxiety and lowest coping scores and CT/C/C marmosets exhibiting low anxiety and high coping. Clinical relevance for the use of genetic information for tailoring "personalized" pharmacological treatments for patients on the basis of genotype was demonstrated in the marmoset model by the observation that the selective serotonin uptake inhibitor citalopram enhanced HIT scores in AC/C/G marmosets, but reduced HIT scores in CT/C/C marmosets.

Positive Valence and Cognitive Systems

This section describes behavioral models in two Domains because the distinction among them is not as clear in animal models as they are in the context of human phenotypes. The Positive Valence System addresses constructs associated with unconditioned and learned/adaptive responses to positive motivational stimuli or context. Among the constructs are processes associated with approach tendencies to innate or learned stimuli (*approach motivation*), reward-seeking behavior and hedonic responses to rewards (*initial responsiveness to reward attainment*), and the biobehavioral consequences of attaining reward (*sustained/longer-term responsiveness to reward attainment*). Learning and cognitive processes are reflected by capacities in reinforcement learning and differentiating among stimulus-reinforcement outcomes (*reward learning*), and the persistence of behavioral responses or cognitive processes associated with reward without excessive cognitive resources and/or in the absence of changes in reinforcement outcomes (*habit*). The Cognitive Systems Domain addresses the continuum of processes associated with detecting environmental stimuli (*attention*), peripheral and central computational processing of these stimuli in single and multiple sensory domains (*perception*), the ability to integrate, via cognitive and affective systems, environmental contexts and select adaptive responses to these contexts (*cognitive control*), and the encoding, maintenance, and recall of relevant information for specific tasks or goal outcomes (*working memory*). The constructs of *declarative memory* and *language* (symbolic representation) will not be considered in this review. A common protocol for generating experimental protocols assessing learning and cognition in marmosets, derived from the Cambridge Neuropsychological Test Automated Battery (CANTAB), can be found in Spinelli et al. [65]. Details on training marmosets to provide response selections using touch-sensitive computer screens can be found in Takemoto et al. [66].

Among the most straightforward tasks for assessing the reinforcing property of stimuli for an organism is the conditioned place preference (CPP). Typically a specific environmental context (chamber, room, or other environmental cue) is repeatedly paired with the presentation of a potential rewarding stimulus, whereas a second distinct context does not lead to the stimulus. The subsequent development of a preference for the context that predicts the delivery of the stimulus is a gauge of the positive rewarding property of the stimulus, whereas avoidance of the context is taken as evidence that the stimulus is a negative reinforcer [67]. Marmosets form a CPP for several reinforcing stimuli, including cocaine [68] and sweet/high-fat food (chocolate) [69].

Reversal learning is a common paradigm for assessing generalized discrimination learning, and in particular to assay response persistence in the face of altered reward consequences. Typically marmosets are presented with two stimulus objects, one associated with reward and the other nonrewarded. Once criterion performance (e.g., 75% choice of the correct stimulus) on that set of stimuli is established, reward contingencies are reversed; the responding to the previously unrewarded stimulus now leads to reward, and vice versa. This protocol has identified both structural and neurochemical correlates of performance in the task. Different neurotransmitters in the medial caudate nucleus appear to be critical for successful reversal learning in marmosets because depletion of DA in the caudate disrupts successful reversal learning, whereas depletion of 5-HT does not [70]. Lesions of the medial striatum and OFC also disrupt rapid reversal learning, whereas amygdala lesions do not affect the transition to new stimulus−reward contingencies [71]. Lacreuse and colleagues have addressed the role of sex steroid hormones in modulating learning processes in marmosets in the context of the reversal task. Estradiol appears to disrupt reversal learning performance because relative to untreated ovariectomized (OVX) females, OVX females given estrogen replacement therapy (ERT) took more trials to reach criterion and exhibited a higher number

of errors in the task [72]. With repeated exposures to sets of reversed reward contingencies, control females made fewer errors to reach criterion performance, whereas estrogen-treated females made more errors. Hormone replacement appears to have sex-specific effects because untreated and testosterone-treated male marmosets did not differ on reversal learning performance [73].

Marmosets also perform well in the more complex reversal paradigm, probabilistic discrimination learning and reversal. In this task, two stimuli are not associated with reward certainty (e.g., selection of stimulus A leads to reward [or nonreward] 100% of the time). Rather, both stimulus cues are associated with differential probabilities of reward, in which responding to the "correct" stimulus leads to reward in 80% of the trials and nonreward in 20%, and to the "incorrect" stimulus leads to reward in 20% of trials and nonreward in 80% of trials. Performance on this task is related to serotonergic activity as demonstrated by site-specific depletion of 5-HT by the local administration of 5,7-DHT [74]. Reducing 5-HT in either the amygdala or the OFC inhibited the acquisition of the initial task and performance in the reversal phases of the task. Reducing 5-HT in the amygdala altered the marmoset's sensitivity to reward contingency, reducing responding to the "correct"' stimulus and enhancing responding to the incorrect stimulus, which results in overall lower reward density for the marmosets. These data suggest that the amygdala and OFC are critical for learning and adjusting to changing reward outcomes, and that lower 5-HT in the amygdala alone serves to mediate complex probabilistic reinforcement contingencies within the context of reversal learning.

A second common behavioral task within these Domains is the barrier-reach task. In the typical experiment, food is made available to the marmoset that is available by performing a fixed motor reach response (e.g., reaching from the right or left side). This is accomplished in a number of ways, but placing food inside a transparent or opaque cube with a single open face to access the food is common. Once a motor response is established by the marmoset in food acquisition, the reaching response required to access the food is altered by modifying the orientation of the cube (e.g., shifting the open face from the left to the right). This task is particularly important for assessing response flexibility (good performance) and perseverative tendencies (poor performance). Performance on this task in marmosets is reduced by drugs known to affect neurotransmitter systems involved in schizophrenia in humans (the DA D3 receptor agonist PD-128,907 and the NMDA-receptor antagonist ketamine) and enhanced by treatment of marmosets with blonanserin, a pharmacological agent that antagonizes DA D2/3 receptors and blocks 5-HT2A receptors [75] but is insensitive to estrogen replacement in OVX female marmosets [72].

In many cases marmosets are useful for experiments that explore the interstices between Negative, Positive, and Cognitive Domains. Shiba et al. [56] is a good exemplar. Marmosets were initially classified as low versus high reactive to a fear/anxiety stimulus in the standard Pavlovian model described above. Marmosets were then presented with two behavioral tasks: one uses the reward value of a food as a discriminative stimulus with unexpected reward outcomes (an OFC-dependent task) and the second task was the barrier-reach task described earlier in this section, which is a PFC-dependent task. In the first task, marmosets were presented with two transparent boxes, within which were located either an unreachable high- or low-preference food item. The reward contingencies for touching either box yielded reversed reward outcomes—touching the box containing the highly preferred was not rewarded, whereas touching the box with the low-preference food item led to the delivery of highly rewarding syrup bread. Thus, the high probability response of touching the box containing the highly preferred food had to be inhibited to receive a reward. The magnitude of conditioned fear and anxiety in the Pavlovian phase of the experiment predicted performance on the two tasks. More perseverative error in the first cognitive task (touching the high-preference food box) was associated with poorer conditioned vigilance in the Pavlovian task, whereas more perseverative error in the barrier-reach task was associated with lower baseline blood pressure in the Pavlovian trials.

Systems for Social Processes

The scope of this Domain is self-evident from its title and includes multiple components of features associated with conspecific sociality. Among these are the quality and patterning of affiliative social interactions and the consequent development of social bonds (*affiliation and attachment*) and the production, perception, interpretation, and responses to the social stimuli that mediate these interactions and sustain the social bonds (*social communication*). Awareness of one's role in social interactions is reflected in the constructs associated with self-awareness and self-agency (*perception and understanding of self*) and in the ability to recognize the identity of partners, their capacity for agency, and to predict or interpret a partner's mental state (*perception and understanding of others*).

Affiliative processes in marmosets have been explored, including caregiver–offspring attachment and "pair-bonding" in adult males and females. Within the context of caregiver–offspring affiliation, the focus has been on two broad areas: features associated with regulatory processes for caregiver interactions with

infants and the consequences of variation in the quality and quantity of caregiving on subsequent offspring development. With regard to the regulation of parental care, correlational studies have implicated a suite of neuroendocrine modulators of parental care, including estradiol, testosterone, glucocorticoids, prolactin, and oxytocin (OT) [76–79]. Experimental models to explore parental motivation include instrumental learning in which the reward state is access to infant stimuli [80] and exposure and response to infants or infant-related stimuli [81–84]. These tasks have revealed that sensitivity to, and interest in, infants and their stimuli are regulated by multiple neuroendocrine systems, and that the behavioral measures are often contingent on age or previous exposure to infants within the social group.

The prominent experimental model to explore the neurobiological and behavioral sequelae to caregiver–infant attachment is the caregiver deprivation model championed by Pryce and colleagues. This model involves short-term, 30–120-min separations of infant marmoset from caregivers from 2 to 28 days of age [85], and the consequence of this disrupted caregiver–infant affiliation is widespread across multiple physiological systems, including behavioral, reward, and cognitive processing, responses to stressors, and gene expression in multiple neurotransmitter systems [86,87]. Less-invasive models include those that examine the impact of normative variation in offspring care on subsequent biobehavioral development. These models demonstrate that "adverse" patterns of early caregiving (e.g., high rates of infant rejection and transfer among caregivers) also produce long-lasting changes in neurobiology and behavior [88–90].

While there is considerable academic argument regarding whether marmosets are strictly "socially monogamous" (e.g., Ref. [91], and articles therein), there is no argument that the close social relationships between adult male and female marmosets, characterized by coordinated activities, high levels of grooming and proximity, cosharing of infant care responsibilities, and joint defense of territories [92], are distinct from other primates considered "nonmonogamous" [53]. Several behavioral protocols have been used to evaluate the establishment, persistence, and strength of this affiliative relationship. The first paradigm is partner preference testing in which marmosets can choose to spend time and/or interact with partners or opposite-sex strangers in a simultaneous choice task [93–95]. With regard to translational potential, the sensitivity of partner preference to environmental and social context should be considered a strength, given the complexities of human social relationships. Partner preference and pair-directed affiliation in marmosets is sensitive to OT manipulations, in that treatment with an OT antagonist reduces affiliative behavior in newly paired marmosets [95] and reduces interest and interactions with an unfamiliar opposite-sex partner in well-established pairs [94]. In addition, correlational studies have revealed that closely bonded family members, including breeding pairs, exhibit highly correlated levels of urinary OT [96], providing additional support for nonapeptide involvement in social affiliation in marmosets.

The second task for assessing pair-related affiliation and attachment involves measuring the behavioral and physiological responses to temporary separation from partners [49,51,97,98]. In heterosexual pairs, partner separation and housing in a novel environment is associated with elevated cortisol, and the presence of the partner [51], but not an opposite-sex stranger [98], can reduce or buffer the stress response in this context. In fact, presentation of phee calls from the partner but not calls from an opposite-sex stranger during separation also buffers the stress response [49]. In long-term same-sex pairs of marmosets, separation stress is buffered by both partners and same-sex strangers in males, but the presence of neither partners nor strangers served to buffer cortisol responses to separation in female marmosets [97]. This would seem an appropriate model system to explore dynamic changes in the socially mediated changes in the HPA axis, and the role of the hippocampus, temporal cortex, and PFC in translating these social buffering effects into physiological and behavioral regulations.

Marmosets have a rich vocal repertoire that mediates a host of intra- and intergroup social interactions. Knowledge of the information content of these social signals and the ways in which they are centrally evaluated in the brain can serve as a useful base to explore normative and atypical vocal communication processes. A standard protocol for assaying information content in marmoset calls involves the playback of recorded marmoset vocalizations and documenting behavioral differences in response to these calls. Information content regarding signalers in marmoset phee calls was experimentally evaluated by Smith et al. [99]. Normative acoustic characteristics of adult phee calls were quantified, and sex differences were noted in numerous acoustic parameters. Synthesized vocalizations that included the important differences in frequency components of the calls were generated, and the responses of marmosets to playback of synthetic and natural calls did not differ; both calls elicited enhanced vigilance, and vigilance was greater for male-typical than female-typical calls. Systematic manipulation of individual components of call structure eliminated differential responding to synthetic phee calls, suggesting that perception and interpretation of the sex of the caller requires a holistic, multivariate assessment of call characteristics. Similar work has been conducted on natural versus synthetic calls in multiple call types, with neural confirmation that these two classes of stimuli are processed

similarly [100]. The potential for studying the behavioral and neural processing of acoustic social signals in real time in marmosets has been enhanced by the development of a sophisticated behavioral model of communicative "conversations" [101,102]. In this model, recorded exemplars of marmosets are played back to subjects with varied probabilities and timing, as "virtual marmosets" in an interaction. The patterning of the vocalization by the real marmoset is contingent on these manipulations in calls from the virtual marmosets [103]. Given that vocal exchange patterns appear to be learned during ontogeny in marmosets [104], this behavioral technique has implications for both adult vocal interactions and vocal development.

Several groups have utilized the expression of immediate early gene (IEG) products, signals of early transcriptional activity within neurons that are responsive to stimuli, to identify brain regions associated with the perception and processing of species-specific acoustic signals in marmosets. Marmosets listening to species-specific vocalizations have differential IEG expression in regions of the brain that differ by task (listening to calls, producing calls, and engaging in antiphonal calling). Perception of calls is associated with IEG expression (cFOS) in the ventrolateral PFC and regions of the auditory cortex: producing calls is associated with distinct activation in the premotor cortex, and vocal exchanges activate the perirhinal cortex in addition to the areas previously mentioned [105]. Using a different IEG marker (Egr-1), Simões et al. [106] demonstrated that vocal exchanges also enhanced IEG expression not only in the PFC but also in the ACC. Single-cell recordings in the premotor cortex also support the role of this region in vocal production in marmosets [107]. For a more complete review of the neurobiology of marmoset vocal communication see Refs. [108,109].

Given that marmosets utilize scent-marking behavior extensively in social interactions and have individual- and sex-specific olfactory "signatures" [110,111], the neurobiology underlying olfactory communication would appear ripe for exploitation. fMRI studies have revealed enhanced BOLD signaling in hypothalamic regions of male marmosets exposed to the odors of sexually receptive females [112] and in cortical and subcortical regions associated with reward and emotional processes [113], suggesting a complex integration of information across the brain. The development of a behavioral conditioning model demonstrating that neutral stimuli can be conditioned with sexually arousing female stimuli in male marmosets [114] anticipates future sophisticated experimental assessments of social olfaction and its peripheral and central processing in marmosets.

Evidence for the ability of marmosets to perceive and understand others derives from several behavioral protocols. A fundamental demonstration that marmosets can perceive that other conspecifics have agency and goals derives from a paradigm in which marmosets watch video presentations of one of three actors spending time with and exploring one of two distinct objects [115]. After a short gap, marmosets are presented with a second video, with the actor either interacting with the same object but in a different location (expected outcome) or interacting with the second object that is now in the same location as the object of interest in the first video (unexpected). As with looking time at visual stimuli in human infants, marmosets spend more time looking at the unexpected than the expected object. The critical manipulation in this experiment is the nature of the model in the video: a marmoset, a quadrupedal marmoset-ish robot, or a black box. As expected, marmosets spent more time looking at the unexpected outcome, but only when the actor was a marmoset or the robot. When given access to the actual objects portrayed in the video, marmosets spent more time with the "correct" object but again only when the video actor was a marmoset or robot, demonstrating social learning only when the model possessed "agency."

Marmosets provide an excellent opportunity to study the perception of others in paradigms that require two or more partners to acquire or distribute food rewards, which speaks to the importance of social life in many aspects of the behavioral biology of this species. Several tasks have been employed that require cooperation or altruism among interacting marmosets, in which both marmosets must respond cooperatively to access food items [116] or act "altruistically" to provide food to others, while not receiving rewards themselves, either in a dyadic context [117,118] or in a context in which an individual provides support to multiple group members [119,120]. Marmosets easily learn to perform cooperative tasks, although like many features of marmoset biology, the ease with which cooperation occurs varies as a function of relatedness and status of cooperating partners [116]. Marmosets do exhibit "other-regarding" sharing of food in the altruistic food-sharing paradigms, although again the nature of social relationships between the donors and recipients, and the social role of the "donor" in the family group determines the probability of altruistic responding [117,118,120]. OT is related to these measures of prosociality. The degree of OT synchrony among dyad members predicts levels of prosociality, with higher dyadic synchrony in OT levels correlated with a higher likelihood of provisioning food to the partner [120]. Experimental manipulation of OT paints a different story; OT reduces sharing in both adult males and females with unfamiliar opposite-sex recipients but does not alter altruistic sharing with long-term pairmates [118]. It is certainly the case that OT synchrony measured in urinary samples provides a different index of OT activity than

pharmacological manipulation of OT, but nonetheless both recent papers point to an important role for OT in cooperative social behavior. These paradigms have the potential to serve as springboards for more detailed explorations of neuroendocrine mediation of complex social traits such as cooperation and altruism and the cortical decision-making circuits that regulate complex decision-making in a social context.

The ability to perceive and understand self-awareness and agency is a difficult concept to study in pre- and nonverbal organisms, and this certainly applies to marmosets. In spite of its faults (of which there are many, e.g., Ref. [121]), the predominant test in NHP for self-awareness remains the "mirror test" [122]. While no studies have been published regarding the performance of common marmosets on this task, two papers have appeared on other closely related callitrichinae species. Pygmy marmosets with lengthy exposure to mirrors in their home cages showed no evidence of mirror-mediated self-directed behavior, although they appeared to use the mirrors to gain visual access to neighboring groups and exhibited aggressive displays toward individuals in these groups [123]. Thus, while pygmy marmosets show no evidence of self-awareness, they "understand" or at least utilize visual information provided by mirrors. Likewise, cotton-top tamarins with long-term exposure to mirrors spent considerable time looking into the mirrors, displayed repeated actions in front of the mirrors, but showed no evidence of self-directed behavior that appeared to be mirror-guided [124]. These negative findings and absence of findings point to two potential interpretations: (1) like most nonhominoid primates [122], marmosets do not possess the cognitive complexity to express self-awareness or (2) we as investigators lack the cleverness and sophistication to assess this question.

Arousal/Modulatory Systems

The final Domain covers neural systems associated with the coordination of responses to environmental stimuli to achieve a homeostatic state or to effect appropriate responses to environmental change and hence an appropriate allostatic state. Constructs in this Domain include generating an appropriate physiological state for the current interoceptive or exteroceptive context (arousal), maintaining appropriate 24-h patterns across multiple organ systems and behavior (circadian rhythms), and the organization of sleep/wake states in the service of optimizing physiological and behavioral functions (sleep and wakefulness).

Marmosets have proven to be excellent models for photic and nonphotic regulation of the circadian rhythm and represent a model species that is diurnal or crepuscular, as opposed to the commonly used nocturnal rodent models. The free-running cycle (τ) in this species under constant 24-h dim lighting conditions has been estimated in multiple studies (e.g., Refs. [125–127]), and with little variation it has been established as 23.3 h. Like other species, entrainment of the circadian cycle under constant 24-h illumination can be accomplished by photic stimulation with a variety of frequency and timing manipulations [125,126]. What is particularly compelling from an RDoC perspective is the sensitivity of circadian rhythmicity to developmental and social variables. There are important age and sex differences in circadian activity profiles in marmosets, with juveniles more active than adults through the active phase, adults showing earlier activity onset than juveniles, adult males showing the earliest phase-onset and -offset for the active period, and a shifting to later activity onset in postpubertal than prepubertal marmosets [128]. Daily rhythms appear to be exquisitely sensitive to social contexts. Entrainment of activity profiles is more tightly coupled in individuals within a family group than between family groups, and the strongest coupling occurs between sibling twin pairs, followed next most closely by male–female breeding pairs [129]. While direct and preferential social interaction, cofeeding, and coincidental allogrooming could be among the mechanisms by which tight activity coupling is mediated, there is also evidence that vocal communication signals can also play an important role. Rates of phee calling in marmosets exhibit a bimodal distribution during the light phase, with the highest rates occurring shortly after light onset. Entrainment to "light onset" can occur in marmosets housed indoors under constant 24-h dim light conditions, under conditions where they can hear phee calls from marmosets exposed to normal light cycles [127].

Marmosets also appear to be a useful model for exploring the circadian and thermoregulatory changes that are associated with menopause in women [130]. Gervais and colleagues [131] utilized implanted biotelemetry to monitor sleep quality (assessed by EEG) and core body temperature in OVX female marmosets before and after ERT. Both high and low doses of estrogen (6 or 12 μg/kg day) significantly reduced core body temperature during the night phase. EEG analyses revealed fewer nighttime arousals and higher delta wave power, both indices of better-quality sleep.

Circulating plasma cortisol concentrations in marmosets follow the circadian pattern typical for diurnal mammals, with rising concentrations as the light phase approaches, highest concentrations in samples collected shortly after activity onset in the morning, with falling concentrations throughout the day until the nadir 2–4 h after the onset of the dark phase [132]. Similar patterns derive from samples that can be collected

noninvasively, including urine [50], saliva [133], and fecal samples [134]. The timing and patterning of circadian cortisol rhythms appear to be sensitive to social context [89,90]. Morning cortisol concentrations in isolated, singly housed marmosets and marmosets in unstable groups with high aggression are higher than those in marmosets housed in stable breeding pairs or family groups. Furthermore, rather than exhibiting the normative reduction in cortisol in the afternoon, cortisol concentrations remain elevated in those marmosets living in unstable or isolated social contexts, and measures of behavioral arousal are strongly correlated with afternoon cortisol levels. In light of the fact that of the multiple parameters that can be measured in the HPA axis, the biggest predictor of risk for depression and other disorders is elevated afternoon cortisol, altered circadian cortisol in marmosets may therefore be a useful proxy measure in models for depression and psychopathology.

Assessing circadian rhythms in marmosets demonstrates the ways in which behavioral models can cut across RDoC domains in meaningful ways, including Arousal and Positive Valence. Marmosets not surprisingly form a CPP for a context and location in which food is available [135]. In an interesting twist, the strength of the CPP was contingent on a match between the time at which associative learning trials were conducted (either in the early morning or late afternoon) and when CPP was assessed. CPP performance was robust when the time of assessment matched the time of training but was effectively eliminated when the times did not match. This result suggests that the phase of the circadian cycle forms an important part of the broad stimulus properties (interoceptive and exteroceptive) to which reward learning in marmosets is sensitive.

SUMMARY

The utility of the marmoset model in behavioral neuroscience is borne out by an NCBI PubMed search on *Marmoset AND* (*Brain OR Behavior*), which yields over 1900 citations, 1300 of which have been published since the year 2000. Interpreting this vast literature is a daunting task, but one that is given structure and becomes more heuristically valuable by adopting the RDoC classification matrix, as illustrated by Oikonomidis et al. [38] and this chapter. This review indicates that explorations of the nature of brain−behavior relationships in the marmoset have the potential to speak to all Domains and most constructs in the RDoC framework. This is especially so in the case of the Social Processes Domain, given the analogous similarities in the social systems of the marmoset with those of humans and the homologies between the human and the nonhuman primate brain. The unique position of the marmoset in this regard has been recognized by others [19,136−138].

This review has identified experimental behavioral models that have been employed in the service of understanding the ways in which the brain generates behavioral and social patterns in marmosets and also the ways in which brain structure and function in turn are altered by environmental and social experiences. The degree of sophistication of the neurobiological methods that have been employed vary primarily as a function of the degree to which the neurobiological measures require invasive or restrictive protocols (e.g., single-cell recording, restraint within an fMRI) or can be conducted with minimally or noninvasive protocols (e.g., measurement of neuropeptide metabolites in urine; oral or nasal administration of neuropeptides). Obviously, the degree of resolution with regard to neural function and organization varies as a consequence of the method used, but so, too, does the ability to study complex, interactive behavior in a complex, interactive, and dynamic social group. In a real sense, then, a form of Heisenberg's Uncertainty Principle applies in this context. Simply paraphrased, Heisenberg pointed out that two key components were required to understand some features of atomic physics—a particle's location and its momentum. By measuring either location or momentum, the ability to measure the other was compromised. To complete the analogy as it applies in the current context, methodologies that provide greater precision, resolution, and timing of neural activity that mediate complex affective, cognitive, and social processes require less complexity and sophistication in the behavioral systems that are under study. This conundrum echoes the cogent arguments of Krakauer et al. [139] that generating meaningful basic and translational research in neuroscience requires that experiments be designed and carried out in light of species-specific evolutionary adaptations, with an eye toward species-specific sensory−motor capacities, and an emphasis on appropriately complex social contexts.

The new methodological innovations that were highlighted at the outset of this chapter may provide a way to reduce the Uncertainty Principle as it applies to marmoset brain−behavior relationships. These include the potential to remotely activate selective neural circuits in freely behaving marmosets via optogenetic stimulation or to alter gene expression during development via transgenic models or in adulthood via shRNA silencing. In that sense, the utility of the marmoset model in behavioral research will likely grow in its stature as an important transitional and translational biomedical model in the neurosciences increases—a 'supermodel', indeed!

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