



## Meetings Report

## Motivation on the Mediterranean: Reward, compulsions and habit formation

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## ARTICLE INFO

## Article history:

Received 9 April 2009

## Keywords:

Addiction  
Compulsion  
Habit  
Motivation  
Obsessive  
Reward

## ABSTRACT

The 2007 Motivational Neuronal Networks meeting, held in Porquerolles, France was organized to generate debate and discussion on issues relating to reward, compulsion, and habit formation. The conference consisted primarily of four workshops that brought researchers from a wide variety of fields together in an informal atmosphere designed to facilitate interaction. This report is based on the detailed notes taken during the wide-ranging discussions, and summarizes major areas of both consensus and disagreement, as well research topics that are likely to be high priorities in the years to come.

## 1. Introduction

In May 2007 the 4th Motivational Neuronal Network meeting was held on the Mediterranean island of Porquerolles, just off the southern coast of France. The purpose of this meeting was to encourage vibrant discussion on issues related to reward, compulsions and habit formation in an informal and congenial atmosphere. Apart from two engaging plenary lectures, delivered by Peter Redgrave of the University of Sheffield and Trevor Robbins of Cambridge University, the format consisted entirely of workshops and poster sessions designed to facilitate interaction. Each of the 84 attendees participated in all four workshops (described in more detail below); to facilitate discourse, each workshop was divided into groups of approximately 30 people, with workshop topics and a list of related questions provided by the organizing committee. This particular format provides an alternative to the panel sessions of more traditional meetings, bringing experts from a number of disciplines into the same room to impart a multidisciplinary flavor that ensured integrative and wide-ranging discussions. Detailed notes were taken in all three discussion groups for each of the four workshops by assigned scribes; these

notes have been integrated and summarized below to provide a brief account of the many lively discussions.

## 2. Workshop I: the dorsal/ventral divide: a dated concept?

*Behavioral similarities/differences between the dorsal/ventral striatum—do they collaborate to orchestrate goal-directed behavior? How?* The first workshop focused on the similarities and differences in the roles of the dorsal and ventral striatum with respect to behavior. Initial discussions supported the idea of a dorsal/ventral divide, focusing on both anatomical differences and the differential effects of dopamine in dorsal and ventral striatum. Anatomically, the striatum was originally divided into its dorsal and ventral components that receive predominantly sensorimotor-related and limbic-related input, respectively (Alexander et al., 1986). Also recognized was the importance of considering the nature of the afferents (i.e. specific versus diffuse projections). Behaviorally, a dorsal/ventral divide is particularly evident with respect to differential effects of dopamine lesions and amphetamine on locomotion in dorsal versus ventral striatum. Furthermore, it was suggested that associations in dorsal striatum are more rigid and inflexible than the ventral striatum, possibly resulting in more efficient processing and less use of neural resources, while ventral striatal associations are more flexible and allow for a greater range of possible actions.

While there is certainly a case to be made for a dorsal/ventral divide of the striatum, other evidence suggests this view may be somewhat simplistic. Differences in drug self-administration,

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conditioned place preference and locomotion due to lesions or pharmacological manipulations of striatal subregions appear to correspond more closely to a medial/lateral, rather than a dorsal/ventral, striatal divide. Moreover, neuronal recordings from the striatum during behavioral tasks rarely show distinct differences in firing rates or patterns in striatal subregions. It was noted that in rodents, the primary striatal distinction is dorsal versus ventral; however, the primate literature may be more useful when attempting to tease apart the relationship between anatomy and function. For example, in primates, discussions on striatal structure and function focus more on differences between caudate and putamen as opposed to dorsal/ventral differences. The somatotopic organization within the striatum is organized such that afferent gradients largely run dorsolateral to ventromedial, as well as anterior to posterior, and not in a strict dorsal/ventral pattern (Voorn et al., 2004). Accordingly, it was suggested that the term “dorsal/ventral divide” is much less accurate than “dorsolateral to ventromedial gradient”. In addition, there was much caution regarding the perils of oversimplification—evidence from many of the laboratories represented suggests that the concept of discrete functional compartmentalization within the striatum may not be entirely accurate. Instead, there are likely to be functional gradients within the striatum on all three (dorsal–ventral, medial–lateral, and rostral–caudal) axes. Furthermore, the distinct functional loops described by Alexander and colleagues are thought to spiral, intersect and interact with other functionally related regions of the basal ganglia to perform goal-directed behaviors, such that both dorsolateral and ventromedial aspects of the striatum are likely to play complementary yet unique roles in goal-oriented behavior. Thus, different afferents and efferents of the dorsolateral and ventromedial striatum coordinate to guide behavior in the most effective way. This coordination arises from a smearing or overlap of function between striatal subregions that can be described by the “Haber loops” (limbic/motivation → cognitive/plan → motor/execution; (see Haber et al., 2000; Haber et al., 2006) and dopamine can facilitate crosstalk within these loops.

*How do amygdalar and hippocampal inputs to ventral striatum influence action plans?* This part of the discussion sought to evaluate the relative contributions of amygdalar and hippocampal input to the ventral striatum in the generation and execution of action plans. An action plan can be described as a series of events that begins with motivation to perform an action and ends with the action itself, and is subserved by limbic, cognitive and motor systems. It was proposed that the hippocampus and amygdala provide salience signals, critical for learning emotional and contextual information, and may thereby contribute to behavioral flexibility. The amygdala is thought to be involved in the behavioral control of conditioned stimulus–unconditioned stimulus associations. Accordingly, it was suggested that amygdala input to ventral striatum reflects emotionality and automaticity of a behavior. In contrast, the hippocampus was thought to be involved in task focus. Supporting these ideas, Floresco et al. (2001) showed that the precise timing of hippocampal and amygdalar inputs is very important when examining striatal firing.

*What are the contributions of the dorsal/ventral striatum to habit?* A habit is defined as a behavior that is insensitive to reward devaluation. How do the firing properties of striatal neurons change with learning, and, in particular, habit learning? It was mentioned that Graybiel's work has addressed this in rodents and primates. In particular, Barnes et al. (2005) tracked the progression of neuronal activity across learning, and through overtraining (i.e. habit), and reported that in early training, activity was scattered over the entire time of task performance, but with extended training activity ultimately clusters at the beginning and end of the task.

It was suggested that, with regard to habit formation/learning, a concern with many experimental tasks is that the animal generally has a very narrow range of task parameters, producing less variability in behavioral and neurophysiological measures than in a natural setting. These issues may cloud the line between a particular behavior and habit. However, if the entirety of the striatum is responsible for habit learning, then lack of variability is perhaps not so surprising. While the striatum has a prominent role in action and habit formation, many other brain regions (e.g., subthalamic nucleus, substantia nigra) are thought to provide monitoring functions that can influence striatum-mediated behavior.

*What is the relationship between the goal-directed behavior and an action plan?* An action plan mediates goal-directed behavior, that is, how to achieve the goal. It was noted that primates in particular have a well-developed ability to evaluate potential outcomes, assessing the probability of achieving a certain goal based on different action plans. There was agreement that the striatum is the neural locus where the most appropriate action plan is selected; however it was thought that action selection and goal selection are probably mediated by anatomically separate areas.

### 3. Workshop II: building and breaking automatized behavioral sequences

*Does reinforcement play a role in maintaining habits? What are the criteria for rodent and monkey models of habit formation and breaking?* The second workshop focused on automaticity and habit formation. Initial discussions on the definition of a habit generally agreed that a habit is considered a predominantly involuntary behavior that is stimulus-evoked and originally goal-oriented. Habits are procedural, involving sensory-motor skill learning derived from action–outcome associations. Indeed, habit formation and procedural learning are difficult to distinguish. Generally, models of habits in animals involve a transfer from action–outcome guided instrumental behavior to stimulus–response guided behavior, effectively representing an overtrained behavior. Despite the insensitivity of habitual behaviors to reward devaluation (e.g., satiating the subject with the primary reinforcer), and punishment, it was thought that reinforcement does play some role in maintaining habits. The bulk of the evidence supporting this notion comes from studies of extinction. Generally, there is a gradient of sensitivity to extinction, and while habitual behaviors are relatively less sensitive to extinction than non-habitual behaviors, they are not completely insensitive, suggesting that the maintenance of behavior is dependent in part upon receipt of the primary reinforcer. Moreover, the particular schedule of reinforcement used can greatly impact habit development, further supporting a role of reinforcement contingency on habitual responding. The possibility was suggested that during the development of habits, the habitual behavior itself becomes reinforcing. However, it is not well known how long habits can persist without reinforcement, or indeed if the strength of a habit depends upon strength or type (positive versus negative) of reinforcement. It was also noted that the transition from goal-directed behavior to habit depends upon the complexity of the behavior; habit formation is slowed with increasing complexity of the behavior.

*Is habit breaking the reverse of formation?* It was generally agreed that habit breaking is *not* the reverse of habit formation. Habit breaking involves new learning, as opposed to unlearning or forgetting, and habits are often easily recovered. Support of this idea came predominantly from the extinction literature where extinction is considered to be new learning; extinction training does not necessarily eliminate a particular behavior, but rather generates a new behavior that displaces or overrides the

previously reinforced one. Physiological evidence also supports this idea; the neural changes that underlie habit formation are generally not reversed in habit breaking or re-learning, but rather can persist for extended periods (though perhaps in weaker form long after periods of non-use). The issue of habit breaking was considered to be of particular clinical relevance for the treatment of a variety of maladaptive behaviors that could be described as “bad habits”; therapies should perhaps focus on learning of competing, more adaptive behaviors.

*How is synaptic plasticity involved in habit formation and breaking?* It was agreed that the neurobiological mechanisms that underlie the transfer from goal-directed behavior into habit are not entirely clear. However, it is likely to involve a transfer of control of behavior from ventromedial to dorsolateral striatum. Balleine and colleagues have shown that lesions to the dorsolateral, but not dorsomedial, striatum reverts behavior from habit into goal-directed instrumental actions (Yin et al., 2004). In addition, Killcross and Coutureau (2003) reported regional specificity of habits versus goal-directed behavior in the mPFC. In this study, lesions of the prelimbic mPFC impaired sensitivity to goal devaluation in early training, resulting in persistent behavior. In contrast, lesions of the infralimbic mPFC produced the opposite result, suppressing the ability of extended training to transform goal-value sensitive behavior into habit. Both these studies lend support to the idea of a transfer of information from one processing loop to another.

With respect to neurotransmitters, it was noted that the dopamine system plays a large role in habit development. Striatal dopamine depletion impairs habit formation, but does not affect the expression of a previously acquired habit. Furthermore, over the course of learning and habit formation, the response of dopamine neurons shifts from unconditioned stimuli to conditioned stimuli and decreases in magnitude as a behavior becomes more habitual. This could potentially reflect a shift in which dopamine neurons are firing, i.e., from VTA to SN. Given the control of the dopamine system by hippocampus and ventral subiculum (among other regions), it is important to recognize that other brain areas also may contribute to habit formation.

#### 4. Workshop III: drug addiction, obsessive-compulsive disorders, Tourette's syndrome and eating disorders

*What are the commonalities and differences with respect to the symptomatology of these disorders?* Each of these disorders can be characterized by repetitive and ritualistic behaviors that can be internally or externally motivated, and by differing degrees of compulsivity (perseveration of behaviors) and impulsivity (loss of inhibitory control of behaviors). Internal drives include intrusive thoughts or cravings, while external triggers may include specific contexts, environmental cues, or stress. It was agreed that while these disorders share some behavioral commonalities, they can differ greatly in terms of symptomatology. For example, drug addiction and eating disorders may be considered more externally driven, while obsessive-compulsive disorder (OCD) and Tourette's syndrome are more internally driven. Moreover, the motivation underlying these behaviors varies considerably across these disorders; behaviors related to drug addiction, OCD and eating disorders can be described as goal-directed, whereas those related to Tourette's syndrome are generally not. Furthermore, behaviors associated with these disorders are maintained by both positive and negative reinforcement. For example, drug addicts take drugs to feel good or euphoric (positive reinforcement), but also to relieve aversive states associated with drug withdrawal (negative reinforcement). While compulsivity may be a hallmark of each of these disorders, the line between compulsion and habit is unclear, complicating the interpretation of specific behaviors. Differences

between these disorders are also reflected in their treatment; effective treatment strategies for OCD include desensitization of behaviors (e.g., exposure and response prevention) and selective serotonin reuptake inhibitors (SSRIs), but these approaches are relatively ineffective for treatment of drug addiction. In addition, the comorbidity of OCD and drug abuse is quite low, further suggesting major distinctions rather than commonalities between these disorders.

*Is corticostriatal dysfunction a common mechanism for these disorders?* There was general consensus that corticostriatal dysfunction is a common feature of each of these disorders, however, the specific changes in corticostriatal function resulting in the behavioral abnormalities in these disorders are likely to be different. For example, OCD is often characterized by frontal cortical hyperactivity whereas the converse holds true in drug addiction. An important role for anterior cingulate cortex is supported by the known involvement of this region in behavioral inhibition. The orbitofrontal cortex (OFC) and its striatal projections appear to be a particularly important network across all of these disorders. OFC lesions result in perseverative responding in rats, and, reduced OFC activity is associated with reduced ventral striatal dopamine D<sub>2</sub> receptor binding. Reduced dopamine D<sub>2</sub> binding in turn correlates with measures of impulsivity and drug abuse (Dalley et al., 2007). Work by Graybiel and colleagues has suggested different roles for the dorsal and ventral striatum in mediating behaviors, where dorsal striatum is associated with “chunking” of behaviors into sequences and ventral striatum is important for mediating goal-directed behaviors. This may relate to the differences in goal-directed versus non-goal-directed behaviors in each of these disorders. Neurochemically, dopamine and serotonin are the most promising neural systems for investigation of impulsive/compulsive behaviors.

*What are the criteria for an effective model of compulsive behavior?* While modeling compulsion in animals has proved challenging, several models of varying validity do currently exist. Compulsive nest building and repeated dopamine agonist treatment are often used as models, but these manipulations may actually reflect repetitive motor patterns or stereotypy rather than compulsive behavior *per se*. Schedule-induced polydipsia, another model of compulsion, does not appear to reflect stereotypy and its validity as a model is enhanced by the fact that this behavior is sensitive to SSRI treatment, currently the pharmacotherapy of choice for OCD. Considerations for the future development of animal models of compulsion include the fact that it is difficult to model the entire spectrum of compulsive behaviors, and one must instead focus on select symptoms or endophenotypes. Promising routes include spontaneous behaviors that can be selectively bred for and developing models where the behavior is resistant to punishment or extinction. It is also important to avoid modeling general traits such as cognitive inflexibility, which may just reflect cortical function. One danger mentioned with respect to model development was over-reliance on a positive response to SSRIs as a measure of model validity, as up to 25% of patients fail to respond to these drugs in the clinic.

*What role, if any, does explicit monitoring and awareness (metacognition) play in the control of habits and compulsions? Can we exploit the awareness of the individual in therapeutic treatment?* While patients with these disorders are often aware that they engage in maladaptive behavior, this awareness nonetheless fails to prevent these behaviors. There may also be a contributing role of distortion/disruption of metacognition that follows the development of the disorders, such that the role of metacognition may change over the course of the disease. The fact that cognitive-behavioral therapy can be beneficial for many of these disorders suggests that improving the awareness of the individuals' cognitive processes can in fact improve prognosis. However, it

was mentioned that this form of treatment is not equally effective for all of these disorders, and that the patient's response to cognitive-behavioral therapy may depend on their individual control of behavior by cognition. Cognitive-behavioral therapy may also improve the patients' coping mechanism for their symptoms, improving outcomes without explicitly reducing symptoms. Unfortunately, it is not clear that meta-awareness can be demonstrated in animals.

#### 5. Workshop IV: nature versus nurture: environmental interactions, why exposure doesn't always lead to addiction and compulsions?

*Do environmental factors and genetic predispositions target the same brain systems in rendering a subject vulnerable to addictive behavior?* The first point raised in the discussion was the importance of addressing exactly how to determine which genetic factors are important. Forward genetic screens (particularly quantitative trait loci mapping for single nucleotide polymorphisms, or in genetically defined rodent lines) can identify genes associated with particular phenotypes. Additionally, rodent lines can be bred for specific traits predicting addictive or compulsive behavior, followed by microarray analysis to identify potential genes or neuronal pathways underlying the phenotype. The contribution of a gene to a particular behavior can be evaluated with reverse genetic approaches, such as in human linkage/association and rodent gene knockout studies. However, caution is necessary when considering non-inducible knockouts with the potential for compensatory alterations during development.

Using the aforementioned approaches, dozens of genes have been associated with aspects of drug abuse. Some of these, such as dopamine D4 receptor gene variants associated with impulsivity and alcoholism, and dopamine D2 receptor gene variants associated with smoking and cocaine abuse, are unsurprising given the prominent role of dopamine in motivated behaviors and reinforcement, but the actual strength of these association remain a matter of some debate. Furthermore, there are numerous other candidate genes of interest that remain relatively unstudied. These factors are heritable and may contribute to the development and maintenance of addictive behaviors, but the currently identified gene variants account for only a small proportion of the variance in addiction-related behaviors and susceptibility to addiction, highlighting the need for large data sets and rigorous analyses in future association studies (Buckland, 2008). It was thought that more longitudinal human studies are needed to better characterize genetic factors such as vulnerability trajectories, developmental neurobiological changes, proteomics/biomarkers and liver enzymes, all of which are likely to play some role in the addictive process.

There are also a number of environmental factors that contribute to addiction, including gender, age, social class, pair bonding, comorbidity with other disorders, drug exposure and stressful life experiences which must be taken into account. Although, a factor like drug exposure does not necessarily predict future addiction liability. For example, opiate use, both therapeutic and recreational, was widespread in American Civil War and Vietnam soldiers. In contrast with Civil war veterans, many of whom became addicted to morphine ("soldier's disease"), a large number Vietnam veterans ceased opiate use after returning home (Robins et al., 1975). This is an example where environmental differences cause very disparate outcomes in two seemingly similar situations, and could be related to factors such as context, availability, legality and/or exposure to drug paired cues.

There was general consensus that genetics, environment, and perhaps most importantly, their interactions, all play a role in the development of addictive/compulsive behaviors. For example,

early life stress combined with certain serotonin transporter polymorphisms may predispose an individual to alcoholism; alternatively, a genetic deficit in basal ganglia function coupled with the environmental factor of drug exposure could lead to addiction through perturbed cortico-basal ganglia information flow. It is important to note that gene–environment interactions are context-dependent; a particular gene may be beneficial in one environment and detrimental in a different environment.

*What are some clinical endophenotypes (e.g., impulsivity, impaired inhibitory control, etc.) that can be modeled in animals?* While it was agreed that modeling endophenotypes in animals is a useful strategy, care must be taken to consider what exactly one wants to model (e.g., alcoholism can be differentiated into distinct categories, type I and type II, that have very different clinical pictures). Traits such as impulsivity and compulsivity were popular candidates as potential endophenotypes. Other traits thought to contribute to endophenotypes related to disorders of reward, compulsion or habit include sense of control over environment, attention, sensitivity to reward, active avoidance, novelty seeking, exploratory behavior, stress reactivity and anxiety. However, it is important to note that endophenotypes may only predict initial drug taking, not necessarily the development of addiction. Indeed, a recent report demonstrated that in rats, high response to novelty predicts initiation of cocaine self-administration, but high impulsivity predicted the development of addictive-like behavior such as persistent drug seeking despite adverse consequences (Belin et al., 2008).

*Do the different monoamine systems play unique or complementary roles in addictive behaviors?* Dopamine has been clearly linked to addictive behaviors, playing a central role in the abuse of various types of drugs. Dopamine agonists increase seeking of a variety of drugs while dopamine antagonists and lesions of the dopamine system disrupt drug seeking. Moreover, dopamine neuron activity has been shown to correlate well with reward and reward cues. While norepinephrine and serotonin are less heavily implicated, evidence suggests that these monoamines also play roles in the addictive process; norepinephrine contributes heavily to the stress response and serotonin is linked to affective states, anxiety and alcohol abuse. The interaction of monoamines with other neuromodulators is also likely to be important; for example, it was speculated that the stress response and associated vulnerability to addiction may arise from monoamine/corticosterone balance or interactions, not from discrete functions of either neurochemical alone.

Knockout mice have provided many interesting clues regarding the role of monoamines in addictive behaviors, though there are conflicting reports in the literature and drawing definitive conclusions can be challenging. An initial report demonstrating cocaine self-administration in dopamine transporter knockout (DAT-KO) mice (Rocha et al., 1998) has not been replicated by others (Thomsen et al., 2009). The discrepancies in self-administration behavior between the different strains of DAT-KO mice may be explained by the differences in extracellular dopamine levels in response to cocaine observed in these two strains. However, cocaine has consistently been shown to produce a conditioned place preference in DAT-KO mice, and it was found that genetic deletion of both the dopamine and serotonin transporters was necessary to abolish cocaine-conditioned place preference, suggesting complementary roles of dopamine and serotonin in drug-related behaviors (Sora et al., 2001). Other studies support the idea of complex monoamine interactions in cocaine reward, such as the report by Hnasko et al. (2009) demonstrating a cocaine-induced conditioned place preference in dopamine-deficient mice that was mediated via the serotonin transporter. Caution is always required when interpreting the effects of developmental knockouts as there are often compensatory adaptations, some of which may underlie



the inconsistencies in the literature. Indeed, there are a variety of other mechanisms by which one monoamine system can indirectly affect other monoamine systems. This presents difficulties when attempting to study the singular effects of a particular monoamine. Moreover, the pharmacology of the monoamine systems is not exclusive; each monoamine can act at another's receptors and transporters, further complicating the interpretation of a particular manipulation.

Unfortunately, there are further difficulties when applying information related to monoamines and addictive behaviors from rodent studies to primates; this is evidenced by the species differences in norepinephrine innervation of the nucleus accumbens in humans and rats. Overall, for addictive and compulsive behaviors, the limbic-cortical-striatal circuit is an obvious candidate and monoamine function within these regions are known relate to differences in behavior. The possibility was raised that each monoamine system provides a layer of a particular behavior, with each system contributing both unique and complementary roles.

*Can stress alone contribute to addictive behaviors in the absence of genetic vulnerability? Do individuals susceptible to addictive behaviors have a different sensitivity to stress, or do those in which stress fails to elicit pathology have protective factors?* Stress can play a substantial role in vulnerability to addiction. However, it was thought that it is unlikely that stress itself can alone drive addiction, as individual variability in stress and drug responses, previous drug exposure and genetic factors would greatly influence the individual response to stress. It is most likely that the interrelationships between inherent genetic susceptibility, magnitude of stress, stage in life and learned stress management strategies are crucial in determining an individual's vulnerability to addiction. Research from Nader and colleagues clearly shows a link between stress and drug taking. In these studies, dominance hierarchy in monkeys was found to correlate with dopamine D<sub>2</sub> receptor expression which also correlated with cocaine intake (more dominant = higher D<sub>2</sub> expression = less cocaine intake) and these measures changed accordingly when the dominance hierarchy was experimentally altered (Morgan et al., 2002). It was also suggested that maternal separation models of early life stress would be a good way to lend support to the link between stress and addiction. This type of model could also shed light on the role of cortical development in these processes.

## 6. Conclusions

Overall, the various discussions highlighted a number of different issues related to motivation, reward, habits, and compulsion, and while there was an encouraging amount of consensus regarding the current state of the science, a number of important points were raised regarding current limitations of the field, particularly with respect to addressing the extremely complex interactions between genes, the environment and behavior. With this in mind, the next MNN conference will hopefully begin to address some of these thorny questions, and generate a whole host of new questions that will continue to move the field forward.

## Acknowledgements

We thank the conference organizers and discussion leaders, particularly Christelle Baunez, Anthony Grace and Jacqueline McGinty. We also thank the following for their contribution of notes from the various workshops: Yukiori Goto, Colleen A. Hanlon, Judith R. Homberg, Sietsa Jonkman, Ronald Keiflin, Ryan T. LaLumiere, Sylvie Lardeux, Yann Pelloux, Daniela Schiller, Kyle S. Smith, Ana Stan, Rachele Stopczynski, Patrick L. Tierney, Derek C. Tucker, Summe Wee, and Catharine A. Winstanley. The meeting was supported in part by NIDA grant R13 DA23350-01, the CNRS Department of Life Sciences, Conseil Régional Provence-Alpes-Côte d'Azur, and the Department of Pharmacology and Physiology, University of Rochester School of Medicine and Dentistry.

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