available at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/brainresrev

BRAIN RESEARCH REVIEWS

Review

Mental fatigue: Costs and benefits

Maarten A.S. Boksem[a,b,d,*], *Mattie Tops*[c,e]

[a]*Department of Social Psychology, Tilburg University, Tilburg, The Netherlands*
[b]*Centre for Justice and Social Decision Making, Tilburg University, Tilburg, The Netherlands*
[c]*Centre for Child and Family Studies, University of Leiden, Leiden, The Netherlands*
[d]*School of Psychiatry, University of New South Wales and Liverpool Hospital, Sydney, Australia*
[e]*Neuroinformatics Centre, University of Oregon, Eugene, USA*

ARTICLE INFO

Article history:
Accepted 2 July 2008
Available online 9 July 2008

Keywords:
Mental fatigue
Motivation
Effort
Reward
Dopamine
DA
OFC
ACC
BLA
NAc
Insula

ABSTRACT

A framework for mental fatigue is proposed, that involves an integrated evaluation of both expected rewards and energetical costs associated with continued performance. Adequate evaluation of predicted rewards and potential risks of actions is essential for successful adaptive behaviour. However, while both rewards and punishments can motivate to engage in activities, both types of motivated behaviour are associated with energetical costs. We will review findings that suggest that the nucleus accumbens, orbitofrontal cortex, amygdala, insula and anterior cingulate cortex are involved evaluating both the potential rewards associated with performing a task, as well as assessing the energetical demands involved in task performance. Behaviour will only proceed if this evaluation turns out favourably towards spending (additional) energy. We propose that this evaluation of predicted rewards and energetical costs is central to the phenomenon of mental fatigue: people will no longer be motivated to engage in task performance when energetical costs are perceived to outweigh predicted rewards.

Contents

* *Corresponding author*. Department of Social Psychology, Warandelaan 2, PO Box 90153, 5000 LE Tilburg, The Netherlands. Fax: +31 13 4662067.
E-mail address: maarten@boksem.nl (M.A.S. Boksem).

0165-0173/$ – see front matter © 2008 Elsevier B.V. All rights reserved.
doi:10.1016/j.brainresrev.2008.07.001

1. Introduction

Mental fatigue refers to the feeling that people may experience after or during prolonged periods of cognitive activity. These feelings are very common in everyday modern life and generally involve tiredness or even exhaustion, an aversion to continue with the present activity, and a decrease in the level of commitment to the task at hand (Holding, 1983; Hockey, 1997; Meijman, 2000). In addition, mental fatigue has been associated with impaired cognitive and behavioural performance (e.g. Boksem et al., 2005; Lorist et al., 2005; Van der Linden and Eling, 2006).

Over the past decades, work has changed to a large extent from demanding physical effort, to demanding mental effort. This has resulted in a substantial increase in complaints related to mental fatigue: in the Netherlands, half of the women in the working population complain about being fatigued, while a third of the men report such complaints. Fifteen years ago, only 38% of the women and 24% of the men reported such complaints. A recent survey of the U.S. workforce (Ricci et al., 2007) showed that 38% of workers reported being fatigued. Of these fatigued workers, 66% reported lost productivity time, compared to 26% of workers without fatigue. Ricci and colleagues estimated that lost productivity time from fatigued workers costs employers an excess of a hundred billion dollars annually, compared to non-fatigued workers. On a more personal level, complaints of fatigue can have a profound and negative impact on people's social and occupational life. Moreover, mental fatigue is a common symptom in a large number of chronic medical conditions such as cancer, Human Immunodeficiency Virus, Multiple Sclerosis, Chronic Fatigue Syndrome, Alzheimer's disease, Huntington's disease and Parkinson's disease (see Chaudhuri and Behan, 2000). It is important to realize however, that fatigue as a symptom of disease may involve different biological substrates compared to acute mental fatigue in otherwise healthy people.

Mental fatigue has been shown to result in various deteri, orations in cognitive functioning. Van der Linden and colleagues (2003a, 2003b, 2006) showed that fatigued subjects had difficulties in focusing their attention, planning, and adaptively changing strategies in the face of negative outcomes. Our own work showed that fatigued subjects had difficulties in adequately preparing their responses (Boksem et al., 2006) and had difficulties in sustaining attention and ignoring irrelevant information (i.e. they suffered from increased distractibility; Boksem et al., 2005). In addition, fatigued subjects corrected their mistakes less often and post error performance adjustment was impaired (Lorist et al., 2005; Boksem et al., 2006).

Common sense would dictate that mental fatigue is the direct result of working for a prolonged period of time: the longer one works on a demanding task, the more fatigue one will experience. This, however, has been shown not to be the case. Fatigue may be experienced after working for a relatively short period of time, while working long hours does not always lead to fatigue (Sparks et al., 1997; Park et al., 2001). Indeed, working long hours has been shown not to lead to fatigue at all when the rewards of working (in terms of payment, but also appreciation by peers and co-workers) are perceived as high (Siegrist, 1996; Van der Hulst and Geurts, 2001).

In other words, high workload only results in fatigue when rewards associated with work are low. Here, we will propose a framework for mental fatigue that involves an integrated evaluation of both expected rewards and energetical costs associated with continued performance, resulting in a reduction in motivation and the effort invested in continued performance.

Two complimentary and interacting motivational systems are proposed to result in producing goal directed behaviour: the motivation to obtain rewards and the motivation to avoid harm and punishment. While both rewards and punishments can motivate to engage in activities, both types of motivated behaviour are associated with energetical costs. In the present review, we will propose that the feeling of fatigue may result from the subconscious analyses of cost and benefits to expend energy, or to conserve energy. People will only expend energy on a certain task when (energetical) costs are comparably low and benefits (high reward, low punishment) are comparably high. However, when tasks have to be performed for prolonged periods of time, the amount of energy invested in performance will build up until it eventually outweighs potential rewards, resulting in a decrease in the motivation to work for rewards that fail to be procured. Thus, we propose that the feeling of fatigue corresponds to a drive to abandon behaviour when energetical costs exceed perceived benefits of continued performance.

The purpose of this review is to provide a coherent framework for mental fatigue. Because of this, we inevitably

focus more on some aspects of this complex phenomenon that on others. This is especially true for the motivational systems and neural substrates we propose are primarily involved. While we focus on the role the 'reward system' of the brain and on the role of the dopamine (DA) neurotransmitter in motivated behaviour, it is certain that other neural structures, neurotransmitters and hormones are also involved. However, by narrowing our focus on these particular aspects of mental fatigue, we are able to present our views on what is a central aspect of this important and complex psychophysiological phenomenon.

2. Goals

So, what is mental fatigue? This question has proved to be very difficult to answer. Despite its mundane nature, mental fatigue appears to be a highly complex phenomenon that involves changes in mood, information processing and behaviour (Desmond and Hancock, 2001), making it a difficult subject to study. Perhaps asking ourselves the opposite question could clarify matters: what makes us tick? What makes us get out of bed every morning and go to work, to school, or do whatever else is planned for the day? Why do we do it? Clearly there must be something to gain, there must be some reward.

From an evolutionary point of view, the ability to seek out rewards is essential for survival and reproduction. The main goal of life, it seems, is to stay alive. Not only does every organism do its utmost not to die, it also goes to great lengths to reproduce and pass on its genes to the next generation to make sure life continues in the future as well. The African cheetah may serve as an example here. To sustain itself, this animal has to go and hunt for food every single day. To obtain the food it needs, it will have to become active and, for example, find a herd of antelopes and try to catch and kill one of these animals. In addition, to be able to reproduce, it will have to go and find a suitable mate to ensure its genes get passed on. In contrast, if the cheetah should encounter a lion that threatens to steal the kill the cheetah has just made, it would be well advised to run, and not try to fight the much stronger lion for the food because of the risk of getting killed in the process. In other words: to reach its goals (sustain life), an organism should try to obtain rewards (e.g. food or sex) and at the same time should try to avoid aversive consequences (e.g. injury or death). The approach of potential rewards and the avoidance of potential punishment are fundamental to all goal directed behaviour (Miller, 2000): for something to constitute a goal, it has to be associated with a high value of predicted reward and low potential risk.

3. Rewards and punishments

There are at least three psychological components of reward (Berridge and Robinson, 2003; Schultz, 2004). First, the consumption of rewards involves feelings of pleasure ('liking'). Second, these pleasurable feelings are highly motivating to obtain this reward more often ('wanting'). Third, in order to do so, one has to learn about the relationships among stimuli and the consequences of actions that led to the procurement of the reward ('learning'). The obvious benefit of such a reward system is that it can bring about goal directed action strategies that enables the organism to select from several possible actions the one that is predicted to result in the best reward. A general distinction can be made between primary rewards, such as food, water and sexual stimuli and secondary rewards such as money. Primary reward can be assumed to positively reinforce the intensity or frequency of a certain behaviour pattern without being learned, while secondary reinforcers reinforce behaviour only after learned association with primary rewards.

To promote reward-seeking activities, the brain is equipped with an elaborate system that signals the rewarding value of events and actions (e.g. Schultz, 2002). The processing of rewards in the brain involves multiple neuroanatomical structures, their interconnections and different types of neurotransmitters. Because our proposed model for mental fatigue relies heavily on the neural systems involved in reward processing, the discussion will benefit from outlining the core components of the 'reward system'. We will briefly review the involvement of the midbrain DA neurons, the orbitofrontal cortex (OFC), the basolateral amygdala (BLA), anterior cingulate cortex (ACC) and the nucleus accumbens (NAc).

3.1. *Midbrain dopamine*

It has long been recognized that activity in midbrain DA neurons is related to rewards and reward-predicting stimuli (see Schultz, 2007 for a review). Most midbrain DA neurons exhibit burst activity following delivery of primary rewards. This DA activity, however, appears to depend on the predictability of the reward, such that unpredicted rewards elicit DA activation (positive prediction error) and an unpredicted non-reward induces a depression in DA activity (negative prediction error), while fully predicted rewards do not elicit DA activity (Schultz, 2002). So, the midbrain DA neurons respond to both rewards (with activation) and punishments/reward omission (mostly with depression; Ungless et al., 2004). Therefore, the DA response has been associated with the 'wanting' aspect of reward processing and not so much with the 'liking' aspect (Berridge, 2007).

It has been shown (e.g. Ljungberg et al., 1992; Mirenowicz and Schultz, 1994) that, while primary rewards initially elicit dopaminergic activation, this activation decreases progressively and is transferred to reward-predicting stimuli when the association between the primary reward and the predicting stimulus is learned. This would suggest top–down control over midbrain DA neurons from structures that have access to reward value information of stimuli and events in the environment. We will briefly review findings regarding these structures below.

Although DA activity has mostly been associated with reward processing, it has been shown that mesolimbic DA neurons not only carry a reward signal, but respond to a large category of salient and arousing events, including appetitive, aversive, high intensity, and novel stimuli (Horvitz, 2000), suggesting a more general role for DA in motivated behaviour (Dayan and Balleine, 2002; Berridge, 2007).

3.2. *Orbitofrontal cortex*

The OFC is a region with dense afferent connections from the primary taste and olfactory cortex as well as from higher visual areas and the somatosensory cortex (Morecraft et al., 1992; Carmichael and Price, 1995). Therefore, the OFC is well suited to integrate information from the different sensory modalities and estimate the reward value of stimuli and ongoing events (Kringelbach, 2005; Walter et al., 2005).

A dissociation appears to exist between the medial OFC (mOFC) and the lateral OFC (lOFC). While the mOFC appears to be involved in the monitoring, memory and learning of reward value, lOFC appears to be involved in the evaluation of punishers and aversive events (O'Doherty et al., 2001; Kringelbach and Rolls, 2004; Seymour et al., 2007). This dichotomy may however prove to be too strict, with OFC coding information on both positive and negative reward value (Coricelli et al., 2005).

Under normal circumstances, multiple stimuli and courses of action, each associated with different reward values, are available from the environment. The OFC has been shown to code reward value compared to other rewards that may be available (Tremblay and Schultz, 1999). In addition, the OFC not only signals current reward value, it also signals expected reward value of stimuli and events and also monitors changes in these expected rewards (Nobre et al., 1999; Gottfried et al., 2003), modifying stimulus–reward associations (Walton et al., 2004).

Thus, the OFC evaluates reward size and possible aversive consequences associated with ongoing events. This way, the OFC provides a kind of running commentary on the value of the present state and courses of action, compared to the value of subsequent predicted states (Schoenbaum et al., 2006).

3.3. *Basolateral amygdala*

Sharing strong reciprocical connections with the OFC (see Öngür and Price, 2000) and also receiving projections from sensory cortex (McDonald, 1998), the BLA and OFC probably provide complimentary information on the reward value of stimuli and events (Baxter et al., 2000). Like the OFC, the BLA codes (relative) reward value (Killcross et al., 1997), signals changes in stimulus–reward contingencies (Salinas et al., 1993; Corbit and Balleine, 2005), and provides information on the value of delayed rewards (Winstanley et al., 2004).

Traditionally the amygdala, with its connections with the lOFC and anterior insula, was thought to be involved in processes related to negative reinforcement and punishment, fear and anxiety (LeDoux, 1996; Seymour et al., 2007). Indeed, the BLA is required for the evaluation of reward omission (Burns et al., 1999) and is involved in harm avoidance (Killcross et al., 1997; Coutureau et al., 2000) and conditioned punishment (Killcross et al., 1995). Nonetheless, the BLA is also involved in evaluating positive reinforcers (Cardinal et al., 2002a).

3.4. *Insula*

Reciprocically connected to the lOFC (Carmichael and Price, 1995) and amygdala (Reynolds and Zahm, 2005), the anterior insula has been shown to be involved in encoding aversive value (Small et al., 2001; Nitschke et al., 2006). In addition to the lOFC and BLA, the insula has also been shown to be involved in the processing of costs and punishments in decision-making. In an fMRI study using a risk-taking decision-making task (Paulus et al., 2003), the degree of insula activation was related to the probability of selecting a "safe" response following a punished response (see also Krain et al., 2006), suggesting a role for the insula in risk aversion and harm avoidance (Kuhnen and Knutson, 2005). Moreover, the degree of insula activation was also positively related to the subjects' harm avoidance and neuroticism scores on personality questionnaires. Knutson and colleagues (2007) showed that, while activity in the NAc reflected anticipation of obtaining desired products, activity in the insula reflected the emotional anticipation of suffering the financial loss involved in paying for it.

3.5. *Anterior cingulate cortex*

The rodent ACC has been shown to be required when multiple stimuli must be discriminated according to their different reward value (Parkinson et al., 2000; Cardinal et al., 2002b). In situations where an organism must choose between response options associated with differential magnitudes of reward, activity of BLA and OFC neurons encode the expected magnitude of reward that each choice may provide. This reward-related information may be relayed to the ACC via ascending glutamatergic projections. In turn, the ACC may integrate these sources of reward information, biasing behaviour in a particular direction that is predicted to yield the highest reward value (Shima and Tanji, 1998; Bush et al., 2002; Williams et al., 2004).

The ACC has been proposed to be required for constructing and/or retrieving a choice–outcome history of both rewards and punishments, to guide behaviour (Kennerley et al., 2006). The heavily interconnected structures of the ACC, OFC and BLA (Carmichael and Price, 1995; Floresco and Ghods-Sharifi, 2007; Öngür and Price, 2000) play complimentary roles in guiding behaviour based on predicted rewards and outcomes of current actions (Kennerley et al., 2006). While OFC and BLA may be involved in monitoring action outcome and changing stimulus–reward contingencies, the ACC is involved in deciding what to do and assessing the consequences of current actions (Kennerley et al., 2006; Walton et al., 2004; Cohen et al., 2005). Once a particular course of action has been determined, the transformation of this strategy into the appropriate behavioral output is likely mediated by coticostriatal connections linking the ACC to the NAc (Floresco et al., 1999; Parkinson et al., 2000).

3.6. *Nucleus accumbens*

The NAc is a major output structure of ACC (Chiba et al., 2001; Sesack et al., 1989), BLA (Floresco et al., 1998) and OFC (Groenewegen et al., 1990) and also receives projections from the insula (Reynolds and Zahm, 2005). These glutaminergic projections to NAc serve to influence response selection and this information is gated or amplified by the dopaminergic innervation of the NAc, probably under control of the amygdala (via the central nucleus of the amygdala (CeA);

Cardinal et al., 2002a; Robledo et al., 1996). DA levels in ventral striatum/accumbens modulate response energizing or response-maintaining effects of motivationally relevant stimuli (Everitt et al., 1989; Salamone et al., 1997), providing the motivational drive for behaviour. While information about reward value is coded in the OFC and BLA and is conveyed to the NAc, where it can be amplified by the DA system, ACC projections to NAc are critical for the intensity of approach behaviour (Devinsky et al., 1995). In turn, the NAc can influence activity in the OFC and ACC through striatal–pallidal–thalamic loops (Cardinal et al., 2002a).

3.7. *Dopamine projections to the prefrontal cortex*

DA projections from the ventral tegmental area (VTA) convey information on reward value to the prefrontal cortex (PFC; Watanabe, 1996, Tremblay and Schultz, 1999). In the PFC, DA influx may strengthen the connections between neuron ensembles that represent goals and the means to achieve them (Miller, 2000). When a certain behaviour is successful, dopaminergic reinforcement signals from the VTA augment the corresponding pattern of PFC activity by strengthening the connections between neurons that are activated by that behaviour. Consolidating the reward value that was associated with a particular stimulus, event, or action, this information is accessible by other structures in the reward system (OFC, ACC, BLA) to estimate the reward value of ongoing events. This will increase the probability that in the future, the same context will elicit reactivation of the PFC activity that led to the rewarded behaviour (Miller and Cohen, 2001). We will discuss the activity of DA in the PFC, and also projections from other neurotransmitter systems to the PFC more extensively in a following paragraph.

3.8. *Summary*

The system involved in promoting goal directed actions by evaluating potential rewards and aversive consequences associated with behaviour towards stimuli in the environment comprises complex interactions of several neural structures (see Fig. 1). Typically, the environment provides multiple response options associated with differential magnitudes of reward. The OFC, BLA and insula are primarily involved in coding the expected appetitive and aversive value that each option may provide. This reward-related information is relayed to the ACC, where these sources of reward information may be integrated to bias behaviour in a particular direction that is predicted to result in the largest reward and the least aversive consequences.

Once a particular course of action has been determined, the transformation of this strategy into the appropriate behavioral output is likely to be mediated by corticostriatal connections linking the ACC to the NAc. In turn, action outcomes are continuously evaluated and when outcomes are better or worse than expected, this information is relayed to the PFC and ACC, strengthening neural connections associated with the successful behaviour (in the case of a positive reward prediction error) or inducing extinction of the current behaviour and behavioural change in the case of a negative reward prediction error.

4. To act or not to act

Despite the importance of the evaluation of potential reward for successful goal directed behaviour, reward seeking activities would only seem to be a part of what constitutes adaptive goal directed behaviour. Rewards always come at a price. To

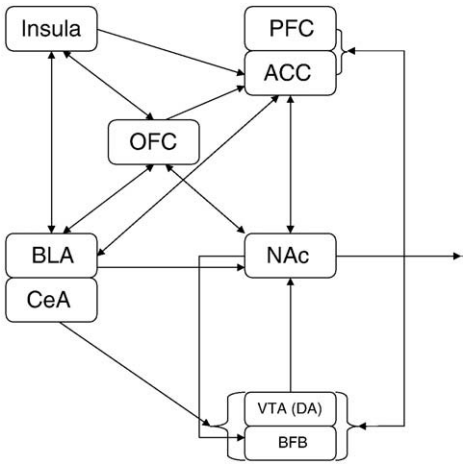

Fig. 1 – The OFC, BLA and insula are primarily involved in coding the expected appetitive and aversive value of potential actions. This reward-related information is relayed to the ACC, where these sources of reward information may be integrated to bias behaviour in a particular direction that is predicted to result in the largest reward and the least aversive consequences. The transformation of this strategy into the appropriate behavioral output is mediated by projections from ACC to the NAc. In turn, action outcomes are continuously evaluated and when outcomes are better or worse than expected, this information is relayed to the PFC and ACC, strengthening neural connections associated with the successful behaviour or inducing extinction of the current behaviour when behaviour was unsuccessful. In addition, decision-making is also guided by evaluating the potential energetical costs associated with behaviour. Multiple brain areas have been shown to be involved in this form of effort based decision making, including the ACC, NAc, BLA and insular cortex. We propose that, in addition to information on reward value, also information on the current physiological state and energetical resources (signalled by the insula), as well as expected effort required to obtain rewards (or avert negative events) is integrated by the ACC, to allow for optimal decision making based on the evaluation of both rewards and potential energetical costs of courses of action. In turn, projections from the ACC impact on activity in the BLA and NAc, modulating the energizing of current behaviour. This way, behaviour is guided by comparing the current state to the predicted future state in terms of both rewards and energetical condition of the body, energizing behaviour only when the predicted state is valued higher than the current state. ACC = Anterior Cingulate Cortex; BLA = Basolateral Amygdala; CeA = Central Nucleus of the Amygdala; OFC = Orbitofrontal Cortex; PFC = Prefrontal Cortex; NAc = Nucleus Accumbens; VTA = Ventral Tegmental Area; BFB = Basal Forebrain; DA = Dopamine; ACh = Acetylcholine.

keep with our example: to catch an antelope, the cheetah will have to leave the safety and comfort of its shelter and venture into the open savannah, spending valuable energy. So, to select the best course of action, an organism has to take into account both the expected reward (and potential risks), and the energetical costs that are involved in obtaining a certain goal.

A growing body of research suggests that the brain is indeed capable to appropriately evaluate current behaviour in terms of both the potential rewards and energetical costs involved. Activity in ACC, NAc and BLA and their interconnections appear to be a prerequisite for behaviour that results in greater rewards at the cost of increased energy expenditure. We will briefly review these findings below.

Salamone and colleagues (1994) conducted experiments to study the role of NAc DA in the performance of a cost/benefit procedure. Rats were trained on a T-maze task in which one arm contained a high reward (pallets of food) and the other arm contained a low reward. Different groups of rats were trained either with unobstructed access to both arms from the start area, or under a condition in which a large vertical barrier was placed in the arm that contained the high reward. After training, the authors depleted the NAc of DA in these animals. Following this procedure, rats that had been trained in the maze with obstructed access to the high reward displayed a significant reduction in the number of selections of the high reward arm when the barrier was present, while the lesion had no effect on arm choice when the barrier was not present (see also Cousins and Salamone, 1994; Denk et al., 2005).

The authors suggested that release of DA in the NAc might be an important part of the neural process that enables organisms to overcome work-related response costs, and that the NAc may indirectly perform cost/benefit analyses, setting constraints on energy expenditure that profoundly influences the relative allocation of instrumental responses toward various alternatives, such that NAc DA depletion biases behaviour in the direction of lower effort alternatives (Salamone et al., 1999).

Similar results were obtained by Walton and colleagues (2002, 2003, see also Schweiber et al., 2005), however, these authors lesioned animals in the ACC instead of the NAc. Like the NAc lesioned rats, rats with lesions to the ACC no longer chose the high reward, high effort option, instead choosing a less preferred reward that required minimal effort to obtain. Cells in the ACC have been shown to respond while working toward or receiving rewards (Akkal et al., 2002; Shidara and Richmond, 2002) and the ACC is bi-directionally (through striatal–pallidal–thalamic loops) connected to the NAc (Berendse et al., 1992; Haber et al., 1995), although exactly how these structures interact in effort-related decisions remains under debate (Walton et al., 2005; Schweiber et al., 2005; Schweiber and Hauber, 2005). In addition, the human ACC has been shown to be involved in effortful task performance (Paus et al., 1997; Winterer et al., 2002; Jensen and Tesche, 2002) and task engagement (Tops et al., 2006a; Boksem et al., in press).

Recently, Floresco and Ghods-Sharifi (2007) showed that bilateral inactivation of the BLA also disrupts effort-based decision making, reducing the preference of lesioned rats to exert greater effort to obtain larger rewards. Importantly, these authors were able to show that disconnecting the BLA and ACC had similar results.

The remarkable similarity between the behavioural effects of ACC, NAc and BLA lesions and disrupting their interconnections, suggest that these interconnected structures are together involved in the evaluation of current behaviour in terms of both potential rewards and energetical costs. Activity in these structures appears to be required for behaviour that results in greater rewards at the cost of increased energy expenditure.

In addition, an important role in the evaluation of effort in decision making may be reserved for the insula. By its reciprocical connections with autonomic and visceral centers of the nervous system such as the hypothalamus, nucleus of the tractus solitarius and the periaquaductal gray (Carmichael and Price, 1995), the insula is the cortical area implicated in monitoring and regulation of peripheral resources like levels of glucose (Allport et al., 2004) and muscle condition (Craig, 2003). Insula activation has been related to perceived physical effort, physical exertion, and "central command" during physical exercise (de Graaf et al., 2004; Williamson et al., 1999, 2003). The anterior insula is involved in monitoring the conditions of peripheral resources and may influence actions by signalling the adequacy of these resources, given the energetical costs of those actions. It has recently been proposed that the insula is involved in the processing of prospective aversive bodily states (Paulus and Stein, 2006), which would account for the role of this structure in both financial loss and punishment and the processing of energetical costs.

A recent study by Herbert et al., 2007 provides an interesting insight into the role of the insula in effort based decision making. In this study, the authors demonstrated that persons that showed a more precise conscious detection of bodily signals (i.e. heartbeat; suggesting increased processing of bodily signals in the insular cortex; Critchley et al., 2004; Pollatos et al., 2005) also invested significantly less physical effort in a situation permitting behavioural self-regulation of effort. This indeed suggests that signals from the insula are involved in effort based decision making (Herbert et al., 2007), by signalling the adequacy of energetical resources.

It is important to distinguish energetical costs from harm and punishment. While both reward and punishments can motivate to engage in activities, both types of motivated behaviour are associated with energetical costs. The results of the experiments described in this section, suggest that neural structures in the brain are capable of comparing predicted rewards associated with performing a task to the energetical costs involved. Behaviour will only proceed if this analysis turns out favourably towards spending (additional) energy.

In summary then, there is good evidence that the brain is well equipped to perform analyses involving both the cost and benefits of behaviour and that this information is used to decide whether or not an action is worth performing (Gehring and Willoughby, 2002; Rushworth et al., 2004). Multiple brain areas have been shown to be involved in this form of effort based decision making, including the ACC, NAc, BLA and insular cortex (see Fig. 1). We propose that, in addition to information on reward value, also information on the current physiological state and energetical resources (signalled by the

insula), as well as expected effort required to obtain rewards (or avert negative events) is integrated, most likely by the ACC, to allow for optimal decision making based on the evaluation of both rewards and potential energetical costs of courses of action. In turn, projections from the ACC impact on activity in the BLA and NAc, modulating the energizing of current behaviour. This way, behaviour is guided by comparing the current state to the predicted future state in terms of both rewards and energetical condition of the body, energizing behaviour only when the predicted state is valued higher than the current state.

Although the majority of experiments described in this section were conducted on animals, these findings apply to humans as well. Granted, our daily activities seem markedly different from a cheetah chasing antelopes on the African plains or from rats trying to climb barriers in some maze to obtain food pallets. But our goals may not be so fundamentally different. As already mentioned, research indicates (e.g. Ljungberg et al., 1992; Mirenowicz and Schultz, 1994) that while primary rewards, like food, initially elicit dopaminergic activation, this activation decreases progressively and is transferred to reward-predicting stimuli when the association between the primary reward and the predicting stimulus is learned (Schultz, 2002). This mechanism makes us find money rewarding (it makes us 'want' money), for example, because money is a very good predictor of us being able to obtain more primary rewards (i.e. we can buy food with it). To take this point further: the pursuit of a career is a goal that at first glance seems rather abstract, but is indeed associated with high expected rewards like the ability to obtain lots of primary food rewards and even with increased chances of finding an attractive mate.

Some interesting results by Erk and co-workers (2002) support this view. In this study, men were presented with photographs of different types of cars: sport cars, middle-sized cars and small cars. More attractive cars elicited stronger activations in several reward related brain areas, including the ventral striatum and mOFC, as well as in the ACC. The authors suggest that sports cars activate the reward system because these cars signal social dominance, which is a strong predictor of primary rewards.

Additionally, one could argue that the definition of effort in studies involving rats climbing barriers (physical effort) may be different from effort that is most relevant for the current discussion (cognitive effort). However, it is important to realize that our brains evolved under circumstances where effort was predominantly physical in nature. It is plausible that these same neural structures are now involved in evaluating effort that is more cognitive or mental in nature. Indeed, it is well established that even the ability to invest physical effort, has a large 'central' component (Schillings et al, 2003). Hence, we propose a neural system evaluating both mental and physical effort that is involved in determining whether a particular mental of physical activity should be engaged in or not.

5. Mental fatigue: The costs of acting

The fact that our brain can process information on both the potential benefits and the potential costs involved in working in order to reach goals enables it not only to determine whether an expected outcome of behaviour is desirable, it can also determine whether a particular action is actually worth performing (Rushworth et al., 2004). For any action to be worth performing, the desirability of the expected outcome should outweigh the potential energetical costs.

We propose that the feeling of fatigue may result from the subconscious analyses of cost and benefits to expend energy, or to conserve energy (Tops et al., 2004; Boksem et al., 2006). People will only expend energy on a certain task when (energetical) costs are comparably low and benefits (high reward, low punishment) are comparably high. This will be the case when behaviour can be expected to bring long-term or short-term rewards, when not performing the task would have negative consequences, or when current behaviour is intrinsically motivating (i.e. the behaviour is 'fun'). However, when tasks have to be performed for prolonged periods of time, the amount of energy invested in performance builds up until it eventually outweighs potential rewards, resulting in a decrease in the motivation to work for rewards that fail to be procured. Thus, we propose that the feeling of fatigue corresponds to a drive to abandon behaviour when energetical costs exceed perceived benefits of continued performance.

Indeed, when the perceived energetical costs of task performance come to exceed the motivation to obtain reward or avoid punishment, the present activities may be abandoned, and perhaps a potentially more rewarding activity will be engaged in. Alternatively, people can try to minimize the energetical costs of performance by choosing behavioural strategies that require minimal levels of effort (Boksem et al., 2006). In doing so, energetical cost are minimized, resulting in a more positive evaluation of costs and benefits.

In one of our own experiments (Boksem et al., 2006), we addressed the issue of the relationship between fatigue and (lack of) motivation to continue task performance. We manipulated motivation by offering our subjects a certain amount of money if they were to be one of the 50% top performing subjects, after they had already performed that task for two consecutive hours. If fatigue can indeed be viewed as involving motivated cost/benefit decisions, the increased reward should lead to a better balance between energetical costs and perceived rewards, thus counteracting the effects of fatigue.

This is exactly what we found. In this experiment, we recorded Event-Related Potentials (ERPs) as well as obtaining behavioural measures. Of special interest to us was the Error-Related Negativity (ERN) or Error Negativity (Ne). The ERN/Ne consists of a large negative shift in the response locked ERP occurring after subjects have made an erroneous response (Falkenstein et al., 1990; Gehring et al., 1990) and is generated in the ACC (Dehaene et al., 1994), which is, as we have seen, a structure of central importance in the processing of reward, punishment and effort demands.

Importantly, Holroyd and Coles (2002) proposed that the ERN/Ne results from a phasic decrease in activity of mesencephalic dopaminergic neurons following an error in reward prediction (i.e. when rewards are less than expected). This decrease in activity in DA activity in the striatum in turn results in a disinhibition of the apical dendrites of motor neurons in the ACC, producing the ERN/Ne (Holroyd and

Yeung, 2003). In addition, many studies have shown the ERN/Ne to be related to motivational processing: when by task instructions the motivation to perform well is reduced, a reduction in ERN/Ne amplitude can be observed (Gehring et al., 1993). Indeed, motivation appears to be essential for observing a robust ERN/Ne (Gehring et al., 1993; Gehring and Knight, 2000) and Bush et al. (2000) argued that ERN/Ne and related ACC activity represent a general evaluative system that processes the motivational significance of events.

What we found was that the ERN/Ne was significantly reduced in fatigued subjects, while motivating these fatigued subjects resulted in increased ERN/Ne amplitudes (Lorist et al., 2005; Boksem et al., 2006). These findings appear to fit well with our hypotheses that mental fatigue involves a negative motivational evaluation of the costs and benefits associated with current behaviour. The ACC, and also the striatum (the NAc in particular) had already been shown to be key structures that enable the brain to perform such analyses (Walton et al., 2002; Salamone et al., 1994). As the ERN/Ne is proposed to result from activity in both striatum and ACC (Holroyd and Coles, 2002), we interpreted our findings of a reduced ERN/Ne in fatigued subjects which can be reversed by providing additional rewards, as strongly corroborating our hypotheses. In addition, because the DA neurotransmitter has a central role in the regulation of the propensity for expending energy (Neill and Justice, 1981; Salamone et al., 1999; Szechtman et al., 1994), and has also been proposed to be involved in generating the ERN/Ne, these findings suggest that DA may be primarily involved in mental fatigue. Indeed, mental fatigue has been causally linked to hampered dopaminergic functioning in striato-thalamo-cortical fibres (Chaudhuri and Behan, 2000, 2004; Lorist and Tops, 2003). Chaudhuri and Behan (2000) propose that fatigue is a symptom of diseases that affect the basal ganglia, disrupting the integration of perceived reward value in the initiation of voluntary activities (Nauta, 1986). The Basal ganglia have been shown to be highly vulnerable to multiple neurodegenerative processes, including invasion of viruses and pro-inflammatory cytokines (Pradhan et al., 1999). Observations in patients suffering from several different diseases with fatigue as a major symptom suggest that the basal ganglia are involved in mental fatigue. Dysfunctions of the basal ganglia have been observed in disorders including Parkinson's disease, Multiple sclerosis, Alzheimer's disease and chronic fatigue syndrome (see Chaudhuri and Behan, 2000 for a review). Further supporting this hypotheses, it has been shown that bilateral lesions of the pallidum (part of the basal ganglia) result in profound fatigue and poor initiative in executive functions (Ghika et al., 1999). Moreover, a generator model of fatigue has been postulated in post poliomyelitis and post viral fatigue syndromes, implicating damage to multiple brain areas including the DA pathways and the basal ganglia (Bruno et al., 1998).

Although mental fatigue as a daily phenomenon most probably does not involve damage to these structures, these findings do suggest that a down regulation of DA in these neural pathways is involved in mental fatigue. As we have seen, these DA pathways and also the basal ganglia (the NAc in particular) are major efferent targets of ACC, OFC, BLA and insula. This way, activity in NAc and midbrain DA is modulated by effort/reward-based decisions, such that increased perceived effort compared to predicted rewards results in a down regulation of DA activity in NAc and midbrain DA.

6. Mental fatigue and control

As already mentioned in the introduction, there will be a reduced probability that the selection of actions will be controlled by high-level regulatory control processes (Lorist et al., 2000; Meijman, 2000), when people become fatigued. Van der Linden and colleagues (2003a, 2003b; 2006) showed that fatigued subjects had difficulties in focusing their attention, planning, and adaptively changing strategies in the face of negative outcomes. In addition, our own work shows that fatigued subjects were less able to prepare themselves for responding (Boksem et al., 2006) and had increasing difficulties in sustaining attention and ignoring irrelevant information (i.e. increased distractibility; Boksem et al., 2005). In addition, we showed that subjects corrected their erroneous responses less often and that post error performance adjustment was impaired (Lorist et al., 2005; Boksem et al., 2006).

The PFC is strongly involved in generating these regulatory cognitive control processes. Because of its connectivity with neocortical sensory and motor systems and various subcortical structures, the PFC provides an ideal infrastructure for integrating the diverse range of information that is needed for complex behaviour. In addition, the PFC projects back to these systems, providing it with a means to exert top–down influence over a large array of brain processes (Pandya and Barnes, 1987; Goldman-Rakic, 1987). Importantly, DA (Durstewitz et al., 1999, 2000; Miller and Cohen, 2001) projections to the PFC have been show to be of central importance to these cognitive control processes.

DA may be involved in sustaining PFC activity over longer periods of time, enabling us to persist toward goals, protecting our goal relevant task representations from disruption by irrelevant, distracting information (Durstewitz et al., 1999, 2000). Indeed, one of the classic signs of PFC damage is increased distractibility: 'frontal' patients seem unable to focus on a task or ignore irrelevant distracting stimuli (Duncan et al., 1996). This is remarkably similar to what has been found with mentally fatigued subjects (e.g. Van der Linden et al., 2003a, 2003b, 2006).

Recently, Sarter et al., (2006) proposed that increasing attentional effort as a result of challenging circumstances (like prolonged task performance) is strongly dependant on the motivation to maintain or recover task performance. They present a model describing the interactions between cortical, mesolimbic and dopaminergic systems that are considered essential for activating attentional systems. Acetylcholine (Ach) projections to the PFC have been shown to be involved in attention and top–down control of behaviour (Sarter et al., 2001; Sarter and Parikh, 2005). In turn, ACh neurons in the basal forebrain receive extensive projections from the brain structures involved in reward processing, most notably the NAc. In their review, Sarter and colleagues provide convincing evidence suggesting that these NAc outputs are capable of activating the PFC circuitry that is involved in attention and

cognitive control (Christakou et al., 2004; Himmelheber et al., 2000; Miner and Sarter, 1999), when motivation to maintain performance is high.

This model also suggests that changes in DA activity in the NAc in response to detrimental challenges, such as prolonged task performance, may attenuate activity in ACh projections to the PFC and thereby lead to reduced attentional performance and cognitive control. Since deficits in attention and top–down control have been observed in fatigued subjects (see above), interactions between the DA and ACh projection systems may prove to be fundamental to the changes in performance due to mental fatigue. Thus, reduced activity in neural structures signalling reward value, may lead to reduced activity in DA and ACh projections to the PFC, resulting in impairments in attention and cognitive control processes.

7. Why fatigue?

Although this seems to suggest that fatigue is only detrimental to performance and goal-directed behaviour, we argue that this is not the case. Instead, we propose that fatigue can best be considered as an adaptive signal that the present behavioural strategy may no longer be the most appropriate, because it continues to demand effort while substantial effort has already been invested and the goal evidently has not yet been achieved. Fatigue may provide the cognitive system with a signal that encourages the organism to lower present goals and/or seek lower effort alternative strategies.

Indeed, we argue that integration of immediate needs, like rest, is essential for realizing long-term goals. Ignoring these short-term goals would have major negative consequences for other, less immediate goals. When people are fatigued, these long term goals suffer more and more competition from these short term goals, that are directed at maintaining general well being. In this view, fatigue may not involve an impairment of goal directed behaviour, but instead involve a change in the goals towards which behaviour is directed; from long-term goals to more immediate goals. Indeed, as Whishaw and Kornelsen (1993) have shown, lesioning the NAc (an integral part of the neural substrate we proposed for mental fatigue) leads rats to still eat their food on the spot, while failing to hoard some of it for later consumption.

We propose that the alterations of DA and ACh influx into the PFC that occur with prolonged task performance is adaptive in the sense that it signals the need to abandon or change the ongoing behaviour in such a way to promote energy conservation or change the focus of attention to other, perhaps more rewarding behaviours. In everyday life, it is rarely useful to keep attention directed at one particular goal for prolonged periods of time, while rewards remain forthcoming. In this view it may even be considered adaptive that the reduced influx of DA and ACh in the PFC results in increased distractibility (i.e. goals become less activated), which would promote exploratory behaviour in search of other, perhaps more rewarding goals.

In summary, the feeling of fatigue provides us with a signal that tells us to put the brakes on. Energy is every organism's most valuable resource and there should be constraints on how it is spent. Efficient spending and conservation of energy results in the greatest chances of survival, which makes the phenomenon of fatigue highly adaptive.

8. Beyond control

Choosing courses of action based on an analysis of costs and benefits is highly adaptive and efficient, but only when one is free to choose between various action alternatives (i.e. the situation is controllable). In everyday life, especially in the work environment, this control over the situation is often lacking. High workload, high demands on cognitive functions, and fixed production quotas limit the possibilities of employees to choose lower effort alternatives when they perceive effort to become too great compared to the perceived rewards.

Ominously, working overtime has been suggested to lead to high blood pressure, cardiovascular disease (Beckers et al., 2004), mental health problems (Van der Hulst, 2003; Sparks et al., 1997), and even death (Harati, 1998). As already mentioned in the introduction however, working overtime per se has not been shown to lead to significant fatigue (Sparks et al., 1997; Park et al., 2001). Indeed, working long hours has been shown not to be detrimental at all, when people can control when they work and how much they work (Hockey and Earle, 2006) and, significantly, when they perceive the rewards of their work (in terms of payment, but also recognition) as high (Siegrist, 1996). Van der Hulst and Geurts (2001) suggest that working overtime does not result in detrimental health, while low job-rewards do. In other words, high workload only results in fatigue when rewards associated with work are low.

When the work situation is uncontrollable, people are forced to override the signal of imminent fatigue that results from an imbalance of perceived costs and benefits associated with their work. The ability to override this signal is in itself adaptive as well, for example in emergency situations, in which case the importance of the emergency outweighs the possible costs. However, overriding this signal for prolonged periods of time comes at a price in the form of stress, which in time can lead to damage (McEwen and Wingfield, 2003). This may be fundamental to disorders that are characterized by long-term fatigue, like burnout.

Although the exact mechanism through which fatigue takes on a more chronic form is poorly understood, it may involve the hypothalamic–pituitary–adrenal axis (HPA axis). In demanding situations (i.e. situations that require increased effort and involve low perceived rewards), the body has to mobilize additional energetical resources to cope with this situation. The hormone cortisol is primarily involved in energy mobilization (Sapolsky et al., 2000), perhaps by indirectly disinhibiting DA function. Cortisol indeed increases dopaminergic activity (Schatzberg et al., 1985; Dallman et al., 2006) and feelings of energy (Tops et al., 2006b, 2007). However, when a stressful situation of high energetical costs and low perceived benefits persists (i.e. the situation of low energetic efficiency is chronic/uncontrollable), this results in a down regulation of cortisol, promoting conservation of energy (Porges, 2001; McEwen and Wingfield, 2003; Tops et al., 2008). This reduction in DA activity, may result in a permanent decrease in the motivation to expend energy, feelings of

detachment and a withdrawal from the work environment (Tops et al., 2007).

Indeed, low levels of cortisol have been found to be characteristic for a highly co-morbid group of syndromes that share the primary symptom of fatigue, like burnout, chronic fatigue syndrome, posttraumatic stress syndrome, atypical depression and fibromyalgia (e.g. Fries et al., 2005). Furthermore, cortisol inhibits activity of pro-inflammatory cytokines, and these immune system communication molecules have been associated with chronic fatigue (Patarca-Montero et al., 2001). Disinhibition of pro-inflammatory cytokine activity by low cortisol levels may induce fatigue and somatic symptoms. Pro-inflammatory cytokines are high in situations when energy is preferably allocated to immune function instead of to mechanisms of behavioural coping (Kelley et al., 2003).

Although there is a striking similarity between the involvement of cortisol in energy efficiency regulation in chronic forms of fatigue and the effort–reward imbalance we propose to be central to acute feelings of fatigue, data on the precise mechanism by which (repeated) acute fatigue results in chronic fatigue is currently lacking. More research is required on the potential role of cortisol in acute fatigue. In addition, structural changes in DA and other neurotransmitter systems in subjects suffering from chronic fatigue symptoms deserve further investigation (see Tops et al., 2007).

9. Individual differences

Are some more at risk for becoming fatigued than others? Several studies have noted that people with personality characteristics that increase chances of overriding the signal of fatigue are at risk. These personality characteristics include high perfectionism (Magnusson et al., 1996; White & Schweitzer, 2000), high neuroticism (Johnson et al., 1996; Prins et al., 2006) and low extraversion (Prins et al., 2006; Watson et al., 1999). All these personality characteristics relate to the way people invest effort and perceive rewards and punishment.

Similar to high neuroticism, low extraversion has been associated with increased perceptions of effort, exertion and fatigue (Morgan, 1994; Watson et al., 1999), as well as lowered preferred exercise intensity (Morgan, 1994) and lower vigour (Depue and Collins, 1999; Watson et al., 1999). The personality trait of extraversion relates to positive affect, vigour, and is thought to reflect reward sensitivity and DA function (Depue and Collins, 1999; Watson et al., 1999). Low scores on extraversion have been identified as a risk factor in the development of burnout (Bellani et al., 1996; Michielsen et al., 2003) and chronic fatigue syndrome (Prins et al., 2006) and play a role in a role in effort–reward imbalances (de Jonge et al., 2000). As extraversion may reflect reward sensitivity, low scores may predispose to perceiving costs as exceeding potential rewards.

Neuroticism is characterized by vigilance and attention to potential threat, caution and avoidance of errors (Eysenck, 1967; Gray, 1987; Perkins and Corr, 2005). People high on neuroticism have been shown to outperform their low-neurotic counterparts when a high level of effort has to be invested (Smillie et al., 2006; Tamir, 2005), possibly sacrificing immediate pleasure or well being to optimise task performance (Tamir, 2005). In consequence, when performance has to be maintained for a prolonged period of time and reward motivation dissipates, these people experience a stronger drive to avoid punishment associated with stopping. This drives them to continue working, even though they do not feel rewarded.

What puts these people high on neuroticism and perfectionism at risk for becoming chronically fatigued is the fact that they persevere even in the face of not reaching their goals and not getting the rewards they work for. As already noted, these rewards not only come in the form of money, but probably primarily as positive social evaluation and appreciation of their work. In other words, these people just do not know when to quit; either because they set their goals too high, are afraid that their achievements will not be perceived as up to the mark by others, or because they are more concerned with being punished for bad results than with being rewarded for good results. Under these circumstances, people perceive the benefits (rewards or non-punishment) of continuing performance as higher than most people would, so they are willing to incur greater energetical and physiological costs. If this stressful situation persists, this could lead to chronic fatigue related illnesses. Indeed, fear of negative social evaluation which is a characteristic feature of perfectionism and neuroticism, has been related to high cortisol responses (Dickerson and Kemeny, 2004). A history of frequent high cortisol responses in these individuals may lead to protective adaptations (low cortisol) that tend to prevent additional responses, thus constraining further energetical output and inducing feelings of fatigue (Miller et al., 2007; Tops et al., 2008).

10. Summary

Our environment typically supports multiple goals, associated with different magnitudes of reward. The OFC, BLA and insula have been shown to be primarily involved in coding the expected appetitive and aversive value that each option may provide. This reward-related information may be relayed to the ACC, where these sources of reward information may be integrated to bias behaviour in a particular direction that is predicted to result in the largest reward value.

In addition to information on reward value, also information on the current physiological state and energetical resources, as well as expected effort required to obtain rewards (or avert negative events) is signalled in the insula and integrated, most likely by the ACC, to allow for optimal decision making based on the evaluation of both rewards and potential engergetical costs of courses of action. Multiple brain areas have been shown to be involved in this form of effort based decision making, including the ACC, NAc, BLA and insular cortex.

The feeling of fatigue may result from the subconscious analyses of cost and benefits to expend energy, or to conserve energy. Energy will only be expended on a certain task when (energetical) costs are comparably low and benefits (high reward, low punishment) are comparably high. Indeed, when

the perceived energetical costs of task performance come to exceed the motivation to obtain reward or avoid punishment, the present activities may be abandoned, and perhaps a potentially more rewarding activity will be engaged in. Alternatively, people can try to minimize the energetical costs of performance by choosing behavioural strategies that require minimal levels of effort.

In summary, we propose that people will only be motivated to engage in or continue activities when potential rewards for performance are high, compared to the effort required for these activities. However, when tasks have to be performed for prolonged periods of time, the amount of energy invested in performance increases compared to potential rewards, resulting in a decrease in the motivation to work for rewards that fail to be procured. Thus, we propose that the feeling of fatigue corresponds to a drive to abandon behaviour when energetical costs continue to exceed perceived rewards of task performance.

Acknowledgments

This work was supported by the Netherlands Organisation for Scientific Research (NWO), as part of the Netherlands concerted research action "Fatigue at Work".

REFERENCES

Akkal, D., Bioulac, B., Audin, J., Burbaud, P., 2002. Comparison of neuronal activity in the rostral supplementary and cingulate motor areas during a task with cognitive and motor demands. Eur. J. Neurosci. 15, 887–904.

Allport, L.E., Butcher, K.S., Baird, T.A., MacGregor, I., Desmond, P.M., Tress, B.M., Colman, P., Davis, S.M., 2004. Insular cortical ischemia is independently associated with acute stress hyperglycemia. Stroke 33, 1886–1891.

Baxter, M.G., Parker, A., Lindner, C.C.C., Izquierdo, A.D., Murray, E.A., 2000. Control of response selection by reinforcer value requires interaction of amygdala and orbital prefrontal cortex. J. Neurosci. 20 (11), 4311–4319.

Beckers, D.G.J., van der Linden, D., Smulders, P.G.W., Kompier, M.A.J., van Veldhoven, M., van Yperen, N.W., 2004. Working overtime hours: relations with fatigue, work motivation, and the quality of work. J. Occup. Environ. Med. 46, 1282–1289.

Bellani, M.L., Furlani, F., Gnecchi, M., Pezzotta, P., Trotti, E.M., Bellotti, G.G., 1996. Burnout and related factors among HIV AIDS health care workers. Aids Care-Psychological and Socio-Medical Aspects of Aids/Hiv 8, 207–221.

Berendse, H.W., Galisdegraaf, Y., Groenewegen, H.J., 1992. Topographical organization and relationship with ventral striatal compartments of prefrontal corticostriatal projections in the rat. J. Comp. Neurol. 316, 314–347.

Berridge, K.C., Robinson, T.E., 2003. Parsing reward. Trends Neurosci. 26, 507–513.

Berridge, K.C., 2007. The debate over dopamine's role in reward: the case for incentive salience. Psychopharmacology 191, 391–431.

Boksem, M.A.S., Lorist, M.M., Meijman, T.F., 2005. Effects of mental fatigue on attention: an ERP study. Cogn. Brain Res. 25, 107–116.

Boksem, M.A.S., Meijman, T.F., Lorist, M.M., 2006. Mental fatigue, motivation and action monitoring. Biol. Psychol. 72, 123–132.

Boksem, M.A.S., Tops, M., Kostermans, E., De Cremer, D., in press. Sensitivity to Punishment and Reward Omission: Evidence From Error-Related ERP Components. Biol. Psychol. doi:10.1016/j.biopsycho.2008.04.010.

Bruno, R.L., Crenage, S.J., Fick, N.M., 1998. Parallels between post-polio fatigue and chronic fatigue syndrome: a common pathophysiology? Am. J. Med. 105, 66S–73S.

Burns, L.H., Everitt, B.J., Robbins, T.W., 1999. Effects of excitotoxic lesions of the basolateral amygdala on conditional discrimination learning with primary and conditioned reinforcement. Behav. Brain Res. 100, 123–133.

Bush, G., Luu, P., Posner, M.I., 2000. Cognitive and emotional influences in anterior cingulate cortex. Trends Cogn. Sci. 4, 215–222.

Bush, G., Vogt, B.A., Holmes, J., Dale, A.M., Greve, D., Jenike, M.A., Rosen, B.R., 2002. Dorsal anterior cingulate cortex: a role in reward-based decision making. Proc. Natl. Acad. Sci. U. S. A. 99, 523–528.

Cardinal, R.N., Parkinson, J.A., Hall, J., Everitt, B.J., 2002a. Emotion and motivation: the role of the amygdala, ventral striatum, and prefrontal cortex. Neurosci. Biobehav. Rev. 26, 321–352.

Cardinal, R.N., Parkinson, J.A., Lachenal, G., Halkerston, K.M., Rudarakanchana, N., Hall, J., Morrison, C.H., Howes, S.R., Robbins, T.W., Everitt, B.J., 2002b. Effects of selective excitotoxic lesions of the nucleus accumbens core, anterior cingulate cortex, and central nucleus of the amygdala on autoshaping performance in rats. Behav. Neurosci. 116, 553–567.

Carmichael, S.T., Price, J.L., 1995. Sensory and premotor connections of the orbital and medial prefrontal cortex of macaque monkeys. J. Comp. Neurol. 363, 642–664.

Chaudhuri, A., Behan, P.O., 2000. Fatigue and basal ganglia. J. Neurol. Sci. 179, 34–42.

Chaudhuri, A., Behan, P.O., 2004. Fatigue in neurological disorders. Lancet 363, 978–988.

Chiba, T., Kayahara, T., Nakanoh, K., 2001. Efferent projections of infralimbic and prelimbic areas of the medial prefrontal cortex in the Japanese monkey, Macaca fuscata. Brain Res. 888, 83–101.

Christakou, A., Robbins, T.W., Everitt, B.J., 2004. Prefrontal cortical–ventral striatal interactions involved in affective modulation of attentional performance: implications for corticostriatal circuit function. J. Neurosci. 24, 773–780.

Cohen, M.X., Heller, A.S., Ranganath, C., 2005. Functional connectivity with anterior cingulate and orbitofrontal cortices during decision-making. Cogn. Brain Res. 23, 61–70.

Corbit, L.H., Balleine, B.W., 2005. Double dissociation of basolateral and central amygdala lesions on the general and outcome-specific forms of pavlovian-instrumental transfer. J. Neurosci. 25, 962–970.

Coricelli, G., Critchley, H.D., Joffily, M., O'Doherty, J.P., Sirigu, A., Dolan, R.J., 2005. Regret and its avoidance: a neuroimaging study of choice behavior. Nat. Neurosci. 8, 1255–1262.

Cousins, M.S., Salamone, J.D., 1994. Nucleus accumbens dopamine depletions in rats affect relative response allocation in a novel cost/benefit procedure. Pharmacol. Biochem. Behav. 49, 85–91.

Coutureau, E., Dix, S.L., Killcross, A.S., 2000. Involvement of the medial prefrontal cortex–basolateral amygdala pathway in fear related behaviour in rats. Eur. J. Neurosci. 12, 156.

Craig, A.D., 2003. Interoception: the sense of the physiological condition of the body. Curr. Opin. Neurobiol. 13, 500–505.

Critchley, H.D., Wiens, S., Rotshtein, P., Ohman, A., Dolan, R.J., 2004. Neural systems supporting interoceptive awareness. Nat. Neurosci. 7, 189–195.

Dallman, M.F., Pecoraro, N.C., La Fleur, S.E., Warne, J.P., Ginsberg, A.B., Akana, S.F., Laugero, K.C., Houshyar, H., Strack, A.M., Bhatnagar, S., Bell, M.E., 2006. Glucocorticoids, chronic stress, and obesity. Prog. Brain Res. 153, 75–105.

Dayan, P., Balleine, B.W., 2002. Reward, motivation, and reinforcement learning. Neuron 36, 285–298.

de Graaf, J.B., Gallea, C., Pailhous, J., Anton, J.L., Roth, M., Bonnard, M., 2004. Awareness of muscular force during movement production: an fMRI study. NeuroImage 21, 1357–1367.
de Jonge, J., Bosma, H., Peter, R., Siegrist, J., 2000. Job strain, effort-reward imbalance and employee wellbeing: a large-scale cross-sectional study. Soc. Sci. Med. 50, 1317–1327.
Dehaene, S., Posner, M.I., Tucker, D.M., 1994. Localization of a neural system for error-detection and compensation. Psychol. Sci. 5, 303–305.
Denk, F., Walton, M.E., Jennings, K.A., Sharp, T., Rushworth, M.F.S., Bannerman, D.M., 2005. Differential involvement of serotonin and dopamine systems in cost-benefit decisions about delay or effort. Psychopharmacology 179, 587–596.
Depue, R.A., Collins, P.F., 1999. Neurobiology of the structure of personality: dopamine, facilitation of incentive motivation, and extraversion. Behav. Brain Sci. 22, 491–517.
Desmond, P.A., Hancock, P.A., 2001. Active and passive fatigue states. In: Desmond, P.A., Hancock, P.A. (Eds.), Stress, Workload and Fatigue. Lawrence Erlbaum Associates, Mahwah, New Yersey, pp. 455–465.
Devinsky, O., Morrell, M.J., Vogt, B.A., 1995. Contributions of anterior cingulate cortex to behavior. Brain 118, 279–306.
Dickerson, S.S., Kemeny, M.E., 2004. Acute stressors and cortisol responses: a theoretical integration and synthesis of laboratory research. Psychol. Bull. 130, 355–391.
Duncan, J., Emslie, H., Williams, P., Johnson, R., Freer, C., 1996. Intelligence and the frontal lobe: the organization of goal-directed behavior. Cogn. Psychol. 30, 257–303.
Durstewitz, D., Kelc, M., Gunturkun, O., 1999. A neurocomputational theory of the dopaminergic modulation of working memory functions. J. Neurosci. 19, 2807–2822.
Durstewitz, D., Seamans, J.K., Sejnowski, T.J., 2000. Dopamine-mediated stabilization of delay-period activity in a network model of prefrontal cortex. J. Neurophysiol. 83, 1733–1750.
Erk, S., Spitzer, M., Wunderlich, A.P., Galley, L., Walter, H., 2002. Cultural objects modulate reward circuitry. Neuroreport 13, 2499–2503.
Everitt, B.J., Cador, M., Robbins, T.W., 1989. Interactions between the amygdala and ventral striatum in stimulus reward associations — studies using a 2nd-order schedule of sexual reinforcement. Neuroscience 30, 63–75.
Eysenck, H.J., 1967. The Biological Basis of Personality. Charles C. Thomas, Springfield, IL.
Falkenstein, M., Hohnsbein, J., Hoormann, J., Blanke, L., 1990. Effects of errors in choice reaction tasks on the ERP under focussed and divided attention. In: Brunia, C.H.M., Gaillard, A.W.K., Kok, A. (Eds.), Psychophysiological Brain Research. Tilburg University Press, Tilburg, pp. 192–195.
Floresco, S.B., Yang, C.R., Phillips, A.G., Blaha, C.D., 1998. Basolateral amygdala stimulation evokes glutamate receptor-dependent dopamine efflux in the nucleus accumbens of the anaesthetized rat. Eur. J. Neurosci. 10, 1241–1251.
Floresco, S.B., Braaksma, D.N., Phillips, A.G., 1999. Thalamic–cortical–striatal circuitry subserves working memory during delayed responding on a radial arm maze. J. Neurosci. 19, 11061–11071.
Floresco, S.B., Ghods-Sharifi, S., 2007. Amygdala-prefrontal cortical circuitry regulates effort-based decision making. Cereb. Cortex 17, 251–260.
Fries, E., Hesse, J., Hellhammer, J., Hellhammer, D.H., 2005. A new view on hypocortisolism. Psychoneuroendocrinology 30, 1010–1016.
Gehring, W.J., Coles, M.G.H., Meyer, D.E., Donchin, E., 1990. The Error-related negativity: an event-related brain potential accompanying errors. Psychophysiology 27, s34.
Gehring, W.J., Goss, B., Coles, M.G.H., Meyer, D.E., Donchin, E., 1993. A neural system for error-detection and compensation. Psychol. Sci. 4, 385–390.
Gehring, W.J., Knight, R.T., 2000. Prefrontal–cingulate interactions in action monitoring. Nat. Neurosci. 3, 516–520.
Gehring, W.J., Willoughby, A.R., 2002. The medial frontal cortex and the rapid processing of monetary gains and losses. Science 295, 2279–2282.
Ghika, J., Ghika-Schmid, F., Fankhauser, H., Assal, G., Vingerhoets, F., Albanese, A., Bogousslavsky, J., Favre, J., 1999. Bilateral contemporaneous posteroventral pallidotomy for the treatment of Parkinson's disease: neuropsychological and neurological side effects — Report of four cases and review of the literature. J. Neurosurg. 91, 313–321.
Goldman-Rakic, P.S., 1987. In: Plum, F. (Ed.), Handbook of Physiology: The Nervous System. American Physiological Society, Bethesda, pp. 373–417.
Gottfried, J.A., O'Doherty, J., Dolan, R.J., 2003. Encoding predictive reward value in human amygdala and orbitofrontal cortex. Science 301, 1104–1107.
Gray, J.A., 1987. The neuropsychology of emotion and personality. In: Stahl, S.M., Iverson, S.D., Goodman, E.C. (Eds.), Cognitive Neurochemistry. Oxford University Press, Oxford, pp. 171–190.
Groenewegen, H.J., Berendse, H.W., Wolters, J.G., Lohman, A.H.M., 1990. The anatomical relationship of the prefrontal cortex with the striatopallidal system, the thalamus and the amygdala — evidence for a parallel organization. Prog. Brain Res. 85, 95–118.
Haber, S.N., Kunishio, K., Mizobuchi, M., Lyndbalta, E., 1995. The orbital and medial prefrontal circuit through the primate basal ganglia. J. Neurosci. 15, 4851–4867.
Harati, T., 1998. Karoshi. Death from overwork. In: Stellman, J.M. (Ed.), Encyclopedia of Occupational Health and Safety. International Labour Office, Geneva, pp. 518–519.
Herbert, B.M., Ulbrich, P., Schandry, R., 2007. Interoceptive sensitivity and physical effort: Implications for the self-control of physical load in everyday life. Psychophysiology 44, 194–202.
Himmelheber, A.M., Bruno, J.P., Sarter, M., 2000. Effects of intra-accumbens infusions of amphetamine or *cis*-flupenthixol on sustained attention performance in rats. Behav. Brain Res. 116, 123–133.
Hockey, G.R.J., 1997. Compensatory control in the regulation of human performance under stress and high workload: a cognitive-energetical framework. Biol. Psychol. 45, 73–93.
Hockey, G.R.J., Earle, F., 2006. Control over the scheduling of simulated office work reduces the impact of workload on mental fatigue and task performance. J. Exp. Psychol. Appl. 12, 50–65.
Holding, D., 1983. Fatigue. In: Hockey, G.R.J. (Ed.), Stress and fatigue in human performance. John Wiley and Sons, Durnham, pp. 145–164.
Holroyd, C.B., Coles, M.G.H., 2002. The neural basis. of human error processing: Reinforcement learning, dopamine, and the error-related negativity. Psychol. Rev. 109, 679–709.
Holroyd, C.B., Yeung, N., 2003. Alcohol and error processing. Trends Neurosci. 26, 402–404.
Horvitz, J.C., 2000. Mesolimbocortical and nigrostriatal dopamine responses to salient non-reward events. Neuroscience 96, 651–656.
Jensen, O., Tesche, C.D., 2002. Frontal theta activity in humans increases with memory load in a working memory task. Eur. J. Neurosci. 15 (8), 1395–1399.
Johnson, S.K., DeLuca, J., Natelson, B.H., 1996. Personality dimensions in the chronic fatigue syndrome: a comparison with multiple sclerosis and depression. J. Psychiatr. Res. 30, 9–20.
Kelley, K.W., Bluthé, R.M., Dantzer, R., Zhou, J.H., Shen, W.H., Johnson, R.W., Broussard, S.R., 2003. Cytokine-induced sickness behavior. Brain Behav. Immunol. 17 (Suppl. 1), S112–S118.
Kennerley, S.W., Walton, M.E., Behrens, T.E.J., Buckley, M.J., Rushworth, M.F.S., 2006. Optimal decision making and the anterior cingulate cortex. Nat. Neurosci. 9, 940–947.

Killcross, A.S., Everitt, B.J., Robbins, T.W., 1995. dissociable effects of selective excitotoxic lesions of the amygdala on instrumental and Pavlovian components of a novel conditioned punishment procedure. Social Neuroscience Abstracts. 25th Annual Meeting, San Diego
Killcross, S., Robbins, T.W., Everitt, B.J., 1997. Different types of fear-conditioned behaviour mediated by separate nuclei within amygdala. Nature 388, 377–380.
Knutson, B., Rick, S., Wimmer, G.E., Prelec, D., Loewenstein, G., 2007. Neural predictors of purchases. Neuron 53, 147–156.
Krain, A.L., Wilson, A.M., Arbuckle, R., Castellanos, F.X., Milham, M.P., 2006. Distinct neural mechanisms of risk and ambiguity: a meta-analysis of decision-making. NeuroImage 32, 477–484.
Kringelbach, M.L., Rolls, E.T., 2004. The functional neuroanatomy of the human orbitofrontal cortex: evidence from neuroimaging and neuropsychology. Prog. Neurobiol. 72, 341–372.
Kringelbach, M.L., 2005. The human orbitofrontal cortex: linking reward to hedonic experience. Nat. Rev. Neurosci. 6, 691–702.
Kuhnen, C.M., Knutson, B., 2005. The neural basis of financial risk taking. Neuron 47, 763–770.
LeDoux, J.E., 1996. The emotional brain. Simon and Schuster.
Ljungberg, T., Apicella, P., Schultz, W., 1992. Responses of monkey dopamine neurons during learning of behavioral reactions. J. Neurophysiol. 67, 145–163.
Lorist, M.M., Klein, M., Nieuwenhuis, S., De Jong, R., Mulder, G., Meijman, T.F., 2000. Mental fatigue and task control: planning and preparation. Psychophysiology 37, 614–625.
Lorist, M.M., Tops, M., 2003. Caffeine, fatigue, and cognition. Brain Cogn. 53, 82–94.
Lorist, M.M., Boksem, M.A.S., Ridderinkhof, K.R., 2005. Impaired cognitive control and reduced cingulate activity during mental fatigue. Cogn. Brain Res. 24, 199–205.
Magnusson, A.E., Nias, D.K., White, P.D., 1996. Is perfectionism associated with fatigue? J. Psychosom. Res. 41, 377–383.
McDonald, A.J., 1998. Cortical pathways to the mammalian amygdala. Prog. Neurobiol. 55, 257–332.
McEwen, B.S., Wingfield, J.C., 2003. The concept of allostasis in biology and biomedicine. Horm. Behav. 43, 2–15.
Meijman, T.F., 2000. The theory of the stop-emotion: on the functionality of fatigue. In: Pogorski, D., Karwowski, W. (Eds.), Ergonomics and safety for global buisiness quality and production. CIOP, Warschaw, pp. 45–50.
Michielsen, H.J., De Vries, J., Van Heck, G.L., 2003. In search of personality and temperament predictors of chronic fatigue: a prospective study. Pers. Individ. Differ. 35, 1073–1087.
Miller, E.K., 2000. The prefrontal cortex and cognitive control. Nat. Rev. Neurosci. 1, 59–65.
Miller, E.K., Cohen, J.D., 2001. An integrative theory of prefrontal cortex function. Annu. Rev. Neurosci. 24, 167–202.
Miller, G.E., Chen, E., Zhou, E.S., 2007. I fit goes up, must it come down? Chronic stress and the hypothalamic–pituitary–adrenal axis in humans. Psychol. Bull. 133, 25–45.
Miner, L.A.H., Sarter, M., 1999. Intra-accumbens infusions of antisense oligodeoxynucleotides to one isoform of glutamic acid decarboxylase mRNA, GAD(65), but not to GAD(67), mRNA, impairs sustained attention performance in the rat. Cogn. Brain Res. 7, 269–283.
Mirenowicz, J., Schultz, W., 1994. Importance of unpredictability for reward responses in primate dopamine neurons. J. Neurophysiol. 72, 1024–1027.
Morecraft, R.J., Geula, C., Mesulam, M.M., 1992. Cytoarchitecture and neural afferents of orbitofrontal cortex in the brain of the monkey. J. Comp. Neurol. 323, 341–358.
Morgan, W.P., 1994. Psychological components of effort sense. Med. Sci. Sports Exerc. 26, 1071–1077.
Nauta, W.H.J., 1986. Circuitous connections linking cerebral cortex, limbic system and corpus striatum. In: Doane, B.K., Livingstone, K.E. (Eds.), The limbic system: functional organization and clinical disorders. Raven Press, New York, pp. 43–54.
Neill, D.B., Justice, J.B., 1981. An hypothesis for a behavioral function of dopaminergic transmission in nucleus accumbens. In: Chronister, R.B., DeFrance, J.F. (Eds.), The neurobiology of the nucleus accumbens. Institute for Electrophysiological Research, Brunswick, ME, pp. 343–350.
Nitschke, J.B., Sarinopoulos, I., Mackiewicz, K.L., Schaefer, H.S., Davidson, R.J., 2006. Functional neuroanatomy of aversion and its anticipation. NeuroImage 29, 106–116.
Nobre, A.C., Coull, J.T., Frith, C.D., Mesulam, M.M., 1999. Orbitofrontal cortex is activated during breaches of expectation in tasks of visual attention. Nat. Neurosci. 2, 11–12.
O'Doherty, J., Kringelbach, M.L., Rolls, E.T., Hornak, J., Andrews, C., 2001. Abstract reward and punishment representations in the human orbitofrontal cortex. Nat. Neurosci. 4 (1), 95–102.
Ongur, D., Price, J.L., 2000. The organization of networks within the orbital and medial prefrontal cortex of rats, monkeys and humans. Cereb. Cortex 10, 206–219.
Pandya, D.N., Barnes, C.L., 1987. In: Percman, E. (Ed.), The Frontal Lobes Revisited. IRBN Press, New York, pp. 41–72.
Park, J.S., Kim, Y.H., Chung, H.K., Hisanaga, N., 2001. Long working hours and subjective fatigue symptoms. Ind. Health 39, 250–254.
Parkinson, J.A., Willoughby, P.J., Robbins, T.W., Everitt, B.J., 2000. Disconnection of the anterior cingulate cortex and nucleus accumbens core impairs Pavlovian approach behavior: Further evidence for limbic cortical–ventral striatopallidal systems. Behav. Neurosci. 114, 42–63.
Patarca-Montero, R., Antoni, M., Fletcher, M.A., Klimas, N.G., 2001. Cytokine and other immunologic markers in chronic fatigue syndrome and their relation to neuropsychological factors. Appl. Neuropsychol. 8, 51–64.
Paulus, M.P., Rogalsky, C., Simmons, A., Feinstein, J.S., Stein, M.B., 2003. Increased activation in the right insula during riks-taking decision making is related to harm avoidance and neuroticism. NeuroImage 19, 1439–1448.
Paulus, M.P., Stein, M.B., 2006. An insular view of anxiety. Biol. Psychiatry 60, 382–387.
Paus, T., Zatorre, R.J., Hofle, N., Caramanos, Z., Gotman, J., Petrides, M., Evans, A.C., 1997. Time-related changes in neural systems underlying attention and arousal during the performance of an auditory vigilance task. J. Cogn. Neurosci. 9 (3), 392–408.
Perkins, A.M., Corr, P.J., 2005. Can worriers be winners? The association between worrying and job performance. Pers. Individ. Diff. 38, 25–31.
Pollatos, O., Kirsch, W., Schandry, R., 2005. Brain structures involved in interoceptive awareness and cardioafferent signal processing: A dipole source localization study. Hum. Brain Mapp. 26, 54–64.
Porges, S.W., 2001. The polyvagal theory: phylogenetic substrates of a social nervous system. Int. J. Psychophysiol. 42, 123–146.
Prins, J.B., Bleijenberg, G., van der Meer, J.W.M., 2006. Chronic fatigue syndrome — Reply. Lancet 367, 1575.
Reynolds, S.M., Zahm, D.S., 2005. Specificity in the projections of prefrontal and insular cortex to ventral striatopallidum and the extended amygdala. J. Neurosci. 25, 11757–11767.
Ricci, J.A., Chee, E., Lorandeau, A.L., Berger, J., 2007. Fatigue in the US workforce: prevalence and implications for lost productive work time. J. Occup. Environ. Med. 49, 1–10.
Robledo, P., Robbins, T.W., Everitt, B.J., 1996. Effects of excitotoxic lesions of the central amygdaloid nucleus on the potentiation of reward-related stimuli by intra-accumbens amphetamine. Behav. Neurosci. 110, 981–990.
Pradhan, S., Pandey, N., Shashank, S., Gupta, R.K., Mathur, A., 1999. Parkinsonian symptoms due to predominant involvement of substantia nigra in Japanese encephalitis. Neurology 53, 1781–1786.

Rushworth, M.F.S., Walton, M.E., Kennerley, S.W., Bannerman, D. M., 2004. Action sets and decisions in the medial frontal cortex. Trends Cogn. Sci. 8, 410–417.
Salamone, J.D., Cousins, M.S., Bucher, S., 1994. Anhedonia or anergia — effects of haloperidol and nucleus-accumbens dopamine depletion on instrumental response selection in a T-maze cost-benefit procedure. Behav. Brain Res. 65, 221–229.
Salamone, J.D., Cousins, M.S., Snyder, B.J., 1997. Behavioral functions of nucleus accumbens dopamine: empirical and conceptual problems with the anhedonia hypothesis. Neurosci. Biobehav. Rev. 21, 341–359.
Salamone, J.D., Aberman, J.E., Sokolowski, J.D., Cousins, M.S., 1999. Nucleus accumbens dopamine and rate of responding: neurochemical and behavioral studies. Psychobiology 27, 236–247.
Salinas, J.A., Packard, M.G., McGaugh, J.L., 1993. Amygdala modulates memory for changes in reward magnitude — reversible post-training inactivation with lidocaine attenuates the response to a reduction in reward. Behav. Brain Res. 59, 153–159.
Sapolsky, R.M., Romero, L.M., Munck, A.U., 2000. How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions. Endocr. Rev. 21, 55–89.
Sarter, M., Givens, B., Bruno, J.P., 2001. The cognitive neuroscience of sustained attention: where top–down meets bottom–up. Brain Res. Rev. 35, 146–160.
Sarter, M., Parikh, V., 2005. Choline transporters, cholinergic transmission and cognition. Nat. Rev. Neurosci. 6, 48–56.
Sarter, M., Gehring, W.J., Kozak, R., 2006. More attention must be paid: the neurobiology of attentional effort. Brain Res. Rev. 51, 145–160.
Schatzberg, A.F., Rothschild, A.J., Langlais, P.J., Bird, E.D., Cole, J.O., 1985. A corticosteroid/dopamine hypothesis for psychotic depression and related states. J. Psychiatr. Res. 19, 57–64.
Schillings, M.L., Hoefsloot, W., Stegeman, D.F., Zwarts, M.J., 2003. Relative contributions of central and peripheral factors to fatigue during a maximal sustained effort. Eur. J. Appl. Physiol. 90, 562–568.
Schoenbaum, G., Roesch, M.R., Stalnaker, T.A., 2006. Orbitofrontal cortex, decision-making and drug addiction. Trends Neurosci. 29, 116–124.
Schultz, W., 2002. Getting formal with dopamine and reward. Neuron 36, 241–263.
Schultz, W., 2004. Neural coding of basic reward terms of animal learning theory, game theory, microeconomics and behavioural ecology. Curr. Opin. Neurobiol. 14, 139–147.
Schultz, W., 2007. Behavioral dopamine signals. Trends Neurosci. 30, 203–210.
Schweiber, J., Hauber, W., 2005. Involvement of the rat anterior cingulate cortex in control of instrumental responses guided by reward expectancy. Learn. Mem. 12, 334–342.
Schweiber, J., Saft, S., Hauber, W., 2005. Involvement of Catecholamine Neurotransmission in the rat anterior cingulate in effort-related decision making. Behav. Neurosci. 119 (6), 1687–1692.
Sesack, S.R., Deutch, A.Y., Roth, R.H., Bunney, B.S., 1989. Topographical organization of the efferent projections of the medial prefrontal cortex in the rat. An anterograde tract-tracing study with phaseolus-vulgaris leucoagglutinin J. Comp. Neurol. 290, 213–242.
Seymour, B., Singer, T., Dolan, R., 2007. The neurobiology of punishment. Nat. Rev. Neurosci. 8, 300–311.
Shidara, M., Richmond, B.J., 2002. Anterior cingulate: single neuronal signals related to degree of reward expectancy. Science 296, 1709–1711.
Shima, K., Tanji, J., 1998. Role for cingulate motor area cells in voluntary movement selection based on reward. Science 282, 1335–1338.
Siegrist, J., 1996. Adverse health effects of high effort/low reward conditions. J. Occup. Health Psychol. 1, 27–41.
Small, D.M., Zatorre, R.J., Dagher, A., Evans, A.C., Jones-Gotman, M., 2001. Changes in brain activity related to eating chocolate — From pleasure to aversion. Brain 124, 1720–1733.
Smillie, L.D., Yeo, G.B., Furnham, A.F., Jackson, C.J., 2006. Benefits of all work and no play: the relationship between neuroticism and performance as a function of resource allocation. J. Appl. Psychol. 91, 139–155.
Sparks, K., Cooper, C., Fried, Y., Shirom, A., 1997. The effects of hours of work on health: a meta-analytic review. J. Occup. Organ. Psychol. 70, 391–408.
Szechtman, H., Talangbayan, H., Ganaran, G., Dai, H., Eliam, D., 1994. Dynamics of behavioral sensitization induced by the dopamine agonist quinpirole and a proposed central energy control mechanism. Psychopharmacology 115, 95–104.
Tamir, M., 2005. Don't worry, be happy? Neuroticism, trait-consistent affect regulation, and performance. J. Pers. Soc. Psychol. 89, 449–461.
Tops, M., Lorist, M.M., Wijers, A.A., Meijman, T.F., 2004. To stress or relax: neurochemical aspects of activity and rest. Gedrag Organ. 17, 32–42.
Tops, M., Boksem, M.A.S., Wester, A.E., Lorist, M.M., Meijman, T.F., 2006a. Task engagement and the relationships between the error-related negativity, agreeableness, behavioral shame proneness and cortisol. Psychoneuroendocrinology 31, 847–858.
Tops, M., van Peer, J.M., Wijers, A.A., Korf, J., 2006b. Acute cortisol administration reduces subjective fatigue in healthy female subjects. Psychophysiology 43, 653–656.
Tops, M., Boksem, M.A.S., Wijers, A.A., van Duinen, H., Den Boer, J.A., Meijman, T.F., Korf, J., 2007. The psychobiology of burnout: are there two different syndromes? Neuropsychobiology 55, 143–150.
Tops, M., Riese, H., Oldehinkel, A.J., Rijsdijk, F.V., Ormel, J., 2008. Rejection sensitivity relates to hypocortisolism and depressed mood state in young women. Psychoneuroendocrinology 33, 551–559.
Tremblay, L., Schultz, W., 1999. Relative reward preference in primate orbitofrontal cortex. Nature 398, 704–708.
Ungless, M.A., Magill, P.J., Bolam, J.P., 2004. Uniform inhibition of dopamine neurons in the ventral tegmental area by aversive stimuli. Science 303, 2040–2042.
Van der Hulst, M., Geurts, S., 2001. Associations between overtime and psychological health in high and low reward jobs. Work Stress 15, 227–240.
Van der Hulst, M., 2003. Long workhours and health. Scand. J. Work Environ. Health 29, 171–188.
Van der Linden, D., Frese, M., Meijman, T.F., 2003a. Mental fatigue and the control of cognitive processes: effects on perseveration and planning. Acta Psychol. 113, 45–65.
Van der Linden, D., Frese, M., Sonnentag, S., 2003b. The impact of mental fatigue on exploration in a complex computer task: rigidity and loss of systematic strategies. Hum. Factors 45, 483–494.
Van der Linden, D., Eling, P., 2006. Mental fatigue disturbs local processing more than global processing. Psychological Research-Psychologische Forschung 70, 395–402.
Walter, H., Abler, B., Ciaramidaro, A., Erk, S., 2005. Motivating forces of human actions — Neuroimaging reward and social interaction. Brain Res. Bull. 67, 368–381.
Walton, M.E., Bannerman, D.M., Rushworth, M.F.S., 2002. The role of rat medial frontal cortex in effort-based decision making. J. Neurosci. 22, 10996–11003.
Walton, M.E., Bannerman, D.M., Alterescu, K., Rushworth, M.F.S., 2003. Functional specialization within medial frontal cortex of the anterior cingulate for evaluating effort-related decisions. J. Neurosci. 23, 6475–6479.
Walton, M.E., Devlin, J.T., Rushworth, M.F.S., 2004. Interactions between decision making and performance monitoring within prefrontal cortex. Nat. Neurosci. 7, 1259–1265.

Walton, M.E., Croxson, P.L., Rushworth, M.F.S., Bannerman, D.M., 2005. The mesocortical dopamine projection to anterior cingulate cortex plays no role in guiding effort-related decisions. Behav. Neurosci. 119, 323–328.

Watanabe, M., 1996. Reward expectancy in primate prefrontal neurons. Nature 382, 629–632.

Watson, D., Wiese, D., Vaidya, J., Tellegen, A., 1999. The two general activation systems of affect: Structural findings, evolutionary considerations, and psychobiological evidence. J. Pers. Soc. Psychol. 76, 820–838.

Whishaw, I.Q., Kornelsen, R.A., 1993. Two types of motivation revealed by ibotenic acid nucleus-accumbens lesions — Dissociation of food carrying and hoarding and the role of primary and incentive motivation. Behav. Brain Res. 55, 283–295.

White, C., Schweitzer, R., 2000. The role of personality in the development and perpetuation of chronic fatigue syndrome. J. Psychosom. Res. 48, 515–524.

Williams, Z.M., Bush, G., Rauch, S.L., Cosgrove, G.R., Eskandar, E.N., 2004. Human anterior cingulate neurons and the integration of monetary reward with motor responses. Nat. Neurosci. 7, 1370–1375.

Williamson, J.W., McColl, R., Mathews, D., Ginsburg, M., Mitchell, J.H., 1999. Activation of the insular cortex is affected by the intensity of exercise. J. Appl. Physiol. 87, 1213–1219.

Williamson, J.W., McColl, R., Mathews, D., 2003. Evidence for central command activation of the human insular cortex during exercise. J. Appl. Physiol. 94, 1726–1734.

Winstanley, C.A., Theobald, D.E.H., Cardinal, R.N., Robbins, T.W., 2004. Contrasting roles of basolateral amygdala and orbitofrontal cortex in impulsive choice. J. Neurosci. 24, 4718–4722.

Winterer, G., Adams, C.M., Jones, D.W., Knutson, B., 2002. Volition to action — An event-related fMRI study. NeuroImage 17 (2), 851–858.