Free Will Versus Survival: Brain Systems That Underlie Intrinsic Constraints on Behavior

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ABSTRACT
This article discusses the neuroanatomical systems involved in the related functions of fear and discernment of the consequences of one’s actions, two internal constraints on free will and action. Both mechanisms are related to a system for control and modulation of visceral function stretching from the spinal cord to the ventromedial prefrontal cortex, including the ventral striatum, ventral pallidum, and mediodorsal thalamus, the amygdala, the hypothalamus, the periaqueductal gray (PAG), and the brainstem reticular formation and autonomic nuclei. Reflexes at the lower levels provide rapid visceral and somatic reactions to threatening stimuli, while the PAG and hypothalamus coordinate these to produce more concerted responses. The amygdala interacts with the cortical sensory systems in the assessment of fear-related stimuli and modulates the reflex responses through projections to the hypothalamus and brainstem. The ventromedial prefrontal cortex, especially the “medial prefrontal network,” is connected to the amygdala, hypothalamus, and PAG, and allows cortical control over the system in relation to a wider set of emotions. This cortical region is involved both in the assessment of reward and in mood disorders and it plays a central role in the ability to discern the consequences of one’s actions and make appropriate behavioral choices. It also forms an interconnected circuit with specific cortical areas in the rostral superior temporal cortex, posterior parahippocampal cortex, and retrosplenial/posterior cingulate cortex. The overall function of this circuit is unclear, but may be involved in introspective monitoring of the individual. J. Comp. Neurol. 493:132–139, 2005.

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The nature of free will has been debated for centuries, and it is still difficult to get a clear definition of what is meant by it. At the least, free will is as the ability to select for or against a course of action in order to fulfill a desire, without extrinsic or intrinsic constraints that compel the choice (O’Connor, 2005). But not everyone would agree with this simple definition. Many would argue that free will and action also require knowledge of the consequences of one’s choices, so that action is not blind. Just about every major philosopher has had something to say about it, and they still cannot agree! In the absence of agreement from the philosophers, a literary or artistic illustration may be useful.

In his extraordinary four-opera cycle, The Ring of the Nibelungs, Richard Wagner constructed a saga in which human-like gods and god-like humans struggle with the need for free will and action, and the difficulty of achieving it. Alberich, the dwarf, has stolen the Rhinegold, fashioned from it a ring of power based on greed and denigration of love, and used it to enslave the race of dwarfs, or Nibelungs. The combination of greed and fear destroys the liberty of the Nibelungs, and they can act only to fulfill Alberich’s ambition. Wotan, the chief of the gods, learns of the ring and steals it from Alberich. He has to surrender it to a giant, however, because he is constrained by past deeds and “evil bargains” (of which he only now recognizes
the consequences), and by his own increasing fear of mortality. Wotan believes that he must regain the ring, but he is bound in by his fear and by his own laws, and cannot act. He therefore attempts to create a free man who can act without external constraint (from the gods) or internal constraint (from fear), kill the giant (who has transmuted into a dragon), and capture the ring. Wotan's first attempt produces magnificent music, but ends in total disaster. Out of the disaster, however, comes Siegfried, the hero who "knows not fear." True to his nature, Siegfried, acting without fear, kills the dragon and obtains the ring. He goes on to woo and mate Brunhilde, Wotan's favorite Valkyrie daughter, and all seems well for a brief time. Siegfried, however, is all too human. While he is not constrained by fear, he has poor judgment, and he does not understand the consequences of his actions. In his moral blindness, Siegfried soon betrays Brunhilde. He is then killed by Hagen, the son Alberich sired to win the ring back for himself. In the end Brunhilde, acting with full understanding and driven by love, not fear, is able to act in true freedom to regain the ring and restore it to the Rhine. In doing so, she sacrifices herself but saves humanity, even as the gods go up in flames. With the death of the gods, humans emerge into a new world in which they alone have the terrifying freedom to determine their destiny.

The principal points that come out of this very brief synopsis are the internal constraints on free will and action. These are first fear, the drive for survival over all else, and second the necessity for discernment, the ability to foresee and understand the consequences of one's actions. Not surprisingly, fear and discernment appear to be closely related within the brain. In this article I will try to outline the brain systems that I believe form the basis for both of these factors.

**BRAINSTEM SYSTEMS**

During the period of development of the first mammals, they were much smaller and weaker than the reptiles and birds that still dominated the landscape. Their chief concern was survival, and mammalian brain systems were developed that allowed them to detect danger and react to it very quickly. The most immediate mechanisms are the spinal and brainstem reflexes that provide automatic responses to pain or threatening stimuli. When you're about to be eaten, fractions of seconds count; you need to jump immediately and worry about free will later. A good example of these mechanisms is the startle response, which provokes a stereotyped jump to a loud noise. This depends on a relatively hardwired brainstem circuit involving the neurons in the root of the cochlear nerve, which connect to cells within the pontine reticular formation that provide descending projections to spinal motor neurons (Fig. 1; Lee et al., 1996).

Simple jumping, however, is a very limited protection against predation. More complex mechanisms involve higher brainstem structures, such as the periaqueductal gray (PAG). This nuclear center receives information from spinal and other afferent sources, especially in relation to pain and other forms of stress, and promotes coordinated responses that involve visceral as well as somatic and behavioral reactions (Bandler et al., 2000). Stimulation of the lateral part of the PAG provokes fight or flight responses, with visceral effects such as increases in heart rate, and behavioral impetus to attack or run away. These are appropriate, active responses to a superficial injury or external threat that you react to openly. In contrast, stimulation of the ventrolateral PAG provokes a quiescence response, in which the animal becomes very quiet and withdrawn, with accompanying decreases in heart rate and other visceral effects. This response is appropriate to deal with a deep, internal wound, disease, or other disorder that you cannot get away from. Your best hope is to be as quiet as possible, in hopes of recovery. In both cases the PAG coordinates a response that combines appropriate visceral reactions, such as cardiovascular changes, and behavioral reactions, such as activation or suppression of motor activity.

**FOREBRAIN MECHANISMS**

These are still relatively automated responses, however, and they offer a limited repertoire of protective mechanisms. The success of mammals, especially as they grew larger and became predators themselves, seems to be re-

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**Abbreviations**

10m, 14c, 14r, 25, 32 Architectonic areas of medial prefrontal cortex
11l, 11m, 11r, 12l, 12m, 12o, 12r, 13m, 13l Architectonic areas of orbital cortex
23 Posterior cingulate cortex
24 Anterior cingulate cortex
29/30 Retrosplenial cortex
35/36 Perirhinal cortex
Aq Cerebral aqueduct
Arh Arcuate nucleus of the hypothalamus
CNP Cuneiform nucleus
dl, dL, l, vl Columns within the PAG
DR Dorsal raphe nucleus
EC Entorhinal cortex
GP Globus pallidus
Ga, Gm, Gs Agranular insular areas
IC Inferior Colliculus
Id Dysgranular insula
LM Lateral lemniscus
LHA Lateral Hypothalamic Area
MD Mediodorsal thalamic nucleus
ML Medial lemniscus
mlf Medial longitudinal fasciculus
MR Median raphe nucleus
OMPC Orbital and medial prefrontal cortex
orc optic tract
PAG Periaqueductal gray
PPT Peripeduncular pontine nucleus
PVN Paraventricular nucleus of the hypothalamus
scp Superior cerebellar peduncle
STGr Rostral part of superior temporal gyrus
STSd, STSv Dorsal and ventral banks of superior temporal sulcus
TEav Anterior cingulate cortex
TF/TH Parahippocampal cortex
TDg, TGr Dorsal and ventral parts of temporal pole
VMH Ventromedial nucleus of the hypothalamus
ZI Zona incerta
lated to the development of forebrain mechanisms that allow more complex and nuanced reactions to the world and its threats or opportunities. In particular, these allow for information to be held over time, so that reactions can be based on memory traces of past experience. These memory traces are not necessarily conscious, but allow for learning.

**Amygdala**

A key structure in this process is the amygdala, a complex of several nuclei that combines both cortical- and striatal-like components. The amygdala appears to integrate sensory information, particularly in relation to fear and anxiety, and to promote appropriate visceral and behavioral reactions (Davis, 1992; LeDoux, 2000). Humans with bilateral lesions of the amygdala are unable to recognize or depict fear (Adolphs et al., 1995). Lesions of the amygdala in animals block the development or expression of a fear response to a conditioned stimulus. The neural circuitry that supports this involves multiple sensory inputs to the amygdala, intra-amygdaloid integrative systems, outputs from the amygdala to visceral control structures, and, most interestingly, interactions with frontal cortex systems (Fig. 2).

Sensory inputs reach the amygdala from all modalities, including vision, audition, somatic sensation, olfaction, and taste/visceral afferents (Price, 2003). Olfactory information reaches the amygdala from the olfactory bulb and cortex (Carmichael et al., 1994), and taste and visceral inputs arise from the nucleus of the solitary tract, parabrachial nucleus, and thalamic taste/visceral relay nucleus (VPMpc) (Norgren, 1976; Beckstead et al., 1980; Yasui et al., 1987). The visual, auditory, and somatic sensory inputs arise mainly from sensory association areas related to each modality. Visual information is projected into the amygdala from the rostral part of the inferior temporal cortex (Turner et al., 1980; Iwai and Yukie, 1987), while auditory and somatic sensory inputs to the amygdala arise from association areas in the superior temporal cortex and posterior insula, respectively (Friedman et al., 1986; Yukie, 2002). Most of these sensory inputs are reciprocated by return projections to the sensory cortical areas, suggesting that the amygdala may influence sensory perception as well as behavioral or emotional reactions. In addition, there are less processed but shorter latency inputs of auditory activity, and probably other modalities, relayed through the posterior “intralaminar” nuclei of the thalamus (Mehler, 1980; Ruscchen, 1982; LeDoux et al., 1985).

Extensive intra-amygdaloid connections integrate these inputs within the amygdala (Amaral et al., 1992). Long-term facilitation and other synaptic changes within the amygdala appear to support learning about fearful or threatening stimuli or situations (Pare et al., 2004). There are then prominent descending outputs from the amygdala (including the basal nucleus as well as the central

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**Fig. 1.** A diagrammatic outline of the brainstem startle reflex, by which loud or unexpected noises produce a very fast, reflex jump. Descending inputs from the amygdala and the PAG enhance the reflex, resulting in a larger response when the animal is in a state of fear, or in response to stress. (Modified from Lee et al., 1996, by permission.)

**Fig. 2.** A diagram of the major interactions of the OMPFC and amygdala with visceral control structures in the hypothalamus and PAG, and with a striato-pallidal-thalamic loop through the ventromedial striatum, ventral pallidum, and mediodorsal thalamic nucleus.
nucleus) to the hypothalamus and brainstem (An et al., 1998; Price, 2003). The targets of these projections include the PAG, pontine and medullary reticular formation, and dorsal vagal nuclei. They provide for modulation of brainstem reflexes such as the startle reflex, or the more complex responses coordinated through the PAG, in relation to fear or other emotions (Price and Amaral, 1981; Amaral et al., 1992; Davis, 1992; Price, 2003). Although the fear or emotion is undoubtedly generated in relation to the cortical input to the amygdala, it is not necessarily conscious; a fearful response may be evoked even when one is not fully aware of being “afraid.”

The amygdala also has extensive interconnections with the hippocampal formation and related cortical areas in the medial temporal lobe that are critically involved in memory processing (Amaral et al., 1992). These may form the basis for the common observation that emotional experiences are more memorable than nonemotional experiences. This memory-enhancing effect depends on the amygdala and involves convergence of noradrenergic, cholinergic, and glucocorticoid modulation of amygdaloid activity. (McGaugh, 2004). In addition to the interactions of the amygdala with the medial temporal lobe structures, the influence of the amygdala on memory may involve amygdaloid connections with the cholinergic nuclei of the basal forebrain and with the sensory association areas (which may store the memory; Mishkin 1982, Miyashita 1993). As with emotion itself, the enhanced memory for emotional experiences may proceed at a relatively subconscious level, without clear awareness.

Orbital and medial prefrontal cortex

The final set of amygdaloid interactions are extensive bidirectional connections with the orbital and medial prefrontal cortex (OMPFC) and unidirectional projections with medial thalamic and ventromedial striatal regions related to the OMPFC. The heaviest cortical projections in monkeys are to areas 24, 25, and 32 on the medial wall of the frontal cortex, areas 11m, 13a, 13b, 14c, and 14r on the gyrus rectus, and areas Iai, 12o, and 12l in the lateral orbital cortex (Amaral and Price, 1984; Carmichael and Price, 1995a). Together, these form the bulk of a system that has been referred to as the “medial prefrontal network,” based on analysis of the cortico-cortical connections within the OMPFC (Fig. 3; Carmichael and Price, 1996). This network stands in contrast to a complementary “orbital prefrontal network” that includes most of the orbital cortex, and which is distinct from the medial network. That is, the areas within the medial or orbital prefrontal networks are mostly interconnected with other areas of the same network and avoid connections with areas of the other network. There are several areas, especially along the gyrus rectus, that are connected to both networks and probably serve as an interface for interactions between them (Ongür and Price, 2000). Although the two networks were based on neuroanatomical experiments in monkeys, parallel architectonic analysis of human OMPFC has allowed the orbital and medial networks to be at least provisionally defined in humans (Fig. 4; Ongür et al., 2003). It is striking that the rostral part of the medial network near the frontal pole (medial and polar parts of area 10) is one of the cortical regions that are very substantially enlarged in humans, as compared to monkeys (Ongür et al., 2003). The orbital network receives inputs from several sensory modalities, including olfaction, taste, vision, and somatic sensation. These arise in other cortical areas or regions, such as the primary olfactory or taste cortex, the inferior temporal cortex (for vision), and several somatic sensory association areas (especially regions that appear to represent the hand and face) (Fig. 3; Carmichael and Price, 1995b). The interconnections within the network appear to function to integrate these modalities, which together suggest sensory qualities of food or feeding. Recordings from the orbital cortex show that single neurons have convergent responses to several food-related modalities, including texture, flavor (taste and olfaction), temperature, and visual aspects of food (Kadohisa et al., 2005). In addition, however, the responses of orbital neu-
rons are also influenced by the presence or expectation of reward, decrease in reward (e.g., from satiety), or aversion (Rolls, 2000; Schultz et al., 2000; Hikosaka and Watanabe, 2000). It is as if a system that evolved in early mammals for the assessment of food, itself a primary reward, has become generalized in primates to serve more abstract aspects of reward.

As interesting as the orbital network is, the medial prefrontal network is more central to the present discussion of free will and discernment. Unlike the orbital network, it does not receive direct unimodal sensory inputs, although it is interconnected with the orbital network and with apparently polysensory areas in the rostral temporal cortex. A major feature of this network is that it has surprisingly substantial outputs to the hypothalamus and the periaqueductal gray, and thereby is the major cortical system that can influence visceral function in response to cortically perceived stimuli (Figs. 3, 5; Ongür et al., 1998; An et al., 1998; Rempel-Clower and Barbas 1998; Barbas et al., 2003). Older reports indicate that electrical stimulation of the medial network areas produces disturbances in functions such as heart rate and respiration (Kaada, 1960). More recent functional MRI (fMRI) studies have shown that activity in the medial prefrontal cortex correlates with visceral activation in response to emotionally evocative stimuli (Critchley et al., 2000; Williams et al., 2000). These and other studies indicate that the medial network provides the basis for visceral modulation in relation to emotion. In turn, as discussed below, this appears to play a critical role in setting mood and guiding appropriate behavioral choices.

Functional imaging studies provide the strongest evidence that the medial prefrontal network, together with the amygdala, is critically involved in regulation of mood and mood disorders. Functional imaging studies indicate that the amygdala, medial prefrontal cortex, and a lateral region in the anterior insula are all abnormally active in depression (Drevets et al., 1992; Drevets, 2000; Mayberg et al., 2003). The lateral region appears to correspond to the lateral component of the medial network. In a remarkable recent article, Mayberg et al. (2005) report that deep brain stimulation in the caudal, medial prefrontal cortex (near area 25) can produce near complete remission of major depressive disorder in severe, treatment-resistant cases. As in previous studies of remission of depression following drug therapy (Mayberg et al., 2000), the stimulation produced decreases in activity in areas of the medial prefrontal network (both on the medial wall of the hemisphere and in anterior insula) and in the hypothalamus. With their connections to the hypothalamus and PAG, it is likely that the medial network and the amygdala are involved in visceral as well as affective or emotional aspects of depression. It is notable that the quiescence response that can be evoked from the PAG (see above, Bandler et al., 2000) resembles many aspects of major depression.

Lesions of the ventromedial prefrontal cortex in humans abolish the normal, automatic visceral response to emotive stimuli, such that when presented with emotional images these individuals do not show a normal skin conductance response (Damasio et al., 1999; Bechara et al., 2000). Remarkably, they are also severely debilitated in terms of their ability to make appropriate choices. Although their cognitive intelligence is intact, and they do not have any overt sensory or motor deficit, their lives are severely disrupted because of faulty decisions made in business, family relations, and other life domains. Often,
they appear to not understand the long-term significance of their actions, and choose in favor of immediate reward without attention to subsequent consequences. Recent observations also indicate that such patients also experience little regret for faulty decisions, and do not anticipate negative consequences of their choices (Camille et al., 2004).

To account for the combined lack of visceral responsiveness and lack of judgment in patients with ventromedial frontal lesions, Damasio and colleagues (1994) proposed what they have termed the “somatic marker hypothesis.” This supposes that the visceral or bodily reaction that normally accompanies emotion (the somatic marker) serves as a subconscious warning or guide that some behaviors are disadvantageous and should be avoided. In phylogenetic terms, it would not be surprising if a system that evolved to provide quick and unambiguous visceral and behavioral reactions to danger should develop into a system that can give a quick analysis of complex situations and produce a bias away from disadvantageous behavior and towards appropriate behavioral responses. While sensation of the actual somatic reaction (e.g., changes in heart rate or sweating) may play a role in some situations, neural “as-if” circuits within the brain are likely to function on their own, independent of the somatic sign. In addition to its descending projections to visceral control centers, the medial prefrontal network also has specific connections with other cortical and subcortical regions that could form the basis of the “as-if” circuit.

Recent studies have suggested that the disability produced by ventromedial prefrontal lesions is more complex than originally postulated. In particular, subjects with ventromedial prefrontal cortex damage show deficits in reversal tasks that indicate an inability to suppress previously learned reactions or associations (Fellows and Farah, 2005). Although these findings have been presented as a challenge to the somatic marker hypothesis (Maia and McClelland, 2004), it is more likely that they represent an additional component of the same mechanism. Experiments in animals indicate that ability to suppress previously learned associations depends on connections of the ventromedial prefrontal cortex with the ventromedial striatum (especially the nucleus accumbens) and the mediodorsal thalamic nucleus (Figs. 2, 6). This circuit, which parallels other cortico-striatal-pallido-thalamic circuits, involves cortico-striate projections from the medial prefrontal network to the ventromedial striatum (Ferry et al., 2000), from there to the ventral pallidum, and then to the portion of the mediodorsal thalamic nucleus that has reciprocal connections with the medial network (Ray and Price, 1993; Ongur and Price, 2000). Experiments in rats and monkeys indicate that lesions in the ventromedial striatum, ventral pallidum, or other points along this pathway produce deficits in the ability to suppress responses to previously rewarded, but now inappropriate stimuli (Roberts et al., 1990; Ferry et al., 2000). Further, because the nucleus accumbens also has a substantial projection into the hypothalamus and brainstem, it provides another pathway from the medial prefrontal network to the visceral control centers.

SUMMARY

To summarize the discussion to this point, the ventromedial prefrontal cortex, and especially the medial prefrontal network, is situated at the top of a system for control and modulation of visceral function. This system also includes the ventral striatum and mediodorsal thalamic nucleus, the amygdala and other limbic structures, the hypothalamus, the PAG, and the reticular formation and autonomic nuclei of the brainstem and spinal cord. Lower parts of the system (brainstem and spinal cord) provide reflex control of viscera to maintain homeostasis and evoke rapid reactions to specific stimuli. The middle parts of the system (PAG and hypothalamus) coordinate multiple visceral functions; the PAG in particular organizes distinct responses to different types of stress, exemplified by superficial and deep pain. The amygdala acts on the middle and lower parts of the system to modulate them in relation to present and past experience, as processed by the forebrain and especially related to fear. The ventromedial prefrontal cortex, and related parts of the basal ganglia and thalamus, provide overall control over the system in relation to a wider set of emotions, and allow behaviors to be suppressed as well as promoted. In doing so, this cortical region plays a critical role in our ability to discern the consequences of our actions (at least in part subconsciously) and make appropriate behavioral choices.

OTHER CORTICAL REGIONS

Of course, the medial prefrontal network does not function in isolation from other parts of the cortex. In addition
It is difficult to discern a concerted function for the circuit involving the medial network. There is evidence that both the parahippocampal cortex and the retrosplenial/posterior cingulate region are involved in processing behaviorally or emotionally salient information (Salzmann et al., 1993; Maddock et al., 2003), but they have more frequently been implicated in spatial memory functions (Olson et al., 1997; Maguire, 2001; Malkova and Mishkin, 2003; Alvarado and Bachevalier, 2005). On the other hand, it is notable that the medial prefrontal cortex and the retrosplenial/posterior cingulate region are both areas that show relatively high ongoing intrinsic activity in “resting” states, and decrease in activity during external, goal-directed tasks. Raichle and Gusnard (2005) suggested that such ongoing activity is related to an intrinsic, self-referential model of expected events and conditions, which can be compared with sensory experience and used to interpret it in relation to past experience and beliefs. It would not be surprising if such a mechanism should involve the ventromedial prefrontal cortex and its associated cortical and subcortical structures. As I have tried to argue, these structures are central to the assessment and modulation of our most basic appetites and emotional drives. After all, it is only by making full use of our emotions, while at the same time keeping control over them, that we are able to act freely and with full understanding of our actions.

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