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Discussion

The roles of the orbitofrontal cortex via the habenula in non-reward and depression, and in the responses of serotonin and dopamine neurons

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ABSTRACT

Cortical regions such as the orbitofrontal cortex involved in reward and in non-reward and which are implicated in depression, and the amygdala, are connected to the habenula via the striatum and pallidum, and via subcortical limbic structures. The habenula in turn projects to the raphe nuclei, the source of the serotonin-containing neurons that project to the forebrain. It is proposed that this provides a route for cortical signals related to reward, and to not obtaining expected rewards, to influence the serotonin-containing neuronal system that is influenced by many antidepressant treatments. This helps to provide a more circuit-based understanding of the brain mechanisms related to depression, and how some treatments influence this system. The habenula also projects via the rostromedial tegmental nucleus to the dopamine-containing neurons, and this, it is proposed, provides a route for reward prediction error signals and other reward- and punishment-related signals of cortical and striatal origin to influence the dopamine system.

This paper is a commentary on the paper "A non-reward attractor theory of depression" that focused on orbitofrontal cortex non-reward attractor networks and their potential relevance to depression (Rolls, 2016b). This commentary draws out the implications of that theory of depression for understanding the functions of the habenula in depression, and the subcortical structures to which it projects including the serotonin (5-HT, 5-hydroxytryptamine) and dopamine systems. This commentary and extension of the theory (Rolls, 2016b) is timely in view of the current interest in the functions of the habenula in depression (Fakhoury, 2017; Loonen and Ivanova, 2015, 2016a, 2017).

The habenula does have neurons that respond to non-reward in macaques (Bromberg-Martin and Hikosaka, 2011; Proulx et al., 2014). Loonen et al. draw attention to this, and consider whether the habenula may be involved in depression (Loonen and Ivanova, 2015, 2016a). That is certainly a possibility. However, it is of interest to consider how the orbitofrontal cortex and its related cortical areas may because of their cortical architecture play an important functional role in non-reward and depression, in a way that may not be possible for the habenula with its different architecture.

Non-reward neurons, that is neurons that respond when the reward obtained (the outcome) is less than that which is expected (the expected reward value), termed negative reward prediction error neurons, were discovered in the orbitofrontal cortex by Thorpe et al. (1983) (see Rolls, 2014). In the lateral habenula, neurons that respond to signaled low reward value or to punishment have been described (Matsumoto and Hikosaka, 2009), and so have neurons that reflect negative reward prediction error (Bromberg-Martin and Hikosaka, 2011). Similar neurons are found in the globus pallidus glutamatergic excitatory habenula-projecting neurons, providing evidence that the necessary computations are not performed in the lateral habenula (Stephenson-Jones et al., 2016).

One key point is that the neocortex with its highly developed local recurrent collateral excitatory connections between the pyramidal cells appears to allow ongoing firing to continue in attractor states, each one of which might represent a short-term memory, an expected value, a long-term memory, the result of a decision just taken, or the recent receipt of non-reward (Rolls, 2016a).

This ability to maintain firing may allow for a stimulus previously associated with a reward to produce expected reward firing, which may continue until the reward is or is not received (the outcome). Another 'non-reward' attractor network may be triggered

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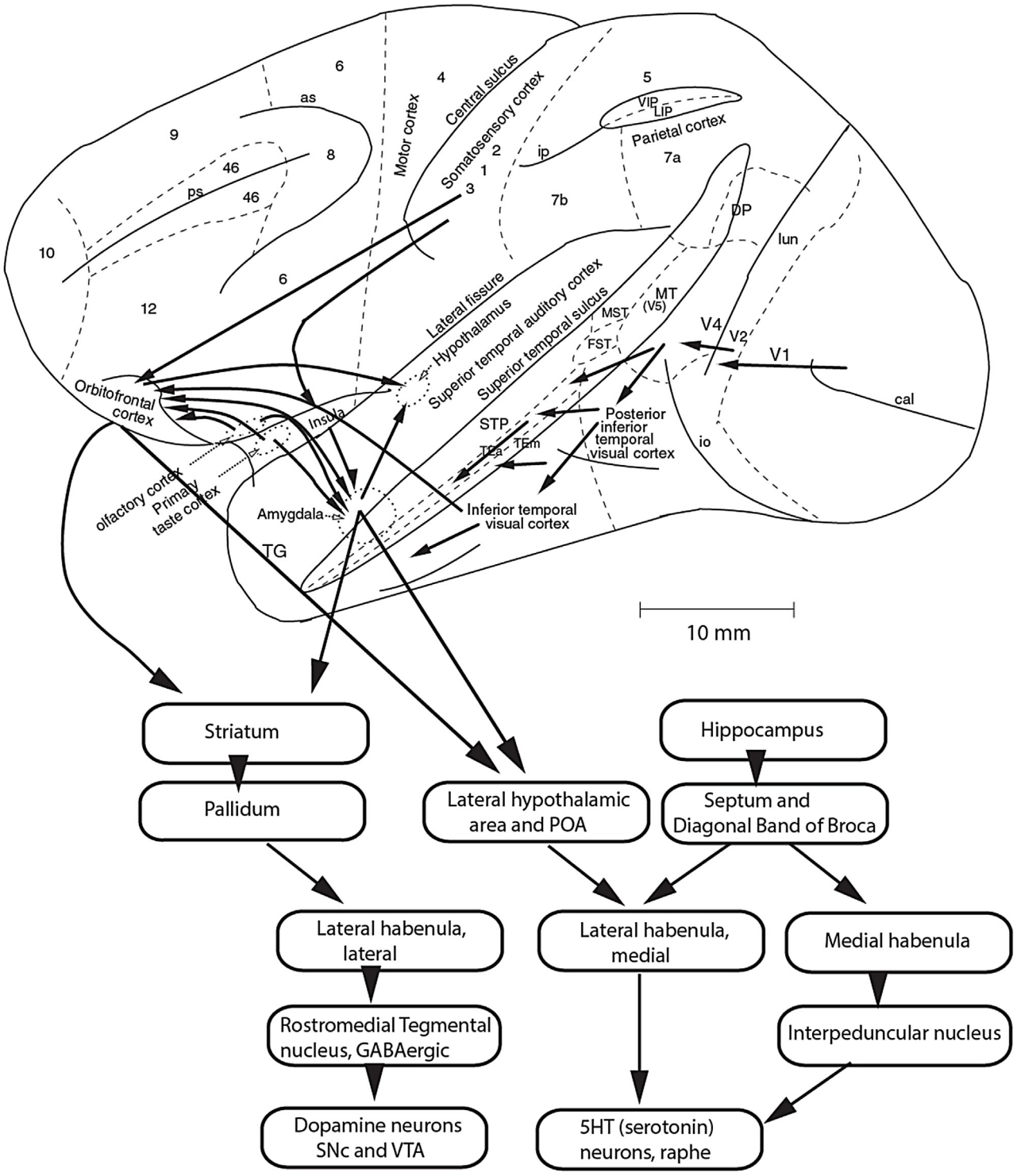

Fig. 1. The orbitofrontal cortex and amygdala systems involved in reward and non-reward can operate via a lateral hypothalamic area/lateral preoptic area (POA) to influence the Lateral Habenula, medial part, which in turn can influence the 5-HT (serotonin) neurons in the raphe nuclei. Many antidepressant drugs may influence this cortical to brainstem pathway by influencing the effects of the 5-HT neurons, which terminate in many brain areas. The hippocampus influence via the septal nuclei and diagonal band of Broca may enable reward context to access the same Lateral Habenula, medial part, to 5-HT-neuron system (Luo et al., 2011; Rolls, 2015). The medial habenula also receives septal inputs, and projects to the interpeduncular nucleus, and thereby to 5-HT neurons (and probably dopamine neurons) (see Fig. 1) (Loonen and Ivanova, 2016b; Proulx et al., 2014). The orbitofrontal cortex, amygdala (and probably anterior cingulate cortex and subgenual cingulate cortex) systems involved in reward and non-reward can operate via a basal ganglia route (striatum, ventral pallidum, and globus pallidus/bed nucleus of the stria terminalis) to influence the Lateral Habenula, lateral part, which in turn via the GABAergic Rostromedial Tegmental nucleus can influence dopamine neurons in the Substantia Nigra pars compacta and ventral Tegmental Area (SNc and VTA). This provides a route for reward, non-reward, and reward prediction error signals of largely cortical origin to influence the dopamine neurons. Details of some of these anatomical connections are provided elsewhere (Loonen and Ivanova, 2016b; Proulx et al., 2014). These connections are shown in the context of some of the pathways involved in reward-related processes and emotion shown on the lateral view of the brain of the macaque monkey in the upper part of the Figure (Rolls, 2014). Connections from the primary taste and olfactory cortices to the orbitofrontal cortex and amygdala are shown. Connections are also shown in the 'ventral visual system' from the visual cortical areas V1 to V2, V4, the inferior temporal visual cortex, etc., with some connections reaching the amygdala and orbitofrontal cortex. In addition,