University of Groningen

Commentary on "A non-reward attractor theory of depression"

Loonen, Anton J M; Ivanova, Svetlana A

Published in:
Neuroscience and Biobehavioral Reviews

DOI:
[10.1016/j.neubiorev.2017.02.007](https://doi.org/10.1016/j.neubiorev.2017.02.007)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2017

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Loonen, A. J. M., & Ivanova, S. A. (2017). Commentary on "A non-reward attractor theory of depression": A proposal to include the habenula connection. *Neuroscience and Biobehavioral Reviews*, 83, 736-741.
<https://doi.org/10.1016/j.neubiorev.2017.02.007>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

Commentary on “A non-reward attractor theory of depression”: A proposal to include the habenula connection

Anton J.M. Loonen^{a,*,2}, Svetlana A. Ivanova^{b,1}

^a Groningen Research Institute of Pharmacy, Unit of Pharmacotherapy, - Epidemiology & - Economics, Department of Pharmacy, University of Groningen, Antonius Deusinglaan 1, 9713 AV Groningen, The Netherlands

^b Mental Health Research Institute, Tomsk National Research Medical Center of the Russian Academy of Sciences, Aleutskaya str., 4, 634014 Tomsk, Russian Federation

ARTICLE INFO

Article history:

Received 9 September 2016

Received in revised form 30 October 2016

Accepted 6 February 2017

Available online 21 February 2017

Keywords:

Depression

Mechanism

Non-reward attractor theory

Orbitofrontal cortex

Habenula

ABSTRACT

The non-reward attractor theory of depression describes this mood disorder as originating from a neuronal dysfunction that arises from increased vulnerability of a cortical network that detects failure to receive an expected reward. From an evolutionary standpoint, the concept that the cerebral cortex determines susceptibility to mood disorders is open to criticism. Instead, using the regulation of reward-seeking, and aversive events-avoiding behaviours of the earliest vertebrates as a start point, the authors have developed a theory of depression in which subcortical regulatory systems that involve the lateral and medial habenula, respectively, play a critical role in regulating these behaviours, and susceptibility to depressive symptoms. As these anatomical structures are well conserved through the evolution of early vertebrates to humans, the authors propose that this subcortical system remains operative. Integrating the evidence that supports the non-attractor theory of depression with this model of a subcortical regulation of behaviour, could offer fresh clues as to how psychological and biological factors interact to cause depression, as well as other mood and anxiety disorders.

© 2017 Elsevier Ltd. All rights reserved.

1. Introduction

In a recent paper, Edmund T. Rolls (2016) describes evidence to support his non-reward attractor theory of mood disorders. Data collected from neurophysiological experiments, neuroimaging, and injury to the orbitofrontal cortex (OFC), have been used by Rolls to propose the existence of an attractor network within the lateral part of the OFC that becomes active when an expected reward fails to materialize. In an evolutionary context, Rolls considers that the development of this network, which enables rapid reversals of stimulus-reward associations, provides for an increased sophistication in the social interactions of primates, including those of humans. Rolls extends his theory to a new hypothesis of depression

which holds that the lateral orbitofrontal network has an essential role in placing, and keeping, the cerebral cortex in a depressive state.

Although the ideas presented in Rolls' paper aptly describe cortical dysfunction in depressive mood disorders, they neglect to consider the extensive interactions of the cerebral cortex with subcortical ganglia. Every part of the cerebral neocortex is connected with the dorsal or ventral striatum (Heimer, 2003), with posterior and anterior extrapyramidal circuits converging through direct (activating), and indirect (inhibitory) pathways, at the same spot on the frontal cerebral cortex (Loonen and Ivanova, 2013). The activities of these extrapyramidal circuits are regulated by midbrain monoaminergic centres, with these, in turn, regulated by the rostromedial tegmental (RMTg) and interpeduncular (IPN) nuclei. In all human craniate ancestors, the activities of the latter nuclei are regulated by a small nuclear system localized within the epithalamus termed the habenula.

In the present commentary we will attempt to integrate current knowledge of the organization of reward-seeking and aversive events-fleeing behaviour within the subcortical forebrain and upper brainstem, with the ideas presented in Rolls' paper. We propose that it is highly likely that the lateral prefrontal cortical

* Corresponding author at: University of Groningen, Department of Pharmacy, Antonius Deusinglaan 1, 9713 AV Groningen, The Netherlands.

E-mail addresses: a.j.m.loonen@rug.nl (A.J.M. Loonen),

svetlana@mail.tomsknet.ru (S.A. Ivanova).

¹ National Research Tomsk Polytechnic University, Lenin Avenue, 30, 634050 Tomsk, Russian Federation.

² GGZ WNB, Mental Health Institution, P.O. Box 371, 4600 AJ Bergen op Zoom, The Netherlands.

attractor network is activated as a target of a ventral cortico-striatal-pallido-thalamo-cortical (CSTC) circuit that regulates the motivation to express reward-seeking behaviour. However, first we will briefly summarize the ideas presented in Rolls' original article.

2. The model as outlined by Edmund T. Rolls

2.1. Evidence for a non-reward attractor network within the lateral prefrontal cortex

Rolls describes an attractor network as a complex system of pyramidal cells in which excitatory inputs to one neuron activates other components of the network through collateral feed-forward connections. Ultimately these collaterals will reactivate the first pyramidal cell, which leads to continuous synchronous activity. Inhibitory interneurons can also receive inputs from these pyramidal cells, and are capable of controlling their activity via negative feedback. The activity level of this network can switch between two preferred energy states, separated by an unattractive energy barrier. Its bi-stable condition makes this attractor network capable of functioning as a flip-flop circuit, which can easily modify complex behavioural patterns depending on the demands of the moment.

Rolls' paper provides evidence that neurons of the lateral OFC may comprise networks that respond to non-reward scenarios by maintaining their firing for several seconds; sustained firing is then used mechanistically to modify reward seeking behaviour. Data collated from neurophysiological experiments with macaques that respond to a visual stimulus in the expectation of receiving fruit juice (the reward), but instead taste aversive saline, would support this notion. A specific population of neurons in the OFC responds to the visual stimulus with continued firing only after reward reversal i.e. when the monkey's behaviour should be changed. This neuron-level evidence is also supported by findings in functional neuroimaging in which the macaque lateral OFC was found to be activated by non-reward during a similar task, with the focus of this activation within the lateral OFC.

These data also agree with human functional neuroimaging that shows evidence of a cortical area in the lateral OFC (Brodmann area (BA) 47/12) that is activated by unexpected, unpleasant, non-rewarding stimuli. After damaging this area of the macaque OFC, these animals were less able to avoid non-rewarding stimuli that had been rewarded prior to reversal.

2.2. Dysfunction of the non-reward attractor network may explain depression

It is well established that the omission or termination of a reward can give rise to sadness when no action can be taken to restore incentive, and to aggression as a possible defence against reward loss. It is hypothesized by Rolls that in depression, the lateral OFC non-reward/punishment attractor network system is activated more frequently, and maintains its non-reward attractor state for longer. This triggers negative cognitive states held on-line in other cortical areas such as the dorsolateral prefrontal cortex. In turn, these other cortical areas maintain the orbitofrontal non-reward system in its active status in a top-down regulatory fashion. According to Rolls, true depression may occur when the recollection of unpleasant memories prolongs negative expectations about the outcome of a recent event, leading to a long-lasting activation of the orbitofrontal non-reward system. This could be the outcome for individuals faced with a major, negatively reinforcing life event that provokes reactive depression. Alternatively, in some individuals, a genetic predisposition could sensitize their lateral orbitofrontal non-reward/punishment system. In his theory, an overly sensitive or responsive short-term non-reward system in the lateral OFC can

produce long-lasting depression because of at least two scenarios. The first involves activation of the dorsolateral prefrontal cortex that re-excites the OFC following rumination over non-reward. A second scenario involves repetitive activation of the OFC by the recollection of sad memories.

This non-reward attractor theory of depression is supported by substantial human neuroimaging evidence that confirms the functional coupling of cortical areas with the lateral OFC and functionally related areas, with specific symptoms of depression. Rolls also describes the relationship between the lateral OFC with other brain areas implicated in depression, particularly the medial OFC, the supracallosal cingulate cortex, the amygdala, the subgenual cingulate cortex, and the insula.

2.3. The non-reward attractor network and mania/bipolar disorder

According to Rolls' theory, the lateral OFC non-reward attractor network may also be involved in bipolar disorder, causing symptoms of mania. Decreased sensitivity of the non-reward system may result in diminished attention to the risks or consequences that can arise from an exaggerated pursuit of reward. This scenario would also result in the pervasive impulsivity that characterizes mania. The activation of the medial and lateral OFC are reciprocally related, with the medial part regulating reward-related affects and inducing impulsivity. Other than these two, short-term attractor systems within the medial and lateral portions of the OFC, a longer loop through the language/planning cognitive system is also purported to exist, which can operate on a much longer time scale. This long-loop attractor might calculate the long-term benefit of certain actions and could also be more sensitive in mania. Rolls in addition proposes that this long-loop attractor involving language cortical areas contributes to ruminating thoughts in depression.

3. But what about the sub-cortex?

3.1. Regulation of the reward-seeking behaviour of lamprey

The regulation of reward-seeking behaviour by the primate non-reward attractor network is very similar to the regulation of comparable behaviours by the lamprey habenula-projecting globus pallidus (GPh) (Stephenson-Jones et al., 2013). Loonen and Ivanova (2015) became interested in the evolution of the forebrain when realizing that even the oldest free-dwelling animals living in the oceans about 560 million years ago must have been capable of obtaining food, warmth, and reproductive possibilities, in addition to having the ability to escape from threats and discomfort. Consequently, their forebrains must have contained a machinery to regulate these behaviours in order to achieve the desired outcomes. The brain of the lamprey is believed to be comparable to our earliest vertebrate ancestors (Loonen and Ivanova, 2015). In lamprey, the part of the pallium (cortical structure) destined to evolve into almost all of the cerebral neocortex, is small and insignificant, as is the dorsal thalamus, which is the main input ganglion of the human neocortex. The dorsal pallium is, unlike the human neocortex, not involved in inducing locomotion. Lamprey have an extrapyramidal system with a similar organization to the analogous system in humans (Robertson et al., 2014; Loonen and Ivanova, 2013). It comprises similar nuclei and has direct and indirect pathways, although with two important differences: the absence of a circuit starting and ending in the dorsal pallium (fore-runner of the neocortex), and direct regulation of motor output by altering motor centres in the lower diencephalon and upper brainstem. The degree of motor output is controlled by a dopaminergic nucleus in the upper brainstem/lower diencephalon, called

the nucleus of the posterior tuberculum, which is comparable to the human ventral tegmental area/substantia nigra pars compacta (VTA/SNc). The forebrain contains a GPh, which regulates the activity of this dopaminergic midbrain nucleus. Behaviours that fail to deliver sufficient reward are inhibited in order to promote other, more rewarding activities. Behaviours that yield positive results are reinforced. The GPh regulates this via the habenula. The habenular nuclei are paired structures that belong to the epithalamus, and comprise the larger lateral (LHb) and smaller, medial (MHb) divisions (Benarroch, 2015b; Klemm, 2004).

3.2. Role of the habenula in human behaviour

Studying the role of the habenula in humans is not a trivial exercise given its small size and subdivision (LHb and MHb), together with a complex circuitry and opposing functions (Batalla et al., in preparation). The habenula cannot be studied with standard functional MRI as its size is reported to be approximately 30 mm³ in each hemisphere (LHb plus MHb) post-mortem (Ranft et al., 2010). However, in vivo estimates report sizes around 18.5 mm³ per hemisphere (Savitz et al., 2011), which means that in each hemisphere the Hb may be even smaller than the standard functional MRI voxel size (i.e. 27 mm³, with a resolution of 3 mm isotropic voxels) (Batalla et al., in preparation). Recently, several groups have employed a high-resolution fMRI approach to examine resting state (Ely et al., 2016; Hetu et al., 2016) and task-related (Furman and Gotlib, 2016; Hennigan et al., 2015; Lawson et al., 2017; Lawson et al., 2013) Hb activity with ≤ 2 mm isotropic voxel sizes, providing novel and more reliable information about the Hb network in humans. Because this resolution is still coarse to study in the Hb in detail, these studies do not distinguish between the lateral and medial parts as in animal studies. Ranft et al. (2010) examined habenular volumes in the post-mortem brains of patients with major depression and with bipolar depression. Significantly, reduced habenular volumes of the medial and lateral habenula were estimated in depressive patients, with a reduction in neuronal cell number and cell area; MRI studies were less conclusive (Carceller-Sindreu et al., 2015; Schmidt et al., 2016). Fortunately, experiments in monkeys have been more straightforward (Hikosaka, 2010). Matsumoto and Hikosaka (2009) found that LHb neurons are inhibited by pleasant events (i.e. rewards) and their predictors, but are excited by reward omission and (predictors of) aversive stimuli. Thereafter, these signals are transmitted to dopaminergic neurons in and around the SNc (Matsumoto and Hikosaka, 2007). This negative reward sensitivity is, at least partly, provided by a distinct group of neurons at the border of the globus pallidus (GPb) (Hong and Hikosaka, 2008, 2013) and ventral pallidum (VPh) (Hong and Hikosaka, 2013). The GPb is believed to be the primate version of the lamprey's GPh, at least within the extrapyramidal system (Stephenson-Jones et al., 2013; Robertson et al., 2014).

The role of the primate MHb has not been studied extensively. Although the MHb is, via the interpeduncular nucleus, more intensively connected with midbrain serotonergic nuclei than the LHb (Benarroch, 2015b; Bianco and Wilson, 2009), serotonergic effects have been largely attributed to the LHb (Hikosaka et al., 2008), although this may prove to be an oversimplification (Proulx et al., 2014).

3.3. Role of the amygdala in humans

The amygdaloid complex can be neuroanatomically divided into “deep nuclei”, “superficial nuclei” and “remaining nuclei” (Benarroch, 2015a; Freese and Amaral, 2009). Both the superficial cortical amygdala nuclei, and the deep basolateral amygdalar nuclear complex, comprise cortex-like cell types (McDonald and Mott, 2016). In contrast, the so-called “extended amygdalar nuclei”

contains predominantly GABA-ergic spiny projection neurons, like the striatum (McDonald and Mott, 2016). Each nucleus of the amygdala has a characteristic set of interconnections with other amygdalar nuclei and extrinsic brain regions (Pitkänen, 2000; Freese and Amaral, 2009). The extended amygdala comprises the ganglionic nuclei, the bed nucleus of the stria terminalis (BST), and their extended amygdala connections (Heimer and Van Hoesen, 2006), and is likely comparable to the complete striato-pallidum of our earliest vertebrate ancestors (Loonen and Ivanova, 2016c). The BST can be considered to be the amygdala-associated globus pallidus (González et al., 2014; Moreno et al., 2012) and contains a section that projects to the lateral habenula (BSTh) (Dong and Swanson, 2006a,b).

A substantial component of amygdaloid output is delivered directly or, via the hippocampus, indirectly, to hypothalamic structures that regulate emotional responses such as sexual desire, hunger, thirst, fear, and nurture, as well as sleep-need and power-dominance drives (Sewards and Sewards, 2003; Loonen and Ivanova, 2016a,b). The connectivity of the deep corticoid amygdaloid complex to and from the hippocampal complex is mediated through parahippocampal regions (Witter, 2002). Via the fornix, the hippocampus sends a GABAergic connection to the medial septum and a glutamatergic connection to the lateral septum (Khakpai et al., 2013; Nieuwenhuys et al., 2008). The septum, particularly the medial septum and the adjacent nucleus of the diagonal band of Broca, is the main input to the MHb (Klemm, 2004; Viswanath et al., 2014; Benarroch, 2015b). Hence, the amygdaloid complex may deliver output to the MHb via the hippocampal complex and septum, as well as to the LHb via the BSTh, which can be considered to be the amygdaloid homologue of the GPh (Fig. 1).

An appropriate description of the functions of the amygdaloid complex is that it analyses complex inputs related to daily life situations within the individual's biotope (nature, flora, fauna, social circumstances) and selects the sensory input most likely to improve personal circumstances (i.e. aversive events-fleeing and reward-seeking). This process refers to (attentive) salience attribution (Loonen and Ivanova, 2016c). The output of the amygdala is modulated by the ventromedial areas of the prefrontal cortex (Kim et al., 2011; Roy et al., 2012; Loonen and Ivanova, 2016a,b). A significant component of the output flows via the hippocampus and fornix, to medial and lateral septal areas (Khakpai et al., 2013; Nieuwenhuys et al., 2008). After comparison with memorized experiences in the hippocampus, and processing within the septal area, this information may reach the MHb. Although the MHb has been subject to much less study than the LHb, experimental data would support the notion that hyperactivity of the MHb is associated with depression, anxiety, and fear (Viswanath et al., 2014).

3.4. The evolution of the amygdala

Studying the development of the human cerebral cortex during subsequent steps of evolution makes clear that until and including a human ancestor with turtle-like brain, animals did not possess a human-like (dorsal) thalamus and cerebral neocortex (Loonen and Ivanova, 2016d). In more recent jawed vertebrates, the input to the dorsal thalamus largely increases, and this in turn leads to a significant expansion of the dorsal pallium into cerebral cortex (Butler, 1994a,b). However, this expansion occurs along different lines in non-synapsid (reptiles, birds) and synapsid (mammals) animals (Butler, 1994b; Montiel et al., 2016). In mammals a true cerebral cortex develops (Butler, 1994b). The expansion of this structure resulted in a total displacement of ventral, dorsal and medial pallial fields of earlier vertebrates. The dorsal and medial pallium became the hippocampus and the ventral pallium became the most caudal edge of the frontal lobe (including olfactory tubercle) and cortical regions of the amygdaloid complex (Loonen and

© A.J.M. Loonen

Fig. 1. Scheme showing the putative connectivity of amygdalo-hippocampal system to the midbrain through the habenular complex.

BSTh = habenula-projecting part of bed nucleus of the stria terminalis; DR = dorsal raphe nucleus; DTg = dorsal tegmental nucleus; IPN = interpeduncular nucleus; LHb = lateral habenula; MHb = medial habenula; PHC = parahippocampal cortex; RMTg = rostromedial tegmental nucleus; sCg = subgenual cingulate gyrus; VTA = ventral tegmental area.

Ivanova, 2016d). As the lamprey striato-pallidum went up into the mammalian extended amygdala, it is justified to consider the human amygdaloid complex to represent the (almost) entire telen-cephalon of human's non-mammalian ancestors. In our opinion, it is very well possible that the regulation of aversive events-fleeing and reward-seeking behavior is still largely confined within these phylogenetically old structures.

3.5. Circuits regulating the intensity of reward-seeking and aversive events-fleeing behaviour

We have previously suggested, that two cortico-striato-pallido-thalamo-cortical re-entry circuits including the nucleus accumbens as a first relay station (Fig. 2), can be thought of as regulating the intensity of reward-seeking and aversive events-fleeing behaviours: the first by the circuit that includes the core region (nucleus accumbens core, NAcBC), and the second by the circuit

© A.J.M. Loonen

Fig. 2. Cortico-striatal-thalamo-cortical re-entry circuits including the core and shell parts of the nucleus accumbens (adapted from Dalley et al., 2008).

The activity of these re-entry circuits (motivating to reward-seeking and aversive event-fleeing behaviour) is regulated by midbrain monoaminergic centres, which are in turn controlled by the output of the habenula.

Note: the existence of the re-entry circuit including the subgenual cingulate cortex is currently hypothetical.

LC = locus coeruleus; VTA = ventral tegmental area. Red arrows = glutamatergic, blue arrows = GABAergic; green arrows = adrenergic; grey arrows = dopaminergic.

which comprises the shell (nucleus accumbens shell, NAcB). The NAcB is part of a re-entry CSTC circuit that starts and ends within the medial OFC (and (dorsal) anterior cingulate cortex, ACC). We previously postulated the existence of a re-entry circuit that began and ended within the (ventral) subgenual anterior cingulate gyrus (sCg), running through the NAcB (Loonen and Ivanova, 2016a). The first circuit regulates the intensity of reward-seeking behaviour and the second, of aversive events-fleeing. The activities of both are regulated by the dopaminergic VTA/SNc, but only the NAcB is innervated by the adrenergic LC (stimulating β adrenoceptors, β -AR) (Loonen and Ivanova, 2016a).

3.6. The role of the medial and lateral habenula

The MHb and LHb play significant roles in regulating the activities of reward-seeking and aversive events-fleeing behaviours by altering the activity of 'controlling' midbrain monoaminergic nuclei (VTA/SNc, DRN, LC). The LHb stimulates the RMTg, and this GABAergic nucleus inhibits the VTA/SNc. The MHb stimulates the LHb and the IPN. The IPN is a singular, unpaired structure located at the ventral midline of the midbrain (Klemm, 2004; Morley, 1986). The major efferent pathways originating in the IPN project to the dorsal tegmental nucleus (Morley, 1986), the VTA (Klemm, 2004) and the raphe nuclei (Bianco and Wilson, 2009; Klemm, 2004). However, the IPN is well known for its widespread projections, both ascending and descending (Klemm, 2004; Morley, 1986).

The cortical part of the amygdaloid cortex and the hippocampal cortex initiate and activate complex emotional responses such as the fear/flight and anger/fight as basic defence mechanisms (Loonen and Ivanova, 2016a). These systems influence the MHb via the septal and diagonal band of Broca nuclei. We would suggest that a homologue of the GPh exists within this limbic system, probably represented by BSTh (Fig. 1), which regulates decisions concerning aversive events-fleeing behaviour.

Within the extrapyramidal system the human homologue of the GPh is likely to alter behaviour by affecting the activities of specific parts of these extrapyramidal CSTC circuits. The non-reward attractor network within the lateral OFC as described by Rolls (2016) may be the target of such a CSTC circuit. This CSTC circuit activates the non-reward attractor network within the lateral OFC. Finally, this network activates dorsal prefrontal areas. At the same time, the GPh inhibits the CSTC circuit which is activating the medial OFC.

4. Conclusion: synthesis of cortical and subcortical regulation

We should emphasize how highly we value Edmund T. Rolls' (2016) paper on the presence of a non-attractor network within the lateral OFC and its possible role in depression and mania. The existence of such a network would enable the individual to rapidly modify reward-seeking behaviour when disappointment ensues. This constitutes a major adaptive advance that allows rapid and flexible changes of behaviour when reinforcement contingencies change (Rolls, 2016). The cerebral cortex with its highly developed recurrent collateral connections which also include a long loop involving language cortical areas may allow for a rule to be looked up by a stimulus, to produce expected reward firing; a mechanism to detect a mismatch if an expected reward is not received; and then continuing firing for at least several seconds to change the behavior, and indeed to switch a rule attractor to indicate that a different stimulus is now rewarded (Rolls and Deco, 2016). The orbitofrontal and ventromedial prefrontal cortices are very suitable to compute the expected value, reward outcome and experienced pleasure for different stimuli (Grabenhorst and Rolls, 2011; Rolls and Grabenhorst, 2008).

However, the change of the attractor state is not necessarily induced by the network itself based upon input through its intra-cortical (top-down) connections. In our opinion, it is perfectly feasible that activation occurs based upon the inputs of a CSTC circuit, as part of a complex response induced by a structure similar to that of our ancestor's GPh, which may be retrieved in the BSTh, the VPh and the GPb. This activation runs through the epithalamus, monoaminergic midbrain nuclei, and probably also includes specific other prefrontal targets. The appropriate response is thereafter computed, initiated, planned and executed by the frontal cortex. However, evaluating the results of this endeavour could still be the preserve of a human version of the GPh within the subcortex.

The lateral and medial habenula may receive input from the amygdalo-hippocampal complex via the BSTh and septal area, respectively (Fig. 1). In turn, the activity of amygdalo-hippocampal complex is inhibited by ventromedial areas of the prefrontal cortex (Kim et al., 2011; Roy et al., 2012). Cheng et al. (2016) measured resting state functional connectivity in patients with major depression and control subjects. They found reduced functional connectivity in depression between medial orbitofrontal cortex with memory systems in the parahippocampal gyrus and medial temporal lobe, especially involving the perirhinal cortex and entorhinal cortex. This may correspond to the finding that anticipation of monetary loss elicited activation in the hippocampus as well as in the amygdala (Hahn et al., 2010). Whether or not the medial or lateral orbitofrontal cortices also directly affect the functioning of habenula remains to be determined.

The prime reason for proposing this adaptation of the non-reward attractor theory of depression is that drugs such as selective serotonin reuptake inhibitors (SSRIs) and N-Methyl-D-Aspartate (NMDA) antagonists (i.e. ketamine) are unlikely to mediate their effects at the cortical level. A subcortical site of action is much more likely as psychotropic drugs in general lack the specificity to influence specific cortical circuitry. In addition, neuroplasticity is unlikely to occur in *specific* cortical targets. Altering the sensitivity of cortical-subcortical interactions is, we believe, a much more likely mechanism of action.

Moreover, as described above, the functioning of specific cortical circuits is controlled by subcortical systems. The latter may lack specificity as a pay off to ensure that the organism adequately responds to changes within its biosphere. Ultimately the response can be far better computed by the cerebral cortex, and humans are probably the best placed of all primates to achieve this due to their well-developed cerebral cortex and profound language capabilities.

References

- Batalla A., Homberg J.R., Lipina T.V., Sescousse G., Luijten M., Ivanova S.A., Schellekens A.F., Loonen A.J., in preparation The role of the habenula in the transition from reward to misery in substance use and mood disorders.
- Benarroch, E.E., 2015a. The amygdala: functional organization and involvement in neurologic disorders. *Neurology* 84, 313–324.
- Benarroch, E.E., 2015b. Habenula: recently recognized functions and potential clinical relevance. *Neurology* 85, 992–1000.
- Bianco, I.H., Wilson, S.W., 2009. The habenular nuclei: a conserved asymmetric relay station in the vertebrate brain: *philos. Trans. R. Soc. Lond. B. Biol. Sci.* 364, 1005–1020.
- Butler, A.B., 1994a. The evolution of the dorsal thalamus of jawed vertebrates, including mammals: cladistic analysis and a new hypothesis. *Brain Res. Brain Res. Rev.* 19, 29–65.
- Butler, A.B., 1994b. The evolution of the dorsal pallium in the telencephalon of amniotes: cladistic analysis and a new hypothesis. *Brain Res. Brain Res. Rev.* 19, 66–101.
- Carceller-Sindreu, M., de Diego-Adelino, J., Serra-Blasco, M., Vives-Gilabert, Y., Martín-Blanco, A., Puigdemont, D., Álvarez, E., Pérez, V., Portella, M.J., 2015. Volumetric MRI study of the habenula in first episode, recurrent and chronic major depression. *Eur. Neuropsychopharmacol.* 25, 2015–2021.
- Cheng, W., Rolls, E.T., Qiu, J., Liu, W., Tang, Y., Huang, C.C., Wang, X., Zhang, J., Lin, W., Zheng, L., Pu, J., Tsai, S.J., Yang, A.C., Lin, C.P., Wang, F., Xie, P., Feng, J., 2016. Medial reward and lateral non-reward orbitofrontal cortex circuits change in opposite directions in depression. *Brain* 139 (Pt 12), 3296–3309.

- Dalley, J.W., Mar, A.C., Economidou, D., Robbins, T.W., 2008. Neurobehavioral mechanisms of impulsivity: fronto-striatal systems and functional neurochemistry. *Pharmacol. Biochem. Behav.* 90, 250–260.
- Dong, H.W., Swanson, L.W., 2006a. Projections from bed nuclei of the stria terminalis, dorsomedial nucleus: implications for cerebral hemisphere integration of neuroendocrine, autonomic, and drinking responses. *J. Comp. Neurol.* 494, 75–107.
- Dong, H.W., Swanson, L.W., 2006b. Projections from bed nuclei of the stria terminalis, anteromedial area: cerebral hemisphere integration of neuroendocrine, autonomic, and behavioral aspects of energy balance. *J. Comp. Neurol.* 494, 142–178.
- Ely, B.A., Xu, J., Goodman, W.K., Lapidus, K.A., Gabbay, V., Stern, E.R., 2016. Resting-state functional connectivity of the human habenula in healthy individuals: associations with subclinical depression. *Hum. Brain Mapp.* 37, 2369–2384.
- Freese, J.L., Amaral, D.G., 2009. Neuroanatomy of the primate amygdala. In: Whalen, P.J., Phelps, E.A. (Eds.), *The human amygdala*, 2009. The Guilford Press, New York, pp. 3–42.
- Furman, D.J., Gotlib, I.H., 2016. Habenula responses to potential and actual loss in major depression: preliminary evidence for lateralized dysfunction. *Soc. Cogn. Affect. Neurosci.* 11, 843–851.
- González, A., Morona, R., Moreno, N., Bandín, S., López, J.M., 2014. Identification of striatal and pallidal regions in the subpallium of anamniotes. *Brain Behav. Evol.* 83, 93–103.
- Grabenhorst, F., Rolls, E.T., 2011. Value, pleasure, and choice in the ventral prefrontal cortex. *Trends Cogn. Sci.* 15, 56–67. Value, pleasure and choice in the ventral prefrontal cortex.
- Hahn, T., Dresler, T., Plichta, M.M., Ehli, A.C., Ernst, L.H., Markulin, F., Polak, T., Blaimer, M., Deckert, J., Lesch, K.P., Jakob, P.M., Fallgatter, A.J., 2010. Functional amygdala-hippocampus connectivity during anticipation of aversive events is associated with Gray's trait sensitivity to punishment. *Biol. Psychiatry* 68, 459–464.
- Heimer, L., Van Hoesen, G.W., 2006. The limbic lobe and its output channels: implications for emotional functions and adaptive behavior. *Neurosci. Biobehav. Rev.* 30, 126–147.
- Heimer, L., 2003. A new anatomical framework for neuropsychiatric disorders and drug abuse. *Am. J. Psychiatry* 160, 1726–1739.
- Hennigan, K., D'Ardenne, K., McClure, S.M., 2015. Distinct midbrain and habenula pathways are involved in processing aversive events in humans. *J. Neurosci.* 35, 198–208.
- Hetu, S., Luo, Y., Saez, I., D'Ardenne, K., Lohrenz, T., Montague, P.R., 2016. Asymmetry in functional connectivity of the human habenula revealed by high-resolution cardiac-gated resting state imaging. *Hum. Brain Mapp.* 37, 2602–2615.
- Hikosaka, O., Sesack, S.R., Lecourtier, L., Shepard, P.D., 2008. Habenula: crossroad between the basal ganglia and the limbic system. *J. Neurosci.* 28, 11825–11829.
- Hikosaka, O., 2010. The habenula: from stress evasion to value-based decision-making. *Nat. Rev. Neurosci.* 11, 503–513.
- Hong, S., Hikosaka, O., 2008. The globus pallidus sends reward-related signals to the lateral habenula. *Neuron* 60, 720–729.
- Hong, S., Hikosaka, O., 2013. Diverse sources of reward value signals in the basal ganglia nuclei transmitted to the lateral habenula in the monkey. *Front. Hum. Neurosci.* 7, 778.
- Khakpai, F., Nasehi, M., Haeri-Rohani, A., Eidi, A., Zarrindast, M.R., 2013. Septo-hippocampo-septal loop and memory formation. *Basic Clin. Neurosci.* 4, 5–23.
- Kim, M.J., Loucks, R.A., Palmer, A.L., Brown, A.C., Solomon, K.M., Marchante, A.N., Whalen, P.J., 2011. The structural and functional connectivity of the amygdala: from normal emotion to pathological anxiety. *Behav. Brain Res.* 223, 403–410.
- Klemm, W.R., 2004. Habenular and interpeduncular nuclei: shared components in multiple-function networks. *Med. Sci. Monit.* 10, RA261–73.
- Lawson, R.P., Drevets, W.C., Roiser, J.P., 2013. Defining the habenula in human neuroimaging studies. *Neuroimage* 64, 722–727.
- Lawson, R.P., Nord, C.L., Seymour, B., Thomas, D.L., Dayan, P., Pilling, S., Roiser, J.P., 2017. Disrupted habenula function in major depression. *Mol. Psychiatry* 22, 202–208, Epub ahead of print.
- Loonen, A.J.M., Ivanova, S.A., 2013. New insights into the mechanism of drug-induced dyskinesia. *CNS Spectr.* 18, 15–20.
- Loonen, A.J.M., Ivanova, S.A., 2015. Circuits regulating pleasure and happiness: the evolution of reward-seeking and misery-fleeing behavioral mechanisms in vertebrates. *Front. Neurosci.* 23, 394.
- Loonen, A.J.M., Ivanova, S.A., 2016a. Circuits regulating pleasure and happiness in major depression. *Med. Hypotheses* 87, 14–21.
- Loonen, A.J.M., Ivanova, S.A., 2016b. Circuits Regulating Pleasure and Happiness – Mechanisms of Depression. *Front. Hum. Neurosci.* 10, 571.
- Loonen, A.J.M., Ivanova, S.A., 2016c. Circuits regulating pleasure and happiness in schizophrenia: the neurobiological mechanism of delusions. In: Shen, Y.-C. (Ed.), *Schizophrenia Treatment – The New Facets*. InTech, Rijeka, Croatia, pp. 109–134, ISBN 978-953-51-4958-3.
- Loonen, A.J.M., Ivanova, S.A., 2016d. Circuits regulating pleasure and happiness: the evolution of the amygdala-hippocampal-habenular connectivity in vertebrates. *Front. Neurosci.* 10, 539.
- Matsumoto, M., Hikosaka, O., 2007. Lateral habenula as a source of negative reward signals in dopamine neurons. *Nature* 447, 1111–1115.
- Matsumoto, M., Hikosaka, O., 2009. Representation of negative motivational value in the primate lateral habenula. *Nat. Neurosci.* 12, 77–84.
- McDonald, A.J., Mott, D.D., 2017. Functional neuroanatomy of amygdalohippocampal interconnections and their role in learning and memory. *J. Neurosci. Res.* 95, 797–820 (Epub ahead of print).
- Montiel, J.F., Vasistha, N.A., Garcia-Moreno, F., Molnár, Z., 2016. From sauropsids to mammals and back: new approaches to comparative cortical development. *J. Comp. Neurol.* 524, 630–645.
- Moreno, N., Morona, R., López, J.M., Domínguez, L., Joven, A., Bandín, S., González, A., 2012. Characterization of the bed nucleus of the stria terminalis in the forebrain of anuran amphibians. *J. Comp. Neurol.* 520, 330–363.
- Morley, B.J., 1986. The interpeduncular nucleus. *Int. Rev. Neurobiol.* 28, 157–182.
- Nieuwenhuys, R., Voogd, J., Van Huijzen, C., 2008. *Telencephalon: Hippocampus and Related Structures*. In: *The Human Central Nervous System*, 4th edition. Springer, Berlin, Heidelberg, pp. 361–400.
- Pitkänen, A., 2000. Connectivity of the rat amygdaloid complex. In: Aggleton, J.P. (Ed.), *The Amygdala – A Functional Analysis*, second edition. Oxford University Press, New York, pp. 31–115.
- Proulx, C.D., Hikosaka, O., Malinow, R., 2014. Reward processing by the lateral habenula in normal and depressive behaviors. *Nat. Neurosci.* 17, 1146–1152.
- Ranft, K., Dobrowolny, H., Krell, D., Biellau, H., Bogerts, B., Bernstein, H.G., 2010. Evidence for structural abnormalities of the human habenular complex in affective disorders but not in schizophrenia. *Psychol. Med.* 40, 557–567.
- Robertson, B., Kardamakis, A., Capantini, L., Pérez-Fernández, J., Suryanarayana, S.M., Wallén, P., Stephenson-Jones, M., Grillner, S., 2014. The lamprey blueprint of the mammalian nervous system. *Prog. Brain Res.* 212, 337–349.
- Rolls, E.T., Deco, G., 2016. Non-reward neural mechanisms in the orbitofrontal cortex. *Cortex* 83, 27–38.
- Rolls, E.T., Grabenhorst, F., 2008. The orbitofrontal cortex and beyond: from affect to decision-making. *Prog. Neurobiol.* 86, 216–244.
- Rolls, E.T., 2016. A non-reward attractor theory of depression. *Neurosci. Biobehav. Rev.* 68, 47–58.
- Roy, M., Shohamy, D., Wager, T.D., 2012. Ventromedial prefrontal-subcortical systems and the generation of affective meaning. *Trends Cogn. Sci.* 16, 147–156.
- Savitz, J.B., Nugent, A.C., Bogers, W., Roiser, J.P., Bain, E.E., Neumeister, A., Zarate Jr., C.A., Manji, H.K., Cannon, D.M., Marrett, S., Henn, F., Charney, D.S., Drevets, W.C., 2011. Habenula volume in bipolar disorder and major depressive disorder: a high-resolution magnetic resonance imaging study. *Biol. Psychiatry* 69, 336–343.
- Schmidt, F.M., Schindler, S., Adamidis, M., Strauß, M., Tränkner, A., Trampel, R., Walter, M., Hegerl, U., Turner, R., Geyer, S., Schönknecht, P., 2016. Habenula volume increases with disease severity in unmedicated major depressive disorder as revealed by 7T MRI. *Eur. Arch. Psychiatry. Clin. Neurosci.* 2016 (February 12) (Epub ahead of print).
- Sewards, T.V., Sewards, M.A., 2003. Representations of motivational drives in mesial cortex, medial thalamus, hypothalamus and midbrain. *Brain Res. Bull.* 61, 25–49.
- Stephenson-Jones, M., Kardamakis, A.A., Robertson, B., Grillner, S., 2013. Independent circuits in the basal ganglia for the evaluation and selection of actions. *Proc. Natl. Acad. Sci., U. S. A.* 110, E3670–9.
- Viswanath, H., Carter, A.Q., Baldwin, P.R., Molfese, D.L., Salas, R., 2014. The medial habenula: still neglected. *Front. Hum. Neurosci.* 7, 931.
- Witter, M., 2002. The parahippocampal region: past, present, and future. In: Witter, M., Wouterlood, F. (Eds.), *The Parahippocampal Region: Organization and Role in Cognitive Function*. University Press, Oxford, UK: Oxford, pp. 3–19.