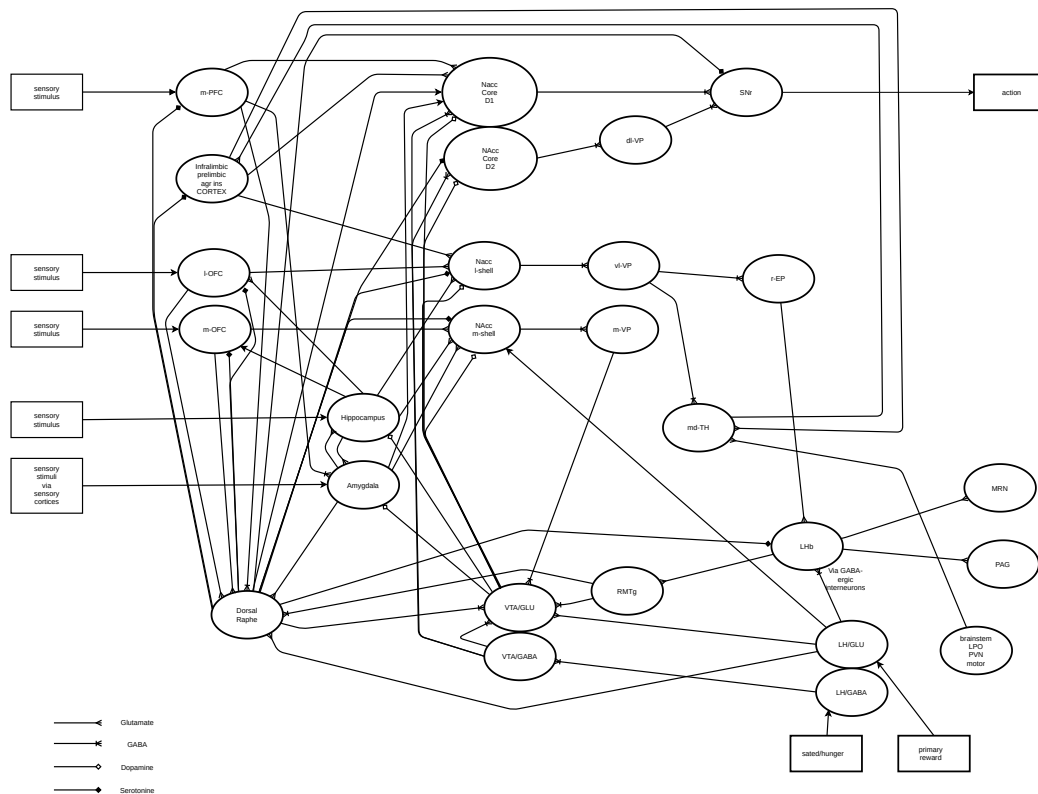


Limbic system map

Bernd Porr*, Maria Thomson and Ailsa Millen

Revision 0.9.0

A hand curated map of the limbic system backed up by anatomical and electrophysiological references.



Online map and as PDF: <https://berndporr.github.io/limbic-system-map/>

*BerndPorr@glasgow.ac.uk

Contents

1	Introduction	4
2	Review articles	5
3	Nucleus Accumbens (NAcc)	5
3.1	Behavioural experiments	6
3.2	Signals	6
3.3	Plasticity	6
3.4	Nucleus Accumbens Core	6
3.4.1	Afferents	6
3.4.2	Efferents	7
3.5	Nucleus Accumbens Shell	7
3.5.1	Medial Shell	7
3.5.2	Lateral Shell	7
3.5.3	Behavioural experiments	7
3.5.4	Function	8
4	Orbitofrontal Cortex (OFC)	8
4.1	Afferents	8
4.2	Efferents	9
4.3	Neuronal activity	9
4.4	Behavioural experiments	9
5	Medial Prefrontal Cortex (m-PFC)	9
5.1	Efferents	10
5.2	Neuromodulation	10
5.3	Behaviour	10
6	Amygdala	10
6.1	Central / Medial	10
6.2	Basolateral / lateral	10
6.3	Efferents	11
6.4	Afferents	11
7	Entopeduncular Nucleus (EP)	11
7.1	Efferents	11
7.2	Function	11

8	Lateral Habenula (l-Hb)	12
8.1	Afferents	12
8.2	Efferents	12
8.3	Function	12
9	Lateral hypothalamus (LH)	13
9.1	Efferents	13
9.2	Afferents	13
9.3	Behavioural experiments	13
10	Rostral Medial Tegmental Nucleus (RMTg)	14
10.1	Afferents	14
10.2	Efferents	14
11	Ventral Pallidum (VP)	14
11.1	Afferents	14
11.2	Efferents	15
12	Dorsal Raphe Nucleus (DRN)	15
12.1	Afferents	15
12.1.1	OFC to DRN	15
12.1.2	mPFC to DRN	15
12.1.3	LHb to DRN	16
12.1.4	LH to DRN	16
12.1.5	Amygdala to DRN	16
12.1.6	Basal Ganglia to DRN	16
12.1.7	Anterior cingulate cortex (ACC)	16
12.2	Efferents	16
12.2.1	Dorsal pathway of the DRN	17
12.2.2	Medial pathway of the DRN	17
12.2.3	Ventral pathway of the DRN	17
12.3	Receptors	18
12.3.1	5HTR1	18
12.3.2	5HTR2	19
12.3.3	5HTR3	19
12.3.4	5HTR4	19
12.4	Activity	20
12.5	Behavioural studies	20

13 Ventral Tegmental Area (VTA)	20
13.1 Afferents	20
13.2 Efferents	20
13.3 Function	21
13.3.1 Phasic activity	21
13.3.2 Tonic activity (DA)	22
13.3.3 Tonic activity (GABA)	22

1 Introduction

This document is a hybrid of a map and commenting text underneath which in turn points to references which back up the connections.

In contrast to “self-organised” models which assume that “objective” data organises itself to a brain map, this project strongly believes that *curation* by a human is essential. There are a number of reasons:

- **Data and papers are biased:** We assume *every paper* and *every dataset* is biased – be it subconscious, conscious or deliberate. It should be a no-brainer as it’s generated by humans for humans. It is thus important to compare different views and then draw conclusions which most likely reflects what is actually happening in the rat brain. I’m a computational neuroscientist. This is both benefit and curse. The advantage is that I can step back and can talk to different camps to find out different intentions, slants or spin. On the other hand the danger is that I force popular machine learning models onto neuroscience. For that reason this map here makes no attempt to be mathematically pure. For example there is no attempt to force TD or deep learning onto this map.
- **Uncertainty of the data:** neurophysiological data rarely provides 100% certainty and a clear-cut interpretation. Data is noisy and there will be almost every time a study which contradicts the current state of the art. However, through experience one learns to distinguish between spurious results and those which will consolidate. This is not a simple process eliminating outliers but to look at the studies from the curator’s experience because a hype or fashion can generate a large amount of publications and again requires stepping back and evaluating publications with possibly at a 10year timeframe to check which of these findings have been reproduced from different sources and over years.

- **Closed loop / Embodied:** At the end an animal needs to act in its environment because the limbic system makes an animal finding rewards (and punishments). This means that the animal generates actions to obtain sensor inputs which in turn generate actions and so forth. The whole map needs to be able to establish a (real or simulated) rat performing reward related behaviour, for example reversal learning. This constraint demands that the limbic map needs to be seen always as a whole being embedded in an environment.

In summary: human curation of data here is as important as humans generating both data and publications. So far no algorithm can fix this. A brain searching for rewards cannot do this while swimming in a vat and thus requires to be embodied.

2 Review articles

- This article by Castro and Berridge promotes their long standing differentiation between 'wanting' and 'liking' ([Berridge, 2009](#)) now updated by 'hedonic hot spots' ([Castro et al., 2015](#)).
- Berthoud's article features fantastic connection diagrams between the different nuclei of the limbic system ([Berthoud, 2004](#)).
- Zahm again provides very detailed anatomical connection diagrams and is a must read ([Zahm, 2000](#)).
- The review by Abbas Khani and Gregor Rainer focusses on the roles of the different nuclei, how they interact, how they implement reinforcement guided decision making and which forms are out there (reversal, go no go etc). A very balanced article which, for example, not just cites the prediction error paradigm of DA but reports also the other roles DA ([Khani and Rainer, 2016](#)).

3 Nucleus Accumbens (NAcc)

The Nacc is the ventral extension of the striatum, and therefore also called the ventral striatum. The ventral striatum contains neurons known as medium spiny neurons (MSN's).

The accumbens has two major subterritories ([Heimer et al., 1991](#)): the shell (section 3.5) and the core (section refcore) where the shell can be further subdivided ([Usuda et al., 1998](#)) in lateral and medial parts and the core rather depending on its D1 or D2 receptors.

3.1 Behavioural experiments

The Nacc core and shell have distinct roles controlling reward based learning:

In **reversal learning** (Dalton et al., 2014) the shell seems to control switching contingencies (i.e. the reward is moved from one site to another) whereas the core controls the actual approach behaviour towards the rewarding site.

Impulsivity is altered by 5HT antagonists which point towards an important role of 5HT in the retrieval of delayed rewards. 5-HT(2A) antagonists reduced decreased impulsive responding and the 5-HT(2C) antagonist increased impulsivity (Robinson et al., 2008).

3.2 Signals

By measuring the DA concentration in both the core and shell (Saddoris et al., 2015) it turns out that Core DA follows the classical prediction error signals where it spikes most to the predicting cue whereas the shell responds to all reward related events during the experiment.

3.3 Plasticity

It's well known the bursts of dopamine cause LTP in conjunction with pre- and (possible) postsynaptic activity (so called 3 factor Hebbian rule) or heterosynaptic LTP. However Goto and Grace (2005) showed that D1 receptors cause LTP on hippocampal fibres whereas D2 receptors control the cortical inputs in the opposite way. It appears to be that 5HT causes retrograde cannabinoid (CB) release which inhibits pre-synaptic GLU release (Burattini et al., 2014). However, also postsynaptic HFS causes CB1 mediated depression. Mathur et al. (2011) tested this more thoroughly in that they conclude that 5HT actually causes presynaptic inhibition via the 5HT1B receptor, with that LTD and that HFS can have a similar effect by releasing CB.

3.4 Nucleus Accumbens Core

3.4.1 Afferents

The NAc core receives inputs from the dorsal-medial prefrontal cortex and the hippocampus (Brog et al., 1993a).

3.4.2 Efferents

There are two distinct output pathways from the NAcc core which have its origins from the two sub-populations of neurons in the NAcc core. The one sub-population carries mainly D1 receptors and the other one carries mainly D2 receptors ([Kelley, 2004](#); [Humphries and Prescott, 2010](#)).

Direct pathway The **D1** receptor carrying neurons feed directly into the SNr and are able to inhibit tonically active SNr neurons, thus the NAcc core is able to disinhibit motor programs.

Indirect pathway There is an indirect pathway via the VP to the SNr originating from the NAcc core. In contrast to the direct pathway these neurons in the indirect pathway carry mainly D2 receptors which are inhibitory in nature. D2 receptors are very sensitive to low DA concentrations and will react to the tonic DA concentrations.

3.5 Nucleus Accumbens Shell

The shell can be further divided into the medial and lateral shell ([Ikemoto, 2007](#); [Usuda et al., 1998](#)) used in the model by ([Humphries and Prescott, 2010](#)).

3.5.1 Medial Shell

The medial Shell projects to the medial Ventral Pallidum (VP) ([Ikemoto, 2007](#)).

3.5.2 Lateral Shell

The lateral shell projects to the ventrolateral Ventral Pallidum (VP) ([Ikemoto, 2007](#)).

3.5.3 Behavioural experiments

The shell seems to be responsible for behavioural flexibility meaning that it controls the animal's ability to shift to another target when the reward is lost ([Aquili et al., 2014](#))

3.5.4 Function

Overall the Shell seems to learn the stimuli which are associated with a reward, and thus enhances the future salience of those stimuli (Cassidy and Tong, 2017).

In this context it is also interesting that shell DA also tracks rather the incentive value than the reward prediction error (Sackett et al., 2017) which probably means that the VTA has regions which work with the shell and that they are distinct from the core.

4 Orbitofrontal Cortex (OFC)

The OFC associates sensory stimuli with reward related information (Schoenbaum et al., 2009) or in other words it computes the (potential) reward value of a sensor cue (Wikenheiser and Schoenbaum, 2016; Bari and Robbins, 2013).

4.1 Afferents

The OFC receives inputs from a wide range of brain areas which allows it to associate sensor cues (and also actions) to rewards. Wikenheiser and Schoenbaum (2016) provides an overview of these inputs which are from the:

- hippocampus
- subiculum
- PFC
- perirhinal cortex, and
- nucleus reuniens

Serotonin seems to have a strong effect on the OFC which has been shown by Zhou et al. (2015). Stimulation of the DRN results in both excitatory activity and inhibitory activity in the OFC. In addition the release of 5HT has a strong impact on plasticity: after pairing an odour stimulus with the release of 5HT the odour stimulus creates long lasting activity in the OFC which starts at the presentation of the stimulus and ends after reward delivery (Zhou et al., 2015).

4.2 Efferents

Its major subcortical targets include the dorsal raphe nucleus (DRN) ([Luo et al., 2015](#)), medial striatum, NAcc, lateral preoptic area, amygdala and the hypothalamus ([Vertes et al., 2012](#)).

- The l-OFC innervates the l-shell and amygdala and
- the m-OFC the m-shell, hippocampus and amygdala ([Brosg et al., 1993b](#); [Noonan et al., 2012](#))

4.3 Neuronal activity

The paper by ([Tremblay and Schultz, 1999](#)) proposed that OFC neurons code the motivational value of rewards. The activity of OFC neurons increased in response to reward-predicting stimuli, during the expectation of rewards, and after the receipt of rewards. Also actions, associated with rewards, increase the firing rates of OFC neurons ([Wikenheiser and Schoenbaum, 2016](#)).

4.4 Behavioural experiments

The review by ([Wikenheiser and Schoenbaum, 2016](#)) presents behavioural experiments involving the OFC which confirm that the OFC computes behavioural reward value computed from sensory cues, such as odour, and actions. They contrast this to the hippocampus which computes reward value in relation to place fields.

Spatial reversal learning is improved by injecting the 5-HT(2C) receptor antagonist into the OFC ([Boulougouris and Robbins, 2010](#)).

Reversal learning is impaired if 5HT processing is disrupted in the OFC ([Bari and Robbins, 2013](#)).

5 Medial Prefrontal Cortex (m-PFC)

The m-PFC is considered by Homberg to be the most important location for top level cognitive functions.

The ventral portion of the m-PFC is called Infralimbic cortex (IL) ([Tsutsui-Kimura et al., 2016](#)).

5.1 Efferents

A well known target of the mPFC is the Nacc core where the Nacc seems to be taking the role for response inhibition and waiting ([Neufang et al., 2016](#); [Feja et al., 2014](#)).

Projections from the m-PFC to the DRN allowing the m-PFC to regulate 5HT firing and therefore control its own 5HT innervation ([Homborg, 2012](#); [Juckel et al., 1999](#)). This projection is inhibitory (see also the DRN page).

5.2 Neuromodulation

5HT plays a significant role in the mPFC which has been shown in great detail in ([Santana and Artigas, 2017](#)) and concluded that 5-HT1A, 5-HT2A, 5-HT2C, and 5-HT3, dopamine D1 and D2 are widely expressed in the mPFC. The receptor 5-HT3 was only expressed on GABAergic interneurons while all the other ones were expressed on both pyramidal and interneurons.

5.3 Behaviour

Lesions to the IL causes more impulsive behaviour ([Tsutsui-Kimura et al., 2016](#)) and reduction in 5HT is also associated with less impulse control ([Neufang et al., 2016](#)).

6 Amygdala

The connectivity of the amygdala has been outlined in these reviews by [Alheid \(2003\)](#); [Sah et al. \(2003\)](#); [Swanson and Petrovich \(1998\)](#).

6.1 Central / Medial

For the the central and medial Amygdala ([Swanson, 2003](#); [Swanson and Petrovich, 1998](#)) have pointed out that these parts contain cells which are similar to those in the striatum (i.e. GABAergic) and thus can be seen as an extension of the striatum dealing with lower executive or autonomic function.

6.2 Basolateral / lateral

The basolateral part of the Amygdala which is related to reward processing and has glutamatergic neurons which have similar roles to that of the cortex and then projects into the striatal parts of the amygdala. See Fig 5 and 6 in [Swanson and Petrovich \(1998\)](#) for detailed connection diagrams.

6.3 Efferents

The anterior basolateral amygdala projects to the NAcc core and the posterior part to the extended amygdala structures (Alheid, 2003).

A projection from the Amygdala to the DRN (Pollak Dorocic et al., 2014) has also been reported.

6.4 Afferents

The basolateral Amygdala has abundant projections from somatosensory cortices (Swanson and Petrovich, 1998), limbic cortices (Ottersen, 1982) and (ventral) hippocampus (Pitkänen et al., 2000).

m-PFC inputs are inhibitory in nature (Rosenkranz and Grace, 2002) but this inhibition can be suppressed by DA release so that in the presence of DA the cortex can drive the BLA.

7 Entopeduncular Nucleus (EP)

The entopeduncular nucleus, also called the GPi in primates, actions are strongly regulated by expected reward outcomes and it is an important output centre of the basal ganglia (Rajakumar et al., 1993).

7.1 Efferents

Different parts of the EP appear to perform different tasks.

- The **caudal part** of the EP has efferents to the (vm-)thalamus and brainstem nuclei and therefore controls motor activity (Rajakumar et al., 1993) (Wallace et al., 2017).
- The **rostral part** of the EP has strong projections to the lateral sub-nuclei of the LHb (including the oval nucleus) LHb (Rajakumar et al., 1993; Hong and Hikosaka, 2008) which are glutamatergic and excitatory (Shabel et al., 2012; Wallace et al., 2017). The LHb then projects primarily to the rostral medial tegmental area (rMTg) which is a GABAergic nucleus that innervates the VTA.

7.2 Function

The reward prediction error is considered to be instigated from the LHb and Barrot et al, 2012 theorized that the EP could play a major role in this

activity as it has such an important input to the LHb ([Barrot et al., 2012](#)) and in turn to the VTA as mentioned above. This relates to the rostral part of the EP.

8 Lateral Habenula (l-Hb)

8.1 Afferents

The 2 strongest forebrain afferents to the LHb are the EP and LH and other connections include the lateral preoptic area and the VP ([Parent et al., 1981](#)).

Araki, 1984, states that the connection from EP to LHb is GABAergic ([Araki et al., 1984](#)) but Shabel 2012 qualifies it as excitatory and glutamergic ([Shabel et al., 2012](#)).

Mok proposed that the actual connection was mainly excitatory ([Mok and Mogenson, 1974](#)). A view supported by Poller who found a strong glutamergic projection that targeted VTA and RMTg projecting neurons ([Poller et al., 2013](#)).

The LHb also receives DA input from the midbrain VTA and SNc ([Kowski et al., 2009](#)) and reciprocally its main, inhibitory projections are to the VTA, SNc and the DRN ([Ji and Shepard, 2007](#); [Christoph et al., 1986](#); [Rajakumar et al., 1993](#)).

8.2 Efferents

The main targets of the LHb are the VTA, Midbrain reticular nucleus (MRN), periaqueductal gray (PAG) and the superior central nucleus raphe (CS) ([Quina et al., 2015](#)).

Slightly puzzling is that the effect on the VTA by the LHb is known to be inhibitory. [Hong et al. \(2011\)](#) theorise that as LHb neurons are largely glutamergic their inhibitory function must be through an intermediary, the RMTg.

8.3 Function

[Bromberg-Martin et al. \(2010\)](#) view LHb as the most important source of reward memory in DA neurons. They cited three potential pathways for transmission; 1) prefrontal cortex to the striatum to the global pallidus to LHb 2) For rats, the mPFC to LHb 3) common sources project reward memory signals to LHb and DA neurons. They found that many LHb and DA

neurons signalled past reward results in their tonic activity, this was surprising as previous studies had reported this was purely the case for phasic activity .

The LHb is considered to be the main source of the negative reward signal that facilitates the DA reward prediction error as LHb innervation inhibits midbrain DA (Shen et al., 2012; Shabel et al., 2012; Matsumoto and Hikosaka, 2007; Barrot et al., 2012).

9 Lateral hypothalamus (LH)

The lateral hypothalamus has both Glutamatergic and GABAergic neurons (Stanley et al., 2011).

9.1 Efferents

The strongest outputs from the LH are to the VTA and the lateral habenula (LHb) (Stuber and Wise, 2016). The projection from the LH to the Habenula is excitatory (Poller et al., 2013) which in turn then projects to the RMTg which has GABA-ergic neurons.

The LH contains both Glu and GABA neurons where the GLU neurons project to the DA neurons in the VTA whereas the GABA neurons in the LH project to the GABA neurons in the VTA which in turn then disinhibit DA neurons in the VTA.

9.2 Afferents

The LH receives many different inputs from different cortical and subcortical areas which are both excitatory and inhibitory. The PFC seems to be an important source of excitatory information, in particular the mPFC. It also receives inputs from the extended Amygdala and the hippocampus (Stuber and Wise, 2016).

9.3 Behavioural experiments

Feeding is stimulated when LH cells are activated by glutamate agonists (Stanley et al., 1993) and that stimulation of GABAergic cells in the LH inhibits feeding (Stanley et al., 2011).

10 Rostral Medial Tegmental Nucleus (RMTg)

The newly discovered rostral medial tegmental nucleus, also called the tail of the VTA, is partially embedded in the VTA ([Bourdy and Barrot, 2012](#)). It has been suggested that it has an ideal location to function as a switch between opposing aversion and reward responding areas and to direct information to DA neurons ([Barrot et al., 2012](#)).

10.1 Afferents

The main afferent to the RMTg is the glutamergic connection from the LHB, which is 7 times stronger than the LHB projection to the VTA ([Barrot et al., 2012](#)) and other afferents include the VTA and SNc ([Lavezzi and Zahm, 2011](#)).

RMTg GABA neurons differ in their targets to the VTA GABA neurons which, for example, target the forebrain in large numbers ([Barrot et al., 2012](#)).

10.2 Efferents

The RMTgs GABA efferents are the principal inhibitory connection to the VTA and SNc and play a critical role in RPE and aversive signalling ([Bourdy and Barrot, 2012](#)). The RMTg also sends projections to other neuromodulatory systems including the raphe nucleus and the locus ceruleus ([Barrot et al., 2012](#)) ([Hong et al., 2011](#)).

11 Ventral Pallidum (VP)

The ventral pallidum is described as the limbic area of the pallidal complex as many reward circuits converge on this region. It encodes reward and motivation information engendered by rewarding stimuli ([Smith et al., 2009](#)). The VP is divided into medial and lateral sections ([Sesack and Grace, 2010](#)).

11.1 Afferents

The VP is innervated by inhibitory GABA connections from the NAcc ([Basar et al., 2010](#)).

See Nacc core/shell for the exact projections.

11.2 Efferents

VP efferents project to the SNr, EP, prefrontal cortex, thalamus, LHb and the VTA ([Groenewegen et al., 1993](#); [Ikemoto, 2007](#)).

The ventral pallidum projects to the mediodorsal thalamic nucleus which in turn then projects to the infralimbic, prelimbic, agranular insular and cingulate cortex ([Ikemoto, 2007](#)).

The m-VP is the main source of GABAergic innervation to the VTA ([Sesack and Grace, 2010](#)).

12 Dorsal Raphe Nucleus (DRN)

The review papers by [Michelsen et al. \(2007\)](#); [Nakamura \(2013\)](#) provide a good overview over the serotonin releasing nucleus.

The DRN seems to generate 5HT to “wait to obtain a reward” behaviour ([Nakamura, 2013](#)).

12.1 Afferents

A detailed tracing / optogenetic study can be found in [Pollak Dorocic et al. \(2014\)](#). LHb, mPFC and LH appear to be the main afferents to the DRN ([Vertes et al., 2010](#); [Sparta and Stuber, 2014](#)) ([Lee et al., 2003](#)).

12.1.1 OFC to DRN

The OFC has strong reciprocal connections to with DRN ([Zhou et al., 2015](#)) where the OFC is probably the main nucleus of the DRN’s ability to track the long term anticipated reward and reversal learning ([Roberts, 2011](#)).

12.1.2 mPFC to DRN

The mPFC (in particular its ventral part) has GLU projections to the DRN ([Gonçalves et al., 2009](#); [Lee et al., 2003](#)).

The conventional view is that the mPFCs glutamergic projections to the DRN connect to locally inhibitory neurons that then target 5HT neurons ([Celada et al., 2001](#)). Stimulation of mPFC neurons usually inhibit DRN neurons which makes a strong case for these scenario.

However, ([Pollak Dorocic et al., 2014](#)) found that the mPFC has direct excitatory control of 5HT which they consider to be potentially critical for the correct function of the serotonergic system.

12.1.3 LHB to DRN

Similarly with regards to LHB projections to the DRN the conventional view is that the LHB neurons target local GABA neurons that then inhibit 5HT. However, ([Pollak Dorocic et al., 2014](#)) found a direct connection to the DRN. Contrary to ([Pollak Dorocic et al., 2014](#)), ([Ogawa et al., 2014](#)) found few monosynaptic connections from the LHB to the DRN and instead posits that the LHB inhibits DRN 5HT via the rostral medial tegmental nucleus (RMTg). This has also been confirmed by ([Sego et al., 2014](#)).

Overall the picture emerges that the LHB exerts its influence via the RMTg and that direct connections from the LHB to the DRN are rare.

12.1.4 LH to DRN

Strong monosynaptic glutamatergic projections have been shown by ([Lee et al., 2003](#)) and ([Aghajanian et al., 1990](#)). It's interesting that of these most prominent projections mentioned above it appears that this is the only excitatory one.

12.1.5 Amygdala to DRN

Tracing studies have shown robust projections from the Amygdala (CEA) to the DRN ([Pollak Dorocic et al., 2014](#)) which are monosynaptic and are most likely glutamatergic ([Swanson and Petrovich, 1998](#)). In contrast to the GABAergic inputs above this seems to be one of the few excitatory inputs.

12.1.6 Basal Ganglia to DRN

Several nuclei from the basal ganglia project to the DRN including SNr and globus pallidus which is inhibitory in nature ([Pollak Dorocic et al., 2014](#)).

12.1.7 Anterior cingulate cortex (ACC)

The paper by [Pollak Dorocic et al. \(2014\)](#) has also shown an excitatory pathway from the ACA to the DR.

12.2 Efferents

Most recently the projections to the limbic cortices have been identified as the strongest ([Linley et al., 2013](#)) ([Roberts, 2011](#)) whereas in this older publication ([Reisine et al., 1984](#)) states that the DRN projects to the striatum and caudate nucleus.

The paper by ([Vertes et al., 2010](#)) claims the DRN efferents include the VTA, SNc, LH and NAcc core. ([Nakamura, 2013](#)) stresses the projections from the DRN to the SNr, the VTA (inhibitory), amygdala, cortex (with inhibition of the mPFC) and to the NAcc where 5HT has at least partially a disinhibitory effect by targeting interneurons.

The actual effect of 5HT depends on the prominent receptor type in the target area. Some 5HT receptors are excitatory, some inhibitory and some ramp up plasticity ([Frazer and Hensler, 1999](#)).

The review paper by [Michelsen et al. \(2007\)](#) makes a distinction between dorsal, medial and ventral pathways:

12.2.1 Dorsal pathway of the DRN

All parts of the striatum ranging from the Nacc shell over core to the dorsal striatum and to a lesser extent the globus pallidus (GP).

12.2.2 Medial pathway of the DRN

The media part projects main to the SNr.

12.2.3 Ventral pathway of the DRN

This pathway targets a large number of different limbic nuclei. In order of density:

- Septum (dense)
- Amygdala (dense)
- Habenula (dense)
- Piriform, insular and frontal cortices (dense)
- Occipital, entorhinal, perirhinal, frontal orbital, anterior cingulate and infralimbic cortices (moderate)
- Thalamic and hypothalamic nuclei (dense to moderate)
- Olfactory bulb. ([Lottem et al., 2016](#)) has shown that the spontaneous activity of the olfactory cortex is suppressed by 5HT release but that odor evoked activity is unaffected by 5HT.
- Hippocampus
- Interpeduncular nucleus

- Geniculate body

12.3 Receptors

In contrast to dopamine 5HT has a vast array of different receptors. While the DRN and MRN generate a global 5HT signal the effects on different brains areas can be vastly different because of every brain area has their own 5HT receptor distribution ([Palacios et al., 1990](#)) ([Carhart-Harris and Nutt, 2017](#)). Before we go into the efferents we present the different receptors and where they are located. If not otherwise cited it's based on the review by ([Mengod et al., 2010](#)) and the classic ([Palacios et al., 1990](#)).

12.3.1 5HTR1

The 5HTR1 has numerous subclasses:

- **5HTR1A** receptors are found on excitatory/pyramidal neurons and inhibit those. This receptor has been called the "limbic" receptor because it is prominent in the limbic areas of the brain: hippocampus, lateral septum, cortex (cingulate/entorhinal) and raphe nucleus. These receptors are often co-expressed with the excitatory 5HT2A receptor. They are located on the soma or dendrite and thus can inhibit the firing of neurons ([Riad et al., 2000](#)).
- **5HTR1B** are found mainly on inhibitory neurons and inhibit those but occasionally also on pyramidal neurons. They are very prominent in the basal ganglia, in particular in the GP, SNR, VP and EP (which are the output nuclei of the BG). They are both auto and heterosynaptic receptors and are located at the axon terminals ([Riad et al., 2000](#)) and control rather the release of transmitter in contrast to 5HTR1A which control spiking.
- **5HTR1D** are located in the caudate putamen, Nacc, olfactory cortex, dorsal raphe nucleus und locus coeruleus. It's predominantly located on axon terminals of both 5HT and and non 5HT neurons and inhibit release of neurotransmitters.
- **5HTR1E** is prominent in the (entorhinal) cortex, caudate putamen and claustrum.
- **5HTR1F** has its highest levels in the cortical regions, olfactory bulb, Nacc, parascicular nucleus, thalamus, medial mamillary nucleus, hippocampus, subiculum and amygdala.

Having both inhibitory 5HT receptors on both excitatory and inhibitory neurons means that this can cancel out in average but will possibly change the dynamics of the network.

12.3.2 5HTR2

- **5HTR2A:** These receptors are excitatory and enhancing inputs when activated meaning they are located on dendrites and on the soma. These receptors are very prominent in the cortex and have been localised on GABAergic interneurons but also glutamatergic projection neurons.
- **5HTR2B:** it's function and localisation is still poorly understood
- **5HTR2C:** has only been found in the CNS and there in the choroid plexus, cortex, NAcc, hippocampus, amygdala, caudate and SNr. They are also postsynaptic but might be also presynaptic.

12.3.3 5HTR3

It's highest concentration is in the dorsal vagal complex of the brainstem.

Is a fast excitatory receptor which is mainly located in the hippocampus (and possibly amygdala) ([Palacios et al., 1990](#)) and is co-expressed with GLU receptors in the hippocampus.

Some evidence points to it controlling DA release ([Mengod et al., 2010](#)).

12.3.4 5HTR4

This receptor seems to control primarily plasticity, for both LTP and LTD ([Peñas-Cazorla and Vilaró, 2015](#)). In an experiment by ([Mlinar et al., 2006](#)) stimulation of this receptor causes LTP in hippocampal slices which were very long lasting for over 2hrs.

Even more impressive are the findings by ([Hagena and Manahan-Vaughan, 2017](#)) who show that 5HTR4 activation shifts the frequency threshold between LTD and LTP: it is generally accepted that under LFS LTD is induced whereas under HFS LTP is induced. The frequency threshold where LTD turns into LTP can be shifted by the 5HTR4 receptor. If this receptor is stimulated even lower frequencies can cause LTP which otherwise would have caused LTD!

In the rat it is located mainly in the limbic system: hippocampus, striatum, inferior colliculus, SNr, ventral pallidum, fundus striatae, olfactory tubercle, septum and amygdala. It has also high concentrations in the parietal cortex.

12.4 Activity

As shown by (Li et al., 2016): the activity increases when "when a mouse voluntarily seeks and acquires sucrose, food, sex and social interaction". 5HT neurons are activated by surprising reward events (such as VTA neurons do) and reward predicting cues is presented. The activity only drops off after the reward has been experienced. In particular the DRN activity stays active while the animal is waiting for a reward.

12.5 Behavioural studies

Numerous studies have reported that 5HT is required for delayed reward scenarios, for example where a rat has to wait in front of a dispenser to retrieve a reward (Khani and Rainer, 2016) as already mentioned above where the activity was measured during a delayed reward scenario (Li et al., 2016).

This has been combined into the proposal by (Miyazaki et al., 2012) that 5HT controls patience and reward.

Premature responding is increased after (Fletcher et al., 2007) application of a 5HT(2A) receptor antagonist and decreased after 5-HT(2C) application. In earlier studies impulsivity could also be increased by 5HT depletion (Harrison et al., 1997).

13 Ventral Tegmental Area (VTA)

Dopamine neurons make up 60-65% of VTA neurons and GABA 30-35% (Sesack and Grace, 2010). More recently also Glutamate Neurons have been identified but little is known (Morales and Margolis, 2017).

13.1 Afferents

Excitatory afferents to the VTA include the LH, PFC and pedunculopontine nucleus (PPTg). Inhibitory, modulatory projections include the NAcc and the VP (Sesack and Grace, 2010).

Electrophysiology suggest that the NAcc projects mainly on the GABAergic neurons in the VTA.

13.2 Efferents

The VTA projects to numerous targets which include (Beckstead et al., 1979):

- Nucleus Accumbens (NAcc)

- Lateral habenula (LHb), nuclei reuniens and centralis medius, and the most medial zone of the mediodorsal nucleus
- posterior hypothalamic nucleus
- Amygdala (central, lateral and medial)
- Bed nucleus of the stria terminalis,
- Nucleus of the diagonal band, and the medial half of the lateral septal nucleus
- Anteromedial (frontocingulate) cortex
- Entorhinal cortex

Although it is principally cited for its DA output GABA also plays a major role in the activity of the VTA. GABA projections from the VTA to the NAcc are reciprocated with GABA projections to the VTA. There is also a large projection of GABA neurons from the VTA to the PFC ([Carr and Sesack, 2000](#)). Local GABA neurons can also inhibit their neighbouring dopamine neurons. ([Sesack and Grace, 2010](#)) and are a strong candidate to calculate the reward prediction error ([Eshel et al., 2015](#)).

13.3 Function

It is very well known that rats self stimulate the VTA indefinitely ([Stuber and Wise, 2016](#)) and that phasic optogenetic activation of the VTA drives behavioural conditioning ([Tsai et al., 2009](#)).

In particular the pathway from the VTA to the NAc core (NAcc) and NAc shell (NAcSh) is instrumental here. VTA dopamine release in response to a rewarding stimulus induces goal-directed behaviour to acquire and consume it ([Morales and Margolis, 2017](#)).

In an experiment where DA release was artificially triggered via an optogenetic stimulation caused robust reward seeking behaviour ([Steinberg et al., 2013](#)).

13.3.1 Phasic activity

Looking at single cell recordings some neurons were excited by the reward (US), some by the reward predicting CS and some reacted to both stimuli ([Cohen et al., 2012](#)). The response to the CS became gradually stronger and the ones to the US smaller.

DA in the VTA signals a reward prediction error resembling that of TD learning which has been first suggested by (Schultz et al., 1997) and then matched quantitatively by (Bayer and Glimcher, 2005).

DA VTA neurons react strongly to unexpected rewards, these responses diminish after repeated presentation of the reward but then rather spike when a CS is presented which predicts the reward.

During omission of the reward the DA activity supposed to experience a 'dip' in activity (Takahashi et al., 2017). However, except of a few examples it is usually a reduction of the DA response after omission.

Also the DA activity won't vanish completely after a reward is expected but is diminished. This behaviour can still be matched on TD learning when using long-lasting eligibility traces (Pan et al., 2005).

However, Sadacca et al. (2016) has recently challenged this view that DA neurons code simply a reward prediction error about an experienced reward but that they also respond to putative cached values of cues which have been previously paired with a reward.

13.3.2 Tonic activity (DA)

On the other hand the VTA generates tonic activity which can be seen as a motivational value signal which is principally sent to the NAcc (Sesack and Grace, 2010; Bromberg-Martin et al., 2010) .

13.3.3 Tonic activity (GABA)

Cohen et al. (2012) found that VTA GABA neurons signalled expected reward so that this can be used to calculate the reward prediction error locally in the VTA.

Nuclei

HC	Hippocampus
PFC	Prefrontal cortex
m-PFC	Medial prefrontal cortex
OFC	Orbitofrontal cortex
DRN	Dorsal Raphe nucleus
NAcc	Nucleus Accumbens
NAcc core	Nucleus Accumbens core
NAcc shell	Nucleus Accumbens shell
m-shell	Medial Nucleus Accumbens shell
l-shell	Lateral Nucleus Accumbens shell
VTA	Ventral tegmental area
VP	Ventral pallidum
m-VP	Medial ventral pallidum
vl-VP	Ventrolateral ventral pallidum
EP	Entopeduncular nucleus
RMTg	Rostral medial tegmental nucleus
LH	Lateral hypothalamus
SNr	Substantia nigra pars reticula
BLA	Basolateral amygdala
LHb	Lateral Habenula
MRN	Midbrain reticular nucleus
PAG	periaqueductal gray
CS	superior central nucleus raphe
ACC	Anterior cingulate cortex

License

This work is licensed under the Creative Commons Attribution-ShareAlike 4.0 International License. To view a copy of this license, visit <http://creativecommons.org/licenses/by-sa/4.0/> or send a letter to Creative Commons, PO Box 1866, Mountain View, CA 94042, USA.

References

- Aghajanian, G. K., Sprouse, J. S., Sheldon, P., and Rasmussen, K. (1990). Electrophysiology of the central serotonin system: receptor subtypes and transducer mechanisms. *Annals of the New York Academy of Sciences*, 600:93–103; discussion 103.
- Alheid, G. F. (2003). Extended amygdala and basal forebrain. *Annals of the New York Academy of Sciences*, 985:185–205.
- Aquili, L., Liu, A. W., Shindou, M., Shindou, T., and Wickens, J. R. (2014). Behavioral flexibility is increased by optogenetic inhibition of neurons in the nucleus accumbens shell during specific time segments. *Learning & memory (Cold Spring Harbor, N.Y.)*, 21(4):223–231.
- Araki, M., McGeer, P. L., and McGeer, E. G. (1984). Retrograde hrp tracing combined with a pharmacohistochemical method for gaba transaminase for the identification of presumptive gabaergic projections to the habenula. *Brain research*, 304(2):271–277.
- Bari, A. and Robbins, T. W. (2013). Inhibition and impulsivity: behavioral and neural basis of response control. *Progress in neurobiology*, 108:44–79.
- Barrot, M., Sesack, S. R., Georges, F., Pistis, M., Hong, S., and Jhou, T. C. (2012). Braking dopamine systems: a new gaba master structure for mesolimbic and nigrostriatal functions. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, 32(41):14094–14101.
- Basar, K., Sesia, T., Groenewegen, H., Steinbusch, H. W. M., Visser-Vandewalle, V., and Temel, Y. (2010). Nucleus accumbens and impulsivity. *Progress in neurobiology*, 92(4):533–557.
- Bayer, H. M. and Glimcher, P. W. (2005). Midbrain dopamine neurons encode a quantitative reward prediction error signal. *Neuron*, 47(1):129–141.

- Beckstead, R. M., Domesick, V. B., and Nauta, W. J. (1979). Efferent connections of the substantia nigra and ventral tegmental area in the rat. *Brain research*, 175(2):191–217.
- Berridge, K. C. (2009). 'liking' and 'wanting' food rewards: brain substrates and roles in eating disorders. *Physiology & behavior*, 97(5):537–550.
- Berthoud, H. (2004). Mind versus metabolism in the control of food intake and energy balance. *Physiol Behav*, 81(5):781–793.
- Boulougouris, V. and Robbins, T. W. (2010). Enhancement of spatial reversal learning by 5-HT_{2C} receptor antagonism is neuroanatomically specific. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, 30(3):930–938.
- Bourdy, R. and Barrot, M. (2012). A new control center for dopaminergic systems: pulling the vta by the tail. *Trends in neurosciences*, 35(11):681–690.
- Brog, J., Salyapongse, A., Deutch, A., and Zahm, D. (1993a). The patterns of afferent innervation of the core and shell in the "accumbens" part of the rat ventral striatum: immunohistochemical detection of retrogradely transported fluoro-gold. *J Comp Neurol*, 338(2):255–278.
- Brog, J. S., Salyapongse, A., Deutch, A. Y., and Zahm, D. S. (1993b). The patterns of afferent innervation of the core and shell in the "accumbens" part of the rat ventral striatum: immunohistochemical detection of retrogradely transported fluoro-gold. *The Journal of comparative neurology*, 338(2):255–278.
- Bromberg-Martin, E. S., Matsumoto, M., and Hikosaka, O. (2010). Dopamine in motivational control: rewarding, aversive, and alerting. *Neuron*, 68(5):815–834.
- Burattini, C., Battistini, G., Tamagnini, F., and Aicardi, G. (2014). Low-frequency stimulation evokes serotonin release in the nucleus accumbens and induces long-term depression via production of endocannabinoid. *Journal of neurophysiology*, 111(5):1046–1055.
- Carhart-Harris, R. L. and Nutt, D. J. (2017). Serotonin and brain function: a tale of two receptors. *Journal of psychopharmacology (Oxford, England)*, 31(9):1091–1120.

- Carr, D. B. and Sesack, S. R. (2000). Gaba-containing neurons in the rat ventral tegmental area project to the prefrontal cortex. *Synapse (New York, N.Y.)*, 38(2):114–123.
- Cassidy, R. M. and Tong, Q. (2017). Hunger and satiety gauge reward sensitivity. *Frontiers in endocrinology*, 8:104.
- Castro, D. C., Cole, S. L., and Berridge, K. C. (2015). Lateral hypothalamus, nucleus accumbens, and ventral pallidum roles in eating and hunger: interactions between homeostatic and reward circuitry. *Frontiers in systems neuroscience*, 9:90.
- Celada, P., Puig, M. V., Casanovas, J. M., Guillazo, G., and Artigas, F. (2001). Control of dorsal raphe serotonergic neurons by the medial prefrontal cortex: Involvement of serotonin-1a, gaba(a), and glutamate receptors. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, 21(24):9917–9929.
- Christoph, G. R., Leonzio, R. J., and Wilcox, K. S. (1986). Stimulation of the lateral habenula inhibits dopamine-containing neurons in the substantia nigra and ventral tegmental area of the rat. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, 6(3):613–619.
- Cohen, J. Y., Haesler, S., Vong, L., Lowell, B. B., and Uchida, N. (2012). Neuron-type-specific signals for reward and punishment in the ventral tegmental area. *Nature*, 482(7383):85–88.
- Dalton, G. L., Phillips, A. G., and Floresco, S. B. (2014). Preferential involvement by nucleus accumbens shell in mediating probabilistic learning and reversal shifts. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, 34(13):4618–4626.
- Eshel, N., Bukwich, M., Rao, V., Hemmelder, V., Tian, J., and Uchida, N. (2015). Arithmetic and local circuitry underlying dopamine prediction errors. *Nature*, 525(7568):243–246.
- Feja, M., Hayn, L., and Koch, M. (2014). Nucleus accumbens core and shell inactivation differentially affects impulsive behaviours in rats. *Progress in neuro-psychopharmacology & biological psychiatry*, 54:31–42.
- Fletcher, P. J., Tampakeras, M., Sinyard, J., and Higgins, G. A. (2007). Opposing effects of 5-HT(2a) and 5-HT(2c) receptor antagonists in the rat and mouse on premature responding in the five-choice serial reaction time test. *Psychopharmacology*, 195(2):223–234.

- Frazer, A. and Hensler, J. (1999). Serotonin receptors. In Siegel, G., Agranoff, B., and Albers, R., editors, *Basic Neurochemistry: Molecular, Cellular and Medical Aspects*. Lippincott-Raven, Philadelphia, 6th edition.
- Gonçalves, L., Nogueira, M. I., Shammah-Lagnado, S. J., and Metzger, M. (2009). Prefrontal afferents to the dorsal raphe nucleus in the rat. *Brain research bulletin*, 78(4-5):240–247.
- Goto, Y. and Grace, A. A. (2005). Dopaminergic modulation of limbic and cortical drive of nucleus accumbens in goal-directed behavior. *Nature neuroscience*, 8(6):805–812.
- Groenewegen, H. J., Berendse, H. W., and Haber, S. N. (1993). Organization of the output of the ventral striatopallidal system in the rat: ventral pallidal efferents. *Neuroscience*, 57(1):113–142.
- Hagena, H. and Manahan-Vaughan, D. (2017). The serotonergic 5-HT₄ receptor: A unique modulator of hippocampal synaptic information processing and cognition. *Neurobiology of learning and memory*, 138:145–153.
- Harrison, A. A., Everitt, B. J., and Robbins, T. W. (1997). Central 5-HT depletion enhances impulsive responding without affecting the accuracy of attentional performance: interactions with dopaminergic mechanisms. *Psychopharmacology*, 133(4):329–342.
- Heimer, L., Zahm, D., Churchill, L., Kalivas, P., and Wohltmann, C. (1991). Specificity in the projection patterns of accumbal core and shell in the rat. *Neuroscience*, 41(1):89–125.
- Homberg, J. R. (2012). Serotonin and decision making processes. *Neuroscience and biobehavioral reviews*, 36(1):218–236.
- Hong, S. and Hikosaka, O. (2008). The globus pallidus sends reward-related signals to the lateral habenula. *Neuron*, 60(4):720–729.
- Hong, S., Jhou, T. C., Smith, M., Saleem, K. S., and Hikosaka, O. (2011). Negative reward signals from the lateral habenula to dopamine neurons are mediated by rostromedial tegmental nucleus in primates. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, 31(32):11457–11471.
- Humphries, M. D. and Prescott, T. J. (2010). The ventral basal ganglia, a selection mechanism at the crossroads of space, strategy, and reward. *Progress in neurobiology*, 90(4):385–417.

- Ikemoto, S. (2007). Dopamine reward circuitry: two projection systems from the ventral midbrain to the nucleus accumbens-olfactory tubercle complex. *Brain research reviews*, 56(1):27–78.
- Ji, H. and Shepard, P. D. (2007). Lateral habenula stimulation inhibits rat midbrain dopamine neurons through a gaba(a) receptor-mediated mechanism. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, 27(26):6923–6930.
- Juckel, G., Mendlin, A., and Jacobs, B. L. (1999). Electrical stimulation of rat medial prefrontal cortex enhances forebrain serotonin output: implications for electroconvulsive therapy and transcranial magnetic stimulation in depression. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology*, 21(3):391–398.
- Kelley, A. (2004). Ventral striatal control of appetitive motivation: Role in ingestive behavior and reward-related learning. *Neurosci Biobehav Rev*, 27(8):765–776.
- Khani, A. and Rainer, G. (2016). Neural and neurochemical basis of reinforcement-guided decision making. *Journal of neurophysiology*, 116(2):724–741.
- Kowski, A. B., Veh, R. W., and Weiss, T. (2009). Dopaminergic activation excites rat lateral habenular neurons in vivo. *Neuroscience*, 161(4):1154–1165.
- Lavezzi, H. N. and Zahm, D. S. (2011). The mesopontine rostromedial tegmental nucleus: an integrative modulator of the reward system. *Basal ganglia*, 1(4):191–200.
- Lee, H. S., Kim, M. A., Valentino, R. J., and Waterhouse, B. D. (2003). Glutamatergic afferent projections to the dorsal raphe nucleus of the rat. *Brain research*, 963(1-2):57–71.
- Li, Y., Zhong, W., Wang, D., Feng, Q., Liu, Z., Zhou, J., Jia, C., Hu, F., Zeng, J., Guo, Q., Fu, L., and Luo, M. (2016). Serotonin neurons in the dorsal raphe nucleus encode reward signals. *Nature communications*, 7:10503.
- Linley, S. B., Hoover, W. B., and Vertes, R. P. (2013). Pattern of distribution of serotonergic fibers to the orbitomedial and insular cortex in the rat. *Journal of chemical neuroanatomy*, 48-49:29–45.

- Lottem, E., Lörincz, M. L., and Mainen, Z. F. (2016). Optogenetic activation of dorsal raphe serotonin neurons rapidly inhibits spontaneous but not odor-evoked activity in olfactory cortex. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, 36(1):7–18.
- Luo, M., Zhou, J., and Liu, Z. (2015). Reward processing by the dorsal raphe nucleus: 5-HT and beyond. *Learning & memory (Cold Spring Harbor, N.Y.)*, 22(9):452–460.
- Mathur, B. N., Capik, N. A., Alvarez, V. A., and Lovinger, D. M. (2011). Serotonin induces long-term depression at corticostriatal synapses. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, 31(20):7402–7411.
- Matsumoto, M. and Hikosaka, O. (2007). Lateral habenula as a source of negative reward signals in dopamine neurons. *Nature*, 447(7148):1111–1115.
- Mengod, G., Corts, R., Vilar, M. T., and Hoyer, D. (2010). Chapter 1.6 - distribution of 5-HT receptors in the central nervous system. In Miller, C. P. and Jacobs, B. L., editors, *Handbook of the Behavioral Neurobiology of Serotonin*, volume 21 of *Handbook of Behavioral Neuroscience*, pages 123 – 138. Elsevier.
- Michelsen, K. A., Schmitz, C., and Steinbusch, H. W. M. (2007). The dorsal raphe nucleus—from silver stainings to a role in depression. *Brain research reviews*, 55(2):329–342.
- Miyazaki, K., Miyazaki, K. W., and Doya, K. (2012). The role of serotonin in the regulation of patience and impulsivity. *Molecular Neurobiology*, 45(2):213–224.
- Mlinar, B., Mascalchi, S., Mannaioni, G., Morini, R., and Corradetti, R. (2006). 5-HT₄ receptor activation induces long-lasting epsp-spike potentiation in CA1 pyramidal neurons. *The European journal of neuroscience*, 24(3):719–731.
- Mok, A. C. and Mogenson, G. J. (1974). Effects of electrical stimulation of the lateral hypothalamus, hippocampus, amygdala and olfactory bulb on unit activity of the lateral habenular nucleus in the rat. *Brain research*, 77(3):417–429.

- Morales, M. and Margolis, E. B. (2017). Ventral tegmental area: cellular heterogeneity, connectivity and behaviour. *Nature reviews. Neuroscience*, 18(2):73–85.
- Nakamura, K. (2013). The role of the dorsal raphe nucleus in reward-seeking behavior. *Frontiers in integrative neuroscience*, 7:60.
- Neufang, S., Akhrif, A., Herrmann, C. G., Drepper, C., Homola, G. A., Nowak, J., Waider, J., Schmitt, A. G., Lesch, K.-P., and Romanos, M. (2016). Serotonergic modulation of ‘waiting impulsivity’ is mediated by the impulsivity phenotype in humans. *Translational psychiatry*, 6(11):e940.
- Noonan, M. P., Kolling, N., Walton, M. E., and Rushworth, M. F. S. (2012). Re-evaluating the role of the orbitofrontal cortex in reward and reinforcement. *The European journal of neuroscience*, 35(7):997–1010.
- Ogawa, S. K., Cohen, J. Y., Hwang, D., Uchida, N., and Watabe-Uchida, M. (2014). Organization of monosynaptic inputs to the serotonin and dopamine neuromodulatory systems. *Cell reports*, 8(4):1105–1118.
- Ottersen, O. P. (1982). Connections of the amygdala of the rat. iv: Corticoamygdaloid and intraamygdaloid connections as studied with axonal transport of horseradish peroxidase. *The Journal of comparative neurology*, 205(1):30–48.
- Palacios, J. M., Waeber, C., Hoyer, D., and Mengod, G. (1990). Distribution of serotonin receptors. *Annals of the New York Academy of Sciences*, 600:36–52.
- Pan, W.-X., Schmidt, R., Wickens, J. R., and Hyland, B. I. (2005). Dopamine cells respond to predicted events during classical conditioning: evidence for eligibility traces in the reward-learning network. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, 25(26):6235–6242.
- Parent, A., Gravel, S., and Boucher, R. (1981). The origin of forebrain afferents to the habenula in rat, cat and monkey. *Brain research bulletin*, 6(1):23–38.
- Peñas-Cazorla, R. and Vilaró, M. T. (2015). Serotonin 5-HT₄ receptors and forebrain cholinergic system: receptor expression in identified cell populations. *Brain structure & function*, 220(6):3413–3434.

- Pitkänen, A., Pikkarainen, M., Nurminen, N., and Ylinen, A. (2000). Reciprocal connections between the amygdala and the hippocampal formation, perirhinal cortex, and postrhinal cortex in rat. a review. *Annals of the New York Academy of Sciences*, 911:369–391.
- Pollak Dorocic, I., Fürth, D., Xuan, Y., Johansson, Y., Pozzi, L., Silberberg, G., Carlén, M., and Meletis, K. (2014). A whole-brain atlas of inputs to serotonergic neurons of the dorsal and median raphe nuclei. *Neuron*, 83(3):663–678.
- Poller, W. C., Madai, V. I., Bernard, R., Laube, G., and Veh, R. W. (2013). A glutamatergic projection from the lateral hypothalamus targets vta-projecting neurons in the lateral habenula of the rat. *Brain research*, 1507:45–60.
- Quina, L. A., Tempest, L., Ng, L., Harris, J. A., Ferguson, S., Jhou, T. C., and Turner, E. E. (2015). Efferent pathways of the mouse lateral habenula. *The Journal of comparative neurology*, 523(1):32–60.
- Rajakumar, N., Elisevich, K., and Flumerfelt, B. A. (1993). Compartmental origin of the striato-entopeduncular projection in the rat. *The Journal of comparative neurology*, 331(2):286–296.
- Reisine, T. D., Soubrié, P., Ferron, A., Blas, C., Romo, R., and Glowinski, J. (1984). Evidence for a dopaminergic innervation of the cat lateral habenula: its role in controlling serotonin transmission in the basal ganglia. *Brain research*, 308(2):281–288.
- Riad, M., Garcia, S., Watkins, K. C., Jodoin, N., Doucet, E., Langlois, X., el Mestikawy, S., Hamon, M., and Descarries, L. (2000). Somatodendritic localization of 5-HT_{1A} and preterminal axonal localization of 5-HT_{1B} serotonin receptors in adult rat brain. *The Journal of comparative neurology*, 417(2):181–194.
- Roberts, A. C. (2011). The importance of serotonin for orbitofrontal function. *Biological psychiatry*, 69(12):1185–1191.
- Robinson, E. S. J., Dalley, J. W., Theobald, D. E. H., Glennon, J. C., Pezze, M. A., Murphy, E. R., and Robbins, T. W. (2008). Opposing roles for 5-HT_{2A} and 5-HT_{2C} receptors in the nucleus accumbens on inhibitory response control in the 5-choice serial reaction time task. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology*, 33(10):2398–2406.

- Rosenkranz, J. A. and Grace, A. A. (2002). Cellular mechanisms of infralimbic and prelimbic prefrontal cortical inhibition and dopaminergic modulation of basolateral amygdala neurons in vivo. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, 22(1):324–337.
- Sackett, D. A., Saddoris, M. P., and Carelli, R. M. (2017). Nucleus accumbens shell dopamine preferentially tracks information related to outcome value of reward. *eNeuro*, 4(3).
- Sadacca, B. F., Jones, J. L., and Schoenbaum, G. (2016). Midbrain dopamine neurons compute inferred and cached value prediction errors in a common framework. *eLife*, 5.
- Saddoris, M. P., Cacciapaglia, F., Wightman, R. M., and Carelli, R. M. (2015). Differential dopamine release dynamics in the nucleus accumbens core and shell reveal complementary signals for error prediction and incentive motivation. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, 35(33):11572–11582.
- Sah, P., Faber, E. S. L., Lopez De Armentia, M., and Power, J. (2003). The amygdaloid complex: anatomy and physiology. *Physiological reviews*, 83(3):803–834.
- Santana, N. and Artigas, F. (2017). Laminar and cellular distribution of monoamine receptors in rat medial prefrontal cortex. *Frontiers in neuroanatomy*, 11:87.
- Schoenbaum, G., Roesch, M. R., Stalnaker, T. A., and Takahashi, Y. K. (2009). A new perspective on the role of the orbitofrontal cortex in adaptive behaviour. *Nat. Rev. Neurosci.*, 10(12):885–92.
- Schultz, W., Dayan, P., and Montague, P. R. (1997). A neural substrate of prediction and reward. *Science (New York, N.Y.)*, 275(5306):1593–1599.
- Sego, C., Gonçalves, L., Lima, L., Furigo, I. C., Donato, J., and Metzger, M. (2014). Lateral habenula and the rostromedial tegmental nucleus innervate neurochemically distinct subdivisions of the dorsal raphe nucleus in the rat. *The Journal of comparative neurology*, 522(7):1454–1484.
- Sesack, S. R. and Grace, A. A. (2010). Cortico-basal ganglia reward network: microcircuitry. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology*, 35(1):27–47.

- Shabel, S. J., Proulx, C. D., Trias, A., Murphy, R. T., and Malinow, R. (2012). Input to the lateral habenula from the basal ganglia is excitatory, aversive, and suppressed by serotonin. *Neuron*, 74(3):475–481.
- Shen, X., Ruan, X., and Zhao, H. (2012). Stimulation of midbrain dopaminergic structures modifies firing rates of rat lateral habenula neurons. *PloS one*, 7(4):e34323.
- Smith, K. S., Tindell, A. J., Aldridge, J. W., and Berridge, K. C. (2009). Ventral pallidum roles in reward and motivation. *Behavioural brain research*, 196(2):155–167.
- Sparta, D. R. and Stuber, G. D. (2014). Cartography of serotonergic circuits. *Neuron*, 83(3):513–515.
- Stanley, B., Willett, V., Donias, H., Ha, L., and Spears, L. (1993). The lateral hypothalamus: a primary site mediating excitatory amino acid-elicited eating. *Brain Res*, 630(1-2):41–49.
- Stanley, B. G., Urstadt, K. R., Charles, J. R., and Kee, T. (2011). Glutamate and gaba in lateral hypothalamic mechanisms controlling food intake. *Physiology & behavior*, 104(1):40–46.
- Steinberg, E. E., Keiflin, R., Boivin, J. R., Witten, I. B., Deisseroth, K., and Janak, P. H. (2013). A causal link between prediction errors, dopamine neurons and learning. *Nature neuroscience*, 16(7):966–973.
- Stuber, G. D. and Wise, R. A. (2016). Lateral hypothalamic circuits for feeding and reward. *Nature neuroscience*, 19(2):198–205.
- Swanson, L. W. (2003). The amygdala and its place in the cerebral hemisphere. *Annals of the New York Academy of Sciences*, 985:174–184.
- Swanson, L. W. and Petrovich, G. D. (1998). What is the amygdala? *Trends in Neurosci*, 21(8):323–331.
- Takahashi, Y. K., Batchelor, H. M., Liu, B., Khanna, A., Morales, M., and Schoenbaum, G. (2017). Dopamine neurons respond to errors in the prediction of sensory features of expected rewards. *Neuron*, 95(6):1395–1405.e3.
- Tremblay, L. and Schultz, W. (1999). Relative reward preference in primate orbitofrontal cortex. *Nature*, 398(6729):704–708.

- Tsai, H.-C., Zhang, F., Adamantidis, A., Stuber, G. D., Bonci, A., de Lecea, L., and Deisseroth, K. (2009). Phasic firing in dopaminergic neurons is sufficient for behavioral conditioning. *Science (New York, N.Y.)*, 324(5930):1080–1084.
- Tsutsui-Kimura, I., Ohmura, Y., Izumi, T., Matsushima, T., Amita, H., Yamaguchi, T., Yoshida, T., and Yoshioka, M. (2016). Neuronal codes for the inhibitory control of impulsive actions in the rat infralimbic cortex. *Behavioural brain research*, 296:361–372.
- Usuda, I., Tanaka, K., and Chiba, T. (1998). Efferent projections of the nucleus accumbens in the rat with special reference to subdivision of the nucleus: biotinylated dextran amine study. *Brain research*, 797(1):73–93.
- Vertes, R. P., Hoover, W. B., and Rodriguez, J. J. (2012). Projections of the central medial nucleus of the thalamus in the rat: node in cortical, striatal and limbic forebrain circuitry. *Neuroscience*, 219:120–136.
- Vertes, R. P., Linley, S. B., and Hoover, W. B. (2010). Pattern of distribution of serotonergic fibers to the thalamus of the rat. *Brain structure & function*, 215(1):1–28.
- Wallace, M. L., Saunders, A., Huang, K. W., Philson, A. C., Goldman, M., Macosko, E. Z., McCarroll, S. A., and Sabatini, B. L. (2017). Genetically distinct parallel pathways in the entopeduncular nucleus for limbic and sensorimotor output of the basal ganglia. *Neuron*, 94(1):138–152.e5.
- Wikenheiser, A. M. and Schoenbaum, G. (2016). Over the river, through the woods: cognitive maps in the hippocampus and orbitofrontal cortex. *Nature Reviews Neuroscience*, 17:513–523.
- Zahm, D. (2000). An integrative neuroanatomical perspective on some sub-cortical substrates of adaptive responding with emphasis on the nucleus accumbens. *Neurosci Biobehav Rev*, 24(1):85–105.
- Zhou, J., Jia, C., Feng, Q., Bao, J., and Luo, M. (2015). Prospective coding of dorsal raphe reward signals by the orbitofrontal cortex. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, 35(6):2717–2730.