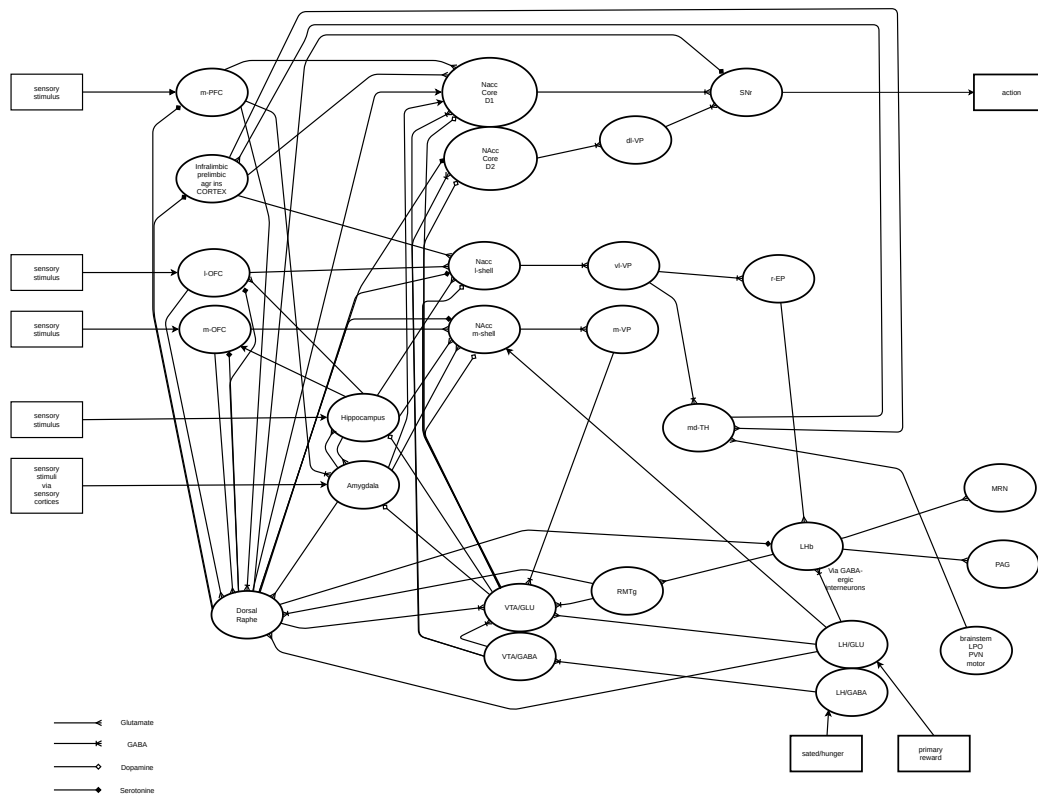


# Limbic system map

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Revision 1.0.0

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/>

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# 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 spurious result can still trigger a large amount of publications and again requires stepping back and evaluating publications with possibly at a 10 year timeframe to check which of these findings have been reproduced from different sources and over years.

- **Closed loop / Embodied:** Crucially, an animal needs to act in its environment because the limbic system makes an animal finding rewards (and avoiding punishments). This means that the animal generates actions and evaluates the resulting 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 embedded in its environment.

In summary: human curation of data 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 focuses 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 NAcc 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 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
- perihirnal 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 pre-optic 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 ([Brog 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 theorised 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 (LHb)

### 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 glutamatergic ([Shabel et al., 2012](#)).

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

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 glutamatergic 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 import 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 glutamatergic 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 glutamatergic 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 and locus ceruleus. It's predominantly located on axon terminals of both 5HT 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 NAcc core (NAcc) and NAcc 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

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

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