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Functional neuroanatomical review of the ventral tegmental area

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ABSTRACT

The ventral tegmental area (VTA) and substantia nigra pars compacta (SNc) are assumed to play a key role in dopamine-related functions such as reward-related behaviour, motivation, addiction and motor functioning. Although dopamine-producing midbrain structures are bordering, they show significant differences in structure and function that argue for a distinction when studying the functions of the dopaminergic midbrain, especially by means of neuroimaging. First, unlike the SNc, the VTA is not a nucleus, which makes it difficult to delineate the structure due to lack of clear anatomical borders. Second, there is no consensus in the literature about the anatomical nomenclature to describe the VTA. Third, these factors in combination with limitations in magnetic resonance imaging (MRI) complicate VTA visualization. We suggest that developing an MRI-compatible probabilistic atlas of the VTA will help to overcome these issues. Such an atlas can be used to identify the individual VTA and serve as region-of-interest for functional MRI.

1. Introduction

The dopaminergic system is associated with many cognitive functions such as reward-based and associative learning (MacInnes et al., 2016; Schultz, 2013) motivation (Berridge and Kringelbach, 2013; Salamone and Correa, 2012), memory (Gillies et al., 2014; Kahn and Shohamy, 2013), and cognitive control in decision-making (Cools and D'Esposito, 2011; Goschke and Bolte, 2014). Human and non-human studies of the DA-system have indicated the importance of two dopamine (DA)–producing structures in the midbrain: the ventral tegmental area (VTA) and the substantia nigra pars compacta (SNc) (Bär et al., 2016; Edwards et al., 2017; Hauser et al., 2017; Howe and Dombeck, 2016; Krebs et al., 2011; Oades and Halliday, 1987; Zhang et al., 2010). Although, some studies treat the VTA and the SN/SNc as a single midbrain DA-complex (D'Ardenne et al., 2012; Düzel et al., 2010; Krebs et al., 2009), the majority of the literature does not indicate a structural and functional unity of VTA and SNc. Although there is likely to be functional and structural overlap between VTA and SNc, it has been shown that they are developmentally, morphologically, and functionally distinct (Fu et al., 2016; van Domburg & ten Donkelaar, 1991). Within this view, the VTA and SNc are separate brain areas that are believed to hold key roles in the neuromodulation of DA related behavior via dopaminergic pathways (Gershman, 2013; Montague et al., 2004; Utter and Basso, 2008). However, although evidence for the SNc as an anatomical and functionally defined region is rather consistent, for the VTA the picture is much more divergent. For example, at the anatomical level, different terminology and definitions exist (Ding et al., 2016; Hall et al., 2014; Halliday and Törk, 1986; Hasirci, Maldonado-Devincci, Beattie, O'Buckley and Morrow, 2017; Mai et al., 2016; McRitchie et al., 1996; Morales and Margolis, 2017; Swanson, 1982). In addition, recent data revealed that neural transmission, in the VTA especially, is not restricted to DA alone (Morales and Margolis, 2017; Root et al., 2016) and that it is functionally involved in more than just DA-related behavior. This is further emphasized by the fact that, at the cellular level, the VTA consists of a heterogeneity of neurons that are organized in neural populations that exhibit gradual rather than abrupt transitions, which makes it hard to define VTA's borders.

Below we will address the divergent findings from studies that investigate the function and structure of the VTA and show that a clear anatomical definition of the VTA is lacking, which hampers in-vivo imaging studies of the VTA as well as comparison of results between studies and species. In order to facilitate future research and comparison of research findings, we suggest to agree on an anatomical definition of the VTA and to develop a high-resolution probabilistic magnetic resonance imaging (MRI) atlas of the VTA.

1.1. Dopaminergic pathways

Although SNc and VTA exhibit connections to mutual regions, such as limbic and brain stem nuclei, they differ in the strength of connections to

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striatal and cortical regions (Williams and Goldman-Rakic, 1998; van Domburg & ten Donkelaar, 1991; Watabe-Uchida et al., 2012), which have been historically organized into nigrostriatal and mesocorticolimbic pathways. The nigrostriatal pathway comprises the dopaminergic projections arising from the SNc to the dorsal striatum (Haber and Fudge, 1997; van Domburg & ten Donkelaar, 1991), hence is part of the basal ganglia loop. The mesocorticolimbic pathways consist of a mesolimbic and a mesocortical part, in which dopaminergic projections from the VTA target the nucleus accumbens (NAcc) in the ventral striatum (Edwards et al., 2017; Haber, 2014; Leemburg et al., 2018; Morales and Margolis, 2017; Yang et al., 2018) and the prefrontal cortex (PFC) respectively (for more information on connectivity, see '1.3 Connectivity and function of neurons in the dopaminergic midbrain'; Ikemoto, 2007; Morales and Margolis, 2017; Oades and Halliday, 1987; Yang et al., 2018).

Functional distinction of the dopaminergic pathways. Both the nigrostriatal and mesocorticolimbic pathways are believed to play a role in different brain functions. Dysfunction of the DA system in the nigrostriatal pathway exclusively has been associated with deficits in locomotion, as seen in neurogenerative disorders such as Parkinson's disease. The mesocorticolimbic pathway receives much attention due to its associated behavioral heterogeneity, as it is involved in cognition, motivation and addiction (Aransay, Rodríguez-López, García-Amado, Clascá and Prensa, 2015; Edwards et al., 2017; Hauser et al., 2017; Yang et al., 2018). Electrophysiology studies show evidence of a functional distinction associated with the origin of each pathway. For example, Howe and Dombeck (2016) were able to show in mice that locomotion-related responses can be found for all targets that originate from the SNc, but only few for neurons that emerge from the VTA. In contrast, the authors show that unexpected reward elicits a response in striatal neurons, but only for those neurons originating from the VTA and not for neurons that originate from the SNc.

However, despite the evidence showing the role of the nigrostriatal pathway in motor behavior, it has been suggested that the nigrostriatal pathway is involved in reward systems and addiction as well (Wise, 2009), making the functional distinction of the pathways less clear. Furthermore, it is assumed that the two pathways interact in modulating complex behavior, like cognitive control. Along this line, Goschke and Bolte (2014) proposed that control emerges by integrating flexible, but also stimulus-dependent behavioral tendencies moderated by the nigrostriatal pathway, and persistent, goal-directed behavioral tendencies moderated by the mesocortical pathway. Along the same lines, Cools and D'Esposito, 2011 have claimed, that the striatum targeted by the nigrostriatal pathway supports flexibility and the prefrontal cortex targeted by the mesocortical pathway propagates goal-persistence. These theoretical accounts of cognitive control suggest that prefrontal and striatal regions represent two (more or less) opposing systems, each promoting persistence or flexibility respectively, and whose interactions build a continuum of cognitive control that is supposed to generate (most) optimal behavior in any given situation.

Besides the substantially differential connectivity profile, the functional distinction between the nigrostriatal and the mesocorticolimbic pathway is likely to be influenced as well by a difference in distributions of DA-receptors in the non-human and human primate brain. Although both, D1-family and D2-family receptors, can be found along the targets of both pathways in which their presence and interactions are crucial for healthy brain functioning (Surmeier et al., 2007), D1-family receptors dominate in the prefrontal targets of the mesocortical pathway and D2-family receptors in the striatal targets of the nigrostriatal pathway (Hurd et al., 2001; Lidow et al., 1991; Takahashi et al., 2008). Findings suggest that varying distributions of D1 and D2 receptors in prefrontal and striatal areas, respectively, affect cognitive functioning by modulating frontal and striatal DA levels (Cools, 2008; Cools and D'Esposito, 2011; Colzato, van den Wildenberg, Van der Does and Hommel, 2010; Colzato, van den Wildenberg and Hommel, 2013; Colzato et al., 2011; Mier et al., 2010). Again, these studies support the claim of a functional dissociation between the mesocortical and nigrostriatal dopaminergic pathway while emphasizing the importance of the interaction of the two pathways for the generation of behavior.

Although these accounts suggest a structural and functional distinction between the DA pathways and their sources, Haber (2014) suggests that the dopaminergic nigrostriatal pathway is not restricted to SNc neurons but extends to VTA neurons, consistent with the findings from Howe and Dombeck (2016). In line with this idea, VTA and SN(c) are sometimes treated as a single midbrain DA complex (D'Ardenne et al., 2012; Düzel et al., 2010; Krebs et al., 2009). Yet, in the following we show that there is a body of evidence indicating a distinction between the dopaminergic midbrain structures.

1.2. Cytoarchitecture & neurochemistry

Developmentally, the neurons of both midbrain DA structures share an embryological origin (Halliday and Törk, 1986), but their DA precursor cells are already controlled by different transcription factors in the fetus stage of human development (Blaess and Ang, 2015; Fu et al., 2016; Hegarty et al., 2013; Veenvliet and Smidt, 2014). While the SNc neurons develop towards a nucleus with homologous neurochemistry, with a high cell density of large, pigmented DA cells, the VTA is comprised of a number of cell populations that are highly heterogeneous with respect to their neurochemical profile and cytoarchitectonic appearance (Fu et al., 2016; Halliday and Törk, 1986; McRitchie et al., 1996; Morales and Margolis, 2017). Yet, it should be noted that first, there are transcription factors expressed by DA precursor cells that lack in regional specificity, in line with the findings by Howe and Dombeck (2016) and Haber (2014). And second, most knowledge of the cytoarchitecture of VTA neurons stems from animal work, as there are limitations in the availability of intact human post-mortem tissue of the ventral tegmentum (Root et al., 2016), rendering generalization of animal findings to humans, problematic.

Classically, both, VTA and SNc are predominantly associated with DA due to the high density of DA-producing neurons. However, anatomical studies have identified other types of neurons in the area of the dopaminergic midbrain. The human SNc has a high density of dopaminergic neurons that are barely intermixed with other neurons, such as glutamatergic or combinatorial neurons (Root et al., 2016).

Compared to the SNc the VTA is less homogeneous: While >80% of the human SNc consists of DA neurons (Root et al., 2016), in the human VTA only 50–80% of the cells are identified as DA neurons (Root et al., 2016), while the rest are GABA-ergic (30%), glutamatergic (5%) (Pignatelli and Bonci, 2015; Root et al., 2016; Yoo et al., 2016), or combinatorial neurons (Morales and Margolis, 2017; Root et al., 2016). This variety of neuron types is associated with an increased functional complexity. For example, Yang et al. (2018) were able to show that GABA mediates powerful feedback loops between NAcc and VTA by inhibition or disinhibition of specific VTA subpopulations, which is thought to generate motivated behavior in mice (see for review Morales and Margolis, 2017).

This heterogeneity in the cytoarchitectonic and neurochemical profile of the VTA might underlie the differences in VTA masks that are developed as regions-of-interest (ROI) in functional imaging studies (see section '4. Imaging & delineation of the DA complex'). Furthermore, it drives the difficulty of defining clear boundaries in structural studies as well. The lack of clear boundaries is evident when considering that, in contrast to the SNc, the VTA is rather a region than a nucleus (Fu et al., 2012; McRitchie et al., 1996; Oades and Halliday, 1987). This becomes apparent in the gradual (rather than nucleoid) transformation in the distribution of the different types of DA cells, namely A10 and A9 cells (Oades and Halliday, 1987) that form the basis of the VTA and SNc distinction (Aransay et al., 2015; Cavalcanti et al., 2016; Dahlström and Fuxe, 1964; Fu et al., 2016; Hall et al., 2014; Halliday et al., 2012; Ungerstedt, 1971). Consequently, even neurobiologists are challenged when it comes to delineating the VTA (Holly and Miczek, 2016; Ikemoto, 2007; Oades and Halliday, 1987). In addition, delineation is further

hampered by variations in the nomenclature of the VTA (see '3. VTA terminology'; Cavalcanti et al., 2016; Fu et al., 2016; Hall et al., 2014; McRitchie et al., 1996; Morales and Margolis, 2017; van Domburg & ten Donkelaar, 1991).

Given the above, it should be noted that, first, the VTA is not solely dopaminergic and, second, that its heterogeneity is not limited to behavior but is already reflected in its cytoarchitectonic and neurochemical profile. Finally, the lack of clear borders in the VTA complicates understanding of the VTA's structure and function due to challenges in defining the VTA also in post-mortem brains.

1.3. Connectivity and function of neurons in the dopaminergic midbrain

Evidence in favour of a functional distinction of the dopaminergic neurons in the midbrain comes from studies on rodents and non-human primates: Lesions of DA neurons in the SNc are primarily associated with impairments of fine motor functions (Pioli et al., 2008), while pathological degeneration of DA neurons in SNc is accompanied by Parkinsonism (Damier et al., 1999; Vaillancourt et al., 2009). In contrast, DA neurons in the VTA code positive reward prediction error in non-human primates (Goschke and Bolte, 2014; Schultz, 2007, 2013) as well as incentive salience in rats (i.e., 'wanting'; Berridge and Kringelbach, 2013; Morales and Margolis, 2017; Smith et al., 2011). Lesions in the VTA impair the ability to control reproductive and ingestive behavior in mice (Oades and Halliday, 1987), and cause perseverative and compulsive behavior in rats (Pioli et al., 2008). Hence, findings from work on the animal dopaminergic midbrain indicate a distinction between DA cells located in VTA and SNc based on their functional involvement, which is in line with the idea of functionally distinct DA-pathways originating from the DA cells of the VTA and SNc.

Functional distinction of VTA and SNc is likely to be caused by differences in cell morphologies with respect to functional projections. Although DA neurons in both, the VTA and SNc, are connected to a great extend with mutual brain regions they differ in the quality of their connections (Morales and Margolis, 2017; Watabe-Uchida et al., 2012). In mice, the SNc is primarily connected with the dorsal striatum in a very powerful loop and most SNc DA neurons receive extensive GABAergic input from neurons located in the dorsal striatum (Watabe-Uchida et al., 2012) and project back to striatal target neurons via highly dense connections (Halliday et al., 2012; Parent and Hazrati, 1995). This primary connection between the striatum and SNc is also reflected in a vast neuronal axon arborization of SNc DA neurons that from a high number of synapses on striatal target neurons in rats (Fu et al., 2016; Matsuda et al., 2009). Findings from a recent tractography and fMRI study on human subjects suggest a functional topography in the organization of nigrostriatal projections, reflecting limbic, associative and cognitive functions respectively (Zhang et al., 2017). Additional glutamatergic input onto SNc neurons comes from somatosensory and motor cortices and the subthalamic nucleus. The SNc also receives input from pallidal projections, the amygdala, and the dorsal raphe nucleus. In addition, the GABAergic neurons in the SNr also synapse on SNc DA neurons in rodents, non-human and human primates (Petri et al., 2002; Watabe-Uchida et al., 2012).

In contrast to the nigrostriatal neurons in the SNc that project to the striatum in a relatively homogenous fashion, the mesocorticolimbic pathway in rodents arises from VTA neurons with various morphologies, as Aransay et al. (2015) showed using single neuron tracing in mice: While some neurons project a single axon to one brain area exclusively (mesocortical, mesolimbic and mesostriatal neurons), other single neurons project to multiple cortical and limbic areas simultaneously (mesocorticolimbic neurons). VTA neurons projecting to the brain stem exhibit multibranched axons also connecting to various forebrain structures. Another major VTA neuron target, specifically of glutamatergic VTA neurons, is the medial PFC (mPFC; Morales and Margolis, 2017).

In contrast to the SNc, the VTA is not predominantly connected to a particular brain region although its main target neurons are located in the ventral striatum, namely the NAcc. Yet, while the NAcc is a major input structure VTA neurons also receive input from various brain regions and are highly connected to other subcortical structures. Besides the NAcc the main input arises primarily from the dorsal raphe, followed by pallidal regions, the central nucleus of the amygdala, hypothalamic regions, the dopaminergic retrorubral field and the parasubthalamic nucleus as shown in mice (Watabe-Uchida et al., 2012). These, and other areas' glutamatergic and GABAergic axons synapse onto VTA DA and non-DA neurons rendering VTA neuronal connectivity highly heterogeneous and complex. It has recently been suggested that these projections form specific VTA circuits that contribute to motivated behavior (Morales and Margolis, 2017).

However, findings from rodent studies using techniques such as viral and molecular tracers and electrophysiology did not yet reveal sufficient consistent findings for clear mapping of the VTAs connectivity profile, especially in the case of the human VTA. For example, it is still unclear whether the NAcc input is mainly on VTA GABA or DA neurons and whether mPFC neurons synapse on VTA DA neurons that project back to the mPFC or to the NAcc (Morales and Margolis, 2017). The challenges in mapping VTA input using viral tracers is likely to be caused by the variety of neurons in the VTA and the lack of clear boundaries, as the viral tracer can spill over to surrounding neurons. Further, the diverse neurons in the VTA (VTA DA, GABA and glutamate neurons) contribute to the complex local VTA micro circuitry by regulating activity of other VTA neurons, and thus complicating understanding of the functional connectivity of VTA neurons. Additionally, it is still unclear how findings from animal studies translate to humans.

1.4. Functional organisation of the dopaminergic midbrain

Given the cellular heterogeneity found in the VTA the question arises whether these differences are reflected in the functional organisation of DA cells. That is, are there functional subdivisions in the VTA that suggest a specific motor, limbic or cognitive profile, as has been shown in the SNc (Haber, 2014; Zhang et al., 2017).

Although a clear functional topography in terms of distinct subdivision has not been identified, data imply a gradual, mostly medio-lateral, transition in the neuronal composition of the VTA (Haber, 2014; Morales and Margolis, 2017; Phillipson, 1979). This topography is likely to reflect a functional topography that is further circumstantiated by receptor-specificity: Evidence in favour of a medio-lateral topography comes from investigations on the mediating effects of GABA on the activity of certain VTA subpopulations, using a range of electrophysiological and histological techniques. For example, Edwards et al. (2017) showed that mouse VTA-GABA and VTA-DA neurons are inhibited via different GABA-receptor types, namely GABA-A and GABA-B receptors respectively. This finding could further be elucidated by Yang et al. (2018) who revealed GABA-mediated pathways between specific NAcc subdivision to certain GABA and DA VTA neural populations representing a feedback loops between the structures in mice. While the powerful pathway connecting the medial shell of the NAcc with the VTA mainly converges in the medial VTA on both GABA and DA neurons, the weaker pathway originating in the lateral NAcc exclusively projects to GABA neurons located in the lateral VTA. With respect to variety of neuron types in the VTA it is likely that VTA functional topography is not restricted to GABA, since VTA DA neurons also contain a number of DA receptor types which renders them also sensitive to DA, besides releasing it (van der Velden et al., 2017).

Taken together, findings indicate a gradual medio-lateral functional topography in the VTA. However, diversity in VTA input paired with the diversity of neuron types located in the VTA complicates full understanding of the (functional) connectivity and micro circuitry of the VTA. This heterogeneity makes it difficult to investigate and define a complete structural and functional profile of the VTA in the midbrain, which is clearer for the SNc that elicits a more homologous histological and connectivity profile.

In sum, there is broad interest in dopaminergic functioning in the brain. The two main DA-producing and neighboring midbrain structures, VTA and SNc, provide input to two main dopaminergic pathways: the nigrostriatal and the mesocorticolimbic pathway. These pathways are thought to be functionally distinct due to the differences in function of their main axonal targets, dorsal striatum and prefrontal cortex, respectively. Animal studies suggests a dissociation between neurons located in the VTA versus SNc but given the lack of clear borders in the VTA, this dissociation is likely to be gradual instead of clear-cut.

Another factor that is likely to influence the functional distinction of the neurons located in the VTA and SNc is the relatively large difference in neuronal heterogeneity in the VTA compared to the more homologous SNc. As a consequence, the VTA is associated with a much larger behavioral diversity compared to the SNc. As most of our knowledge on the dopaminergic midbrain stems from animal work, it remains to be seen how dissociations from animal findings translate to humans, especially in view of considerable anatomical differences between species in the fact that the human VTA is much more complex than the VTA of rodents (Halliday et al., 2012; Watabe-Uchida et al., 2012).

2. Topological atlases

Historically, functional VTA research on the living brain was restricted to animal work. Today, advances in neuroimaging allow to test more and more findings from animal studies non-invasively in human subjects, which is reflected in a recent increase in fMRI studies focusing on VTA activity. Yet, in contrast to the SN, there is a lack in availability of digital, anatomically precise VTA atlases derived from high-resolution data that serve as a visual aid in the identification of the full VTA body in MRI data.

While the issue of identification of the entire VTA body might be less import for animal studies, such as studies in which the VTA is identified by its electrophysiological profile using cell-recordings (Holly and Miczek, 2016), the field of human neuroimaging relies on visual identification or, if available, topological or digital atlases. Available atlases provided by neuroimaging software, such as FMRIB Software Library 5.0 (FSL), provide no information on the location of the VTA. Consequently, researchers depend on extensive anatomical knowledge for visual identification of the VTA.

Hence, for reasons of anatomical reliability, a three-dimensional description of the structure is necessary. Topological brain atlases, that are based on precise cytoarchitectonic reconstructions of an entire brain (e.g. Ding et al., 2016; Mai et al., 2016; Paxinos and Huang, 1995), can be used to provide priors of shape and size of a structure which in turn can be employed to identify nuclei on MR images. However, different atlases are not always in accordance with each other when it comes to the shape and volume of the VTA. This difference is also reflected in the nomenclature applied by the authors.

Another reason for the inconsistency of VTA representations across topological atlases is that topological atlases fail to account for inter-individual variations in anatomy, as they are based on only a single brain (Cabezas et al., 2011; Ding et al., 2016; Mai et al., 2016; Paxinos et al., 2012). Recent developments in neuroscience try to overcome this lack of incorporating anatomical variability by constructing digital brain atlases based on a higher number of subjects, referred to as probabilistic atlases (Cabezas et al., 2011). By using in-vivo, high-resolution MRI, such as 7 T MRI, probabilistic digital atlases of human anatomy are computed using segmentations of regions – of – interest (ROIs) on images of multiple individuals. The resulting probabilistic maps of those ROIs can be registered to standard space, such as the Montreal Neuroscience Institute (MNI152) brain (Evans et al., 1994; Forstmann and Wagenmakers, 2015), which in turn allows for transfer and comparison between different experimental findings. However, in contrast to the SN, currently there is no (probabilistic) MRI atlas for the VTA that is based on precise anatomical reconstruction and maximal resolution we can gain with structural MRI today. Thus, researchers that aim to provide anatomical precision in their neuroimaging efforts are restricted to the use of topological atlases for localization and delineation of the individual VTA. Yet, the VTA representations in topological atlases differ which is likely to be due to differences in VTA terminology, besides interindividual variability in anatomy.

3. VTA terminology

Historically, the VTA was first identified in the opossum and labeled nucleus tegmenti ventralis (Tsai, 1925). Follow-up studies identified corresponding areas in the cat, rat, non-human primate, and human, and labeled an increasing number of distinct cell populations in the midbrain region (Fallon and Moore, 1978; German and Manaye, 1993; Halliday and Törk, 1986; Olszewski and Baxter, 1954; Phillipson, 1979; Poirier et al., 1983; Taber, 1961). Yet, the nomenclature of the VTA, and component nuclei, differ between cytoarchitecture studies on the VTA to a substantial extend (see Table 1). Many neuroimaging studies refer to the VTA as the entire region, defined by its location with respect to landmark structures (Ballard et al., 2011; Barry et al., 2013; D'Ardenne et al., 2008; Eapen and Gore, 2009; Murty et al., 2014), whilst others, mainly cytoarchitecture studies, distinguish between the arrangement of neural populations of the overall VTA and refer to its components as anatomically distinct nuclei (see Fig. 1; Ding et al., 2016; Hall et al., 2014; Hasirci et al., 2017; Mai et al., 2016; McRitchie et al., 1996; Morales and Margolis, 2017; Paxinos et al., 2012). This lack in agreement in VTA nomenclature was already present in early cytological studies (Halliday and Törk, 1986; McRitchie et al., 1996; Swanson, 1982) and this issue remains unsolved (see Fig. 1).

This lack of common nomenclature not only makes it difficult to compare studies (Morales and Margolis, 2017), it naturally also has implications for the assumed size and shape of the VTA. With regard to the VTA and its role in many cognitive and motivational processes (Berridge and Kringelbach, 2013; Colzato et al., 2016; Cools and D'Esposito, 2011; Goschke and Bolte, 2014; Salamone and Correa, 2012; Schultz, 2013), a clear understanding of the anatomical appearance of this region is essential to reliably report activity in this region.

Although the VTA was originally described as a single brainstem nucleus (Tsai, 1925), a broader VTA definition has been introduced based on the findings of Dahlström and Fuxe (1964). The authors identified distinct A8, A9, and A10 cell populations in the rodent midbrain and introduced the term VTA to refer to the midbrain region containing A10 DA neurons and the nucleus described by Tsai (1925). However, recent findings seem to support the 'nucleus-like' VTA which is not in agreement with Dahlström and Fuxe (1964) VTA terminology (Ding et al., 2016; Hall et al., 2014; Halliday et al., 2012; Hasirci et al., 2017; Mai et al., 2016; McRitchie et al., 1996; Paxinos et al., 2012). For clarity, in the following paragraphs, the term *VTA* is used to refer to the entire A10 region, whereas *VTA nucleus* is used for a specific cell population within the A10 region.

In general, the VTA can be roughly divided into a lateral and medial part (Björklund and Dunnett, 2007; Hall et al., 2014; Morales and Margolis, 2017; Zhang et al., 2010). The parabrachial pigmented nucleus (PBP) is located most laterally of all VTA nuclei, so that it is frequently referred to as the *lateral VTA*, sometimes in combination with the paranigral nucleus (PN; Halliday and Törk, 1986; Morales and Margolis, 2017) or the rostral VTA (VTAR; Paxinos and Watson, 2007; Fu et al., 2012; Paxinos et al., 2012; Medeiros et al., 2016; Root et al., 2016; Viereckel et al., 2016). The lateral VTA comprises, according to (Swanson, 1982), the region that Tsai (1925) originally defined as VTA (*Nc. Tegmentalis ventralis*) and represents the area that is labeled as VTA in rodents by McRitchie et al. (1996). Recent studies that refer to a VTA *nucleus* within the VTA region, define this nucleus to be located between the PN and PBP (Ding et al., 2016; Hall et al., 2014; Halliday et al., 2012; Mai et al., 2016; McRitchie et al., 1996; Paxinos et al., 2012; Paxinos and Huang, 1995). Accordingly, the VTA nucleus can be considered part of the lateral or mediolateral VTA (Fig. 2D). Whether this nucleus

Table 1
Ventral tegmental area component nuclei reported in histological studies.

Year	Author	Species	N	PBP	PN	IF	RLi	CLi	VTAR	PIF	VTA nc	PaP	VTAC	Total
1961	Taber	C	5	x	X		x							1
1978	Fallon & Moore	R	10	x	X						x[1]			4
1979	Phillipson	R	–	x	X	x		x						4
1983	Poirier et al.	C	–	x[2]	X	x	x	x			x[3]			5
		R	–	x[2]	X	x		x			x[3]			5
		P	–	x[2]	X	x		x			x[3]			5
1986	Halliday & Törk	P	5	x	X	x	x	x						5
		C	6	x	X	x	x	x						5
		P	10	x	X	x	x	x						5
		H	1	x	X	x	x	x						5
1993	German & Manaye	R	4	x	X	x	x	x			x			6
1996	McRitchie et al.	H	–	x	X	x	x	x			x	x		7
2007	Paxinos & Watson	R	–	x	X				x	x				4
2008	Ferreira et al.	R	–	x	X	x	x	x					x	6
2008	Nair-Roberts et al.	R	10	x	X	x	x			x				5
2012	Fu et al.	M	15	x	X	x	x	x	x	x				7
2014	Hall et al.	H	40	x	X	x	x	x			x	x		7
2015	Aransay et al.	R	16	x	X	x	x	x	x	x			x	8
2016	Ding et al.	H	1	x	X	x				x	x			5
2016	Mai et al.	H	1	x	X	x	x	x			x	x		7
2016	Cavalcanti et al.	P	–	x	X	x	x	x	x	x				7
2017	Hasirci et al.	H	65	x	X	x	x	x			x	x		7

1 VTA of Tsai; 2 PBP considered part of SN; 3 nucleus proper of the VTA; Abbreviations: VTA nc = VTA nucleus; VTAR = rostral VTA; VTAC = caudal VTA; PBP = Parabrachial pigmented nucleus; PN = paranigral nucleus; IF = interfascicular nucleus; PaP = Parapeduncular nucleus; PIF = Parainterfascicular nucleus; RLi = Rostral linear nucleus; CLi = caudal (or central) linear nucleus; C = Cat; R = Rat; M = Mice; H = Human.

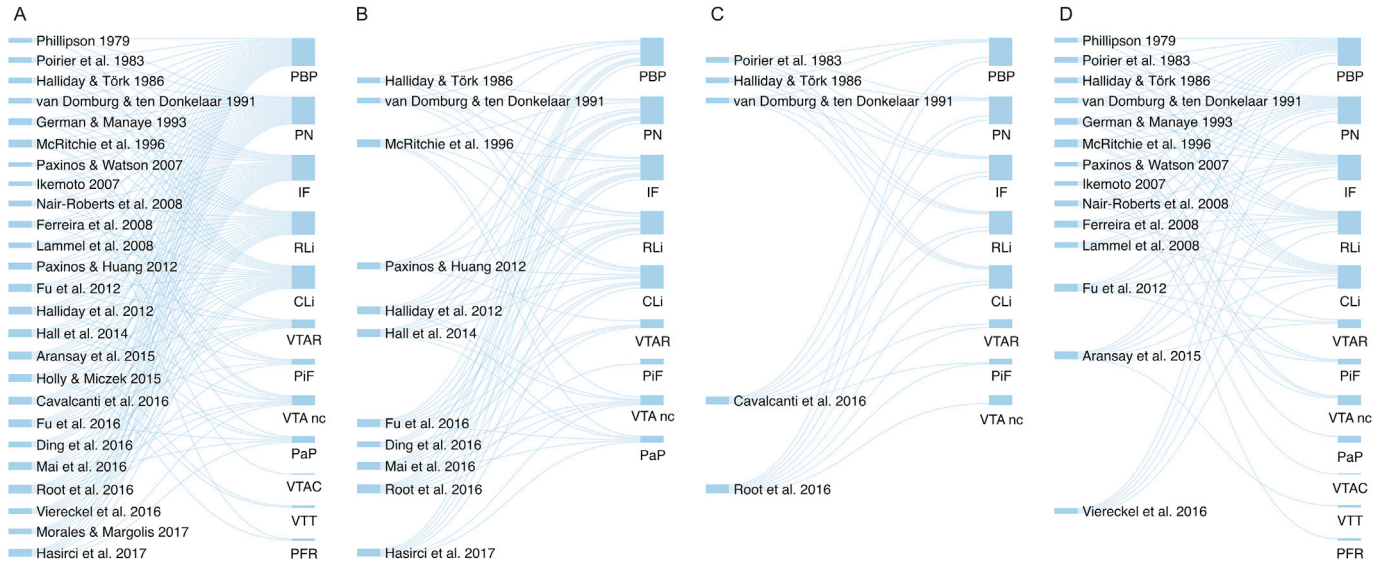

Fig. 1. VTA component nuclei mentioned in the literature as a function of the number of reports. Studies depicted since Phillipson (1979), who introduced the IF and thus, was the first to report all three nuclei, PBP, PN, and IF, as VTA components. **A)** VTA component nuclei across species. **B)** VTA component nuclei in human studies. **C)** VTA component nuclei in non-human primate studies. **D)** VTA component nuclei in rodent studies. Abbrevations: PBP = Parabrachial pigmented nucleus; PN = paranigral nucleus; IF = interfascicular nucleus; VTA nc = VTA nucleus; VTAR = rostral VTA; VTAC = caudal VTA; VTT = Tail of VTA; PaP = Parapeduncular nucleus; PIF = Parainterfascicular nucleus; RLi = Rostral linear nucleus; CLi = caudal (or central) linear nucleus; (PFR) = parafasciculus retroflexus area (https://actrutti.github.io/VTA_component_nuclei/).

represents the *nucleus proper of the VTA,* originally proposed by Poirier et al. (1983), is unclear.

When it comes to the *medial VTA*, there is substantial variation in nomenclature. While there is common agreement on the interfascicular nucleus (IF) as a VTA component nucleus, there is less but growing agreement for the parainterfascicular nucleus (PIF) and parapeduncular nucleus (PaP). Both, the PiF and the PaP, were mentioned mainly in recent studies (Cavalcanti et al., 2016; Fu et al., 2012, 2016; Hall et al., 2014; Mai et al., 2016; Medeiros et al., 2016; Paxinos et al., 2012). Paxinos and Watson (2007) labeled the PiF as the rat homologue of the human PaP and suggested the usage of the term PiF to avoid further confusion. As shown in Fig. 1, this suggestion was not consistently followed. Given that the authors excluded the IF in their subsequent definition of the VTA, the PiF appears to cover the area of the IF. The midline linear raphe nuclei, rostral linear nucleus (RLi) and caudal linear nucleus (CLi; also referred to as central linear nucleus) are mentioned regularly, although early studies do not distinguish between the rostral and caudal parts (Fallon and Moore, 1978; Oades and Halliday, 1987) or report only one linear nucleus (German and Manaye, 1993; Phillipson, 1979; Poirier et al., 1983; Taber, 1961). The caudal VTA (VTAC; Root et al., 2016;

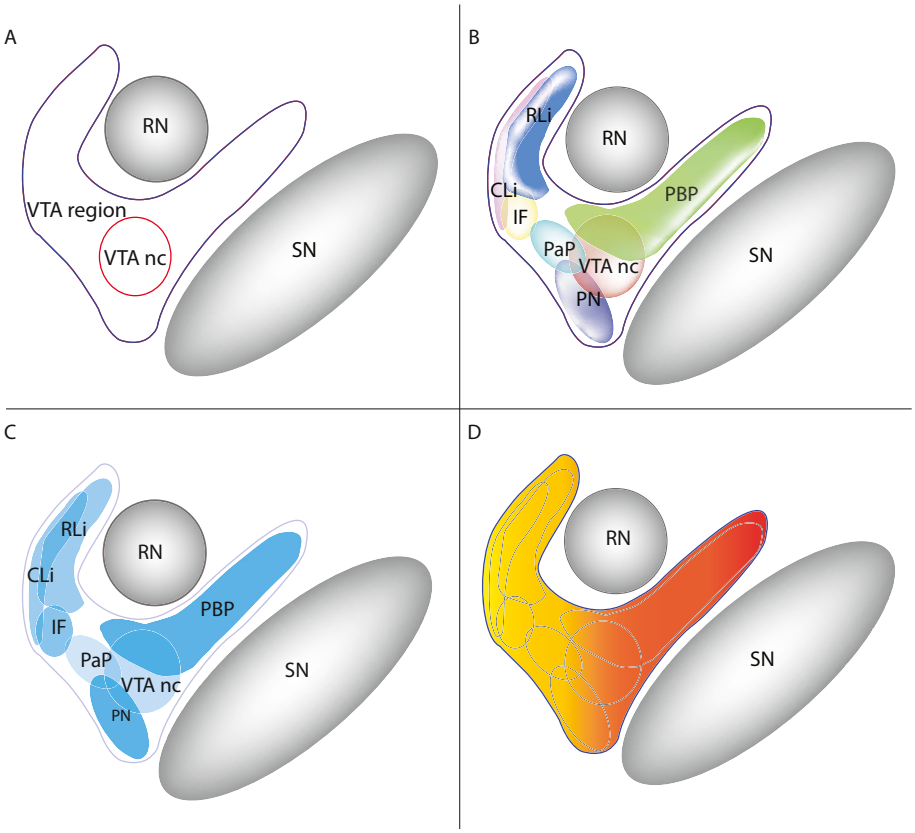

Fig. 2. Schematic two-dimensional representations of the human VTA reconstructed from human post-mortem work and topological atlases with Figures A and B visualising how the shape of the VTA region is affected by the nomenclature. Note: None of the figures is based on histological or MRI reconstruction but rather integrates information from various histological reconstructions, as it is currently not possible to delineate the subpopulations in MRI. Accordingly, three-dimensional information is reduced to a two-dimensional plane. **A:** Reconstruction of the two, main conflicting VTA terminologies with VTA as a region (blue outline) and VTA as a nucleus (red outline); **B:** Two-dimensional representation of the location of VTA subpopulations that give rise to various VTA terminologies due to the arrangement of different nuclei combinations, from a rostral view (information on depth indicated by luminosity, i.e. PBP nucleus is a VTA sub-nucleus that is located rostrally and spans along the rostro-caudal dimension of the VTA, and the RLi nucleus is located rostrally to the CLi nucleus). **C:** Opacity-coded representation of the VTA sub-nuclei with respect to the frequency of being reported as VTA component with a higher report frequency represented by higher opacity. **D:** Schematic representation of the gradual medio-lateral functional topography in the VTA including superimposed nuclei location (see 'Functional subdivisions' part in introduction). There are a several VTA sub-nuclei, for example the VTA nucleus, that are likely to fall within the transition zone between the medial and lateral VTA region. Abbrevations: PBP = Parabrachial pigmented nucleus; PN = paranigral nucleus; IF = interfascicular nucleus; VTA nc = VTA nucleus; PaP = Parapeduncular nucleus; RLi = Rostral linear nucleus; CLi = Caudal (or central) linear nucleus; SN = Substantia nigra; RN = Red nucleus.

Ferreira et al., 2008) and the tail of VTA (VTT; Holly and Miczek, 2016; Ikemoto, 2007) have been mentioned more frequently. The VTT was introduced by Perrotti et al. (2005) and equals to VTAC according to Ferreira et al. (2008). Holly and Miczek (2016) introduced the parafasciculus retroflexus area (PFR), which covers the rostral area of VTA (Aransay et al., 2015). For both, the VTAC (vs VTT) and VTAR (vs PFR), subsequent studies differentially employed the nomenclature (s. Fig. 1) and it is therefore unclear too what extend findings are translatable. Unfortunately, many of the recently introduced VTA sub-nuclei and regions are not (yet) depicted in topological atlases of the human brain and are therefore difficult to reconstruct in MRI. Hence, we excluded them in our efforts of schematic representations of the VTA (see Figs. 2 and 3).

In sum, based on the aforementioned literature, there is common agreement on three nuclei as being part of the VTA: the PBP, PN, and IF (Fig. 1). Those nuclei make up 75% of the VTA volume and 86% of the midbrain A10 cells in humans according to Halliday and Törk (1986). Interestingly, these three nuclei are in accordance with the terminology of the anterior and ventral tegmental nuclei, as agreed upon by experts of the Federative Committee for Anatomical Terminology (FCAT, 1998) that discuss the terminology for structures of the human body.

Given that the VTA is characterised by a large cellular variety of dopaminergic, glutamate-ergic, GABAergic and combinatorial neurons (Morales and Margolis, 2017; Pignatelli and Bonci, 2015), paired with a complex connectivity profile (Edwards et al., 2017; Morales and Margolis, 2017; Yang et al., 2018), raises the question whether the previously introduced VTA component nuclei represent distinct functional subdivisions. However, there is little evidence that the VTA component nuclei represent neural populations specialised and distinct in function. Only in the case of the largest and most laterally located VTA nucleus PBP it has been shown that it is particularly strong connected to the lateral NAcc and therefore suggested to be predominantly involved in reward related behaviour (Yang et al., 2018).

Taken together, there is considerable inconsistency in the terminology of the VTA: Not only does the number of nuclei differ between studies, but the term VTA is also utilised for both the A10 region and the VTA *nucleus,* which is believed to be a component nucleus of the VTA region (Fu et al., 2012). These inconsistencies are likely to lead to anatomically questionable or imprecise definition of the VTA region, which in turn can lead to incorrect and unreliable results. For example, an imprecise definition of the ROI could potentially yield false ideas about the functional significance of the VTA. Furthermore, unclear definitions might result in a higher probability of ignoring VTA components (nuclei) in past studies (Holly and Miczek, 2016; Williams et al., 2014; Zhang et al., 2010), which may suggest that our current knowledge of the VTA is biased. Findings from functional studies do not support the VTA parcellation stemming from neuro-architectural studies but indicate a media-lateral functional topography in the VTA. This parcellation is likely to cover an area that contains these five VTA component nuclei PBP, PN, IF (PiF), CLi, and RLi.

4. Imaging & delineation of the DA complex

Given the broad research interest in dopaminergic functioning in humans, a large number of imaging studies attempted to measure VTA and SN activity in functional MRI experiments (Büchel et al., 2017; Chen et al., 2016; Duarte et al., 2017; Eapen et al., 2011; Hadley et al., 2014; Krebs et al., 2011; Takahashi et al., 2004; Tomasi and Volkow, 2014). Although visualising small structures like this in the subcortex has proven

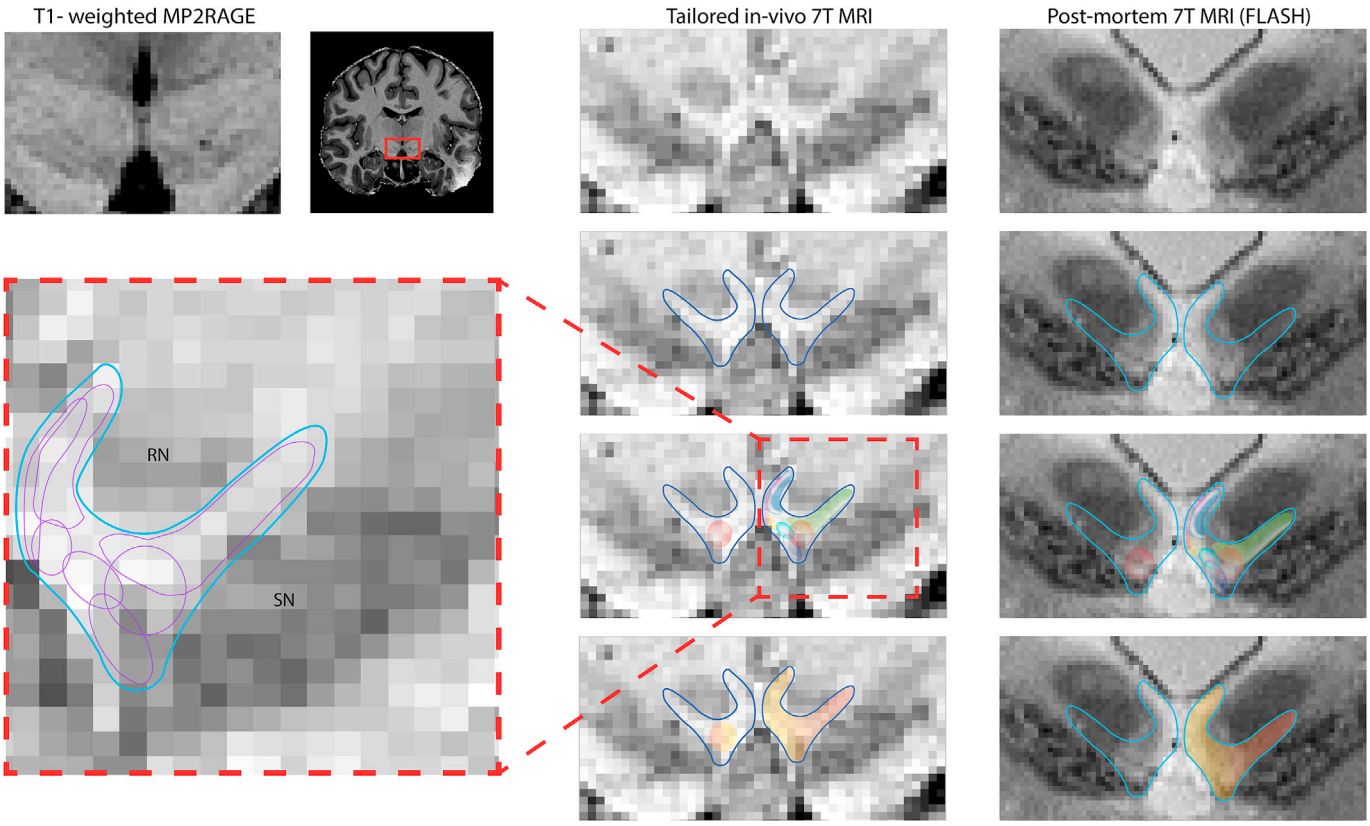

Fig. 3. Delineation of the VTA as both, a region and a nucleus, and schematic representation of VTA subpopulations superimposed on, but not reconstructed from 7 T MR images (Please note that visualization and reconstruction of the entirety of VTA sub-nuclei is not possible in in-vivo MRI given the limitations in subcortical MRI. Standard T1-weighted sequences do not provide enough SNR and CNR to visualize and delineate the VTA (upper left). In contrast, tailored sequences in- and ex-vivo increase VTA visibility and thus enable VTA delineation (right side). In this case, the midbrain-optimised sequence ('Tailored in-vivo 7T MRI') outperforms the 'Post-mortem 7T MRI (FLASH)' image with respect to VTA segmentation feasibility, even so it does not enable segmentation of distinct VTA sub-nuclei as the enlarged image shows (red outline). The midbrain-optimised sequence displays higher contrast differences to surrounding landmarks, although the post-mortem scan provides much higher resolution. One possible explanation for the difference in VTA visualization between the in-vivo and ex-vivo MRIs is the extremely inflated third ventricle in the post-mortem scan which appears to put pressure on the ventrally located midbrain structures. Differences in ventricle volume are likely to be caused by the different age ranges in the provided MRI data (in-vivo scan: 18–30 years; post-mortem scan: > 70 years), as ventricles inflate with age.

to be challenging (Alkemade et al., 2013; Barry et al., 2013; Keuken et al., 2014; Lenglet et al., 2012) delineation and segmentation of the region of interest helps to specify the localisation of the activity.

Given that in PD the degeneration of DA-neurons is associated (almost) exclusively with the SNc, there is major clinical interest in imaging the human SN for diagnostic, as well as research purposes. Although it is difficult to distinguish between the compacta (SNc) and reticulata part (SNr) of the SN due to scattered rather than a clear bipartite subdivision (Ding et al., 2016; Halliday et al., 2012; van Domburg & ten Donkelaar, 1991), several (probabilistic) atlases of the SN exist (Chakravarty et al., 2006; Keuken et al., 2014; Pauli et al., 2018; Xiao et al., 2017).

In the case of the VTA, only a few studies delineated the individual VTA on structural MR images (Ballard et al., 2011; Barry et al., 2013; Eapen et al., 2011; Murty et al., 2014) in order to define the ROI prior to fMRI analysis. This seems worrying, as the small size and complex shape of the VTA (Halliday and Törk, 1986) renders interpretations of blood oxygen level dependence (BOLD)-signals speculative when no a priori ROI is defined. In addition to that, available digital VTA atlases show striking dissimilarities which are likely to be caused by VTA definitions as a nucleus (Pauli et al., 2018) versus VTA as a region (Murty et al., 2014). This seems rather worrying as the user is likely to be unaware of the variability in VTA terminology rendering comparison of results difficult between studies employing different ROIs.

Generally, there are several limitations in imaging subcortical structures which is reflected in the number of structures in MRI atlases. Only 7% of the 455 sub-cortical nuclei are captured by the currently available MRI atlases, highlighting the general difficulty in mapping smaller subcortical structures (Alkemade et al., 2013; Forstmann et al., 2017). First, there is a low signal-to-noise ratio (SNR) caused by the increased distance to the coil relative to the cortex (Barry et al., 2013; Keuken et al., 2014; Lenglet et al., 2012). Second, anatomical features such as the neighborhood to a dense vene-system (the circle of Willis) causes signal distortions. These issues make imaging the VTA challenging but not impossible as have been shown by studies using high-field (quantitative) MRI on subcortical regions (Eapen et al., 2011; Forstmann et al., 2017, 2014; Keuken et al., 2013, 2015; Keuken and Forstmann, 2015).

Yet, the VTA is difficult to identify as a whole from MR images, as the heterogeneous anatomical nature of the VTA fails to elicit homologous MR signal (Eapen et al., 2011). This is due to the variability of cell populations within the VTA that vary with respect to their anatomical and neurochemical properties (Morales and Margolis, 2017; Holly and Miczek, 2016; Root et al., 2016; Aransay et al., 2015; Lammel et al., 2008; McRitchie et al., 1996; van Domburg & ten Donkelaar, 1991)—properties that all affect the MR signal. This anatomical heterogeneity and the additional lack in clear delineation from surrounding nuclei complicate segmentation on MRI images, as there is no aid defining the VTAs borders. As a result, the studies that attempt to delineate the VTA on MRI images vary substantially in reported VTA volume (Eapen et al., 2011; Hadley et al., 2014; Murty et al., 2014; Tomasi and Volkow, 2014; Pauli et al., 2018) which is corroborated by differences to post-mortem estimates (Halliday and Törk, 1986; Paxinos and Huang, 1995).

However, using multi-parameter high-field MRI can help to increase the contrast to noise ratio between the VTA and surrounding landmarks, making delineation of the VTA borders more reliable.

In sum, there has been a lot of progress in the recent years in optimising MR sequences to improve image resolution and increase tissue specific contrasts. Although, digital atlases are consequently updated to cover subcortical structures, there are few including the VTA. And those that exist vary substantially in volume. This is not surprising, since a crucial aspect for the construction of an atlas is to define the anatomical boundaries, which is difficult for the VTA given the lack of consensus on the exact neuroanatomy of the VTA in the current literature (Ding et al., 2016; Eapen et al., 2011; Halliday and Törk, 1986; Halliday et al., 2012; Hasirci et al., 2017; Mai et al., 2016; Morales and Margolis, 2017).

5. Future directions

Given the great interest in the VTA and its functioning we believe that the neuroscientific field will benefit from a (3D) histological reconstruction of the VTA. This will aid research and result in a consistent view on the anatomical borders of the VTA. Finally, it will provide a new framework to further investigate the possible subdivisions and their functions of the VTA in relation to other brain areas. In the following we propose development of a probabilistic atlas, preferably based on agreement in terminology. Such an atlas can be used on the one hand, in order to optimize SNR for neuroimaging studies and on the other hand, in order to further functionally parcellate the atlas for the purpose of functional subdivision. Finally, we suggest to use ex-vivo methods for reasons of validation and precision.

First, it would be of great benefit to the field if inconsistencies in VTA terminology were overcome, as identification of subpopulations and consequently delineations of the VTA are naturally also of importance for cytological studies. This is especially relevant when taking into account novel VTA definitions, which deviate to a substantial extend from the aforementioned literature (Ikemoto, 2007; Holly and Miczek, 2016). In spite of that and given our extensive literature search, we argue to for a A10 cell - based VTA definition. This is because findings from animal studies on VTA functioning are very likely to be recorded from neurons within the A10 DA cell region since it contains the most frequently mentioned VTA neuronal subpopulations (see Fig. 2). Hence, employing a A10 cell-based VTA terminology reduces the likelihood of disregarding particular VTA functions as all functional subdivision are likely to be included in the ROI. Of course, it should be noted that an increase in ROI volume goes hand in hand with a reduction in likelihood to find activation, given that activation can be cancelled out. Yet, we believe that using anatomically defined, A10-based VTA ROI will help constructing functionally specific VTA atlases, for example, using functional parcellation.

Next, we suggest to develop a high-resolution probabilistic atlas of the VTA using tailored MRI sequences. Since the MRI signal varies with respect to tissue properties, VTA visualization would benefit from the development of a tailored sequence that is specifically designed to increase the contrast to noise in that area. Standard T1/T2 weighted images might not capture the VTA-specific contrast which makes them less suitable for border-delineation. Instead, we opt for sequences using a high-resolution (7T) multi-parameter imaging protocol by which we can obtain quantified maps that are specific for the underlying tissue properties (Weiskopf et al., 2015). Using such an approach would help to acquire specific T1 and T2* relaxation times for the VTA (T1/T2*map) which in turn provides us the optimal echo-times for other (f)MRI sequences. In addition, using a multi-parameter sequence will allow for calculations and combinations of different images, increasing border specific contrasts (Metere et al., 2017). Further, we argue for the use of 7T as the high field strength improves image resolution compared to lower field strengths, and consequently increases the number of voxels that cover the area of a specific structure. Especially in the case of the relatively small and complex-shaped VTA, the increase in resolution is naturally a crucial factor.

Despite the fact that imaging the VTA is difficult we believe that such an endeavor would provide more detail to define the outer borders, using both contrast-differences and landmarks known from the existing histological atlases. Although the lack of agreement on terminology make border definitions difficult, efforts in contrast optimisation enable visibility of the A10-cell area (Fig. 3). Hence, consistent segmentation of the VTA on MRI images of different individuals is possible, which in turn can be used to develop a probabilistic atlas. Naturally, such an atlas considers the anatomical variability across individuals and might be useful for fMRI research.

A probabilistic atlas of the VTA would not only help to bring consensus across the neuroscientific field but it might also benefit functional imaging studies as well. In general, the midbrain area suffers from susceptibility artefacts that affect the SNR of the MR signal (e.g. Barry et al., 2013). A probabilistic atlas of a specific ROI can aid optimising the scan sequence for functional imaging studies as it can be used to define the ROI and quantify specific relaxation times. For example, it has been shown that the SNR of an fMRI sequence benefits from a theoretically optimal echo time that is close to the T2* relaxation value of the region of interest (de Hollander et al., 2017). To this end, the atlas of the VTA can be applied to obtain the optimal TE by extracting the T2* values for the VTA from a T2*map.

Once a delineation is reached, the next steps should involve connectivity approaches in order to further functionally subdivide the VTA atlas, for example by means of functional parcellation (Tittgemeyer et al., 2018). This might be especially relevant and of interest in the case of the VTA due to its structural and functional heterogeneity. However, whether or not we can visualize the VTA subdivisions with high-field MRI has to be investigated. For this purpose, a multi-disciplinary approach using both, in-vivo and ex-vivo methods, might help to understand the nature of the VTA subdivisions. For example, in-vivo functional imaging methods can also help to investigate the VTA structure. By using tailored fMRI sequences (i.e., with echo times based on the T2* values within the VTA region), resting state signals can be measured to investigate sub-divisions by clustering regions with similar signal-patterns. Such a functional parcellation would help to visualize the borders of the sub-nuclei (or deviant functional subdivisions) of the VTA, based on their functional signal: There is growing evidence for a medio-lateral functional topography in the VTA, where lateral and medial nuclei have different functional involvement based on connectivity, neurochemistry, gene expression and functional activity (Aransay et al., 2015; Holly and Miczek, 2016; Lammel et al., 2012; Lammel et al., 2011; Viereckel et al., 2016; Yang et al., 2018). Functional parcellations have already proven to be successful to delineate subdivisions of subcortical structures such as the striatum (Janssen et al., 2015). Whether or not the in-vivo resolution of fMRI can be increased to deliver the necessary detail has to be investigated.

While in-vivo scanning might not be sufficient to detect smaller subregions, imaging post-mortem brains might be useful to obtain more detail due to the fact that longer scanning-times and higher-resolutions are allowed. In turn, post-mortem images can provide more detailed information for the MRI atlas, and will help to translate between MRI and histology-based images. At the microscopic level, knowledge of the VTA and its cytoarchitecture can help to define sub-divisions as well. Given that historically, the brain was studied at a microscopic level by means of histological staining (Halliday and Törk, 1986; Oades and Halliday, 1987; van Domburg & ten Donkelaar, 1991) early studies on the dopaminergic midbrain have shown that discrimination of VTA and SNc is based on the distribution of A10 and A9 cell groups (Dahlström and Fuxe, 1964; German et al., 1983; McRitchie et al., 1996; Oades and Halliday, 1987). Consequently, a histological reconstruction of the full A10 VTA body is possible and allows, in combination with recent developments in computer sciences and neuroimaging, the digital representation of the histology-based VTA reconstruction within an image of the whole brain (Meyer et al., 2006). This complex approach enables identification of the

exact location and shape of the VTA with respect to neighboring structures, and the identification of the MR signal from the VTA. However, such an approach is very labor-, cost-, and time-consuming. Therefore, creating a probabilistic MRI atlas of the VTA based on multiple in-vivo images to account for inter-individual variations in anatomy is a first step. Nevertheless, a histological approach would aid in precise reconstruction of the shape and location of the VTA and its sub-divisions within a standard brain template, such as MNI.

6. Conclusion

There are substantial differences in structure and function between SNc and VTA that argue for a distinction of the structures when investigating the functions of the dopaminergic midbrain regions. Unlike the SNc, the VTA is not a nucleus, which makes it difficult to delineate the structure due to lack of clear anatomical borders. This, in combination with a low signal- and contrast-to-noise ratio, makes the visualization of the VTA by means of MRI difficult. Therefore, identification and delineation of the area depends highly on two-dimensional topological atlases that lack information of inter-individual differences and are not consistent in VTA shape and nomenclature. Consequently, construction of a probabilistic VTA atlas is a promising perspective for future studies as DA-associated behaviour is of interest in many psychological research fields (Colzato et al., 2010; Duarte et al., 2017; Krebs et al., 2009, 2011; Peters et al., 2011; Ranaldi, 2014). However, several obstacles have to be resolved in order to construct an anatomically valid VTA atlas. First, it would be beneficial if consensus was reached on the nomenclature that is used to describe the VTA. We suggest to include an area that covers the location of five VTA neural populations that are most consistently mentioned in the literature comprising the VTA (PBP, PN, IF, RLi and CLi). Given that SN and VTA were historically distinguished based on the location and distribution of A9 and A10 cells, respectively, and were subsequently subdivided further in cytological and electrophysiological animal studies based on their structure and function, we propose this deductive approach to be a valid approach to study the human VTA.

Conflicts of interest

The authors declare no competing financial interest.

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