Summary

Recent advancements in neurophysiological methods have enabled us to investigate subcortical nuclei with increased precision. High-field magnetic resonance imaging (MRI) scanner field strengths, such as 7 Tesla (T), even allow the examination of brain regions located deep in the brain, far away from the brain's cortical surface. This dissertation investigates the structure and function of the human dopaminergic midbrain, with a specific emphasis on the ventral tegmental area (VTA). Historically overshadowed by the substantia nigra (SN) in research, the VTA has been shown to play a central role in behaviours related to cognitive functions such as reward-based learning, motivation, and cognitive control. However, the VTA's cellular complexity, lack of clear anatomical borders and location deep in the brain pose challenges for accurate study using standard MRI techniques. This dissertation describes a combination of different methodological approaches in order to tackle these challenges: A critical evaluation of historical and recent publications on VTA anatomy, identification and delineation of the VTA on high-resolution MRI data, as well as investigations into the structural connectivity and functional characteristics of the structure in humans.

Chapter 2 reviews the literature with the aim of defining the VTA as a distinct brain region and highlights its neuronal diversity and complex structure. In contrast with its neighbour, the SN, the VTA exhibits gradual transitions between its heterogeneous cell populations and is associated with a more diverse connectivity profile. The chapter also emphasises challenges in VTA research, including inconsistent nomenclature and difficulties in MRI identification due to low signal- and contrast-to-noise ratios. In response to these difficulties, in Chapter 3, a new probabilistic atlas of the human VTA based on high-resolution 7 T MRI data is presented. This atlas, which can serve as an aid in navigating the brain and as a region of interest in structural and functional neuroimaging analyses, was developed through manual segmentation of MRI scans from 27 participants. It offers enhanced anatomical precision compared to previous atlases and considers the inconsistent nomenclature by delineating a region that captures the VTA neural populations that have the highest agreement in the literature. It considers the lack of anatomical border by including a 'tailored' MRI contrast as the basis for delineation based on a combination of multiple scans that enhance the contrast to surrounding tissue.

As the VTA and the SN, together as dopamine-producing neurons containing regions of the midbrain, represent the main sources of dopamine in the brain, Chapters 4-7 explore the structural and functional characteristics of both using

high-resolution MRI methods. Chapter 4 investigates the fibre connections between the VTA and SN, respectively, and a large number of other brain regions by reconstructing the white matter pathways using probabilistic tractography on diffusion MRI data. This structural connectivity analysis revealed similar connectivity profiles but differences in white matter tract density.

Given that dopamine plays a central role in executive functions, such as working memory and learning both represent promising cognitive functions to elucidate the functional topography of the dopaminergic midbrain. Specifically, working memory updating has been linked to brain regions closely related to the VTA and SN, like the prefrontal cortex and the striatum. Hence, as a first step towards functionally investigating the VTA and SN, Chapter 5 reviews working memory updating mechanisms, highlighting the benefit of model-based cognitive neuroscience methods to understand the neural mechanisms involved in working memory updating. As a next step, Chapter 6 employs model-based 7T fMRI to examine subcortical neural correlates during working memory updating, emphasising the role of the VTA and SN in dopamine-related processes. It challenges existing models like the famous prefrontal cortex-basal ganglia-working memory model (PBWM) by suggesting subcortical involvement in working memory substitution rather than gating mechanisms.

Finally, Chapter 7 focuses on the reward prediction error (RPE), a prominent reward-based learning signal encoded by midbrain dopamine neurons. The chapter describes an investigation of the neural correlates of the RPE with a special focus on subcortical regions, including the striatum, VTA and SN, using a reversal-learning task and model-based fMRI. Despite the robust association between the dopamine neurons of the midbrain and the RPE, the study failed to provide evidence for RPE-related neural activity in either VTA or SN. A possible explanation is that RPE-encoding neural populations are not accurately mapped by the VTA and SN masks. Both, VTA and SN masks used in this thesis include various neural populations associated with that particular region, but functional and structural subdivisions are not accounted for. As a consequence, RPE-related activations might be cancelled out.

Overall, this dissertation advances our understanding of the dopaminergic midbrain, in particular the VTA's anatomical complexity and functional significance, using state-of-the-art neuroimaging techniques. It provides essential tools like the probabilistic atlas to enhance precision in brain research and applies this tool in both structural and functional MRI. Critically, this dissertation expands our views of

neural mechanisms behind working memory updating and the accuracy of current working memory models.