Identifying the Functional Architecture of the Human Ventral Tegmental Area and the Substantia Nigra using High Resolution Magnetic Resonance Imaging

Mariam Eapen and John C. Gore*[§]

The ventral tegmental area (VTA) and the substantia nigra pars compacta (SNc) are subcortical areas within the ventral midbrain that are primary synthesizers of the neurotransmitter, dopamine (DA). Dopaminergic neurons from these areas have widespread projections to many subcortical and cortical parts of the brain. However, to date, the functional architecture of these midbrain regions in humans remains unclear. *In vivo* studies in rodents and non-human primates have shown that the dopaminergic neurons in the VTA and SNc are similar in their firing properties and release of DA[1,2,39]. However, these firing patterns are believed to facilitate multiple functional roles associated with reward related learning, motivation, and other goal directed behaviors[1,50,51,60].

Since most of the studies on the VTA and SNc have been done in non-human species, it is difficult to translate this work into humans and accurately characterize the functional role of these two regions in normal human brain function. Non-invasive functional magnetic resonance imaging (fMRI) is one technique used to study human brain function in vivo. In particular, high resolution fMRI performed in ultra high field magnets (7 Tesla) can be especially beneficial in segmenting the anatomical substructure of brain areas in close proximity. This paper reviews the anatomical layout and functional significance of the VTA and SNc and proposes the use of ultra high field high resolution MRI to study the functional architecture of these two midbrain areas.

**Neuroscience Graduate Program, Vanderbilt University Medical School, U1205 Medical Center North, Nashville, TN 37232, USA.*

§Department of Radiology and Radiological Sciences, Vanderbilt University, Nashville, TN 37232, USA. Correspondence to M.E. e-mail: mariam.eapen@vanderbilt.edu

ANATOMY OF THE VTA AND SNc

The anatomy of the VTA and SNc is unique and challenging to study because of its location in the brain, cellular profile and complex interconnections. Nonetheless, an overview of the anatomy is essential to localize the source of an MRI signal, optimize the parameters required to image this part of the brain and correlate it with brain function.

The VTA and SNc are located in the ventral portion of the midbrain brain stem area, and they both vary in size and cytoarchitecture. The VTA is approximately 60mm^3 in size[3] and consists of heterogeneous groups of neurons that are part of the A10 dopaminergic system[5,6]. The SNc is approximately 1100mm in size[3-4] and is part of the A9 dopaminergic system[5,6]. A10 DA fibers contained within the ventromedial midbrain, consist of small diameter (15-30µm), non-myelinated axons that ascend in the medial forebrain bundle (MFB)[7,8]. The A9 DA fibers, on the other hand, vary in size (20-40µm) and extend from the medial lemniscus to the lateral border of the cerebral peduncles[9].

The VTA is further subdivided into separate nuclei based on their location and cellular profile[10,15], and the neuronal populations in these subdivisions tend to be mediolaterally arranged[11]. The SN is topographically divided into two subdivisions, the pars compacta and pars reticulata[9]. The compacta cells (SNc) have larger cell bodies, thicker and longer dendrites, more numerous dendritic segments and denser neuromelanin granules compared to the reticulata cells[12,13,14].

The DA neurons in the VTA have widespread reciprocal connections with sub-cortical and cortical areas of the brain, making this region a major site of information integration. It has reciprocal connections with limbic cortices through the mesolimbic pathway, including the nucleus accumbens (NAc), amygdala, cingulate cortex, and the hippocampal complex[15]. It has efferent and afferent associations with the prefrontal cortex, insular cortex, some sensory, motor and association areas (the mesocortical pathway), and with various nuclei of the thalamus and hypothalamus[15,16,17]. It is also reciprocally connected to the dorsal raphe nuclei, locus ceruleus, various brain stem nuclei, the superior colliculus, reticular formation periaqueductal gray, and the spinal cord[15,17,18,19,20]. Mesocortical projections tend to have their origin dorsorostrally in the VTA[21,22], and the mesolimbic projections originate in the ventrocaudal

VTA[15]. Within the midbrain, the VTA receives glutamatergic input from the laterodorsal tegmentum (in the mesopontine brainstem)[23], and cholinergic input from the pedunculopontine tegmentum[24,25].

Within the ventral midbrain, there is a dorsoventral topography of the DA neurons[26,27,28]. In primates, the dorsal tier of neurons forms a medio-lateral continuum of DA cell groups that include the dorsal SNc, the retrorubral area and the VTA[9,12]. The neurons in this tier are calbindin-D_{28k}-positive, contain low levels of mRNA for DA D2 receptor[27], have dendrites that are oriented mediolaterally, and project to the ventral forebrain as the mesolimbic pathway. In contrast, the ventral tier of neurons consists of the ventral SNc (densocellular zone) and the cell columns extending into the pars reticulata. These neurons are calbindin-D_{28k}-negative, have relatively high levels of mRNA for the DA D2 receptor[27], contain dendrites oriented ventrally, and project to the dorsolateral striatal regions as the niagrostriatal pathway. The neurons in the densocellular zone project to both the ventral and sensorimotor-related striatum[28].

The majority of efferent and afferent pathways of the SNc form the niagrostriatal and striatonigral pathways. The SNc receives topographically organized input from different parts of the striatum in an inverse dorsoventral fashion[32]. Sensorimotor areas of the striatum project to the ventrolateral pallidum and ventrolateral SNc cell columns[29,30,31]. Projections from the central striatum terminate more centrally in both the pallidum and ventral densocellular SNc. Ventral striatum projects topographically into the ventral pallidum, VTA and densocellular SNc[32].

Therefore, the VTA and SNc vary in their cellular architecture along the ventral mediolateral span of the midbrain. Projections to and from the VTA and medial SNc seem to be associated with the limbic areas, whereas the lateral and ventral SNc regions are connected to the association and motor related areas. The next section reviews the functional significance of these structural connections.

FUNCTIONAL PROPERTIES OF DOPAMINE NEURONS IN THE VTA AND SNc

Electrophysiological recordings from the VTA/SNc and their projection sites show DA neurons having a characteristic pattern of activity comprising: (i) a hyperpolarized, inactive state; (ii) a slow, irregular, single spike or 'tonic' firing pattern; and (iii) a burst or 'phasic' pattern of activity[33,34]. Interactions between these distinct firing patterns are known to encode behaviorally relevant signals that facilitate reward related learning, motivation, novelty assessment and other goal directed behaviors.

The phasic firing pattern is dependent on afferent input into the neuron and constitutes a rapid, high concentration efflux of DA released into the synaptic space[35]. This burst release of DA is believed to be the functionally relevant signal sent to post synaptic sites to indicate reward and other goal directed behaviors[1,36]. The DA released in this manner may function selectively on DA receptors localized within or around the synapse and therefore affect only a selected number of post synaptic neurons (for example, in the NAc and striatum) [37].

On the other hand, the single-spike or tonic firing pattern is driven by an intrinsic pacemaker potential[38] that results in a slow changing, low tonic concentration of DA released into the extra-synaptic space[37,39]. The overall activity of DA tonic firing is thus more spatially distributed affecting a large pool of post synaptic neurons (for example, in the ventral striatum) and modulating input from other neurons. The phasic and tonic firing patterns were both observed in the VTA[37] as well as the SNc[33,35,38]. The unique behavioral significance of these two firing patterns is reviewed next.

Single unit studies in non-human primates conducted by Schultz and colleagues[1,40,41,42,43] showed that the phasic firing pattern of midbrain DA neurons (primarily in the VTA and SNc) encodes a learning signal that predicts the error in the occurrence of a rewarding or aversive stimulus. These neurons responded robustly to primary food and liquid rewards and conditioned cues predicting the reward[40,41,44,**45**]. However, they seemed to respond much less to aversive stimuli like air puffs, saline drops to the mouth and foot pinches[46,47]. Even though most of the midbrain neurons measured in the reward prediction error studies were DA in nature, the non-DA neurons, in contrast, were shown to respond robustly to aversive stimuli[47]. Human neuroimaging studies using fMRI have corroborated Schultz's evidence, showing that the VTA and ventral striatum are involved in processing positive prediction errors during conditional associative tasks using appetitive or monetary rewards[**48**,49]. However, due to the limited spatial and temporal resolution of the blood oxygen level dependent (BOLD) response, it is not conclusively credible that the activity seen in the VTA is contributed solely by the phasic firing pattern of the DA neurons.

In contrast, the slowly changing and low concentration tonic firing pattern is thought to be involved in setting up a motivational state, providing initial input to other neuronal systems subserving reward seeking or general goal-directed functions[50,51]. Voltammetry studies[52], micro dialysis studies[53,54] and electrophysiological experiments[55] conducted in the NAc (a major projection site of the VTA) indicate that DA release is maximum during the performance of a behavior or the presentation of a stimulus that triggers a behavioral response. This activity in the NAc is

attributed to its role in engaging with other brain structures to influence parameters for motor activity[56,57]. Thus, the NAc in association with the midbrain DA neurons appears to be involved in higher order sensorimotor functions that are important for motivational processes.

Schultz's studies also showed that the DA neurons in the VTA and SNc fired phasically when the animals were exposed to unexpected or novel aspects of the reward (novel magnitude or reinforcing properties of the reward or novel time of reward delivery)[40,44,45]. Human neuroimaging studies using fMRI also found that the SNc/VTA region preferentially responded to stimulus novelty over other forms of stimulus salience like rareness, target response and negative emotional arousal[58]. However, the spatial resolution in these neuroimaging studies was not feasible to differentiate activity between the VTA and the SNc.

While DA is known to be involved in reward processing, it is more specifically involved in directing attention to salient stimuli in order to prepare an appropriate behavioral response[40,42]. Haber and colleagues[32,59,60] suggested that the process from detecting a salient stimulus to preparing an appropriate behavioral response involves a complex chain of events that recruits an ascending spiral feed-forward organization of the niragro-striatal-niagro pathways. It begins with motivation in the dorsal tier DA cells (VTA, SNc and their connections with the NAc shell), proceeds through cognitive processing in the ventral tier DA cells (SNc and its connections with the NAc core and central striatum); and finally shapes motor outcomes though the ventral tier DA cell columns of the SNc and its connections with the dorsolateral striatum.

In summary, the studies reviewed thus far indicate that the midbrain DA neurons are known to be involved in reward related learning when responding to an unpredicted reward or a cue that reliably predicts the reward. Moreover, they respond preferentially to novel aspects of the stimulus compared to other salience properties. While it is difficult to draw a fine distinction between the role of the VTA and SNc DA neurons, these studies suggest that the VTA DA neurons seem to respond to the motivational, novelty and salience aspects of the stimulus. On the other hand, the SNc DA neurons seem to be associated with preparing an appropriate behavioral response to the stimulus. The role of the midbrain DA neurons in human brain function was not well characterized in the above mentioned fMRI studies. Advanced imaging techniques that can accurately localize the MR signal can provide better insight into the fine grained functional architecture of midbrain substructures like the VTA and SN. Understanding how to achieve this step in imaging technology is discussed in the next section.

IMAGING THE VTA AND SNc

The aforementioned studies have attempted to characterize the function of the VTA and SNc in rodents and non-human primates. However, very little work has been done to functionally delineate the midbrain DA neurons in humans. Given DA's role in reward related learning, novelty assessment and motivation, it would be important to understand how DA produced in these midbrain areas are relevant in human brain function.

While DA release can be directly imaged using PET (Positron Emission Tomography), this technique does not provide high spatial resolution required to segment brain regions in close proximity. Anatomical MR imaging affords the visualization of high resolution images of the human brain and was initially developed for diagnostic purposes. With the advent of current high resolution MRI techniques, areas like the brainstem can be segmented, revealing details approaching those seen in histological specimens[61]. Current three dimensional high resolution MR methods can produce images with an isotropic voxel dimension of 700μm in a 7 Tesla magnet (**Figure 1**).

MRI based on the BOLD response is a potential way to study the functional roles of brain stem areas like the VTA and the SNc. Most fMRI studies involving the brain stem to date have been conducted in low field scanners (1.5 Tesla or 3 Tesla) with imaging protocols that have certain limitations on sensitivity and signal to noise ratios (SNR). However, at higher field strengths (7 Tesla or higher), some of these limitations can be ameliorated because of the ability to view smaller voxel dimensions from more localized regions, and because BOLD signals increase with increasing field strength. However, higher field strength imaging has various technical challenges, especially when imaging the midbrain. Some of these challenges include signal artifacts and distortions caused by magnetic susceptibility variations in the brain and the behavior of radio frequency coils at high frequency.

The location of the midbrain (apposing the interpeduncular cistern) is such that the tissue magnetic susceptibility varies within and across the region, thereby distorting the applied magnetic field. This results in signal artifacts like geometric distortions (macroscopic spatial image distortion) and variations in signal intensity (microscopic, due to dephasing of the proton spins). In order to compensate for susceptibility artifacts, techniques like asymmetric spin echo imaging[62], modified single shot echo planar and spiral imaging[63,64,65], multiple linear gradients[66], and higher order gradients[67] have been used. A recent study used the magnetic susceptibility differences (phase changes) across tissues in a human

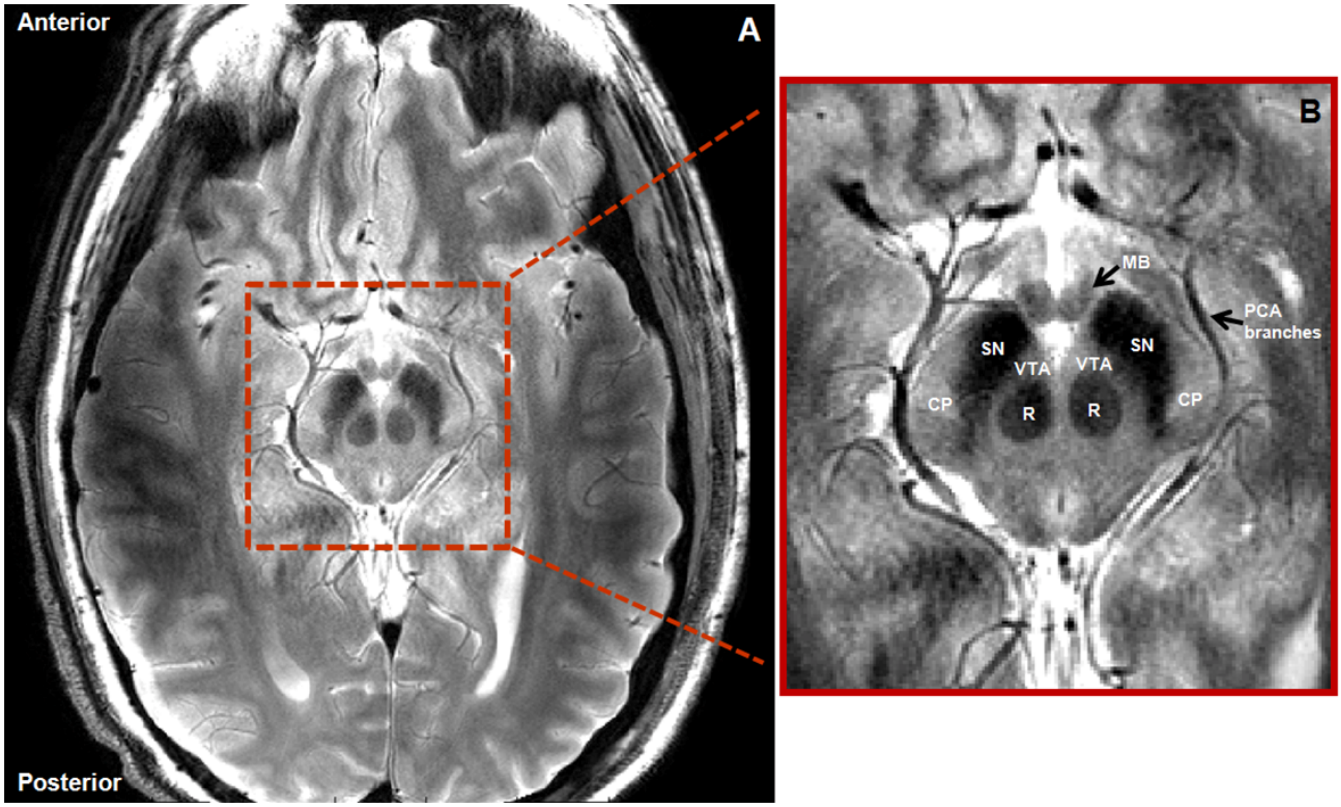

Figure 1 | **7 Tesla MRI image from a T2 weighted GRASE (Gradient And Spin Echo) pulse sequence. a** | Axial image of the midbrain at the level of the superior colliculus; **b** | Enlarged view of the midbrain area highlighted in A. **CP** = Cerebral Peduncles; **SN** = Substantia Nigra; **R** = Red nucleus; **VTA** = Ventral Tegmental Area; **PCA** = Posterior Cerebral Artery; **MB** = Mammillary Body.

7 Tesla to generate high contrast to noise ratios in cortical structures[68]. While none of these techniques can completely eliminate the distortion and signal dropout observed at high field, in various combinations they can be used to improve image quality.

Noise also increases as you go to higher field strengths. The intrinsic noise (thermal noise in the body and from scanner electronics) increases linearly with increasing frequency; while the physiological noise caused by head motion, respiration, and cardiac cycles also increases with increasing field strength. However, specific technical advances are possible to overcome these fields, such as the use of array coils[69] and dynamic shimming[70,76].

While the above mentioned techniques can help to improve image quality, they are not sufficient for accurately localizing fMRI signal (both spatially and temporally) with respect to neuronal activity. The BOLD signal measures neuronal activity indirectly by detecting relative changes in deoxygenated and oxygenated hemoglobin in the vascular region adjacent to the activation site. In order to spatially localize the BOLD signal, different techniques such as diffusion weighted imaging, perfusion weighted imaging (imaging blood flow in capillaries), MR angiography and susceptibility weighted imaging (imaging the venous system at the region of activation) can be used. At higher fields, these methods become more practical because of the higher SNR.

The temporal resolution of fMRI is on the order of seconds, limited mainly by the delay in the hemodynamic correlate of neuronal activity, though in practice, the ability to assess the onset of events is limited by the SNR. Methods to improve the temporal resolution of the data acquisition time include multiple channel acquisition (by using more receiver coils), partial k-space imaging[71] and the development of efficient k-space trajectories that use both x and y gradients to sample k-space in a diagonal or spiral direction[65]. These techniques may only improve the image data acquisition time, but the temporal resolution is still limited by the BOLD dynamics. However, at high resolution, we have the ability to parse out different parts of the BOLD signal as the SNR is higher at higher field strengths.

Apart from reward prediction error tasks, several human fMRI studies conducted in low field magnets have shown BOLD activation in the mesolimbic regions like VTA, SNc, hippocampus and amygdala. These were observed in tasks using pleasant tasting

stimuli[72], monetary rewarding tasks[73], novelty and memory recall tasks[74], reward anticipation and reward related memory recall tasks[75]. However, these studies have not accurately mapped the spatial and temporal profile of the BOLD signal within the midbrain, especially at a resolution required to delineate functional differences between the VTA and SNc.

fMRI techniques mentioned above using high resolution imaging in ultra high filed magnets (like 7 Tesla) promises to improve the localization of the BOLD signal from functionally important areas like the midbrain VTA and SNc. Optimization of already existing imaging techniques and the use of complementary imaging protocols (perfusion weighted imaging, susceptibility weighted imaging, proton density imaging) tailored to the midbrain area would enable us to achieve this.

CONCLUSION AND FUTURE DIRECTIONS

Given what we know of the distinct anatomy and structural connections of the VTA and the SNc, and their functional relevance in various goal directed behaviors, it would be a likely next step to parse out the individual function of these two areas, especially within the human brain. As described in this review, neuroimaging techniques, particularly those using high resolution imaging, offers a plausible approach to investigate the functional architecture of these midbrain regions. This would enable us to ask ecologically valid questions about the role of these midbrain areas in humans, which is typically challenging to do in non-human species. Moreover, the advancement of research methodologies used to examine these midbrain areas can potentially translate into the clinical realm to investigate the role of DA in midbrain related pathologies.

REFERENCES

1. Schultz W (1998). Predictive reward signal of dopamine neurons. *J. Neurophysiol*. **80**: 1–27.
2. Goto Y, Otani S, Grace AA (2007). The Yin and Yang of dopamine release: a new perspective. *Neuropharmacology.* **53**: 583-587.
3. Paxinos G and Huang X (1995). *Atlas of the Human Brainstem*. Academic Press, San Diego, CA.
4. Mai JK, Paxinos G and Voss T (2008). *Atlas of the Human Brain*. Academic Press, New York.
5. Dahlstrom A and Fuxe K (1964). Evidence for the existence of monoamine-containing neurons in the central nervous system. I. Demonstration of monoamines in the cell bodies of brain stem neurons. *Acta Physiol. Scand.* **62**: 1–80.
6. McRitchie D A, Hardman CD and Halliday GM (1996). Cytoarchitectural distribution of calcium binding proteins in midbrain dopaminergic regions of rats and humans. *J. Comp. Neurol.* **364**: 121–150.
7. Nieuwenhuys R, Geeraedts LMG and Veening JG (1982). The medial forebrain bundle of the rat. *J. Comp. Neuro.* **206**: 49-82.
8. Takagi H, Shiosaka M, Tohyama E, Senba E and Sakanaka M (1980). Ascending components of the medial forebrain bundle from the lower brain stem in the rat with special reference to raphe and catecholamine cell groups. A study by the horseradish peroxidase method, *Brain Res.* **193**: 315-337.
9. Poirier LJ, Giyere M and Marchand R (1983). Comparative morphology of the substantia nigra and ventral tegmental area in the monkey, cat and rat. *Brain Res. Bull.* **11**: 371-397.
10. Tork I, Halliday G, Scheibner T and Turner S, The organization of the mesencephalic ventromedial (VMT) in the cat. In *Modulation* of *Sensorimotor Activity during Alterations in Behavioural States* (Ed. R. Bandler) 39-73. (Alan Liss, New York, 1984)
11. McRitchie DA, Cartwright H, Pond SM, van der Schyf CJ, Castagnoli N Jr, van der Nest DG, and Halliday GM (1998). The midbrain dopaminergic cell groups in the baboon Papio ursinus. *Brain Res Bull.* **47** (6): 611-23.
12. Francois C, Yelnik J and Percheron G (1987). Golgi study of the primate substantia nigra. II. Spatial organization of dendritic arborizations in relation to the cytoarchitectonic boundaries and to the striatonigral bundle. *J. Comp. Neurol.* **265**: 473-493.
13. Yelnik J, Francois C, Percheron G and Heyner S (1987). Golgi study of the primate substantia nigra. I. Quantitative morphology and typology of nigral neurons. *J. Comp. Neurol.* **265**: 455-472.
14. Braak H and Braak E (1986). Nuclear configuration and neuronal types of the nucleus niger in the brain of the human adult. *Hum Neurobiol.* **5**: 71-82.
15. Oades RD and Halliday GM (1987). Ventral Tegmental Area (A10) system: neurobiology. 1. Anatomy and connectivity. *Brain Research Reviews* **12**: 117-165.
16. Phillipson OT (1979). Afferent projections to the ventral tegmental area of Tsai and interfascicular nucleus: a horseradish peroxidase study in the rat. *J. Comp. Neural.,* **187** (1): 117-144.
17. Woolf NJ and Butcher LL (1985). Cholinergic systems in the rat brain. II. Projections to the interpeduncular nucleus, *Brain Res. Bull.* **14***:* 63-83.
18. Simon H, Le Moal M and Calas A (1979). Efferents and afferents of the ventral tegmental-A10 region studied after local injection of [^{3}H]leucine and horseradish peroxidase. *Brain Res.* **178**: 17-40.
19. Beckstead RM, Domesick VB and Nauta, WJH (1979). Efferent connections of the substantia nigra and ventral tegmental area in the rat. *Brain Res.* **175**: 91-217.
20. Adell A and Artigas F (2004). The somatodendritic release of dopamine in the ventral tegmental area and its regulation by afferent transmitter systems. *Neurosci Biobehav Rev*. **28**: 415-431.
21. Levitt P, Rakic P and Goldman-Rakic PS (1984). Region specific distribution of catechoiamine afferents in primate cerebral cortex: a fluorescence histochemical analysis, 1. *Comp. Neural.* **227**: 23-36.
22. Brown RM and Goldman PS (1977). Catecholamines in neocortex of rhesus monkeys: regional distribution and ontogenetic development, *Brain Res.,* **124**: 576-580.
23. Cornwall J, Cooper JD and Phillipson OT (1990). Afferent and efferent connections of the laterodorsal tegmental nucleus in the rat. *Brain Res Bull.* **25**: 271–284.
24. Blaha CD, Allen LF, Das S, Inglis WL, Latimer MP, Vincent SR and Winn P (1996). Modulation of

dopamine efflux in the nucleus accumbens after cholinergic stimulation of the ventral tegmental area in intact, pedunculopontine tegmental nucleus-lesioned, and laterodorsal tegmental nucleus-lesioned rats. *J Neurosci.* **16**:714–722.
25. Woolf NJ (1991). Cholinergic systems in mammalian brain and spinal cord. *Prog Neurobiol*. **37**: 475–524.
26. Gerfen CR, Herkenham M and Thibault J (1987). The neostriatal mosaic: II. Patch- and matrix-directed mesostriatal dopaminergic and non-dopaminergic systems. *J. Neurosci.* **7**: 3915-3934**.**
27. Lavoie B and Parent A (1991). Dopaminergic neurons expressing calbindin in normal and parkinsonian monkeys. *NeuroReport.* **2**: 601-604**.**
28. Lynd-Balta E and Haber SN (1992). Organization of dopaminergic striatal projections in relation to peptidergic innervation of the substantia nigra in primate. *Soc. Neurosci. Abstr*. **18**: 306.
29. Szabo J (1979). Strionigral and nigrostriatal connections: anatomical studies. *Appl. Neurophysiol.* **42**: 9–12.
30. Selemon LD and Goldman-Rakic PS (1990). Topographic intermingling of striatonigral and striatopallidal neurons in the rhesus monkey. *J Comp Neurol.* **297**: 359–376.
31. Hedreen JC and DeLong MR (1991). Organization of striatopallidal, striatonigal, and nigrostriatal projections in the Macaque. *J Comp Neurol.* **304**: 569–595.
32. Haber SN, Fudge JL and McFarland NR (2000). Striatonigrostriatal pathways in primates form an ascending spiral from the shell to the dorsolateral striatum. *J Neurosci*. **20**: 2369 –2382.
33. Grace AA and Bunney BS (1983). Intracellular and extracellular electrophysiology of nigral dopaminergic neurons–1. Identification and characterization. *Neuroscience* **10**: 301–315.
34. Grace AA (1990). Evidence for the functional compartmentalization of spike generating regions of rat midbrain dopamine neurons recorded in vitro. *Brain Res.* **524**: 31–41.
35. Grace AA and Bunney BS (1984). The control of firing pattern in nigral dopamine neurons: burst firing. *J. Neurosci.* **4**: 2877–2890.
36. Berridge KC and Robinson TE (1998). What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? *Brain Res. Rev.* **28**: 309–369.
37. Floresco SB, West AR, Ash B, Moore H and Grace AA (2003). Afferent modulation of dopamine neuron firing differentially regulates tonic and phasic dopamine transmission. *Nat. Neurosci.* **6**: 968–973.
38. Grace AA and Bunney BS (1984a). The control of firing pattern in nigral dopamine neurons: single spike firing. *J. Neurosci.* **4**: 2866–2876.
39. Grace AA (1991). Phasic versus tonic dopamine release and the modulation of dopamine system responsivity: a hypothesis for the etiology of schizophrenia. *Neuroscience* **41**: 1–24.
40. Schultz W and Romo R (1990). Dopamine neurons of the monkey midbrain: contingencies of responses to stimuli eliciting immediate behavioral reactions. *J Neurophysiol*, **6**: 607-624.
41. Romo R and Schultz W (1990). Dopamine neurons of the monkey midbrain: contingencies of responses to active touch during self-initiated arm movements. *J Neurophysiol* **63**: 592-606.
42. Schultz W (1997). Dopamine neurons and their role in reward mechanisms. *Current Opinion in Neurobiology* **7**:191-l97.
43. Schultz W and Dickinson A (2000). Neuronal coding of prediction errors. *Annu. Rev. Neurosci*. **23**: 473–500.
44. Ljungberg T, Apicella P and Schultz W (1992). Responses of monkey dopamine neurons during learning of behavioral reactions. *J. Neurophysiol*. **67**: 145–163.
45. Hollerman JR and Schultz W (1998). Dopamine neurons report an error in the temporal prediction of reward during learning. *Nature Neuroscience.* **1** (4): 304-309.
A single unit recording study in non-human primates showing the role of the midbrain DA neurons in reward related learning.
46. Mirenowicz J and Schultz W (1996). Preferential activation of midbrain dopamine neurons by appetitive rather than aversive stimuli. *Nature.* **379**: 449-451.
47. Ungless MA, Magill PJ and Bolam JP (2004). Uniform Inhibition of Dopamine Neurons in the Ventral Tegmental Area by Aversive Stimuli. *Science.* **303**, 2040-2042.
48. D'Ardenne K, McClure SM, Nystrom LE and Cohen JD (2008). BOLD Responses Reflecting Dopaminergic Signals in the Human Ventral Tegmental Area. *Science.* **319**: 1264-1267.
This is a seminal paper that characterizes the function of the VTA in a reward prediction error paradigm using high resolution fMRI in a 3 Tesla magnet.
49. Berns GS, McClure SM, Pagnoni G and Montague PR (2001). Predictability modulates human brain response to reward. *J. Neurosci.***21**: 2793–2798.
50. Blackbum JR, Pfaus JG and Phillips AG (1992). Dopamine functions in appetitive and defensive behaviours. *Prog. Neurobiol.* **39**: 247-279.
51. Salamone JD (1996). The behavioral neurochemistry of motivation: methodological and conceptual issues in studies of the dynamic activity of nucleus accumbens dopamine. *Journal of Neuroscience Methods.* **64**: 137- l49.
52. Kiyatkin EA and Gratton A (1994). Electrochemical monitoring of extracellular dopamine in nucleus accumbens of rats lever pressing for food. *Brain Res.* **652**: 225-234.
53. McCullough LD and Salamone JD (1992b). Involvement of nucleus accumbens dopamine in the motor activity induced by periodic food presentation: a microdialysis and behavioral study. *Brain Res.* **592**: 29-36.
54. Salamone JD, Cousins MS, McCullough LD, Carriero DL and Berkowitz RJ (1994b). Nucleus accumbens dopamine release increases during instrumental lever pressing for food but not food consumption. *Pharmacol. Biochem. Behav.* **49**, 25-31.
55. Kosobud AE, Harris GC and Chapin JK (1994). Behavioral associations of neuronal activity in the ventral tegmental area of the rat. *J. Neurosci*., **14**: 7117-7129.
56. Salamone JD, Steinpreis RE, McCullough LD, Smith P, Grebel D and Mahan K (1991). Haloperidol and nucleus accumbens dopamine depletion suppress lever pressing for food but increase free food consumption in a novel food-choice procedure. *Psychopharmacology*, **104**: 515-521.
57. Salamone JD, Cousins MS and Bucher S (1994a).

Anhedonia or anergia? Effects of haioperidol and nucleus accumbens dopamine depletion on instrumental response selection in a T-mare cost/benefit procedure. *Behav. Brain Res.* **65**: 221-229.
58. Bunzeck N and Duzel E (2006). Absolute Coding of Stimulus Novelty in the Human Substantia Nigra/VTA. *Neuron* **51**: 369–379.
59. Lynd-Balta E and Haber SN (1994). The organization of midbrain projections to the striatum in the primate: sensorimotor-related striatum versus ventral striatum. *Neuroscience.* **59** (3): 625-640.
60. Haber SN (2003). The primate basal ganglia: parallel and integrative networks. *Journal of Chemical Neuroanatomy* **26**: 317–330.
61. Novak P, Novak V, Kangarlu A, Abduljalil AM, Chakeres DW and Robitaille PM (2001). High Resolution MRI of the Brainstem at 8 T. *Journal of Computer Assisted Tomography*. **25** (2): 242–246.
62. Stables LA, Kennan RP and Gore JC (1998). Asymmetric Spin-Echo Imaging of Magnetically Inhomogeneous Systems: Theory, Experiment, and Numerical Studies. *Magn Reson Med.* **40**: 432-442.
63. Song AW (2001). Single shot EPI with signal recovery from susceptibility induced losses. *Mag Res Med.* **46**: 407-411.
64. Guo H and Song AW (2003). Single-shot spiral image acquisition with embedded z-shimming for susceptibility signal recovery. *J.Magn.Reson.Imaging.* **18** (3): 389-395.
65. Glover GH and Law CS (2001). Spiral-in/out BOLD fMRI for increased SNR and reduced susceptibility artifacts. *Magn. Res. Med.,* **46** (3): 515-522.
66. Frahm J, Merboldt KD and Hanicke W (1988). Direct FLASH MR imaging of magnetic field inhomogenieties by gradient compensation. *Mag. Res. Med.,* **6**: 474-480.
67. Cho ZH and Ro YM (1992). Reduction of susceptibility artifact in gradient echo imaging. *Mag. Res. Med.* **23**: 193-196.
68. Duyn JH, van Gelderen P, Li TQ, de Zwart JA, Koretsky AP and Fukunaga M (2007). High-field MRI of brain cortical substructure based on signal phase. *Proc Natl Acad Sci USA*. **104** (28): 11796-801.
This article shows how we can harness magnetic susceptibility differences seen in different parts of brain to generate high contrast to noise ratios in the MR signal.
69. Lin FH, Witzel T, Mandeville JB, Polimeni JR, Zeffiro TA, Greve DN, Wiggins G, Wald LL and Belliveau JW (2008). Event-related single-shot volumetric functional magnetic resonance inverse imaging of visual processing. *Neuroimage.* **42** (1): 230-47.
70. Koch KM, McIntyre S, Nixon TW, Rothman DL and de Graaf RA (2006). Dynamic shim updating on the human brain. *J Magn Reson.* **180** (2): 286-96.
71. Jesmanowicz A, Bandettini PA and Hyde JS (1998). Single-shot half k-space high-resolution gradient recalled EPI for fMRI at 3Tesla. *Magn. Reson. Med.* **40** (5): 754-762.
72. O'Doherty JP, Deichmann R, Critchley HD and Dolan RJ (2002). Neural responses during anticipation of a primary taste reward. *Neuron.* **33**: 815–826.
73. Knutson B and Cooper JC (2005). Functional magnetic resonance imaging of reward prediction. *Current Opinion in Neurology*. **18**: 411–417.
74. Schott BH, Sellner DB, Lauer CJ, Habib R, Frey JU, Guderian S, Heinze HJ and Düzel E (2004). Activation of midbrain structures by associative novelty and the formation of explicit memory in humans. *Learning&Memory*. **11**: 383–387.
75. Wittmann BC, Schott BH, Guderian S, Frey JU, Heinze HJ and Duzel E (2005). Reward-related FMRI activation of dopaminergic midbrain is associated with enhanced hippocampus-dependent long-term memory formation. *Neuron*. **45**: 459–467.
76. van Gelderen P, de Zwart JA, Starewicz P, Hinks RS and Duyn JH (2007). Real-Time Shimming to Compensate for Respiration-Induced *B*0 Fluctuations. *Magn Reson Med.* **57** (2): 362-8.
This article details one method by which we can deal with physiological noise associated with respiration.
77. Napadow V, Dhond R, Kennedy D, Hui KK and Makris N (2006). Automated Brainstem Co-registration (ABC) for MRI. *Neuroimage.* **32** (3): 1113-9.

FURTHER INFORMATION

John Gore's Lab: http://www.vuiis.vanderbilt.edu/