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Development and function of the midbrain dopamine system: what we know and what we need to

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Abstract

The past two decades have seen an explosion in our understanding of the origin and development of the midbrain dopamine system. Much of this work has been focused on the aspects of dopamine neuron development related to the onset of movement disorders such as Parkinson's disease, with the intent of hopefully delaying, preventing or fixing symptoms. While midbrain dopamine degeneration is a major focus for treatment and research, many other human disorders are impacted by abnormal dopamine, including drug addiction, autism and schizophrenia. Understanding dopamine neuron ontogeny and how dopamine connections and circuitry develops may provide us with key insights into potentially important avenues of research for other dopamine-related disorders. This review will provide a brief overview of the major molecular and genetic players throughout the development of midbrain dopamine neurons and what we know about the behavioral- and disease-related implications associated with perturbations to midbrain dopamine neuron development. We intend to combine the knowledge of two broad fields of neuroscience, both developmental and behavioral, with the intent on fostering greater discussion between branches of neuroscience in the service of addressing complex cognitive questions from a developmental perspective and identifying important gaps in our knowledge for future study.

Keywords

Development; midbrain dopamine; nurr1; pitx3; substantia nigra pars compacta; ventral tegmental area

Dopaminergic neurons in the ventral mesodiencephalon (mdDA), also known as midbrain dopamine neurons, are a class of neurons critical for controlling voluntary movement, creating associations with rewarding stimuli, attending to salient environmental stimuli, motivating behavior, maintenance of working memory and the regulation of emotion. Just as proper function of these neurons is critical to basic behavior of animals, changes to this neural population are implicated across many neurological and psychiatric disorders, including Parkinson's disease, schizophrenia and drug addiction. The mdDA neurons and their connectivity therefore represent a critical link between learning, memory and the expression of these cognitive aspects via movement (behavior). Understanding the

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development of mdDA neurons and their connectivity will provide a framework for understanding how genetic and molecular insults through development ultimately impact learning, memory and behavior.

While the term mdDA neuron refers to all DA-expressing neurons in the midbrain, it is important to note that these neural populations are somewhat distinct, in terms of connectivity and neurodevelopment. DA neurons in the ventral tegmental area (VTA) strongly innervate the ventral striatum and the prefrontal cortex, constituting the mesostriatal and mesocortical DA pathways, respectively (Braver *et al.* 1999; Koob 1996; Redgrave *et al.* 1999b; Sawaguchi & Goldman-Rakic 1994). These two pathways are often grouped together and called the mesocorticolimbic pathway. Mesocorticolimbic projections are known to be critical for the creation of reward associations, and recent data suggest a role in signaling aversive outcomes (Bromberg-Martin *et al.* 2010; Comoli *et al.* 2003; Matsumoto & Hikosaka 2009; Redgrave *et al.* 2008; Satoh *et al.* 2003; Tzschentke & Schmidt 2000) (Fig. 1). Changes in this pathway are associated with several mental illnesses, from drug addiction to schizophrenia (Di Chiara 2002; Grace 1991; Kapur 2003; Meyer-Lindenberg *et al.* 2005; Robinson & Berridge 1993; Zahniser & Sorkin 2004).

A separate population of mdDA neurons constitutes the substantia nigra pars compacta (SNc). These neurons are critical for the control of voluntary movement, which is regulated by the SNc projections to dorsal striatum via the nigostriatal pathway, and loss of these neurons leads to the impaired motor function observed in Parkinson's disease (Frank 2005; Hikida *et al.* 2010; Hikosaka 2007; Jin & Costa 2010; Kravitz *et al.* 2010; Marshall *et al.* 1976; Schultz 1986). Interestingly, though classically considered from the motor perspective, recent data implicate SNc DA neurons as also report reward prediction errors (PEs) (Matsumoto & Hikosaka 2009) and perhaps more critically, salience (Brischoux *et al.* 2009; Matsumoto & Hikosaka 2009; Mirenowicz & Schultz 1996; Nomoto *et al.* 2010). While the role of these neurons in maintaining dopaminergic tone critical for allowing voluntary movement is known, how modulations in dopaminergic tone in dorsal striatum are impacted by changes in salience of environmental stimuli still requires research (Fig. 1). While the connectivity and anatomical location of the cell bodies of these two populations of dopamine neurons are somewhat distinct, it is somewhat of an oversimplification, as cells from the VTA do sometimes target striatal cells, and SNc neurons do sometimes project to limbic or cortical regions (Bromberg-Martin *et al.* 2010; Fallon & Loughlin 1982; Loughlin & Fallon 1984; Swanson 1982) and these projections likely carry different types of neural signals (Haruno & Kawato 2006; Lau & Glimcher 2008).

Thus, this little population of neurons [approximately 400 000–600 000 in humans (Pakkenberg *et al.* 1991)] in the midbrain represents a critical control system, with their activity impacting basic functions such as voluntary motor control and influencing the interface between emotional regulation, reward processing and actions. Understanding the neurodevelopmental influences that drive development of this small but powerful population of neurons represents a first step in developing therapeutic interventions to enhance or maintain their activity. While much has been learned about the molecular influences on mdDA neuron development, interfacing this knowledge with more complex cognitive behavior has remained tenuous. This review will highlight the basics of the

neurodevelopment of mdDA neurons, their connectivity and any associations of disruptions through neurodevelopment with changes in behavioral outcomes. Finally, we will attempt to link animal research to human studies, with the goal of illuminating critical unanswered research questions.

Neurodevelopment of mesodiencephalic dopamine neurons

The mdDA ontogeny occurs through a well-regulated series of steps that determine their migration, location, differentiation, specification and connectivity, which are regulated both in space and time. While adult mdDA neurons may be identified by immunolabeling of the tyrosine hydroxylase (TH) enzyme, the rate-limiting enzyme in the synthesis of dopamine, or for the dopamine transporter (DAT), which recovers dopamine and transports it back into the cell (Blanchard *et al.* 1994), there is a need for ways to label specific populations of mdDA neurons throughout development. Maintenance of mdDA specification throughout the life of an organism is continued by the expression of certain transcription factors, among them PITX3, LMX1b, OTX2 and NURR1 (Abeliovich & Hammond 2007). These postmitotic transcription factors have been critical in identifying developmental differences within populations of mdDA neurons.

Migration and differentiation

The mdDA neurons are derived from progenitor cells located on the ventral midline of the neural tube floor plate (Ono *et al.* 2007). During early neurodevelopment, the midbrain/hindbrain border is determined through signaling from the isthmic organizer (Liu & Joyner 2001; Rhinn & Brand 2001). The mdDA neurons are born around E10.5 and arise from the floor plate along the ventral midline (Ono *et al.* 2007; Ye *et al.* 1998). Signaling from the isthmic organizer (which will determine the anterior/posterior patterning) and from the notochord floor plate (which will determine the dorsal/ventral patterning) will produce a border based on differential concentration gradients of their produced morphogens (Nakamura & Watanabe 2005). The isthmus produces fibroblast growth factor 8 (FGF8) (McMahon & Bradley 1990; McMahon *et al.* 1992) and where FGF8 and sonic hedgehog (SHH) expression from the notochord meet, mdDA neuroprogenitors are born (Hynes *et al.* 1995; Ye *et al.* 1998). The expression of *fgf8* is dependent upon WNT1 (McMahon & Bradley 1990; McMahon *et al.* 1992), as are the activation of engrailed genes *En1*/*En2* (Castelo-Branco *et al.* 2003; Danielian & McMahon 1996). Later, *wnt1* expression will be critical for differentiation of mdDA progenitors into specific mdDA subtypes (Brodski *et al.* 2003).

The mesodiencephalon ventricular zone (VZ) induces mitotic cells into postmitotic cell mdDA precursor neurons (Ono *et al.* 2007). The expression of developmental factors such as OTX1, OTX2, SHH and LIM homeobox transcription factor (LMX) from the VZ influences cell fate along a dorsal and ventral axis (Puelles *et al.* 2004; Smidt & Burbach 2007; Smits *et al.* 2006; Vernay *et al.* 2005). Several different transcription factors are critical for the maintenance of differentiation of mdDA neurons, notably PITX3 and LMX1B (Alavian *et al.* 2008; Chakrabarty *et al.* 2012; Puelles *et al.* 2004; Smidt *et al.* 1997, 2000; Smits *et al.* 2006; Vernay *et al.* 2005). In addition to these transcription factors, Engrailed-1 and 2 (EN1,

EN2), neurogenin 2 (NGN2), NURR1 and TGFβ also influence mdDA differentiation. These mdDA progenitors migrate from the ventral midline floor plate following radial glia ventrally and then laterally to populate areas that will become the VTA and SNc (Kawano *et al.* 1995; Shults *et al.* 1990). Around E12 in rats (Gates *et al.* 2006), mdDA neuroprogenitors begin to produce TH (Puelles & Verney 1998), identifying their end neuronal phenotype. Critically, expression of the dopamine neurotransmitter phenotype is dependent upon the NURR1 transcription factor, which regulates proteins critical for dopamine synthesis, such as TH and DAT, and receptor-related proteins such as vesicular monoamine transporter 2 and RET receptor tyrosine kinase (Saucedo-Cardenas *et al.* 1998; Smits *et al.* 2003; Wallen *et al.* 2001; Zetterstrom *et al.* 1997).

However, as mentioned above, the development and maintenance of TH expression (and cell viability) is dependent upon continued expression of several different transcription factors. *Lmx1b* is co-expressed with *Pitx3* and *TH* through development and into adulthood (Dai *et al.* 2008) and the loss of *Lmx1b* leads to a failure to express *Pitx3* later in development and the eventual loss of *Pitx3* expressing mdDA neurons (Smidt *et al.* 2000). *Nurr1* expression begins around the time mdDA progenitors are born (~E10.5) and is also maintained into adulthood. *Lmx1b* mutant mice have mdDA neuroprogenitors that, while failing to express *Pitx3*, normally express *Nurr1* (Smidt *et al.* 2000) and hence, *Th*. The continued expression of *Nurr1* is critical for survival of mdDA neurons. While *Nurr1*-deficient mice display normal mdDA development and mdDA progenitors migrate to the appropriate locations while expressing *Lmx1b*, *Pitx3* and *En1* (Saucedo-Cardenas *et al.* 1998; Wallen *et al.* 1999), the neurons that express *Pitx3* are lost in later development (Saucedo-Cardenas *et al.* 1998). Interestingly, while *Nurr1* expression begins early, it is independent of SHH and FGF8 signaling (Sakurada *et al.* 1999) and induction of *Nurr1* expression might depend on *Foxa1* and *Foxa2* expression (Ferri *et al.* 2007; Lee *et al.* 2010). The continued expression of *Foxa2* appears critical for continued survival of mdDA neurons, with mutations to *Foxa2* leading to Parkinson-like symptoms in mice (Kittappa *et al.* 2007).

After mdDA precursors migrate to their final locations (~E11.5), *Pitx3* expression begins (Smidt *et al.* 1997, 2004a,b; van den Munckhof *et al.* 2003). In mice with mutations to the *Pitx3* gene (*aphakia* mice), mdDA development proceeds normally until around E12.5, when more lateral *TH*-expressing mdDA neurons decrease in number (Hwang *et al.* 2003; Nunes *et al.* 2003; van den Munckhof *et al.* 2003). This lateral population of mdDA neurons normally develops into the SNc, and *Pitx3* mutations lead to a decrease in mdDA neurons in developing SNc. The *aphakia* mice have decreased nigrostriatal projections, while leaving VTA mdDA population unscathed (Hwang *et al.* 2003; Nunes *et al.* 2003; van den Munckhof *et al.* 2003). This was among the first evidence suggesting that there may be different developmental plans for VTA and SNc dopamine neurons. The expression of *Pitx3* is important for the expression of BDNF in mdDA SNc neurons, and supplementation of BDNF not only prevents SNc cell death in *Pitx3* null mice but also prevents cell death when treated with 6-OHDA (Peng *et al.* 2011). Thus, *Pitx3* expression is critically linked not only to neurotransmitter phenotype and *DAT* expression but also to the survival of the more lateral mdDA population of neurons. This information potentially implicates both *Nurr1* and *Pitx3* expression in SNc normal development, and in abnormalities that may underlie detrimental changes to nigrostriatal pathway and ultimately to movement deficits observed

in Parkinson's disease patients. Interestingly, some recent data have implicated SNc projections in attention and salience monitoring (Berridge 2007; Berridge & Robinson 1998; Bromberg-Martin *et al.* 2010), which will be a topic of discussion below. The mdDA neurons also being to express *En1* and *En2* around E11.5, which, like *Nurr1* and *Pitx3* expression, is maintained throughout adulthood (Alberi *et al.* 2004; Li & Joyner 2001; Liu & Joyner 2001; Simon *et al.* 2001). Data suggest that the expression of *En1* and *En2* is necessary for cell survivability in postmitotic mdDA neurons (Alberi *et al.* 2004). Like *Pitx3* mutants, mutations impacting *En1*/*En2* lead to cell death selectively in the SNc population and lead to eventual motor deficits (Sgado *et al.* 2006; Sonnier *et al.* 2007). *Pitx3* expression is different between VTA and SNc, with VTA mdDA neurons expressing *Pitx3* around six times more than SNc neurons (Korotkova *et al.* 2005). As noted, much of our understanding of the development and survivability of mdDA populations has revolved around timing and expression differences among the future SNc populations. It remains to be seen whether SNc mdDA neurons develop differently than VTA mdDA neurons simply owing to additional neurodevelopmental steps, or whether there are as-yet-unknown molecular and genetic developmental plans that distinguish future VTA neurons from future SNc neurons early in development.

Connectivity

While the development and differentiation of mdDA neurons is critical, ultimately neural connectivity determines what functional aspects of an animal's life these DA neurons are capable of influencing. Critically, the manner and amount with which mdDA neurons innervate other neural structures may play an essential role in aspects as simple as motivating basic movement and complex as cognition. Indeed, changes in connectivity of mdDA with other neural structures have been associated with drug use and addiction (Robinson & Kolb 2004), as have changes to the expression of axon guidance cues (Flores *et al.* 2006; Halladay *et al.* 2000; Zhang *et al.* 2004, 2005). Despite this fundamental role, little is known about the development of mdDA neuron connectivity, especially relating to mesocortical DA pathways, as most research has focused on developing mdDA connectivity with the striatum and control of voluntary movement as a function of Parkinson's disease. What is known focuses on increases in available DA in areas like the prefrontal cortex (Kalsbeek *et al.* 1988; Rosenberg & Lewis 1994, 1995). Additionally, even less is known about the neurodevelopment of mdDA fibers targeting the hippocampus, lateral habenula and amygdala beyond approximate developmental timing and our knowledge of the importance of DA in the function of mature versions of these neural structures (Kim *et al.* 2011; Lisman & Grace 2005).

Among the first data delineating axon guidance, NTN1–DCC and ROBO–SLIT have been shown to be necessary signaling complexes. NTN1–DCC has been shown to be localized to the mdDA (Serafini *et al.* 1996). While NTN1 and DCC null mice exist, it is unknown if any defects in mdDA axon guidance are observed in the adult mice (Nishikawa *et al.* 2003; Serafini *et al.* 1996). While gross neuroanatomy in these animals appears intact, these mice do show amphetamine sensitization (Flores *et al.* 2005), suggesting some form of altered striatal DA transmission. Axons from mdDA neurons appear to be repulsed by the expression of receptors such as ROBO1 (expressed by both VTA and SNc neurons) and

ROBO2 (expressed only by SNc neurons) and axon guidance molecules such as SLIT1, SLIT2 and SLIT3 (Hivert *et al.* 2002; Holmes *et al.* 1998; Lin *et al.* 2005; Marillat *et al.* 2002). The combined action of this repulsion works to direct axon growth toward the rostral brain (Bagri *et al.* 2002; Gates *et al.* 2004, 2006; Marillat *et al.* 2002). Further, repulsive signaling by the dorsal midbrain expressing SLIT1 later in development (E15) keeps mdDA axon growth along a ventral, rather than dorsal, trajectory (Gates *et al.* 2004). However, these molecules only reflect repulsive cues, as the chemoattractant cues that orient and attract mdDA axons toward striatum and the forebrain remains unknown.

As mdDA axon growth proceeds rostrally, it will find fertile ground in the striatum. Limited slit expression is observed in the striatum of rodents before adulthood, suggesting that the striatum is a hospitable environment for mdDA projections. However, SLIT2 expression is detected in a sparse population of striatal neurons, which are presumed to be cholinergic striatal inhibitory interneurons. Additionally, SLIT2 expression begins around postnatal day 5, suggesting a potential pruning mechanism for mdDA projections expressing ROBO (Dimitrova *et al.* 2008; Ozdinler & Erzurumlu 2002; Pasterkamp *et al.* 2009; Smidt & Burbach 2009). Interestingly, neither the mesostriatal pathway nor the mesolimbic pathways appear to display a preference for dorsal or ventral striatum (Hu *et al.* 2004). This specificity presumably arises by selective pruning of VTA or SNc axons, though the exact mechanism for this pruning remains unknown and though common neurotrophic support in the form of GDNF, BDNF or neurotrophins 3, 4, 5 may play a role.

The mdDA axon growth forming the medial forebrain bundle relies upon Nkx2.1 to maintain a direct projection, as the MFB crosses the midline in Nkx2.1 mutant animals, likely owing to a loss of repulsive molecules from the hypothalamic area, notably SLIT2 and semaphorin 3A (Kawano *et al.* 2003). As these projections move more rostrally, the MFB chemoattractant must be reduced, else mdDA projections would remain here, rather than continuing in their rostral and eventual dorsal pathway. Interestingly, embryonic neo-cortex is repulsive to mdDA axons (Gates *et al.* 2004), though mdDA projections will eventually innervate some, but not other, frontal cortical regions (Hemmendinger *et al.* 1981a,b). Survivability of these neurons and their axon outgrowths have been linked to expression of *Engrailed 1* (Fuchs *et al.* 2012). Important remaining questions include how to differentiate SNc from VTA efferents in embryonic tissue and how SNc mdDA projections innervate dorsal striatal regions, while VTA DA projections innervate ventral striatal and frontal cortical regions. Identifying the chemoattractants and axon pruning mechanisms involved in determining the nigrostriatal and mesocortical pathways will be helpful for understanding the final development of mdDA connectivity and will likely uncover promising new avenues of research into the etiology of different neuropsychiatric disorders.

Behavioral implications

Much of what is known about mdDA development surrounds SNc cell development and survivability. However, given the importance of both VTA and SNc in complex behaviors beyond voluntary movement, discussion on this topic is warranted. A central pillar of learning theory rests upon the ability of an organism to learn cause and effect as it navigates the world. This associative learning occurs when an outcome of an action leads to a better-

than-expected outcome. A positive outcome should become associated with the previous action, such that the previous action would become reinforced and the organism will repeat this action in the future (Fig. 2). When an outcome of an action is worse-than-expected, the previous association should either degrade or be avoided. These central points are elegantly described as positive or negative prediction errors, respectively (Rescorla & Wagner 1972). Populations of mdDA neurons have been implicated in signaling these positive and negative PE signals (Schultz 1997, 1998; Schultz & Dickinson 2000). *In vivo* recordings of single neuron activity in animals (Hollerman & Schultz 1998; Jo *et al.* 2013; Mirenowicz & Schultz 1994; Pan *et al.* 2005; Roesch *et al.* 2007a; Waelti *et al.* 2001), human imaging (D'Ardenne *et al.* 2008), fast-scan cyclic voltammetry (Day *et al.* 2007; Hart *et al.* 2014; Oleson *et al.* 2012) and recently, optogenetic experiments (Steinberg *et al.* 2013) support and affirm the hypothesis that phasic activity changes of mdDA neurons signal reward PEs, meaning that mdDA neurons increase firing to signal positive PE, and briefly pause firing to signal negative PE. Thus, mdDA neuronal firing may act as a teaching mechanism, updating the probability of selecting a future rewarded action (Bromberg-Martin *et al.* 2010; Da Cunha *et al.* 2009; Montague *et al.* 1996; Schultz 1998; Schultz *et al.* 1997).

However, much of the previous research has investigated how mdDA neurons signal PEs in an evaluative role. That is, these forms of research investigate how neural activity related to different valued response option, either positive or negative PEs, or differences in the values between cues [for example, neural activity between large or small valued outcomes (Roesch *et al.* 2007b)]. The vast majority of this research has focused on the DA neurons of the VTA. Recent research suggests that there are dissociable activity patterns based on mdDA location. Unlike neural activity in VTA, the activity of SNc mdDA neurons might play a more critical role in signaling salience (Kakade & Dayan 2002; Matsumoto & Hikosaka 2009), signaling when outcomes are unexpected, either positively or negatively. This salience signal could play an additional critical role in learning, making cues associated with the previous action more salient (Bissonette & Roesch 2015; Bromberg-Martin *et al.* 2010; Redgrave & Gurney 2006; Redgrave *et al.* 1999a). Thus, the combination of mdDA neurons in SNc signaling salience after unexpected outcomes and mdDA neurons from VTA assigning the value of the unexpected outcome (positive or negative) may represent a complementary and powerful approach to learning (Fig. 2).

While functionally dissociable populations of mdDA neurons may generally segregate between the VTA and SNc, there is a greater role for mdDA neurons than signaling PEs and attention/salience or providing tonic DA levels necessary for voluntary movement. By signaling incentive salience, mdDA neurons may promote behavioral responding in additional ways than by signaling PEs, which may only represent a readout of other upstream regions that are reflecting learning (Berridge 2007). This additional hypothesis of the role of DA is that mdDA is responsible for the 'wanting' aspects of rewards, but not the 'liking' or 'learning' aspects (Berridge & Robinson 1998). By developing the 'wanting' aspects of stimuli, the incentive salience hypothesis posits that DA release makes stimuli 'wanted' in that the incentive of that stimuli increases, thus grabbing more attention. An additional feature of the incentive salience hypothesis is that by incenting stimuli through increasing the salience of the stimuli, motivation to seek out the stimulus is increased. The relative strength of the incentive salience signal may also be modulated by homeostatic

mechanisms (e.g. hunger or thirst) where animals 'want' a particular stimuli more than others, depending on their physiological state (Berridge 2007).

This research is striking, partially because such a small group of neurons [~500 000 in adult humans, representing about 0.0005% of total neurons in the human brain (Pakkenberg *et al.* 1991)] play such a fundamental role in movement, learning, motivation, decision making, value encoding and attention, each of which represents an essential aspects of life. Despite representing the critical nexus between action and learning, and despite our growing knowledge of the molecular and genetic aspects of mdDA development, very little discussion is given to how changes throughout development may impact this teaching system. As discussed above, mdDA neurons destined for VTA or SNc appear to have slightly different developmental trajectories. How might small differences, not just in survivability but in differentiation and connectivity impact the differences in cognition between animals or the development of mental illness?

The vast majority of behavioral research investigating developmental perturbations to the mdDA system is focused on neural degeneration and Parkinson's disease modeling through motor deficits. While these animals provide an opportunity to behaviorally study and attempt to characterize the implications of developmentally manipulated mdDA system, it is important to note that this is not a perfect model. Parkinson's disease patients do not always show DA-dependent cognitive impairments (Robbins & Cools 2014) though on some occasions these impairments are sensitive to treatment with L-DOPA (Downes *et al.* 1989; Lange *et al.* 1992) and certain aspects of cognition may be related to several genetic factors in humans including catecholamine-*O*-methyltransferase (COMT) Val158Met polymorphism (Mattay *et al.* 2003; Rakshi *et al.* 1999). Implicit in the reward prediction error model of dopamine function is the idea that decreased release of dopamine will track with a decreasing capability to perform stimulus-response and reinforcement learning. In humans with PD, sometimes L-dopa does not improve reinforcement learning deficits (Shiner *et al.* 2012) and might worsen them (Hiebert *et al.* 2014; Macdonald *et al.* 2013) though other experiments have shown improved reinforcement learning while on PD medication, increasing learning rates from positive, rewarded outcomes without impacting potential negative prediction errors on negative outcomes (Frank *et al.* 2004, 2007). While this outcome may call into question how reliable the RPE hypothesis of mdDA function is regarding humans, it is still difficult to account for all variables in clinical scenarios. As SNc cell loss is associated with the severity of PD, rather than VTA DA cell loss, the majority of RPE signaling mdDA neurons may be spared in PD patients. Regardless, this topic requires further investigation and caution should be taken when considering how the RPE hypothesis performs in relation to human PD patient data and the following animal data.

Mice heterozygous for the *Engrailed 1* gene, *En1*+/−, show progressive loss of SNc mdDA neurons starting from postnatal week 8, while also displaying a decrease in mdDA VTA neurons at week 48 (Sonnier *et al.* 2007). The *En1*+/− mice moved less in an open field, reared less, spent more time immobile and consumed less saccharin water compared with wild-type (WT) animals (Sonnier *et al.* 2007). *En1*+/−; *En2*−/− mice exhibit a 67% decrease in SNc, but not VTA neurons in adulthood (Sgado *et al.* 2006). Additionally, *En1*+/−; *En2*−/− mice move less in an open field, hang for shorter duration, freeze more during a swim test

and interestingly, eat less and gain less weight when compared with *En2*−/− mice (Sgado *et al.* 2006). Pitx3-deficient mice (*aphakia* mice) have been shown to have a selective decrease in SNc dopamine neurons, leading to a 90% decrease in dorsal striatal DA (Hwang *et al.* 2003; Nunes *et al.* 2003), which corresponds with the development of sensorimotor deficits on locomotor tests. *Aphakia* mice take longer to traverse a beam test, make more steps to do so and rear less compared with WT mice. These motor deficits were brought back to baseline in terms of time to traverse and step number for a beam crossing test by the administration of L-DOPA, and spontaneous activity was increased after L-DOPA administration (Hwang *et al.* 2005). Although Pitx3-deficient mice present with motor deficits that may be rescued by L-DOPA, it is important to consider that this may not be a pure motor deficit, but that these tests reflect aspects of sensorimotor capabilities as well. Additionally, neural degeneration was already observed in newborn mice, complicating the question of what normal motor development and associated deficits actually reflect (Hwang *et al.* 2003).

Recently, there have been efforts to tie the function of dopamine for both expression of motor behaviors and learning (see Taylor *et al.* 2010 for a good review on Parkinson's disease models in particular). Beeler *et al.* (2010) used *aphakia* mice to demonstrate an impairment in learning novel motor-driven behaviors, such as maintaining balance on a rotarod and running on a treadmill, which was rescued by administration of L-DOPA (Beeler *et al.* 2010). This same group had previously demonstrated a loss of cocaine locomotor sensitization in *aphakia* mice in terms of distance traveled in an open field (Beeler *et al.* 2009). Attempts have been made to use diminished sucrose consumption in *aphakia* mice as a model of depression, in addition to the Parkinson's disease model (Kim *et al.* 2014a,b). Along with rotarod deficits additional differences have been observed in *aphakia* mice in a swimming or dry T-maze task investigating egocentric spatial responding in a task where mice swim to find a platform (escape the water), or learn to turn left or right for a food reward. *Aphakia* mice were slower than WT mice in finding the platform. In a dry T-maze, *aphakia* mice were faster than WT mice in finding their correct food reward, though they did not 'improve' their latency that was viewed as a deficit (Ardayfio *et al.* 2008). Recently, altered striatal dopamine type 2 receptor overexpression in mice demonstrated decreased social investigation and vocalizations (Kabitzke *et al.* 2015) throughout different developmental time points. Importantly and as noted above, it is not always the case that learning deficits develop along with Parkinson's disease in humans (Robbins & Cools 2014) and so any deficits to learning or flexible behavior observed in developmental mouse models need to be understood with the caveat that no single animal model will completely demonstrate construct and content validity.

Studies of humans have implicated chromosome 7q as a region containing genes with susceptibility for Autism. Among these genes are ones critical for mdDA development, including *WNT2* and *Engrailed2*. Association work has linked *Engrailed 2* (located at chromosome 7q36) with ASD (Gharani *et al.* 2004) in humans. We know from developmental work that *En1*/*En2* are implicated in mdDA development (Alberi *et al.* 2004) and others have suggested that mutant *Engrailed* mice may be useful in studying aspects of ASD (Moy *et al.* 2006). For example, *En2*−/− mice engage in decreased social behaviors, including decreased social sniffing, play, allogrooming and in the resident intruder assay,

while also displaying increased escape latency in a Morris water maze task (Cheh *et al.* 2006; Moy & Nadler 2008). Additionally, *En2*−/− mice never improved above chance in terms of time spent in different quadrants, suggesting that they failed to learn the location of the hidden platform (Cheh *et al.* 2006). These results have been repeated recently (Brielmaier *et al.* 2012) and expanded to include deficits in both cued and contextual fear memory expression, but not during training. Interestingly, though *En2*−/− mice displayed significantly decreased social behaviors, their performance on a novel object recognition task was intact (Brielmaier *et al.* 2012), again suggestive of an ASD association. Other associations with ASD may stem from *Otx* mutant mice (Silverman *et al.* 2010), which display decreased social interactions and vocalizations (Winslow *et al.* 2000) though the results are not as clear as with mutations to *Engrailed* (Crawley 2007).

As of yet, the critical implication of developmental SNc perturbations on motivation salience, incentive salience and PE signaling remains uncharacterized and not well understood. While the important role of DA signaling in signaling motivational salience is well documented (Berridge & Robinson 1998; Lex & Hauber 2008; Rutledge *et al.* 2015; Salamone & Correa 2012; Salamone *et al.* 2007; Smith *et al.* 2011), understanding how particular DA neurons signal motivational salience rather than PEs is still a field of active research. Further, dissociating the role of mdDA neurons in signaling salience or PEs and incentive salience requires additional research. While signals of salience and PEs appear to have a rough dorsal–ventral segregation in the VTA and SNc, respectively, it remains unknown if there is any such anatomical segregation of neurons signaling incentive salience. What is known is that DA release in the core and shell of the nucleus accumbens seems to reflect different types of DA signals, where DA release in the core reflects PE signals, while DA release in the shell better reflects incentive salience signal (Saddoris *et al.* 2015). Perhaps the majority of mdDA neurons contribute to an incentive salience signal while a minority broadcast discrete PE or salience signals. What this means for animal models that manipulate the development of mdDA neurons is unclear. Although decreased motivation is a clinical component of disorder like Parkinson's disease, it is perhaps a symptom related to a decrease in the 'wanting' aspect of mdDA neural degeneration. Testing rodents in behavioral paradigms designed to dissociate 'wanting' from 'liking' would provide direct answers (Berridge 2007; Berridge & Robinson 1998; Smith *et al.* 2011).

There are clear avenues to pursue based off human literature. Nurr1 expression in dopamine neurons is decreased in chronic human cocaine abusers (Bannon *et al.* 2002). As Nurr1 regulates DAT expression by impacting DAT transcription and DAT expression is also decreased in chronic cocaine users, it is possible that Nurr1 expression may be impacted by drugs of addiction, thereby impacting behavior (Bannon *et al.* 2002). Alterations in Nurr1 genes leading to diminished Nurr1 expression have also been observed in humans with schizophrenia (Buervenich *et al.* 2000). Mutations to the gene for COMT involving the common V(108/158)M substitution, which reduced DA catabolism, are associated with decreased circuit interaction of mdDA and prefrontal cortical areas, notably dorsolateral prefrontal cortex (Meyer-Lindenberg *et al.* 2005). These results are associated with reward responsivity, but not risk-seeking behaviors, suggesting implications for clinical symptoms of anhedonia (Lancaster *et al.* 2015). Additionally, symptoms associated with the rare genetic disorder Williams–Beuren syndrome may have origins in altered mdDA

development. Williams syndrome is caused by a microdeletion of 21 genes on chromosome 7q11.23 and, along with hypersociability and stereotypical faces, there are extrapyramidal symptoms associated with the motor system including involuntary, choreiform movements and dystonia, which are hypothesized to be related to altered SNc development (Gagliardi *et al.* 2007; Thompson *et al.* 2005). Other neurodevelopmental disorders, such as dystonias and attention-deficit hyperactivity disorder, are theorized to originate from developmental perturbations to the dopamine system (Madras *et al.* 2005; Perlmutter & Mink 2004; Walker & Shashidharan 2003) though more research will be needed to identify specific developmental perturbations associated with each disorder. Future studies using sophisticated behavioral, *in vivo* electrophysiological, optogenetic and molecular techniques will be needed to tease apart the complex interaction of altered mdDA neuron development and aspects of decision making in the face of altered associative circuitry. Given our growing knowledge of mdDA development, dissociating the developmental trajectories of these different functional neural populations remains an area of high importance and as our behavioral, genetic and molecular tools develop, we will begin to address these questions.

Future directions

Over the past two decades, modern scientific research has made tremendous strides in discerning the developmental process of midbrain dopamine neurons. The majority of these efforts have been made with an eye toward preventing the development of neurodegenerative disorders involving the dopamine system, like Parkinson's disease. However, with more data implicating changes to the mdDA system in complex psychiatric disorders with much earlier onsets, such as Autism or schizophrenia, there is a growing need to understand how early developmental differences to the mdDA population of cells impact organisms. Specifically, it is important to understand what perturbations early in life may lead to long-term significant impacts to the mdDA system. Some of the main unanswered and remaining topics for investigation are summarized in Fig. 3. Once the importance of these changes has been determined, targeted early interventions and novel therapeutics may be developed. But first, we need to develop a more firm understanding of how mdDA neurons impact animal decisions and behavior, and to identify the individual developmental trajectories of each of these populations of neurons.

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References

Abeliovich A, Hammond R. Midbrain dopamine neuron differentiation: factors and fates. Dev Biol. 2007; 304:447–454. [PubMed: 17331494]

Alavian KN, Scholz C, Simon HH. Transcriptional regulation of mesencephalic dopaminergic neurons: the full circle of life and death. Mov Disord. 2008; 23:319–328. [PubMed: 18044702]

Alberi L, Sgado P, Simon HH. Engrailed genes are cell-autonomously required to prevent apoptosis in mesencephalic dopaminergic neurons. Development. 2004; 131:3229–3236. [PubMed: 15175251]

Ardayfio P, Moon J, Leung KK, Youn-Hwang D, Kim KS. Impaired learning and memory in Pitx3 deficient aphakia mice: a genetic model for striatum-dependent cognitive symptoms in Parkinson's disease. Neurobiol Dis. 2008; 31:406–412. [PubMed: 18573342]

Bagri A, Marin O, Plump AS, Mak J, Pleasure SJ, Rubenstein JL, Tessier-Lavigne M. Slit proteins prevent midline crossing and determine the dorsoventral position of major axonal pathways in the mammalian forebrain. Neuron. 2002; 33:233–248. [PubMed: 11804571]

Bannon MJ, Pruetz B, Manning-Bog AB, Whitty CJ, Michelhaugh SK, Sacchetti P, Granneman JG, Mash DC, Schmidt CJ. Decreased expression of the transcription factor NURR1 in dopamine neurons of cocaine abusers. Proc Natl Acad Sci USA. 2002; 99:6382–6385. [PubMed: 11959923]

Beeler JA, Cao ZF, Kheirbek MA, Zhuang X. Loss of cocaine locomotor response in Pitx3-deficient mice lacking a nigrostriatal pathway. Neuropsychopharmacology. 2009; 34:1149–1161. [PubMed: 18704092]

Beeler JA, Daw N, Frazier CR, Zhuang X. Tonic dopamine modulates exploitation of reward learning. Front Behav Neurosci. 2010; 4:170. [PubMed: 21120145]

Berridge KC. The debate over dopamine's role in reward: the case for incentive salience. Psychopharmacology (Berl). 2007; 191:391–431. [PubMed: 17072591]

Berridge KC, Robinson TE. What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? Brain Res Brain Res Rev. 1998; 28:309–369. [PubMed: 9858756]

Bissonette, GB., Roesch, MR. Current Topics in Behavioral Neuroscience. Springer; Berlin/Heidelberg: 2015. Neurophysiology of reward-guided behavior: correlates related to predictions, value, motivation, errors, attention, and action; p. 1-32.

Blanchard V, Raisman-Vozari R, Vyas S, Michel PP, Javoy-Agid F, Uhl G, Agid Y. Differential expression of tyrosine hydroxylase and membrane dopamine transporter genes in subpopulations of dopaminergic neurons of the rat mesencephalon. Brain Res Mol Brain Res. 1994; 22:29–38. [PubMed: 7912404]

Braver TS, Barch DM, Cohen JD. Cognition and control in schizophrenia: a computational model of dopamine and prefrontal function. Biol Psychiatry. 1999; 46:312–328. [PubMed: 10435197]

Brielmaier J, Matteson PG, Silverman JL, Senerth JM, Kelly S, Genestine M, Millonig JH, DiCicco-Bloom E, Crawley JN. Autism-relevant social abnormalities and cognitive deficits in engrailed-2 knockout mice. PLoS One. 2012; 7:e40914. [PubMed: 22829897]

Brischoux F, Chakraborty S, Brierley DI, Ungless MA. Phasic excitation of dopamine neurons in ventral VTA by noxious stimuli. Proc Natl Acad Sci USA. 2009; 106:4894–4899. [PubMed: 19261850]

Brodski C, Weisenhorn DM, Signore M, Sillaber I, Oesterheld M, Broccoli V, Acampora D, Simeone A, Wurst W. Location and size of dopaminergic and serotonergic cell populations are controlled by the position of the midbrain-hindbrain organizer. J Neurosci. 2003; 23:4199–4207. [PubMed: 12764108]

Bromberg-Martin ES, Matsumoto M, Hikosaka O. Dopamine in motivational control: rewarding, aversive, and alerting. Neuron. 2010; 68:815–834. [PubMed: 21144997]

Buervenich S, Carmine A, Arvidsson M, Xiang F, Zhang Z, Sydow O, Jonsson EG, Sedvall GC, Leonard S, Ross RG, Freedman R, Chowdari KV, Nimgaonkar VL, Perlmann T, Anvret M, Olson L. NURR1 mutations in cases of schizophrenia and manic-depressive disorder. Am J Med Genet. 2000; 96:808–813. [PubMed: 11121187]

Castelo-Branco G, Wagner J, Rodriguez FJ, Kele J, Sousa K, Rawal N, Pasolli HA, Fuchs E, Kitajewski J, Arenas E. Differential regulation of midbrain dopaminergic neuron development by Wnt-1, Wnt-3a, and Wnt-5a. Proc Natl Acad Sci USA. 2003; 100:12747–12752. [PubMed: 14557550]

Chakrabarty K, Von Oerthel L, Hellemons A, Clotman F, Espana A, Groot Koerkamp M, Holstege FC, Pasterkamp RJ, Smidt MP. Genome wide expression profiling of the mesodiencephalic region identifies novel factors involved in early and late dopaminergic development. Biol Open. 2012; 1:693–704. [PubMed: 23213462]

Cheh MA, Millonig JH, Roselli LM, Ming X, Jacobsen E, Kamdar S, Wagner GC. En2 knockout mice display neurobehavioral and neurochemical alterations relevant to autism spectrum disorder. Brain Res. 2006; 1116:166–176. [PubMed: 16935268]

Comoli E, Coizet V, Boyes J, Bolam JP, Canteras NS, Quirk RH, Overton PG, Redgrave P. A direct projection from superior colliculus to substantia nigra for detecting salient visual events. Nat Neurosci. 2003; 6:974–980. [PubMed: 12925855]

Crawley JN. Mouse behavioral assays relevant to the symptoms of autism. Brain Pathol. 2007; 17:448–459. [PubMed: 17919130]

Da Cunha, C., Wietzikoski, EC., Bortolanza, M., Dombrowski, PA., dos Santos, LM., Boschen, SL., Miyoshi, E., Vital, MA., Boerngen-Lacerda, R., Andreatini, R. Birth, Life and Death of Dopaminergic Neurons in the Substantia Nigra. Springer; Berlin/Heidelberg: 2009. Non-motor function of the midbrain dopaminergic neurons; p. 147-160.

Dai JX, Hu ZL, Shi M, Guo C, Ding YQ. Postnatal ontogeny of the transcription factor Lmx1b in the mouse central nervous system. J Comp Neurol. 2008; 509:341–355. [PubMed: 18512225]

Danielian PS, McMahon AP. Engrailed-1 as a target of the Wnt-1 signalling pathway in vertebrate midbrain development. Nature. 1996; 383:332–334. [PubMed: 8848044]

D'Ardenne K, McClure SM, Nystrom LE, Cohen JD. BOLD responses reflecting dopaminergic signals in the human ventral tegmental area. Science. 2008; 319:1264–1267. [PubMed: 18309087]

Day JJ, Roitman MF, Wightman RM, Carelli RM. Associative learning mediates dynamic shifts in dopamine signaling in the nucleus accumbens. Nat Neurosci. 2007; 10:1020–1028. [PubMed: 17603481]

Di Chiara G. Nucleus accumbens shell and core dopamine: differential role in behavior and addiction. Behav Brain Res. 2002; 137:75–114. [PubMed: 12445717]

Dimitrova S, Reissaus A, Tavosanis G. Slit and Robo regulate dendrite branching and elongation of space-filling neurons in Drosophila. Dev Biol. 2008; 324:18–30. [PubMed: 18817767]

Downes JJ, Roberts AC, Sahakian BJ, Evenden JL, Morris RG, Robbins TW. Impaired extra-dimensional shift performance in medicated and unmedicated Parkinson's disease: evidence for a specific attentional dysfunction. Neuropsychologia. 1989; 27:1329–1343. [PubMed: 2615934]

Fallon JH, Loughlin SE. Monoamine innervation of the forebrain: collateralization. Brain Res Bull. 1982; 9:295–307. [PubMed: 6129040]

Ferri AL, Lin W, Mavromatakis YE, Wang JC, Sasaki H, Whitsett JA, Ang SL. Foxa1 and Foxa2 regulate multiple phases of midbrain dopaminergic neuron development in a dosage-dependent manner. Development. 2007; 134:2761–2769. [PubMed: 17596284]

Flores C, Manitt C, Rodaros D, Thompson KM, Rajabi H, Luk KC, Tritsch NX, Sadikot AF, Stewart J, Kennedy TE. Netrin receptor deficient mice exhibit functional reorganization of dopaminergic systems and do not sensitize to amphetamine. Mol Psychiatry. 2005; 10:606–612. [PubMed: 15534618]

Flores JA, Galan-Rodriguez B, Ramiro-Fuentes S, Fernandez-Espejo E. Role for dopamine neurons of the rostral linear nucleus and periaqueductal gray in the rewarding and sensitizing properties of heroin. Neuropsychopharmacology. 2006; 31:1475–1488. [PubMed: 16292327]

Frank MJ. Dynamic dopamine modulation in the basal ganglia: a neurocomputational account of cognitive deficits in medicated and nonmedicated Parkinsonism. J Cogn Neurosci. 2005; 17:51–72. [PubMed: 15701239]

Frank MJ, Seeberger LC, O'Reilly RC. By carrot or by stick: cognitive reinforcement learning in parkinsonism. Science. 2004; 306:1940–1943. [PubMed: 15528409]

Frank MJ, Samanta J, Moustafa AA, Sherman SJ. Hold your horses: impulsivity, deep brain stimulation, and medication in parkinsonism. Science. 2007; 318:1309–1312. [PubMed: 17962524]

Fuchs J, Stettler O, Alvarez-Fischer D, Prochiantz A, Moya KL, Joshi RL. Engrailed signaling in axon guidance and neuron survival. Eur J Neurosci. 2012; 35:1837–1845. [PubMed: 22708594]

Gagliardi C, Martelli S, Burt MD, Borgatti R. Evolution of neurologic features in Williams syndrome. Pediatr Neurol. 2007; 36:301–306. [PubMed: 17509461]

Gates MA, Coupe VM, Torres EM, Fricker-Gates RA, Dunnett SB. Spatially and temporally restricted chemoattractive and chemorepulsive cues direct the formation of the nigrostriatal circuit. Eur J Neurosci. 2004; 19:831–844. [PubMed: 15009130]

Gates MA, Torres EM, White A, Fricker-Gates RA, Dunnett SB. Re-examining the ontogeny of substantia nigra dopamine neurons. Eur J Neurosci. 2006; 23:1384–1390. [PubMed: 16553799]

Gharani N, Benayed R, Mancuso V, Brzustowicz LM, Millonig JH. Association of the homeobox transcription factor, ENGRAILED 2, 3, with autism spectrum disorder. Mol Psychiatry. 2004; 9:474–484. [PubMed: 15024396]

Grace AA. Phasic versus tonic dopamine release and the modulation of dopamine system responsivity: a hypothesis for the etiology of schizophrenia. Neuroscience. 1991; 41:1–24. [PubMed: 1676137]

Halladay AK, Yue Y, Michna L, Widmer DA, Wagner GC, Zhou R. Regulation of EphB1 expression by dopamine signaling. Brain Res Mol Brain Res. 2000; 85:171–178. [PubMed: 11146119]

Hart AS, Rutledge RB, Glimcher PW, Phillips PE. Phasic dopamine release in the rat nucleus accumbens symmetrically encodes a reward prediction error term. J Neurosci. 2014; 34:698–704. [PubMed: 24431428]

Haruno M, Kawato M. Different neural correlates of reward expectation and reward expectation error in the putamen and caudate nucleus during stimulus-action-reward association learning. J Neurophysiol. 2006; 95:948–959. [PubMed: 16192338]

Hemmendinger LM, Garber BB, Hoffmann PC, Heller A. Selective association of embryonic murine mesencephalic dopamine neurons in vitro. Brain Res. 1981a; 222:417–422. [PubMed: 7284789]

Hemmendinger LM, Garber BB, Hoffmann PC, Heller A. Target neuron-specific process formation by embryonic mesencephalic dopamine neurons in vitro. Proc Natl Acad Sci USA. 1981b; 78:1264–1268. [PubMed: 7015330]

Hiebert NM, Seergobin KN, Vo A, Ganjavi H, MacDonald PA. Dopaminergic therapy affects learning and impulsivity in Parkinson's disease. Ann Clin Transl Neurol. 2014; 1:833–843. [PubMed: 25493274]

Hikida T, Kimura K, Wada N, Funabiki K, Nakanishi S. Distinct roles of synaptic transmission in direct and indirect striatal pathways to reward and aversive behavior. Neuron. 2010; 66:896–907. [PubMed: 20620875]

Hikosaka O. Basal ganglia mechanisms of reward-oriented eye movement. Ann N Y Acad Sci. 2007; 1104:229–249. [PubMed: 17360800]

Hivert B, Liu Z, Chuang CY, Doherty P, Sundaresan V. Robo1 and Robo2 are homophilic binding molecules that promote axonal growth. Mol Cell Neurosci. 2002; 21:534–545. [PubMed: 12504588]

Hollerman JR, Schultz W. Dopamine neurons report an error in the temporal prediction of reward during learning. Nat Neurosci. 1998; 1:304–309. [PubMed: 10195164]

Holmes GP, Negus K, Burridge L, Raman S, Algar E, Yamada T, Little MH. Distinct but overlapping expression patterns of two vertebrate slit homologs implies functional roles in CNS development and organogenesis. Mech Dev. 1998; 79:57–72. [PubMed: 10349621]

Hu Z, Cooper M, Crockett DP, Zhou R. Differentiation of the midbrain dopaminergic pathways during mouse development. J Comp Neurol. 2004; 476:301–311. [PubMed: 15269972]

Hwang DY, Ardayfio P, Kang UJ, Semina EV, Kim KS. Selective loss of dopaminergic neurons in the substantia nigra of Pitx3-deficient aphakia mice. Brain Res Mol Brain Res. 2003; 114:123–131. [PubMed: 12829322]

Hwang DY, Fleming SM, Ardayfio P, Moran-Gates T, Kim H, Tarazi FI, Chesselet MF, Kim KS. 3,4-Dihydroxyphenylalanine reverses the motor deficits in Pitx3-deficient aphakia mice: behavioral characterization of a novel genetic model of Parkinson's disease. J Neurosci. 2005; 25:2132–2137. [PubMed: 15728853]

Hynes M, Porter JA, Chiang C, Chang D, Tessier-Lavigne M, Beachy PA, Rosenthal A. Induction of midbrain dopaminergic neurons by Sonic hedgehog. Neuron. 1995; 15:35–44. [PubMed: 7619528]

Jin X, Costa RM. Start/stop signals emerge in nigrostriatal circuits during sequence learning. Nature. 2010; 466:457–462. [PubMed: 20651684]

Jo YS, Lee J, Mizumori SJ. Effects of prefrontal cortical inactivation on neural activity in the ventral tegmental area. J Neurosci. 2013; 33:8159–8171. [PubMed: 23658156]

Kabitzke PA, Simpson EH, Kandel ER, Balsam PD. Social behavior in a genetic model of dopamine dysfunction at different neurodevelopmental time points. Genes Brain Behav. 2015; 14:503–515. [PubMed: 26176662]

Kakade S, Dayan P. Dopamine: generalization and bonuses. Neural Netw. 2002; 15:549–559. [PubMed: 12371511]

Kalsbeek A, Voorn P, Buijs RM, Pool CW, Uylings HB. Development of the dopaminergic innervation in the prefrontal cortex of the rat. J Comp Neurol. 1988; 269:58–72. [PubMed: 3361004]

Kapur S. Psychosis as a state of aberrant salience: a framework linking biology, phenomenology, and pharmacology in schizophrenia. Am J Psychiatry. 2003; 160:13–23. [PubMed: 12505794]

Kawano H, Ohyama K, Kawamura K, Nagatsu I. Migration of dopaminergic neurons in the embryonic mesencephalon of mice. Brain Res Dev Brain Res. 1995; 86:101–113. [PubMed: 7544698]

Kawano H, Horie M, Honma S, Kawamura K, Takeuchi K, Kimura S. Aberrant trajectory of ascending dopaminergic pathway in mice lacking Nkx2.1. Exp Neurol. 2003; 182:103–112. [PubMed: 12821380]

Kim MJ, Loucks RA, Palmer AL, Brown AC, Solomon KM, Marchante AN, Whalen PJ. The structural and functional connectivity of the amygdala: from normal emotion to pathological anxiety. Behav Brain Res. 2011; 223:403–410. [PubMed: 21536077]

Kim H, Quan X, Seong Y, Kim J. Impaired motor coordination in Pitx3 overexpression mice. Biochem Biophys Res Commun. 2014a; 446:1211–1218. [PubMed: 24680684]

Kim KS, Kang YM, Kang Y, Park TS, Park HY, Kim YJ, Han BS, Kim CH, Lee CH, Ardayfio PA, Han PL, Jung BH. Pitx3 deficient mice as a genetic animal model of comorbid depressive disorder and parkinsonism. Brain Res. 2014b; 1552:72–81. [PubMed: 24480473]

Kittappa R, Chang WW, Awatramani RB, McKay RD. The foxa2 gene controls the birth and spontaneous degeneration of dopamine neurons in old age. PLoS Biol. 2007; 5:e325. [PubMed: 18076286]

Koob GF. Hedonic valence, dopamine and motivation. Mol Psychiatry. 1996; 1:186–189. [PubMed: 9118342]

Korotkova TM, Ponomarenko AA, Haas HL, Sergeeva OA. Differential expression of the homeobox gene Pitx3 in midbrain dopaminergic neurons. Eur J Neurosci. 2005; 22:1287–1293. [PubMed: 16190884]

Kravitz AV, Freeze BS, Parker PR, Kay K, Thwin MT, Deisseroth K, Kreitzer AC. Regulation of parkinsonian motor behaviours by optogenetic control of basal ganglia circuitry. Nature. 2010; 466:622–626. [PubMed: 20613723]

Lancaster TM, Heerey EA, Mantripragada K, Linden DEJ. Replication study implicates COMT val158met polymorphism as a modulator of probabilistic reward learning. Genes Brain Behav. 2015; 14:486–492. [PubMed: 26096878]

Lange KW, Robbins TW, Marsden CD, James M, Owen AM, Paul GM. L-dopa withdrawal in Parkinson's disease selectively impairs cognitive performance in tests sensitive to frontal lobe dysfunction. Psychopharmacology (Berl). 1992; 107:394–404. [PubMed: 1615139]

Lau B, Glimcher PW. Value representations in the primate striatum during matching behavior. Neuron. 2008; 58:451–463. [PubMed: 18466754]

Lee HS, Bae EJ, Yi SH, Shim JW, Jo AY, Kang JS, Yoon EH, Rhee YH, Park CH, Koh HC, Kim HJ, Choi HS, Han JW, Lee YS, Kim J, Li JY, Brundin P, Lee SH. Foxa2 and Nurr1 synergistically yield A9 nigral dopamine neurons exhibiting improved differentiation, function, and cell survival. Stem Cells. 2010; 28:501–512. [PubMed: 20049900]

Lex A, Hauber W. Dopamine D1 and D2 receptors in the nucleus accumbens core and shell mediate Pavlovian-instrumental transfer. Learn Mem. 2008; 15:483–491. [PubMed: 18626092]

Li JY, Joyner AL. Otx2 and Gbx2 are required for refinement and not induction of mid-hindbrain gene expression. Development. 2001; 128:4979–4991. [PubMed: 11748135]

Lin L, Rao Y, Isacson O. Netrin-1 and slit-2 regulate and direct neurite growth of ventral midbrain dopaminergic neurons. Mol Cell Neurosci. 2005; 28:547–555. [PubMed: 15737744]

Lisman JE, Grace AA. The hippocampal-VTA loop: controlling the entry of information into long-term memory. Neuron. 2005; 46:703–713. [PubMed: 15924857]

Liu A, Joyner AL. Early anterior/posterior patterning of the midbrain and cerebellum. Annu Rev Neurosci. 2001; 24:869–896. [PubMed: 11520921]

Loughlin SE, Fallon JH. Substantia nigra and ventral tegmental area projections to cortex: topography and collateralization. Neuroscience. 1984; 11:425–435. [PubMed: 6201780]

MacDonald AA, Seergobin KN, Owen AM, Tamjeedi R, Monchi O, Ganjavi H, MacDonald PA. Differential effects of Parkinson's disease and dopamine replacement on memory encoding and retrieval. PLoS One. 2013; 8:e74044. [PubMed: 24086309]

Madras BK, Miller GM, Fischman AJ. The dopamine transporter and attention-deficit/hyperactivity disorder. Biol Psychiatry. 2005; 57:1397–1409. [PubMed: 15950014]

Marillat V, Cases O, Nguyen-Ba-Charvet KT, Tessier-Lavigne M, Sotelo C, Chedotal A. Spatiotemporal expression patterns of slit and robo genes in the rat brain. J Comp Neurol. 2002; 442:130–155. [PubMed: 11754167]

Marshall JF, Levitan D, Stricker EM. Activation-induced restoration of sensorimotor functions in rats with dopamine-depleting brain lesions. J Comp Physiol Psychol. 1976; 90:536–546. [PubMed: 8470]

Matsumoto M, Hikosaka O. Two types of dopamine neuron distinctly convey positive and negative motivational signals. Nature. 2009; 459:837–841. [PubMed: 19448610]

Mattay VS, Goldberg TE, Fera F, Hariri AR, Tessitore A, Egan MF, Kolachana B, Callicott JH, Weinberger DR. Catechol O-methyltransferase val158-met genotype and individual variation in the brain response to amphetamine. Proc Natl Acad Sci USA. 2003; 100:6186–6191. [PubMed: 12716966]

McMahon AP, Bradley A. The Wnt-1 (int-1) proto-oncogene is required for development of a large region of the mouse brain. Cell. 1990; 62:1073–1085. [PubMed: 2205396]

McMahon AP, Joyner AL, Bradley A, McMahon JA. The midbrain-hindbrain phenotype of Wnt-1-/Wnt-1- mice results from stepwise deletion of engrailed-expressing cells by 9.5 days postcoitum. Cell. 1992; 69:581–595. [PubMed: 1534034]

Meyer-Lindenberg A, Kohn PD, Kolachana B, Kippenhan S, McInerney-Leo A, Nussbaum R, Weinberger DR, Berman KF. Midbrain dopamine and prefrontal function in humans: interaction and modulation by COMT genotype. Nat Neurosci. 2005; 8:594–596. [PubMed: 15821730]

Mirenowicz J, Schultz W. Importance of unpredictability for reward responses in primate dopamine neurons. J Neurophysiol. 1994; 72:1024–1027. [PubMed: 7983508]

Mirenowicz J, Schultz W. Preferential activation of midbrain dopamine neurons by appetitive rather than aversive stimuli. Nature. 1996; 379:449–451. [PubMed: 8559249]

Montague PR, Dayan P, Sejnowski TJ. A framework for mesencephalic dopamine systems based on predictive Hebbian learning. J Neurosci. 1996; 16:1936–1947. [PubMed: 8774460]

Moy SS, Nadler JJ. Advances in behavioral genetics: mouse models of autism. Mol Psychiatry. 2008; 13:4–26. [PubMed: 17848915]

Moy SS, Nadler JJ, Magnuson TR, Crawley JN. Mouse models of autism spectrum disorders: the challenge for behavioral genetics. Am J Med Genet C Semin Med Genet. 2006; 142C:40–51. [PubMed: 16419099]

van den Munckhof P, Luk KC, Ste-Marie L, Montgomery J, Blanchet PJ, Sadikot AF, Drouin J. Pitx3 is required for motor activity and for survival of a subset of midbrain dopaminergic neurons. Development. 2003; 130:2535–2542. [PubMed: 12702666]

Nakamura H, Watanabe Y. Isthmus organizer and regionalization of the mesencephalon and metencephalon. Int J Dev Biol. 2005; 49:231–235. [PubMed: 15906236]

Nishikawa S, Goto S, Yamada K, Hamasaki T, Ushio Y. Lack of Reelin causes malpositioning of nigral dopaminergic neurons: evidence from comparison of normal and Reln(rl) mutant mice. J Comp Neurol. 2003; 461:166–173. [PubMed: 12724835]

Nomoto K, Schultz W, Watanabe T, Sakagami M. Temporally extended dopamine responses to perceptually demanding reward-predictive stimuli. J Neurosci. 2010; 30:10692–10702. [PubMed: 20702700]

Nunes I, Tovmasian LT, Silva RM, Burke RE, Goff SP. Pitx3 is required for development of substantia nigra dopaminergic neurons. Proc Natl Acad Sci USA. 2003; 100:4245–4250. [PubMed: 12655058]

Oleson EB, Gentry RN, Chioma VC, Cheer JF. Subsecond dopamine release in the nucleus accumbens predicts conditioned punishment and its successful avoidance. J Neurosci. 2012; 32:14804–14808. [PubMed: 23077064]

Ono Y, Nakatani T, Sakamoto Y, Mizuhara E, Minaki Y, Kumai M, Hamaguchi A, Nishimura M, Inoue Y, Hayashi H, Takahashi J, Imai T. Differences in neurogenic potential in floor plate cells along an anteroposterior location: midbrain dopaminergic neurons originate from mesencephalic floor plate cells. Development. 2007; 134:3213–3225. [PubMed: 17670789]

Ozdinler PH, Erzurumlu RS. Slit2, a branching-arborization factor for sensory axons in the Mammalian CNS. J Neurosci. 2002; 22:4540–4549. [PubMed: 12040061]

Pakkenberg B, Moller A, Gundersen HJ, Mouritzen Dam A, Pakkenberg H. The absolute number of nerve cells in substantia nigra in normal subjects and in patients with Parkinson's disease estimated with an unbiased stereological method. J Neurol Neurosurg Psychiatry. 1991; 54:30–33. [PubMed: 2010756]

Pan WX, Schmidt R, Wickens JR, Hyland BI. Dopamine cells respond to predicted events during classical conditioning: evidence for eligibility traces in the reward-learning network. J Neurosci. 2005; 25:6235–6242. [PubMed: 15987953]

Pasterkamp RJ, Smidt MP, Burbach JP. Development and engineering of dopamine neurons. Preface. Adv Exp Med Biol. 2009; 651:v–vi. [PubMed: 19731545]

Peng C, Aron L, Klein R, Li M, Wurst W, Prakash N, Le W. Pitx3 is a critical mediator of GDNF-induced BDNF expression in nigrostriatal dopaminergic neurons. J Neurosci. 2011; 31:12802–12815. [PubMed: 21900559]

Perlmutter JS, Mink JW. Dysfunction of dopaminergic pathways in dystonia. Adv Neurol. 2004; 94:163–170. [PubMed: 14509670]

Puelles L, Verney C. Early neuromeric distribution of tyrosine-hydroxylase-immunoreactive neurons in human embryos. J Comp Neurol. 1998; 394:283–308. [PubMed: 9579394]

Puelles E, Annino A, Tuorto F, Usiello A, Acampora D, Czerny T, Brodski C, Ang SL, Wurst W, Simeone A. Otx2 regulates the extent, identity and fate of neuronal progenitor domains in the ventral midbrain. Development. 2004; 131:2037–2048. [PubMed: 15105370]

Rakshi JS, Uema T, Ito K, Bailey DL, Morrish PK, Ashburner J, Dagher A, Jenkins IH, Friston KJ, Brooks DJ. Frontal, midbrain and striatal dopaminergic function in early and advanced Parkinson's disease A 3D [(18)F]dopa-PET study. Brain. 1999; 122(Pt. 9):1637–1650. [PubMed: 10468504]

Redgrave P, Gurney K. The short-latency dopamine signal: a role in discovering novel actions? Neuroscience. 2006; 7:967–975. [PubMed: 17115078]

Redgrave P, Prescott TJ, Gurney K. The basal ganglia: a vertebrate solution to the selection problem? Neuroscience. 1999a; 89:1009–1023. [PubMed: 10362291]

Redgrave P, Prescott TJ, Gurney K. Is the short-latency dopamine response too short to signal reward error? Trends Neurosci. 1999b; 22:146–151. [PubMed: 10203849]

Redgrave P, Gurney K, Reynolds J. What is reinforced by phasic dopamine signals? Brain Res Rev. 2008; 58:322–339. [PubMed: 18055018]

Rescorla, RA., Wagner, AR. A theory of Pavlovian conditioning: variations in the effectiveness of reinforcement and nonreinforcement. In: Black, A., Prokasy, WF., editors. Classical Conditioning II: Current Research and Theory. Appleton-Century-Crofts; New York: 1972. p. 64-99.

Rhinn M, Brand M. The midbrain--hindbrain boundary organizer. Curr Opin Neurobiol. 2001; 11:34–42. [PubMed: 11179870]

Robbins TW, Cools R. Cognitive deficits in Parkinson's disease: a cognitive neuroscience perspective. Mov Disord. 2014; 29:597–607. [PubMed: 24757109]

Robinson TE, Berridge KC. The neural basis of drug craving: an incentive-sensitization theory of addiction. Brain Res Brain Res Rev. 1993; 18:247–291. [PubMed: 8401595]

Robinson TE, Kolb B. Structural plasticity associated with exposure to drugs of abuse. Neuropharmacology. 2004; 47(Suppl 1):33–46. [PubMed: 15464124]

Roesch MR, Calu DJ, Schoenbaum G. Dopamine neurons encode the better option in rats deciding between differently delayed or sized rewards. Nat Neurosci. 2007a; 10:1615–1624. [PubMed: 18026098]

Roesch MR, Calu DJ, Schoenbaum G. Dopamine neurons encode the better option in rats deciding between differently delayed or sized rewards. Nat Neurosci. 2007b; 10:1615–1624. [PubMed: 18026098]

Rosenberg DR, Lewis DA. Changes in the dopaminergic innervation of monkey prefrontal cortex during late postnatal development: a tyrosine hydroxylase immunohistochemical study. Biol Psychiatry. 1994; 36:272–277. [PubMed: 7986893]

Rosenberg DR, Lewis DA. Postnatal maturation of the dopaminergic innervation of monkey prefrontal and motor cortices: a tyrosine hydroxylase immunohistochemical analysis. J Comp Neurol. 1995; 358:383–400. [PubMed: 7560293]

Rutledge RB, Skandali N, Dayan P, Dolan RJ. Dopaminergic modulation of decision making and subjective well-being. J Neurosci. 2015; 35:9811–9822. [PubMed: 26156984]

Saddoris MP, Cacciapaglia F, Wightman RM, Carelli RM. Differential dopamine release dynamics in the nucleus accumbens core and shell reveal complementary signals for error prediction and incentive motivation. J Neurosci. 2015; 35:11572–11582. [PubMed: 26290234]

Sakurada K, Ohshima-Sakurada M, Palmer TD, Gage FH. Nurr1, an orphan nuclear receptor, is a transcriptional activator of endogenous tyrosine hydroxylase in neural progenitor cells derived from the adult brain. Development. 1999; 126:4017–4026. [PubMed: 10457011]

Salamone JD, Correa M. The mysterious motivational functions of mesolimbic dopamine. Neuron. 2012; 76:470–485. [PubMed: 23141060]

Salamone JD, Correa M, Farrar A, Mingote SM. Effort-related functions of nucleus accumbens dopamine and associated forebrain circuits. Psychopharmacology (Berl). 2007; 191:461–482. [PubMed: 17225164]

Satoh T, Nakai S, Sato T, Kimura M. Correlated coding of motivation and outcome of decision by dopamine neurons. J Neurosci. 2003; 23:9913–9923. [PubMed: 14586021]

Saucedo-Cardenas O, Quintana-Hau JD, Le WD, Smidt MP, Cox JJ, De Mayo F, Burbach JP, Conneely OM. Nurr1 is essential for the induction of the dopaminergic phenotype and the survival of ventral mesencephalic late dopaminergic precursor neurons. Proc Natl Acad Sci USA. 1998; 95:4013–4018. [PubMed: 9520484]

Sawaguchi T, Goldman-Rakic PS. The role of D1-dopamine receptor in working memory: local injections of dopamine antagonists into the prefrontal cortex of rhesus monkeys performing an oculomotor delayed-response task. J Neurophysiol. 1994; 71:515–528. [PubMed: 7909839]

Schultz W. Responses of midbrain dopamine neurons to behavioral trigger stimuli in the monkey. J Neurophysiol. 1986; 56:1439–1461. [PubMed: 3794777]

Schultz W. Dopamine neurons and their role in reward mechanisms. Curr Opin Neurobiol. 1997; 7:191–197. [PubMed: 9142754]

Schultz W. Predictive reward signal of dopamine neurons. J Neurophysiol. 1998; 80:1–27. [PubMed: 9658025]

Schultz W, Dickinson A. Neuronal coding of prediction errors. Annu Rev Neurosci. 2000; 23:473–500. [PubMed: 10845072]

Schultz W, Dayan P, Montague PR. A neural substrate of prediction and reward. Science. 1997; 275:1593–1599. [PubMed: 9054347]

Serafini T, Colamarino SA, Leonardo ED, Wang H, Beddington R, Skarnes WC, Tessier-Lavigne M. Netrin-1 is required for commissural axon guidance in the developing vertebrate nervous system. Cell. 1996; 87:1001–1014. [PubMed: 8978605]

Sgado P, Alberi L, Gherbassi D, Galasso SL, Ramakers GM, Alavian KN, Smidt MP, Dyck RH, Simon HH. Slow progressive degeneration of nigral dopaminergic neurons in postnatal Engrailed mutant mice. Proc Natl Acad Sci USA. 2006; 103:15242–15247. [PubMed: 17015829]

Shiner T, Seymour B, Wunderlich K, Hill C, Bhatia KP, Dayan P, Dolan RJ. Dopamine and performance in a reinforcement learning task: evidence from Parkinson's disease. Brain. 2012; 135:1871–1883. [PubMed: 22508958]

Shults CW, Hashimoto R, Brady RM, Gage FH. Dopaminergic cells align along radial glia in the developing mesencephalon of the rat. Neuroscience. 1990; 38:427–436. [PubMed: 1979855]

Silverman JL, Yang M, Lord C, Crawley JN. Behavioural phenotyping assays for mouse models of autism. Nat Rev Neurosci. 2010; 11:490–502. [PubMed: 20559336]

Simon HH, Saueressig H, Wurst W, Goulding MD, O'Leary DD. Fate of midbrain dopaminergic neurons controlled by the engrailed genes. J Neurosci. 2001; 21:3126–3134. [PubMed: 11312297]

Smidt MP, Burbach JP. How to make a mesodiencephalic dopaminergic neuron. Nat Rev Neurosci. 2007; 8:21–32. [PubMed: 17180160]

Smidt MP, Burbach JP. Terminal differentiation of mesodiencephalic dopaminergic neurons: the role of Nurr1 and Pitx3. Adv Exp Med Biol. 2009; 651:47–57. [PubMed: 19731549]

Smidt MP, van Schaick HS, Lanctot C, Tremblay JJ, Cox JJ, van der Kleij AA, Wolterink G, Drouin J, Burbach JP. A homeodomain gene Ptx3 has highly restricted brain expression in mesencephalic dopaminergic neurons. Proc Natl Acad Sci USA. 1997; 94:13305–13310. [PubMed: 9371841]

Smidt MP, Asbreuk CH, Cox JJ, Chen H, Johnson RL, Burbach JP. A second independent pathway for development of mesencephalic dopaminergic neurons requires Lmx1b. Nat Neurosci. 2000; 3:337–341. [PubMed: 10725922]

Smidt MP, Smits SM, Bouwmeester H, Hamers FP, van der Linden AJ, Hellemons AJ, Graw J, Burbach JP. Early developmental failure of substantia nigra dopamine neurons in mice lacking the homeodomain gene Pitx3. Development. 2004a; 131:1145–1155. [PubMed: 14973278]

Smidt MP, Smits SM, Burbach JP. Homeobox gene Pitx3 and its role in the development of dopamine neurons of the substantia nigra. Cell Tissue Res. 2004b; 318:35–43. [PubMed: 15300495]

Smith KS, Berridge KC, Aldridge JW. Disentangling pleasure from incentive salience and learning signals in brain reward circuitry. Proc Natl Acad Sci USA. 2011; 108:E255–E264. [PubMed: 21670308]

Smits SM, Ponnio T, Conneely OM, Burbach JP, Smidt MP. Involvement of Nurr1 in specifying the neurotransmitter identity of ventral midbrain dopaminergic neurons. Eur J Neurosci. 2003; 18:1731–1738. [PubMed: 14622207]

Smits SM, Burbach JP, Smidt MP. Developmental origin and fate of mesodiencephalic dopamine neurons. Prog Neurobiol. 2006; 78:1–16. [PubMed: 16414173]

Sonnier L, Le Pen G, Hartmann A, Bizot JC, Trovero F, Krebs MO, Prochiantz A. Progressive loss of dopaminergic neurons in the ventral midbrain of adult mice heterozygote for Engrailed1. J Neurosci. 2007; 27:1063–1071. [PubMed: 17267560]

Steinberg EE, Keiflin R, Boivin JR, Witten IB, Deisseroth K, Janak PH. A causal link between prediction errors, dopamine neurons and learning. Nat Neurosci. 2013; 16:966–973. [PubMed: 23708143]

Swanson LW. The projections of the ventral tegmental area and adjacent regions: a combined fluorescent retrograde tracer and immunofluorescence study in the rat. Brain Res Bull. 1982; 9:321–353. [PubMed: 6816390]

Taylor TN, Greene JG, Miller GW. Behavioral phenotyping of mouse models of Parkinson's disease. Behav Brain Res. 2010; 211:1–10. [PubMed: 20211655]

Thompson PM, Lee AD, Dutton RA, Geaga JA, Hayashi KM, Eckert MA, Bellugi U, Galaburda AM, Korenberg JR, Mills DL, Toga AW, Reiss AL. Abnormal cortical complexity and thickness profiles mapped in Williams syndrome. J Neurosci. 2005; 25:4146–4158. [PubMed: 15843618]

Tzschentke TM, Schmidt WJ. Functional relationship among medial prefrontal cortex, nucleus accumbens, and ventral tegmental area in locomotion and reward. Crit Rev Neurobiol. 2000; 14:131–142. [PubMed: 11513242]

Vernay B, Koch M, Vaccarino F, Briscoe J, Simeone A, Kageyama R, Ang SL. Otx2 regulates subtype specification and neurogenesis in the midbrain. J Neurosci. 2005; 25:4856–4867. [PubMed: 15888661]

Waelti P, Dickinson A, Schultz W. Dopamine responses comply with basic assumptions of formal learning theory. Nature. 2001; 412:43–48. [PubMed: 11452299]

Walker RH, Shashidharan P. Developments in the molecular biology of DYT1 dystonia. Mov Disord. 2003; 18:1102–1107. [PubMed: 14534912]

Wallen A, Zetterstrom RH, Solomin L, Arvidsson M, Olson L, Perlmann T. Fate of mesencephalic AHD2-expressing dopamine progenitor cells in NURR1 mutant mice. Exp Cell Res. 1999; 253:737–746. [PubMed: 10585298]

Wallen AA, Castro DS, Zetterstrom RH, Karlen M, Olson L, Ericson J, Perlmann T. Orphan nuclear receptor Nurr1 is essential for Ret expression in midbrain dopamine neurons and in the brain stem. Mol Cell Neurosci. 2001; 18:649–663. [PubMed: 11749040]

Winslow JT, Hearn EF, Ferguson J, Young LJ, Matzuk MM, Insel TR. Infant vocalization, adult aggression, and fear behavior of an oxytocin null mutant mouse. Horm Behav. 2000; 37:145–155. [PubMed: 10753584]

Ye W, Shimamura K, Rubenstein JL, Hynes MA, Rosenthal A. FGF and Shh signals control dopaminergic and serotonergic cell fate in the anterior neural plate. Cell. 1998; 93:755–766. [PubMed: 9630220]

Zahniser NR, Sorkin A. Rapid regulation of the dopamine transporter: role in stimulant addiction? Neuropharmacology. 2004; 47(Suppl 1):80–91. [PubMed: 15464127]

Zetterstrom RH, Solomin L, Jansson L, Hoffer BJ, Olson L, Perlmann T. Dopamine neuron agenesis in Nurr1-deficient mice. Science. 1997; 276:248–250. [PubMed: 9092472]

Zhang H, Cotecchia S, Thomas SA, Tanoue A, Tsujimoto G, Faber JE. Gene deletion of dopamine beta-hydroxylase and alpha1-adrenoceptors demonstrates involvement of catecholamines in vascular remodeling. Am J Physiol Heart Circ Physiol. 2004; 287:H2106–H2114. [PubMed: 15231500]

Zhang L, Bai J, Undie AS, Bergson C, Lidow MS. D1 dopamine receptor regulation of the levels of the cell-cycle-controlling proteins, cyclin D, P27 and Raf-1, in cerebral cortical precursor cells is mediated through cAMP-independent pathways. Cereb Cortex. 2005; 15:74–84. [PubMed: 15238444]

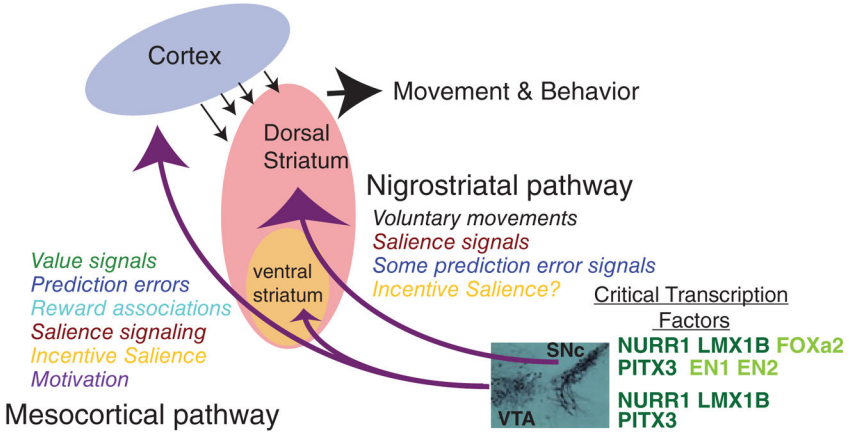

Figure 1. Major projections of mdDA neurons and known functions

In this simplified diagram of the major mdDA projections (shown as purple arrows), mesocortical pathway is shown emanating mainly from the VTA and sending major projections to ventral striatum (nucleus accumbens) and to cortex. This pathway is critical for creating reward associations, for signaling incentive salience and for providing value, PE and salience signals. The nigrostriatal pathway is shown emanating mainly from the SNc, providing the dopaminergic tone necessary for voluntary movements and also carrying salience and PE signals. As mdDA neurons in each of these pathways are not only located in either SNc or VTA, these neural areas are shown to overlap slightly. Corticostriatal input is shown as small black arrows, while the final outcome of this circuit is shown as bodily movement, also known as behavior. Critical transcription factors that determine the expression of the dopamine neuron phenotype and survivability of mdDA neurons in either the SNc or VTA are listed and color coded to illuminate which transcription factors are important for both SNc and VTA, and which are important for SNc development. The mdDA VTA and SNc histology image, taken at × 10, of diaminobenzidine reaction to tyrosine hydroxylase stain (1:2500; Sigma Chemical Co, St. Louis, MO, USA) using a Leica DMRX microscope (Leica Microsystems GmbH, Wetzlar, Germany).

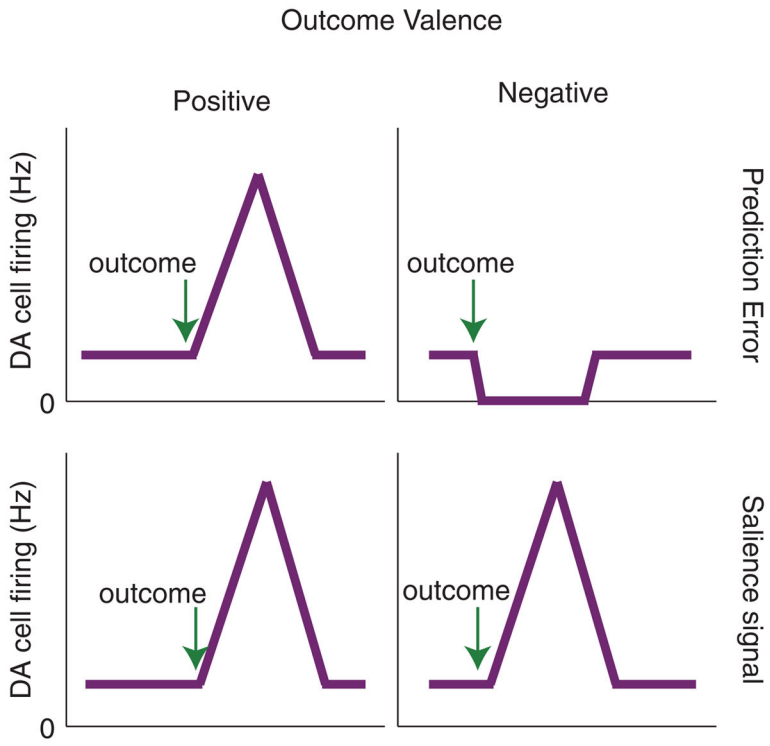

Figure 2. Theoretical dopamine cell firing showing either PE or salience signaling

Purple line represents the firing of a theoretical mdDA neuron while an animal is engaged in some form of activity which permits learning. When the valence (positive or negative) of an outcome is better or worse than expected, an mdDA neuron carrying PE information will either increase or decrease firing, respectively. However, if the mdDA neuron is signaling salience, then it will increase firing for both a better-than-expected and a worse-than-expected outcome. These example neural responses are to unexpected outcomes, but after learning, mdDA neurons that signal PE and salience also respond in a similar fashion to cues that predict negative or positive events.

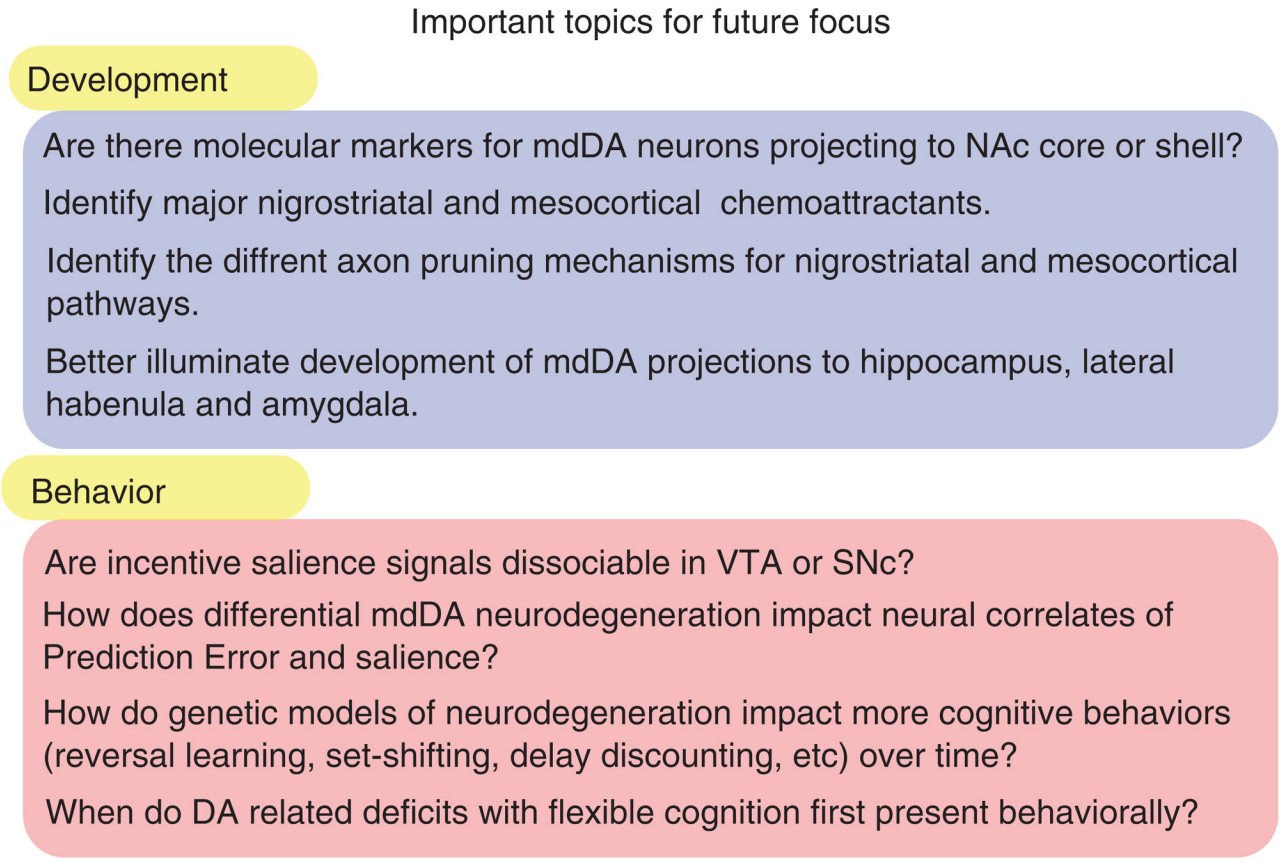

Figure 3. List of major questions remaining for developmental and behavioral neuroscience

Broken down between questions and topics that can be answered by either developmental or behavioral neuroscience, this list identifies major unanswered questions. Developmental questions focus on better understanding how mdDA neurons connect with other brain areas, both in terms of the chemoattractants and regarding pruning of synapses, while expanding the knowledge beyond the nigrostriatal and mesocortical pathways. Behavioral questions focus on using existing and future animal models of altered mdDA development to address questions of flexible cognition, separate from motor and sensorimotor questions currently being addressed. Additionally, the combination of developmental perturbations with *in vivo* electrophysiological techniques will be a powerful approach for studying the impact of altered mdDA development on PE, salience and incentive salience signals.