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Abstract

Play is an important part of normal childhood development and can be readily studied in the laboratory rat in the form of rough-and-tumble play. Given the robust nature of rough-and-tumble play, it has often been assumed that the basal ganglia would have a prominent role in modulating this behavior. Recent work using c-fos expression as a metabolic marker for neural activity combined with temporary inactivation of relevant corticostriatal regions and pharmacological manipulations of opioid, cannabinoid, and dopamine systems has led to a better understanding of how basal ganglia circuitry may be involved in modulating social play in the juvenile rat. Studies using selective play deprivation have also provided insight into the consequences of playful experiences on basal ganglia function. Data reviewed in this paper support a role for the basal ganglia in social play and also suggest that corticostriatal functioning also benefits from playful activities.

Keywords

dopamine, play, striatum, rat

Disciplines

Behavioral Neurobiology | Developmental Psychology | Psychology

Basal Ganglia Involvement in the Playfulness of Juvenile Rats

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Abstract

Play is an important part of normal childhood development and can be readily studied in the laboratory rat in the form of rough-and-tumble play. Given the robust nature of rough-and-tumble play it has often been assumed that the basal ganglia would have a prominent role in modulating this behavior. Recent work using c-fos expression as a metabolic marker for neural activity combined with temporary inactivation of relevant corticostriatal regions and pharmacological manipulations of opioid, cannabinoid, and dopamine systems has led to a better understanding of how basal ganglia circuitry may be involved in modulating social play in the juvenile rat. Studies using selective play deprivation have also provided insight into the consequences of playful experiences on basal ganglia function. Data reviewed in this paper support a role for the basal ganglia in social play and also suggests that corticostriatal functioning also benefits from playful activities.

Introduction – the road to UCLA

Judging by the list of contributors to this special issue, the focus of this particular contribution might be seem a bit out of place to many readers on an intellectual level but should be familiar to most on a more personal level. The primary focus of my research before and after my post-doctoral years in Mike Levine's lab at UCLA has been to gain a better understanding of the neurobiological substrates of mammalian playfulness. As a young graduate student in the early 1980s, I was eager to identify brain areas that were particularly important for play to occur in juvenile rats. The hope was that I could be part of a research enterprise that would eventually map out a neural circuit for playfulness. Using the best available techniques at the time to ablate brain areas and then looking at the effects of these lesions on play a small handful of labs began to systematically puzzle through how the brain might be modulating play in the rat. These early studies primarily assessed the involvement of limbic structures (Beatty, Dodge, Traylor, Donegan, & Godding, 1982; Meaney, Dodge, & Beatty, 1981), hypothalamus (Beatty & Costello, 1983), thalamus (Siviy & Panksepp, 1985, 1987), and cortex (Normansell & Panksepp, 1984; Panksepp, Normansell, Cox, & Siviy, 1994; Pellis, Pellis, & Whishaw, 1992).

Given the vigorous nature of play in the rat, striatal involvement seemed almost certain. Unfortunately, early attempts to assess striatal involvement in play were unsuccessful as lesion techniques at that time were not readily applicable to the striatum and resulted in rats unable to survive the procedure, let alone play (Panksepp, Siviy, & Normansell, 1984). So in 1988 when Mike Levine offered me an opportunity to join his group as a post-doctoral trainee at UCLA to help study the neurophysiology of the basal ganglia, I was quite excited. It didn't take long, however, to realize that brain slices did not engage in a lot of playful behavior so I found myself instead focusing on the physiology of medium spiny neurons as a function of development and plasticity (Siviy, Buchwald, & Levine, 1991; Siviy et al., 1993). While my research trajectory did not continue down the path of striatal neurophysiology after moving on from UCLA, I continued to study the neurobiology of play and, in this paper, will briefly summarize current thinking about the role of the basal ganglia in mammalian playfulness.

Play in the laboratory rat

First, it would be helpful to explain what play is, how we quantify it, and what might be the benefits associated with this behavior. Play is a particularly rambunctious behavior and occurs with regularity in the behavioral repertoire of a wide variety of mammalian species, along with some reptiles and birds (Burghardt, 2005). The standard laboratory rat has proven to be an optimal model system for studying the neurobiology of play. Rats begin to engage in playful interactions prior to weaning and this continues throughout the juvenile period, peaking at around 35 days of age, and then steadily decreasing as the animals reach puberty (Panksepp, 1981). Play in the rat primarily takes the form of "rough-and-tumble" activity; rats will vigorously chase each other, pounce on each other's dorsal surface, nuzzle and nip at the nape, and pin each other (Panksepp et al., 1984; Pellis & Pellis, 2009; Siviy & Panksepp, 2011; Vanderschuren, Niesink, & Van Ree, 1997; Vanderschuren & Trezza, 2014). Yet, despite the seemingly chaotic nature of these encounters there are a number of easily identifiable and stable behavioral endpoints that can be used to reliably quantify playfulness. We and others have focused on two major postures that are commonly seen during play but rare in other non-playful social encounters – pounces and pins. A pounce is defined as occurring when one rat vigorously pounces at the nape of the other rat with either its snout or front paws. A pin occurs when one rat rolls onto its back with the other rat on top. Pins often, but not always, occur in response to a nape contact and are thought to prolong a play bout and/or signal playful intent (Panksepp et al., 1984; Pellis, Field, Smith, & Pellis, 1997; Vanderschuren & Trezza, 2014) Far from being subtle, social forms of play such as rough-and-tumble activities seen in rats and other mammals can be especially demanding on both sensory and motor systems. Play involves rapid switching between different behavior patterns and requires continual give-and-take between participants for the interaction to remain playful. At one moment a rat will be vigorously pouncing on its partner's nape, which may result in that rat pinning the other, and then find that it is being pinned soon thereafter. This cycle of pinning and being pinned continues throughout the play bout.

Play is highly motivated and under fairly tight regulatory control, in that the amount of play exhibited by rats during a discrete observation period is a direct function of the amount of

time that has lapsed since the last opportunity to play. For example, rats that have not had any opportunity for social contact in 24 hours will play more than rats that have not had any social contact for 4 hours (Panksepp & Beatty, 1980). Play is also fun. Rats will prefer to return to a unique environment where play was experienced over an environment not associated with play (Calcagnetti & Schechter, 1992; Trezza, Damsteegt, & Vanderschuren, 2009). Rats will also readily navigate a T-maze when one arm is baited with another juvenile rat (Humphreys & Einon, 1981; Normansell & Panksepp, 1990) and will perform an operant response when an opportunity to play is the reward (Achterberg et al., 2016; Trezza, Campolongo, & Vanderschuren, 2011).

Finally, play is important for the overall development of those animals that readily engage in play. When deprived of the opportunity to play as juveniles and then assessed as adults, rats are impaired socially, emotionally, and cognitively (Baarendse, Counotte, O'Donnell, & Vanderschuren, 2013; Van den Berg et al., 1999; Von Frijtag, Schot, van den Bos, & Spruijt, 2002). This would suggest that the young mammalian brain is programmed and motivated to engage in playful behaviors, with adverse consequences resulting when opportunities for play are thwarted. The importance of play in normal childhood development has been highlighted on several occasions by the American Academy of Pediatrics, most recently in 2018 when it was recommended that all pediatricians "prescribe" hefty doses of play when children come in for scheduled exams (Ginsburg, 2007; Yogman, Garner, Hutchinson, Hirsh-Pasek, & Golinkoff, 2018). Gaining a solid foot-hold on how the brain modulates playful behaviors in young rats will help us to better understand the full benefits that play may bestow on our own children as they navigate their way to adulthood.

What do we know about the basal ganglia and play?

Given the behavioral richness and sensorimotor complexity associated with rough-and-tumble play and the reciprocity needed to maintain the playfulness of these interactions, let alone the affective and motivational properties of play, it would not be unexpected to find a prominent role for the basal ganglia in the modulation of playful behaviors. Indeed, the relative size of the striatum within a subset of non-human primates predicts the amount of social play in those species (Graham, 2011), suggesting that higher amounts of play in a particular primate

species is associated with a larger striatum. When play-induced striatal activity is assessed by c-fos expression, significant increases have been reported in both dorsal and ventral striatum (Gordon, Kollack-Walker, Akil, & Panksepp, 2002; van Kerkhof et al., 2014), suggesting widespread activation of striatal neurons during play behavior. Within the dorsal striatum, activity is particularly pronounced in the dorsolateral striatum and since this region is primarily associated with somatosensory input (Voorn, Vanderschuren, Groenewegen, Robbins, & Pennartz, 2004) it is suggested that dorsal striatum may be particularly important for the spatial and temporal organization of rough-and-tumble play. Play also results in differential activation of prefrontal areas, along with correlated activity between prefrontal regions and striatal targets (van Kerkhof et al., 2014). These authors suggest that prefrontal-dorsomedial striatal circuitry may be particularly relevant for sequential and temporal organization of play while prefrontal-ventral striatal circuitry may be more relevant for rewarding aspects of play. On the output side, play-induced decreases in fos expression were found in globus pallidus, which would be consistent with the increases observed in the dorsal striatum. There was no play-induced decrease or increase in fos expression in the ventral pallidum, although there was a positive correlation between activity in the NAc core region and ventral pallidum in animals that had an opportunity to play (van Kerkhof et al., 2014). While this would not have been expected in light of current models of basal ganglia circuitry (e.g., Gerfen & Bolam, 2010), there was an expected negative correlation between dorsal striatum and ventral pallidum activity in the animals not allowed to play. The authors report that this is not without precedent and conclude that both the globus pallidus and ventral pallidum appear to have a role in the modulation of play.

With the data strongly pointing towards correlated activation between play and basal ganglia circuitry, causal links between specific regions of the basal ganglia and play have also begun to emerge. An early attempt to assess the effects of compromising striatal functioning assessed the effects of neonatal 6-OHDA lesions of the striatum on play in juvenile rats (Pellis, Casteneda, McKenna, Tran-Nguyen, & Whishaw, 1993). These lesions severely compromised dopaminergic functioning within the dorsal and ventral striatum and disrupted the patterning of play between participants. As mentioned earlier, contacts directed to the nape can often

result in the rat responding by allowing it to be pinned. However, this is only one possibility. Rats may also respond to nape contacts by running away and Pellis et al. (1993) report that 6-OHDA lesioned rats tend to run away from these contacts much more than non-lesioned controls. Based on these results it was suggested that the striatum may be involved in the selection of behavioral elements that are more likely to maintain a play sequence. Neonatal lesions to the medial prefrontal cortex have also been shown to result in a rat that is more likely to run away when solicited by a play partner (Bell, McCaffrey, Forgie, Kolb, & Pellis, 2009), suggesting that prefrontal-dorsal striatal circuitry may act in concert and help maintain the normal ebb and flow of a play bout.

While the lesion studies described above make a compelling argument for a modulatory influence for cortical and striatal areas on play, it is important to keep in mind that these were permanent lesions that were made shortly after birth. Consequently, one cannot discount the possibility that any of the observed effects are due to either compensatory mechanisms and/or alterations in normal developmental processes. To help address this uncertainty, a more recent study looked at striatal involvement in play, along with corresponding prefrontal regions, using a temporary inactivation strategy (van Kerkhof, Damsteegt, Trezza, Voorn, & Vanderschuren, 2013). Temporary inactivation of the dorsomedial striatum with the AMPA/kainite antagonist DNQX increased pouncing, pinning, and overall play duration. These effects on play were behaviorally specific as non-playful social exploration and locomotor activity were unaffected by DNQX infusions. Combined infusion of the $GABA_A$ agonist muscimol and the $GABA_B$ agonist baclofen into the dorsomedial striatum resulted in a non-significant trend for an increase in pounces. On the other hand, temporary inactivation of either the prelimbic cortex, infralimbic cortex, or medial/ventral orbitofrontal cortex reduced both nape contacts and pins while having no effect on, or slightly increasing, social exploration. Taken together, these data suggest that the dorsomedial striatum may normally inhibit active social behaviors such as play, with temporary inactivation leading to disinhibited behavior, while prefrontal cortical areas may serve to prolong active playful interactions (van Kerkhof et al., 2013; Vanderschuren, Achterberg, & Trezza, 2016). To the best of my knowledge, no studies have looked at inactivation of the dorsolateral striatum.

The ventral striatum has a well-established role in motivation and reward (Alcaro, Huber, & Panksepp, 2007; Berridge, 2007; Ikemoto & Panksepp, 1999; Robinson & Berridge, 1993) so involvement of the nucleus accumbens (NAc) has received considerable attention. Inactivation of the core region of the NAc with muscimol and baclofen increased the length of play bouts while having no effect on the frequency of either pins or pounces, suggesting that inactivation of the NAc core region prolongs playful interactions, perhaps by enhancing the rewarding value associated with playful interactions (van Kerkhof et al., 2013; Vanderschuren et al., 2016). Indeed, infusions of μ-opioid agonists into either the core or shell regions of the NAc increase play whereas μ-opioid antagonists reduce play, block the play-enhancing effect of agonists, and prevent the establishment of a play-induced conditioned place preference (Trezza, Damsteegt, Achterberg, & Vanderschuren, 2011). These data suggest that the release of endogenous opioids into the NAc enhances play by modulating the reward value or emotional valence of playful social interactions. Opioids acting in the nucleus accumbens are also believed to interact with the endogenous cannabinoids anandamide and 2-AG in modulating play. In particular, preventing the metabolic breakdown of either anandamide (Trezza et al., 2012) or 2-AG (Manduca et al., 2016a) within the nucleus accumbens increases social play. Furthermore, increases in play following systemic administration of morphine is blocked by intra-accumbens infusion of the CB1 antagonist SR141716 and increases in play following systemic administration of the 2-AG hydrolysis inhibitor JZL184 is blocked by intra-accumbens infusion of the μ-opioid antagonist naloxone (Manduca et al., 2016a). These data suggest that the nucleus accumbens may be a critical nexus for the interactive effects of endogenous opioids and endogenous cannabinoids on social play.

Strain differences in play, the basal ganglia, dopamine, and another UCLA connection

As with many other motivated behaviors, brain dopamine (DA) systems have long been thought to be an important neuromodulator for play (Siviy & Panksepp, 2011; Trezza, Baarendse, & Vanderschuren, 2010; Vanderschuren et al., 2016). As mentioned earlier, neonatal 6-OHDA lesions to the striatum disrupts the sequencing of play behavior (Pellis et al., 1993). And while DA antagonists uniformly reduce play, obtaining robust and reliable increases

in playfulness with systemically administered dopamine agonists has been elusive and, when present, can be quite subtle and hard to replicate (Beatty, Costello, & Berry, 1984; Niesink & Van Ree, 1989; Siviy, Fleischhauer, Kerrigan, & Kuhlman, 1996). Being somewhat unsatisfied with the lack of robust play-enhancing effects associated with dopamine agonists (Siviy et al., 1996), I began to look for alternative models. At that time, we had been using exclusively outbred rats of the Sprague-Dawley strain and I began to wonder if another strain might be somewhat more sensitive to dopamine agonists. Indeed, a little background searching into the literature led to a few articles indicating that the inbred F344 rat might be more amenable to pharmacological manipulations of the DA system (Guitart, Beitner-Johnson, Marby, Kosten, & Nestler, 1992; Helmeste, 1983; Helmeste, Seeman, & Coscina, 1981). Before planning any specific pharmacological experiments it seemed worthwhile to get some initial data on overall levels of playfulness in rats of this strain. While I assumed that this would be a quick study and we would quickly move forward with assessing selective dopamine agonists and antagonists, it was quite surprising to find that rats of this strain did not play at the same level as other strains (Siviy, Baliko, & Bowers, 1997; Siviy, Love, DeCicco, Giordano, & Seifert, 2003).

After these initial studies characterizing strain differences in play, any further work looking at a role for DA in play was put on hold while I digressed into other aspects of play behavior. My interest in the F344 rat was rekindled a few years later while catching up over dinner with another alum from Mike Levine's lab, John Walsh, at the 2008 Society for Neuroscience meeting. As it turned out, John's lab was also interested in the F344 strain; rats of this strain seem to be particularly vulnerable to mitochondrial distress and this was reflected in altered DAergic functioning as measured in striatal slices (Akopian et al., 2008). This led to a fruitful collaboration between our labs looking for parallels between cortico-striatal DA dysfunction and the dysfunctional play of the F344 rat. Using fast-scan cyclic voltammetry of brain slices in the dorsal striatum and nucleus accumbens, we found that F344 rats release less DA in response to electrode stimulation (Siviy, Crawford, Akopian, & Walsh, 2011). Using high performance liquid chromatography, Cynthia Crawford, another alum from Mike's lab, showed that F344 rats had higher DA content in the striatum and prefrontal cortex while showing less DA turnover relative to SD rats at both sites. Together, these data suggested that F344 rats

may have a deficit in the packaging of DA into vesicles, leading to a build-up of DA in the cytoplasm and a corresponding dysfunction in vesicular release. If this is the case, and if F344 rats are sequestering DA in the cytoplasm, we thought it possible that some of the behavioral differences observed in F344 rats may be attributable to problems associated with DA handling and release.

In a subsequent study (Siviy et al., 2015) we sought to test this hypothesis by further exploring the neurochemical differences in DA functioning in brain slices obtained from F344 and SD rats and using these data to inform behavioral hypotheses. If, as suggested by our earlier work, there is an accumulation of cytoplasmic non-vesicular DA then this should be detectible by treating brain slices with amphetamine, due to enhanced cytoplasmic DA release through reverse transport at DA transporters (DATs). Consistent with this hypothesis, we found that amphetamine caused a more rapid and greater release of DA in striatal slices from F344 rats. To further test this hypothesis in a behavioral model, we assessed the effectiveness of amphetamine to increase locomotor activity in an open field. As predicted, amphetamine was found to be more effective at increasing activity in F344 rats when strain differences in baseline activity were taken into account. This suggests that F344 rats are more susceptible to the stimulant properties of amphetamine and is consistent with the hypothesis that rats of this strain are more susceptible to non-vesicular release of DA through amphetamine-mediated reverse transport.

Finding support for our hypothesis that F344 rats have deficits in the handling and delivery of vesicular DA using a neurochemical assay and a robust behavioral assay, we then sought to determine if the dysfunctional play of F344 rats may be related to reductions in vesicular release of DA (Siviy et al., 2015). If F344 rats are less playful because of impaired vesicular release of DA within the striatum it seemed reasonable to hypothesize that increased synaptic availability of DA through amphetamine-induced non-vesicular release of DA may lead to an increase in play in rats of this strain. This hypothesis was not supported as amphetamine reduced play to a comparable extent in both F344 and SD rats. So while there is a clear difference in how these two strains handle DA in the pre-synaptic terminal and that these

differences can have behavioral consequences, it is still unclear as to whether impaired DA functioning within the striatum can readily account for the relative lack of play in the F344 rat.

While dysfunction in DA functioning may not easily account for the low levels of play in the F344 rat, recent studies have bolstered the notion that DA acting within the ventral striatum provides an important modulatory influence over playfulness. Infusions of either amphetamine or the DA agonist apomorphine into the NAc increases play, with the increases seen with amphetamine blocked by co-infusion of either D1 or D2 antagonists (Manduca et al., 2016b). There are also several lines of converging evidence suggesting that DA may be particularly important for enhancing motivation to play (Achterberg et al., 2016) and this may be due to increased DAergic activity within the NAc. Rats will emit high frequency 50kHz ultrasonic vocalizations (USVs) when playing (Burgdorf et al., 2008; Manduca et al., 2014) and when anticipating play (Siviy & Panksepp, 2011). Playback of 50 kHz USVs also leads to approach in juvenile rats (Wöhr & Schwarting, 2007) and increased release of DA in the NAc as assessed by fast scan cyclic voltammetry (Willuhn et al., 2014). Similarly, social interactions can increase DA release in the NAc of both adolescent and adult rats (Robinson, Zitzman, Smith, & Spear, 2011). Taken together, these data strongly suggest that DA release in the nucleus accumbens has an important modulatory role in various aspects of social play in the rat.

Conclusions

For the rat, behavioral and postural flexibility is needed in order to fully engage in active playful behaviors and maintain the give-and-take needed to keep these social interactions playful. In turn, having ample opportunities to play will result in an adult that has more behavioral and cognitive flexibility as it encounters novel and uncertain situations in an ever-changing world. It is perhaps through playful social interactions during juvenile and adolescent periods that young mammals develop flexible behavioral strategies that can be beneficial when these types of situations are encountered later in life (Pellis & Pellis, 2009; Spinka, Newberry, & Bekoff, 2001; Vanderschuren & Trezza, 2014) and basal ganglia circuitry may be primary beneficiaries of this added flexibility to the behavioral repertoire. We can see several examples of this when rats are deprived of opportunities to play as juveniles by either housing

individually or with a non-playful adult, re-housed socially after puberty, and then assessing basal ganglia function after a period of re-socialization. Using this type of protocol, dendritic complexity of pyramidal neurons within the medial prefrontal cortex has been shown to be sensitive to play experience as a juvenile (Bell, Pellis, & Kolb, 2010). Pyramidal neurons in the medial prefrontal cortex in rats that had been play-deprived during the 3rd and 4th weeks of life, and then re-housed socially, are less sensitive to modulation by dopamine (Baarendse et al., 2013). We have also reported impaired DA-mediated plasticity in the prefrontal cortex and dorsal striatum of the non-playful F344 rat (Siviy et al., 2011), further suggesting that play, or the lack thereof, may have an impact on basal ganglia functionality.

The data reviewed in this paper suggest that the basal ganglia not only has an important modulatory role in the control of play behavior in rats but also is the recipient of benefits that arise from engaging in playful behaviors. But since this special issue is a "birthday present" for Mike Levine I thought it proper to see if I could relate this work to what I did during my time at UCLA in Mike's lab. The primary focus of my post-doctoral traineeship was to study development and plasticity in striatum using an *in vitro* slice preparation. One of the projects that I became involved in was to study NMDA receptor activation in the developing cat caudate nucleus (Siviy et al., 1991). Recording from cat striatal neurons ranging in age from 19 to 79 days we were able to detect NMDA-enhanced post-synaptic responses in these neurons and noticed bursts of action potentials in the youngest neurons. The ages at which bursting could be readily observed coincided with ages at which the animals were beginning to establish more developed (adult-like) patterns of motor control. This suggested to us that the enhanced NMDA receptor activated response might reflect increased neuroplasticity at a time when these neurons were being called into action as the animal begins to walk. Perhaps a similar type of neuroplasticity within basal ganglia circuitry occurs during the juvenile/adolescent period as animals engage in dynamic social interactions. Understanding how the basal ganglia, along with other associated brain circuitry, is involved in both modulating and benefiting from play should provide significant insight into a crucial aspect of childhood development.

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