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Stephen M. Sivy
Gettysburg College

Jaak Panksepp

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Keywords

play, development, rat, adolescence, review, affect, emotions, juvenile

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In Search of the Neurobiological Substrates for Social Playfulness in Mammalian Brains

Stephen M. Sivy¹ and Jaak Panksepp²

¹Department of Psychology
Gettysburg College
Gettysburg, PA 17325 USA

²Department of Veterinary and Comparative Anatomy, College of Veterinary Medicine
Washington State University
Pullman, WA 99164-6520 USA

Correspondence to

Stephen M. Sivy
Department of Psychology
Gettysburg College
Gettysburg, PA 17325
USA

Phone: 717-337-6180
Fax: 717-337-6172
e-mail: ssivy@gettysburg.edu

Abstract

Play behavior is a fundamental and intrinsic neurobehavioral process in the mammalian brain. Using rough-and-tumble play in the juvenile rat as a model system to study mammalian playfulness, some of the relevant neurobiological substrates for this behavior have been identified, and in this review this progress. A primary-process executive circuit for play in the rat that includes thalamic intralaminar nuclei, frontal cortex and striatum can be gleaned from these data. Other neural areas that may interact with this putative circuit include amygdala, ventral hypothalamus, periaqueductal gray (PAG), and deep tectum, as well as ascending dopamine systems which participate in all types of seeking urges. At the neurochemical level, considerable evidence points to specific cholinergic and dopaminergic controls, but also endogenous opioids and cannabinoids as having a positive modulatory influence over playfulness, with all neuropeptides known to have aversive effects to reduce play. Monoamines such as norepinephrine and serotonin certainly modulate play, but they influence all psychobehavioral systems, suggesting non-specific effects. We proceed to discuss how increased insights into the neurobiological mechanisms of play can inform our understanding of normal and abnormal childhood development.

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1. Introduction

Play behavior is such a common occurrence among so many mammals and is so prevalent among our own species that it often seems amazing how relatively little research, until recently, has been directed towards identifying the brain mechanisms that mediate this social-emotional process (for a comprehensive recent summary, see Pellis & Pellis, 2009). This was especially the case in the late 1970's when we turned our investigative and theoretical eye towards the play behavior of rats as part of a larger research program aimed at identifying the brain mechanisms of primary-process emotions (Panksepp, 1982). No neuroscientists at that time were studying concepts as nebulous as social emotions, let alone something seemingly as frivolous as play. Although the number of labs studying play from neurobiological perspectives has not exactly mushroomed since then, there is increased interest in the affective lives of mammals, and the extent to which playfulness may have an important impact on the overall brain development, health and well-being of humans and other animals. As a result, the amount of work on how the brain integrates playfulness has substantially increased.

Play not only occurs in most mammals, but has also been reported to occur in many avian species and even among some reptiles and invertebrates; indeed Gordon Burghardt (2005) devoted a whole chapter to play in reptiles. The widespread prevalence of play among a variety of species suggests that play as a behavioral phenotype probably evolved fairly early. Although rudiments of play seem to be evident in a wide range of species, social play became a major psychobehavioral process in mammals. There is now good evidence that the play urge is highly heritable, as highlighted by robust and consistent differences in play seen among different strains of rats (Ferguson & Cada, 2004; Siviy et al., 1997; Siviy et al., 2003) and between rats that have been selectively bred on other related components such as affective vocalizations (Brunelli et al.,

2006; Burgdorf et al., 2005) and susceptibility to amygdala kindling (Reinhart et al., 2006; Reinhart et al., 2004). All of this suggests that play is a fundamental neurobehavioral process in mammalian brains, arising from specific neural circuits. At present, the most efficient and thoroughly studied model system for identifying these brain networks lies in studies with domestic rats.

2. Play in the rat: Historical antecedents

During the waning years of the 19th century, the first major scientific publication on the play behaviors of rat appeared. In 1898, Karl Groos (1898) published a translated version of a still-cited book on play in animals, followed shortly by a remarkably prescient paper describing the development of the young white rat from birth until 28 days of age (Small, 1899). Willard Small noted that the first hints of play among infant rats began by around 18 days of age, increasing gradually and remaining at high levels throughout adolescence. But not much more laboratory work was published about play in rats until the last quarter of the 20th century, reflecting a shift from behaviorist learning models to increasing interests in the brain mechanisms of spontaneous animal behaviors using ethological approaches. Indeed, in mid-century, Frank Beach (1945) lamented on the relative lack of attention by comparative and physiological psychologists towards understanding the play of animals and tried to provide a framework for better understanding. A few years later, Schlosberg (1947) countered with a highly critical commentary on Beach's paper, suggesting that playful activity as a category "is so loose that it is almost useless for modern psychology" (p. 231). Only a little work continued in developmental psychology, focusing on human children, of course. Also, field workers taking ethological approaches also provided descriptions of play in a variety of species (Aldis, 1975;

Fagen, 1981). These efforts kept interest in play alive, but provided no well-controlled paradigms that might have encouraged neuroscientists to analyze the underlying brain mechanisms.

It wasn't until the late 1970s that systematic inquiries into the behavior of play in rodents were initiated. Neuroscientific work had to wait for the 1980s. In the mid 1970s, a few studies describing the play behavior of rats and mice were reported by Poole and Fish (Poole & Fish, 1975, 1976). Soon thereafter, a series of studies from Jane Stewart's lab at Concordia University provided detailed behavioral descriptions of play in juvenile rats in the complexities of their home environments, using a 'focal-observation' approach where individual animals were targets of observation for set periods (Meaney & Stewart, 1981; Olioff & Stewart, 1978).

These early studies provided useful insights into what play in the rat looks like in a semi-naturalistic setting. However, the experimental approaches being used still had significant limitations for neuroscientific inquiries. One potential obstacle at that time was the lack of clear and unambiguous indicator variables for playfulness in the rat. In other words, the study of play was not really amenable to what we now call "high-throughput research". Rough-and-tumble activity in young rats still seemed to be about as haphazard and random as it might be in human children wrestling on the floor, when the mood hit them. Closer observation of the animals, however, showed that indicator variables were not hard to identify and the motivation could be brought under tight experimental control using play-deprivation procedures, using what came to be known as the "paired-encounter" procedure, typically used with pairing of the same animals. In other words, there are certain ways in which the animals interact with one another that occur with relatively high frequency during bouts of what is aptly called rough-and-tumble play. Most notable was the frequent occurrence of 'wrestling' with one rat pinning the other for brief moments of time, with animals apparently taking turns, very unlike the aggression that was being

described in adult rats. A pin is essentially when one rat is on its back and the other on top in what looks like a dominant posture. Frequency of pinning is sensitive to the amount of isolation prior to testing (Panksepp & Beatty, 1980) and such repeated and frequent short pins, with both animals 'taking turns' to describe it mildly, are generally not seen in non-playful social encounters, albeit in adult fighting there are sustained, infrequent pins, almost always just by dominant animals. Pins with each animal scored independently are also remarkably easy to quantify, yielding clear developmental patterns (Panksepp, 1981a) and have high inter-rater reliability (Panksepp et al., 1984). Pins are often preceded by contacts directed to the nape of the neck so these contacts can also be used to quantify playful solicitations. This type of "paired encounter" methodology has now become standard in the field.

Another obstacle to efficient neuroscience research was how to obtain a reasonable sample of play behavior in a short observation period. This problem becomes particularly acute when using discrete manipulations such as drug treatments, where one needs stable baselines of the behavioral activities being monitored. But, as it turned out, play behavior is regulated in much the same way as other more traditionally studied motivated behaviors such as feeding and drinking. So when young rats are housed individually, thus being prevented from engaging freely in play behavior, and then given only limited opportunities to interact, the amount of play exhibited during discrete observation periods was systematically related to the amount of prior social deprivation (Panksepp & Beatty, 1980). Rats isolated for 4 hours played significantly more than rats housed socially and 8 hrs of deprivation was even more effective, and 24 hours much more so. So by isolating rats prior to testing one can easily titrate the amount of play that is exhibited during short observation periods (e.g., 5 – 15 minutes). With these protocols in hand,

investigators were now in a position to begin systematically investigating the unknown brain mechanisms that control playfulness in rats.

In this paper we will focus primarily on what we currently know about the neuroanatomical and neurochemical substrates of play in the rat. We will also discuss how this work can perhaps inform us as to the putative function(s) of play. Although most of the discussion will focus on laboratory rats, whose brains are remarkably playful, we will also consider other species for which there is some relevant evidence.

3. The motivational and affective side of play

As mentioned above, the amount of play that occurs during a short observation period can be readily titrated by varying the amount of isolation, indeed specific play-deprivation, prior to having that opportunity to play. This suggests that young rats are intrinsically highly motivated to play and given how tightly regulated play is in their brains, it is likely that the lack of social play in young rats changes the sensitivity of relevant neural substrates such that rats will be sensitized to engage playfully when the opportunity presents itself. As we describe below, brain dopamine systems have an important role in regulating play behavior, so changes in the sensitivity of dopamine systems probably provides part of the affective motivation and reward for play (Burgdorf et al., 2007).

In a preliminary experiment to evaluate this, we sought to determine whether 3 days of isolation housing could change the responsiveness of rats to novelty and to a moderate dose (1 mg/kg) of amphetamine, which was one of the first drugs found to dramatically reduce play (Beatty et al., 1982). Juvenile Lewis and Fischer rats were used since these 2 strains differ reliably in their overall levels of playfulness (Siviy, et al., 2003) and were tested in a novel open

field for 60 minutes, injected with amphetamine (1 mg/kg) and returned to the open field for an additional 90 minutes. Rats were either socially housed or housed individually for 3 days prior to testing. This amount of isolation was chosen as it has been previously shown to be sufficient for changing the analgesic response to morphine (Panksepp, 1980). As can be seen in Figure 1, three days of isolation housing was sufficient to increase baseline activity as well as amphetamine-induced activity. Interestingly, the two strains were affected to a comparable extent suggesting that the relative lack of play in the Fischer 344 rat is not due to a differential sensitivity to isolation in this strain. The response of rats from both of these inbred strains to a relatively acute period of isolation is similar to what has been observed in other strains with considerably longer periods of isolation-housing (Jones et al., 1992; Jones et al., 1990; Sahakian et al., 1975; Weiss et al., 2001) and, while the neurochemical specificity of this effect needs to be further explored, it suggests that brain dopamine systems may be sensitized following a period of isolation housing and, presumably, play deprivation.

In addition to being highly motivated, play is also fun for the participants. While this statement is fairly obvious when discussing the play of human children, more objective empirical evidence is needed when trying to reach the same conclusion for play in the rat. Rats will readily traverse a maze when an opportunity to play is the reward (Humphreys & Einon, 1981; Normansell & Panksepp, 1990) and will show a clear place preference for a context previously associated with play (Calcagnetti & Schechter, 1992; Douglas et al., 2004; Trezza et al., 2009), suggesting that playful experiences are indeed enjoyable to rats. Rats will also emit short (< 0.5 seconds) bursts of high frequency (~ 50 kHz) vocalizations when playing and when placed in a context where they have previously played (Knutson et al., 1998). Similar ultrasonic vocalizations (USVs) have been observed in male rats when anticipating a sexual encounter

(McIntosh & Barfield, 1980), in contexts associated with amphetamine or morphine (Knutson et al., 1999), when anticipating electrical stimulation of the medial forebrain bundle (Burgdorf et al., 2000), and in young rats that are manually “tickled” by an experimenter (Burgdorf et al., 2008; Burgdorf & Panksepp, 2001). From this we can see that all of these stimuli can evoke 50 kHz USVs and are also capable of evoking approach. Indeed, latency of rats to run towards a human hand that provides tickling is inversely related to the amount of 50 kHz USVs emitted while being tickled (Panksepp & Burgdorf, 2000). In other words, those rats emitting the most vocalizations while being tickled are also those that run fastest to the hand that tickles them.

In a recent preliminary study, we sought to look more closely at the acquisition of USVs when rats are anticipating a play bout. In our first experiment, rats were placed individually in a testing chamber and 50 kHz USVs were manually counted for 2 minutes in one group before a 5 minute opportunity to play in the same chamber (play group) and in another group that was returned to their home cage and did not have an opportunity to play in the test chamber (control group). As can be seen in Figure 2A, USVs gradually increased over the course of 8 testing days in those rats that were about to play. In a subsequent experiment, rats were either allowed to play with the same partner every day (as in the preceding experiment) or with a different partner every day. These results are shown in Figure 2B and indicate that social familiarity had a subtle effect on acquisition of USVs. In particular, those rats playing with a familiar partner every day were vocalizing more by the end of the 7 days of testing than those playing with a novel partner every day. It is also noteworthy that psychostimulants can sensitize the underlying anticipatory 50 kHz USV substrates of play (Panksepp et al., 2002).

These two experiments show that there is a steady increase in USVs as the predictive ability of the chamber that has been associated with play presumably increases. The results of the

second experiment further suggest that rats may be quicker to make that connection when their play partner remains the same every day. Differences in playfulness have also been reported for rats when playing with either familiar or unfamiliar partners, although the direction of these differences is dependent on both the measure of play used and the gender of the rats (Cirulli et al., 1996). Duration of overall rough-and-tumble activity is higher in both males and females when playing with an unfamiliar partner. However, males solicit more play when paired with a familiar partner while females solicit more play when paired with an unfamiliar partner. These data highlight not only the need for considering social familiarity when studying play but also the need for monitoring USVs during these playful encounters.

3. Neuroanatomical substrates of play

One approach towards framing the neuroanatomy of play has been to use Paul MacLean's heuristic of the "triune brain" (MacLean, 1985, 1990) and this was very influential in guiding some of the early lesion work designed to identify relevant neural structures. According to this conceptualization the most relevant neural circuitry for guiding mammalian play would most likely be found among older limbic structures. The neocortex, on the other hand, should have minimal influence on playfulness. In an initial paper testing this hypothesis (Murphy et al., 1981) it was reported that complete removal of the neocortex in hamsters did not have a major impact on the prevalence of play exhibited as juveniles. If the damage extended to limbic structures, however, play tended to decline. With some caveats, this initial finding by MacLean's group has been confirmed in rats (Panksepp et al., 1994; Pellis et al., 1992). For example, we (Panksepp, et al., 1994) found that decorticates pinned each other less than controls when allowed to play with other neo-decorticates, but overall rough-and-tumble play facilitated

overall motor activity (as monitored by stabilimeter platforms) was not reduced, since the animals still exhibited comparable play solicitations, as monitored with dorsal contacts (Normansell & Panksepp, 1984). Likewise, play dominance of decorticates did not differ from controls when paired with controls. Similarly, Pellis and colleagues (1992) reported that decorticates did not differ from control rats in terms of the frequency of playful nape contacts nor in the overall likelihood of responding to these contacts. However, partial decortication, as with selective lesions of the somatosensory cortex did reduce play (Panksepp, et al., 1994) while selective frontal lesions increased play markedly, even if done unilaterally (Panksepp et al., 2003).

Overall though, rats without a neocortex exhibit all of the elements of play behavior, although subtle differences among decorticate rats suggests that some type of modulation of play occurs at the level of the cortex. These differences can become particularly salient when more detailed observations of play are made and when these observations are followed into early adulthood. For example, Pellis and his colleagues have compared the play of juveniles to that of young adults and have characterized age-related shifts in how intact rats respond to playful solicitations as they mature (Pellis & Pellis, 1990; Pellis et al., 1993). As juveniles, intact male rats are most likely to respond to playful solicitations by rotating completely onto their back (i.e., a pin) but as these rats mature, they are less likely to be pinned since they tend to only rotate partially, often with their hind paws still firmly planted on the ground. As adults, intact rats also modulate how they respond to playful solicitations depending upon the status of the rat that they happen to be playing with. When playing with a dominant male, subordinate males continue responding to playful contacts by allowing themselves to be pinned. But when paired with another subordinate, these rats respond mostly with partial rotations.

In their initial paper on play of decorticated rats, Pellis and colleagues (1992) noted that decorticate rats were more likely to respond to nape contacts with partial rotations both before and after puberty suggesting that decorticate play more closely resembled adult play in rats. These rats also did not modulate their responses based on the status of the partner. Subsequent studies from Pellis' group found that different areas of the cortex appear to be modulating these different aspects of play. For example, rats with lesions to the motor cortex do not show age-related changes in play tactics in that males continue to respond predominantly with complete rotations after puberty (Kamitakahara et al., 2007). On the other hand, rats with damage to the orbitofrontal cortex fail to modulate their play based on the status of the partner (Pellis et al., 2006), while rats with damage to the medial prefrontal cortex simply use less complex play tactics (e.g., they are more likely to run away) when solicited (Bell et al., 2009). While these studies indicate that play is modulated in fairly subtle ways by cortical processes, it is still likely that subcortical systems are the targets of such modulation, and the cortical regulation may largely be learned (an important issue to be resolved empirically).

A number of subcortical structures have been suggested to be particularly relevant for play to occur, yet no clear "play circuit" has emerged. A role for the mesolimbic dopamine system in motivation and reward is well established (Alcaro et al., 2007; Berridge, 2007; Ikemoto & Panksepp, 1999; Robinson & Berridge, 1993) so it is likely to have a pivotal role in play as well. Although the definitive experiments have yet to be done, there is ample indirect evidence to make a case for mesolimbic involvement in at least the appetitive and/or affective response to play. As mentioned earlier, rats will readily emit ultrasonic vocalizations (USVs) in the 50-55 kHz range both during play and when they are anticipating play (Burgdorf, et al.,

2008; Knutson, et al., 1998) and the mesolimbic dopamine system strongly controls the production of 50 kHz USVs (Burgdorf, et al., 2007).

Given the importance of somatosensory processing during this kind of chasing and ‘wrestling’ play (Siviy & Panksepp, 1987b) it was perhaps not surprising to find that discrete damage limited to subcortical areas known to process somatosensory input, such as the parafascicular area of the thalamus (PFA), results in a robust, long-lasting, and selective impairment of play (Siviy & Panksepp, 1985, 1987a), without compromising complex sensory-motor processes such as foraging for food. The PFA, perhaps along with other components of the intralaminar thalamic nuclei, may then be a critical hub in an executive circuit for mammalian playfulness; receiving direct somatosensory input from the spinal cord and sending excitatory projections to areas such as the frontal cortex and striatum (Cesaro et al., 1985; Nakamura et al., 2006; Voorn et al., 2004). As mentioned above, there is evidence for some modulation of play by the prefrontal cortex (Bell, et al., 2009; Kamitakahara, et al., 2007; Pellis, et al., 2006) and the striatum is likely to be important for playful behaviors as well (Gordon et al., 2002; Graham, 2011; Pellis et al., 1993) so these areas may help transduce playful somatosensory input into the fluid motor sequences seen during play. Recent evidence suggesting that PFA input to the dorsal striatum facilitates behavioral flexibility (Brown et al., 2010) may be particularly salient in this regard.

Within the limbic system there is some evidence for amygdala involvement in play, but the functions remain unclear. When social play frequency and size of amygdala were compared in a variety of non-human primates, it was found that the size of the amygdala predicted amounts of social play (Lewis & Barton, 2006) suggesting the abundance of social play is associated with a larger amygdala at least within a sub-set of non-human primates. A similar relationship has

been reported between striatum and social play (Graham, 2011). In rats, relatively large ibotenic acid lesions to the amygdala on postnatal day 21 have been shown to reduce play when tested one week later while open field activity in these animals and other social behaviors unrelated to play were largely unaffected by the lesions (Daenen et al., 2002; Wolterink et al., 2001). While this suggests a selective effect of these lesions on play behavior, the interpretation of these data remains debatable. For instance, we have also found that large electrolytic lesions of the amygdala reduce play, although these animals also show deficits when required to forage for food (Panksepp, et al., 1984).

Use of metabolic mapping techniques have also produced mixed results with relatively little overall change in c-fos mRNA activity seen as a result of play in higher brain region in rats except for parietal somatosensory regions, while many subcortical areas exhibited substantial activation--including dorsal PAG and other adjacent deep tectal areas, the inferior colliculus as well as both the dorsal and ventral striatum (Gordon, et al., 2002). Increases in c-fos protein have also been reported for the medial amygdala of hamsters after play (Cheng et al., 2008). While an executive function for the amygdala in play remains unlikely, the amygdala may still be a recipient of information about playful activities along with reciprocal modulation of play expressions, perhaps via affective rewarding properties. Overall, the above data strongly support a subcortical locus of control for play, and affirm that the mesolimbic SEEKING system may be especially influential for promoting play (Burgdorf, et al., 2007). We also note that play has been shown to increase the transcription of brain derived neurotrophic factor (BDNF) in the amygdala, as well as in the dorsolateral frontal cortex (Gordon et al., 2003), and more recently a host of other changes in cortical gene expressions, especially insulin-like growth factor 1 (Burgdorf et al., 2010).

Since the behavioral patterns observed with play tend to co-opt those utilized in other situations (e.g., reproductive behavior, defensive behavior, aggression) circuits involved in the execution of these behavior patterns may also be recruited and modulated by executive circuitry for play. For example, the dorsal PAG is activated by play behavior in both rats and hamsters (Cheng, et al., 2008; Gordon, et al., 2002). The PAG has been suggested to be critical for switching between different behavior patterns (Sukikara et al., 2006), which is another defining characteristic of rough-and-tumble play and the PAG is a major recipient of activity arising from the medial hypothalamic defensive-fear circuit (Canteras, 2002).

Because of its sensory and motor complexity, identifying specific neuroanatomical substrates for mammalian play remains a challenge, although continued use of traditional brain lesion methods in tandem with careful behavioral observations that rule out general behavioral deficits, increased use of established metabolic mapping techniques (Cheng, et al., 2008; Gordon, et al., 2002) and novel molecular tools (Burgdorf et al., 2010) are likely to add to our understanding of how play maps onto neural networks in mammalian brain.

4. Neurochemical substrates of play

Given the robust nature of rough-and-tumble play, disentangling the relevant neurochemical systems involved in modulating the behavior has also been a challenge. Nevertheless, several neurotransmitters have emerged as strong candidates for modulating play. Building off of the theoretical framework that endogenous opioids are critical for positive social affect (Panksepp, 1981b, 1982; Panksepp et al., 1980) it seemed logical that opioids would also be important for play. Indeed, endogenous opioids are released in many brain areas during play (Panksepp & Bishop, 1981; Vanderschuren et al., 1995) and a number of studies have shown that

low doses of opioid agonists, such as morphine (i.e., 1 mg/kg and less), can reliably increase play in juvenile rats while opioid antagonists decrease play (Niesink & Van Ree, 1989; Panksepp et al., 1985; Trezza & Vanderschuren, 2008b; Vanderschuren et al., 1995a, 1995b, 1996).

Morphine does not appear to enhance any particular component of play nor does it increase non-playful social behaviors, which are in fact often reduced (Panksepp et al., 1979). Thus, modest facilitation of brain opioid activity seems to specifically promote active engagement in playful behaviors (Vanderschuren et al., 1995b; Vanderschuren, et al., 1996), perhaps increasing play by sustaining positive affective play motivation of the rat (Normansell & Panksepp, 1990; Panksepp, et al., 1985). These data suggest that endogenous opioids have an overall modulatory influence on play in juvenile rats, with mild increases in opioid activity resulting in an affective state that is especially compatible with playfulness, and perhaps high levels of endogenous opioids, just like higher doses of morphine, reducing play with a sense of satisfaction that enough play has been had.

More recent work has shown that enhancing activity in endogenous cannabinoid systems can also make rats more playful (Trezza & Vanderschuren, 2008a, 2008b, 2009). In this same vein, administration of compounds that prolong the action of endogenous cannabinoids in active synapses increase play while direct cannabinoid agonists consistently decrease play. Since endocannabinoids are only manufactured and released on demand (Piomelli, 2003), this suggests that a sub-set of synapses with CB₁ receptors are activated during play and it is at these synapses where enhanced cannabinoid activity makes rats more playful. There also appears to be considerable overlap between opioid and cannabinoid involvement in play as increases with morphine can be blocked by both opioid and cannabinoid CB₁ antagonists while increases in play following enhanced endocannabinoid signaling can be blocked by opioid and cannabinoid

CB₁ antagonists. While these data suggest that opioids and cannabinoids act on similar substrates to modulate play, effects associated with each can still be dissociated. For example, dopamine antagonists can block increases in play due to indirect cannabinoid agonists while being ineffective when combined with opioid agonists (Trezza & Vanderschuren, 2008a). In either case, the evidence to date points strongly towards both endogenous opioids and cannabinoids having a specific role in modulating play.

One of the earliest pharmacological studies with play behavior showed that psychomotor stimulants such as amphetamine and methylphenidate (Ritalin[®]) were extremely potent in reducing play (Beatty et al., 1984; Beatty, et al., 1982; Panksepp, 1979) suggesting that monoamines may be important for modulating levels of playfulness (Normansell & Panksepp, 1985a, 1985b). More recent work has shown that the methylphenidate-induced reduction in play is due to enhanced release of norepinephrine (Vanderschuren et al., 2008). In particular, these investigators reported that reductions in play following methylphenidate were blocked by the α_2 noradrenergic antagonist RX821002 but not by α_1 or β noradrenergic antagonists nor by a dopamine antagonist. The effect of methylphenidate could also be mimicked by the selective noradrenergic reuptake inhibitor atomoxetine but not by the dopamine reuptake inhibitor GBR-12909. These data suggest that increased noradrenergic activity at post-synaptic α_2 receptors is incompatible with play. This might also suggest that the play enhancing effect of α_2 noradrenergic antagonists (Siviy et al., 1990; Siviy & Baliko, 2000) is due to blockade of this same population of post-synaptic receptors and that dampening noradrenergic activity is compatible with playfulness. It is then noteworthy that some of the more recent pharmaceuticals being used in the treatment of ADHD, such as atomoxetine (Strattera[®]) or the selective alpha-2 agonist guanfacine (Intuniv[®]) act selectively on noradrenergic systems, perhaps by stimulating

alpha-2 receptors in the prefrontal cortex (Arnsten et al., 1996; Robbins & Arnsten, 2009). This also leads us to wonder whether the symptomatic benefits of these drugs in treating ADHD is, at least in part, due to reduction of play urges in young children.

Both noradrenergic and serotonergic systems have fairly extensive and diffuse projections throughout the forebrain and are both likely to have some modulatory involvement in play. As described above, the evidence suggests that enhanced noradrenergic tone would be incompatible with play. Serotonin is thought to have considerable impact on a wide range of neurobehavioral processes including affective regulation (Dayan & Huys, 2009; Hariri & Holmes, 2006), establishing and maintaining dominance (Huber et al., 2001; Raleigh et al., 1991), and defensive behavior (Blanchard et al., 1998; Graeff, 2002), to name just a few, so it is very likely that serotonin may also be involved in at least some aspect of play, as it is in practically all behavioral processes (Panksepp, 1998a). Manipulations that can enhance serotonin functioning such as fluoxetine or MDMA (“Ecstasy”) reduce play when both rats are treated similarly (Homberg et al., 2007; Knutson et al., 1996). Homberg and colleagues (2007) also reported less play among serotonin transporter knockout rats as well. Although this would suggest that enhanced serotonergic functioning is incompatible with play, a more complex pattern emerges when only one rat of a pair is treated and attention is paid to the reciprocal interactions between the two rats of the testing pair. When rats were allowed to establish a dominance relationship such that one rat accounted for more pinning than the other (this being the dominant rat) the effects of either fluoxetine or serotonin depletion depended on the status of the rat. Augmenting serotonin levels through fluoxetine reduced the pinning asymmetry when the dominant rat was treated (Knutson, et al., 1996) while depleting serotonin enhanced the pinning asymmetry (Knutson & Panksepp, 1997). Treating the subordinate rat had no effect on

the pinning asymmetry. Furthermore, playful solicitations were not affected in this set of experiments. These data suggest a more subtle role for serotonin in modulating play behavior that may be more sensitive to interactive cues between the play partners.

We have spent many years looking at the effects of the selective 5HT_{1A} agonist 8-OH-DPAT on play starting with a relatively simple working hypothesis that dampening serotonergic activity would tend to increase play. We had then predicted that low auto-receptor selective doses of 8-OH-DPAT would tend to increase play. While small increases have been observed from time to time, these have not been very robust nor have they been easily replicable (some of this work is described in Siviy, 1998). In light of the results described above with fluoxetine and serotonin depletion we recently began a series of studies to assess the effects of 8-OH-DPAT when administered to only one rat of the testing pair. Rather than allowing rats to establish a dominance/subordinate relationship, rats in this experiment played with a new partner on each test day. One rat of the pair was tested with each of 4 doses of (±)-8-OH-DPAT plus a vehicle and the untreated partner was chronically isolated while the treated rat was isolated for only 4 hours prior to testing. As can be seen in Figure 2 this created a natural asymmetry in dorsal contacts between the untreated and treated rat after vehicle presumably due to the higher motivation to play in the untreated, and chronically isolated, partner. This asymmetry in dorsal contacts collapsed at the two lower doses of 8-OH-DPAT and returned after the higher two doses, presumably due to non-specific effects with these higher doses. The likelihood of a dorsal contact resulting in a pin was not affected by 8-OH-DPAT.

These data are consistent with the possibility that fluctuations in serotonergic functioning change the dynamics of a playful interaction between two rats when there is some baseline asymmetry in that interaction. Given that the doses that produced the effects should have been

affecting autoreceptors this would suggest that an acute decrease in serotonergic tone through stimulation of autoreceptors may be accounting for these behavioral effects. However, caution should be used when interpreting results from adolescent rats when using drugs that affect both pre-synaptic and post-synaptic receptors. For example, we had assumed that the enhanced play seen with low doses of α_2 antagonists was due to blocking pre-synaptic autoreceptors (Siviy, et al., 1990; Siviy & Baliko, 2000) whereas it is more likely to be due to blockade of post-synaptic receptors (Vanderschuren, et al., 2008). Given that the relative sensitivity of autoreceptors and post-synaptic heteroreceptors may fluctuate over the peri-adolescent period (Spear, 2000), any interpretations associated with 8-OH-DPAT must remain highly tentative at present. Definitive resolution of this issue would probably require the evaluation of pharmacological effects in animals where pre-synaptic serotonin neurons are destroyed with serotonin specific neurotoxins (Olivier et al., 1991).

Given the exuberant nature of play and the amount of positive affect associated with play (Burgdorf, et al., 2008; Calcagnetti & Schechter, 1992; Humphreys & Einon, 1981; Normansell & Panksepp, 1990) there are many *a priori* reasons to suppose that brain dopamine systems may have a role in playful behaviors. Indeed, dopamine utilization increases during play bouts (Panksepp, 1993), dopamine antagonists uniformly reduce play (Beatty et al., 1984; Niesink & Van Ree, 1989; Siviy et al., 1996), and neonatal 6-OHDA lesions impair the sequencing of behavioral elements during play bouts (Pellis et al., 1993). While it has been difficult to obtain consistent increases in play with dopamine agonists (Beatty et al., 1984; Field & Pellis, 1994; Siviy et al., 1996) increases in play following alcohol, nicotine, and indirect cannabinoid agonists can all be blocked by silent doses of dopamine antagonists (Trezza et al., 2009; Trezza & Vanderschuren, 2008a). Taken together, these data suggest that play is associated with

increased release of dopamine (Robinson et al., 2011), and it has been suggested that an optimal level of dopamine functioning is necessary for play to occur (Trezza et al., 2010).

Dopamine may also have a preparatory, or appetitive, function in much the same way as it does for other motivated behaviors (Berridge, 2007; Berridge & Robinson, 1998; Ikemoto & Panksepp, 1996, 1999; Pfaus & Phillips, 1991). Play can be readily dissociated between appetitive and consummatory components; rats will display an anticipatory increase in activity when placed in an environment previously associated with play and this can be attenuated with the dopamine antagonist haloperidol (Siviy, 1998). As mentioned earlier, rats will also emit ultrasonic vocalizations in the 50-55 kHz range when placed in an environment previously associated with play (Burgdorf et al., 2008; Knutson et al., 1998), and it seems clear that these kinds of vocalizations are dopamine-mediated (Burgdorf et al., 2007).

Central cholinergic systems may also have a modulatory influence on play. In some of our earlier work we found that nicotine reduced play while blocking cholinergic receptors with the nicotinic antagonist mecamylamine modestly increased play (Panksepp et al., 1984). However, a more recent study has shown that nicotine increases play (Trezza et al., 2009) and that this increase was blocked by a dose of mecamylamine that had no effect in and of itself. While obtaining opposite results with nicotine in these two studies seems initially problematic, several methodological differences could readily account for these differences. For example, the dose used by Trezza and colleagues (0.1 mg/kg) was lower than the lowest dose used in our work (0.125 mg/kg), which had a minimal effect on play. A more robust reduction in pinning only became apparent in our hands at higher doses that may have resulted in a non-specific impairment. Another potentially important methodological difference between these two studies is the extent to which the rats were familiar with each other prior to testing. In almost all of our

pharmacological work rats have been paired with either cage-mates or with the same rat every day over the course of an experiment. On the other hand, the Trezza et al. (2009) study, along with most other recent studies from Vanderschuren's group, tests rats that are unfamiliar with each other. It is possible that social familiarity may be a factor in determining the nature of some of these pharmacological effects and is probably a variable that should be examined in more detail. We've already seen earlier that the 50 kHz USVs emitted in anticipation of play may be sensitive to the familiarity of the partner and others have shown that levels of play are sensitive to familiarity of the play partner (Cirulli et al., 1996).

Since both muscarinic agonists and antagonists reduce play (Wilson et al., 1986) any cholinergic involvement is more than likely limited to nicotinic receptors. However, increases in play with nicotine are blocked by not only the nicotinic antagonist mecamylamine but also by opioid, cannabinoid, and dopamine antagonists (Trezza et al., 2009). Emerging from these data is a complex neurochemical picture that involves interactions between opioid, cannabinoid, dopaminergic, and cholinergic systems in the regulation of play. Positive affect associated with play may be a common thread by which all of these systems modulate playfulness. As described earlier, play can be used as an unconditioned stimulus in a conditioned place preference (CPP) paradigm such that rats will spend more time in an environment that has previously been associated with play (Calcagnetti & Schechter, 1992). When doses of nicotine or cocaine that are insufficient to yield a CPP by themselves are combined with moderate levels of play that are also insufficient for inducing a CPP, a robust place preference is obtained (Thiel et al., 2008, 2009). Drugs which act on these systems and which tend to increase play may be doing so by enhancing the positive affect associated with playful social interactions.

5. Clinical and Developmental Implications of Play Research

Briefly, let us consider the functions of play in brain, mind and behavioral development, which are bound to be many (Spinka et al., 2001). First, we should be confident that play is an intrinsic function of the brain, since it emerges promptly in rats in mid-adolescence even if they have had no previous opportunity to play (Ikemoto and Panksepp, 1992). Hence, just like all the basic emotions of the brain, it is an experience expectant process that allows animals to adjust their behavior to facilitate survival. It is highly likely that this anticipatory effect relates mostly to the emergence of social competence, a likelihood that currently has little good data at the animal behavioral levels (but see Van den Berg et al., 1999). However, various human studies suggest such functions (Brown, 2010; Grossman, et al., 2002). These are very sensible approaches to this scientifically unsolved problem, but here we would briefly discuss how playfulness may relate to psychiatric/clinical issues. It may have special implications for treating childhood disorders such as Attention Deficit Hyperactivity Disorders (ADHD) and depression at all ages.

A case has been made for the possibility that our current epidemic of childhood ADHD may reflect our increasing family and societal regimentation of early childhood activities, where free rough-and-tumble play that children themselves initiate, is often frowned on. However, in addition to the fact that play promotes various growth factors in the brain (Burgdorf, et al., 2010; Gordon, et al., 2002), it is clear that play is regulated both in terms of daily activities (Panksepp and Beatty, 1980) as well as the whole adolescent period of development (Panksepp, 1981a). If a young rat has not had play for a while during a day, or during early phases of development, it will exhibit an elevated desire for play later on (Ikemoto & Panksepp, 1992; Panksepp et al., 1984). In a well-regulated society, such urges may be deemed to be impulse-control disorders by

adults (Panksepp, 2007a). Might play-starved children be more liable to be diagnosed with ADHD, and given psychostimulants which, as we have already seen, are very effective in reducing play in rats? Since play does activate brain growth factors in frontal regions of the brain (Gordon et al., 2003), might play deprivation reduce the maturation of frontal executive areas of the brain (Panksepp, 2001)?

We evaluated this possibility quite simply--by preparing animals with frontal lobe damage that markedly increased motor activity and also playfulness (Panksepp et al., 2003). We then provided half of the ADHD type rats and half of the controls either very little play during development, or a well-controlled hour of play each day, in two 30 minute play periods, morning and evening, following the natural diurnal pattern of play in most mammalian youngsters. When given an opportunity for "play therapy", levels of activity and playfulness in lesioned animals returned to control levels. These results indicated that brain damaged ADHD-type rats that had abundant play were better regulated than littermates who had had no play. This, taken in combination with the profound ability of ADHD medications like Ritalin to reduce playfulness (Beatty et al., 1982; Panksepp, 1998b; Vanderschuren et al., 2008), should at least alert us to the fact that ADHD in our society may be as much of a social-developmental disorder as something that is intrinsically wrong in children's brains. If so, it would be wise for us to establish social policies, perhaps "play sanctuaries" that promote childhood play (Panksepp, 2007a).

The other psychiatric issue where a fuller consideration of the benefits of playfulness needs to be considered is depression, a sustained form of psychological pain and emptiness, that is widely considered to arise largely from sustained life stressors, especially those arising from social loss (for full review, see Watt and Panksepp, 2009). Since playfulness promotes social bonding, happiness and laughter (Panksepp, 2007b; Scott & Panksepp, 2003), would it be too

far-fetched to suggest that facilitation of playfulness might reduce depression, even in the context of psychotherapeutic interactions? We think that is a reasonable possibility, and we already have some pre-clinical pilot data suggesting such benefits in the animal models of depression we have been studying (for a summary see Burgdorf et al., this issue).

When we consider these momentous issues for the kind of social structures we need to promote, we wonder why there is so little research in the developmental literature on physical-social playfulness in human children, without toys. When we had already conducted over three decades of systematic research on the playfulness of rats, with no such work ever having been published for our own species, we decided to conduct the study ourselves (Scott and Panksepp, 2003). Boys and girls having a mean age of about 5 years old were tested for 30 minutes in same-gender pairings in a room with a cushioned floor but without any toys. The children were shown a brief video clip of children engaged in rough-and-tumble play and simply told to enjoy themselves. As expected, pre-school children readily engaged in physical rough-and-tumble activity that was accompanied by laughter. Much like our work with rats, these children showed a steady decline in play and laughter over the course of the 30 minute observation period, perhaps reflecting satiety. This study demonstrates that rough-and-tumble play is as easily quantifiable in human children as it is in the rat and will hopefully serve as a model for future studies as we continue to draw parallels between the rough-and-tumble worlds of the young rat and the human child.

In sum, mammalian play urges, clearly built into the nervous systems, are likely to be social experience-expectant processes that allow the young to learn the specific social nuances of their species. Play not only helps the young to acquire and refine social skills, depending on ecological demands which were not built into their nervous systems by evolution, but it does so

in the safety of supportive adult social groups that can provide feedback on their behaviors. The mock battles surely also prime their skills for social competition, and in stable social societies, probably allow animals to be integrated into their social structures, whether as dominant or submissive members, without the serious conflicts that sometime characterize social interactions among strange adults. The fact that systematic play research had a slow start in behavioral neuroscience reflects the need for complementary perspectives that take affective processes seriously, as reflections of primal emotional mechanisms that facilitate survival (Panksepp, 1998a; 1998c; Siviy, 1998).

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Figure captions

Figure 1. Distance traveled in a novel open field before (Baseline) and after an injection of 1 mg/kg amphetamine (Post-amphetamine) in both Lewis and Fischer rats. Rats were either socially housed or isolated for 3 days prior to testing. The data from the baseline period were analyzed using a 2 x 6 Analysis of Variance (ANOVA) and there was found to be a significant time x housing interaction, $F(4,140) = 5.52$, $p < .001$. No effects were associated with strain of the rat. When the post-amphetamine data were analyzed with a 2 x 9 ANOVA there was found to be a significant time x strain interaction, $F(8,224) = 3.23$, $p = .002$, and a significant main effect of housing, $F(1,28) = 4.79$, $p = .037$.

Figure 2. Panel A: Mean (\pm SEM) number of 50 kHz vocalizations emitted in a 2 minute period in rats that were returned to their home cage immediately afterwards (Control) or allowed to play with a same-age conspecific for 5 minutes (Play). All rats were housed individually. At least several hours after testing, those rats in the control group were allowed to play with another male rat of the same age in a chamber that differed in size, texture of floor, and lighting. This chamber was also placed in a different room from the testing chamber. Vocalizations were not monitored on the first two days of testing. The presence of a significant day of testing X group interaction, $F(5,70) = 6.58$, $p < .001$, indicated that the difference in vocalizations between the two groups became more pronounced as testing progressed. Panel B: Mean (\pm SEM) number of 50 kHz vocalizations emitted in a 2 minute period prior to either a 5 minute opportunity to play with the same partner or a different partner every day. The presence of a significant day of testing X group interaction, $F(6,102) = 5.03$, $p < .001$, indicated that rats allowed to play with the

same partner every day were vocalizing significantly more than those that played with a different partner every day by the last three days of acquisition.

Figure 3. Mean (\pm SEM) number of dorsal contacts in rats treated with 8-OH-DPAT or vehicle. Untreated rats were individually housed throughout testing while the 8-OH-DPAT treated rats were isolated for 4 hours prior to testing. Analysis of these data with a 2 X 5 ANOVA yielded a significant dose x group interaction, $F(1,14) = 8.214$, $p = .012$. * indicates significant difference between the treated and untreated rats.

Figure 1
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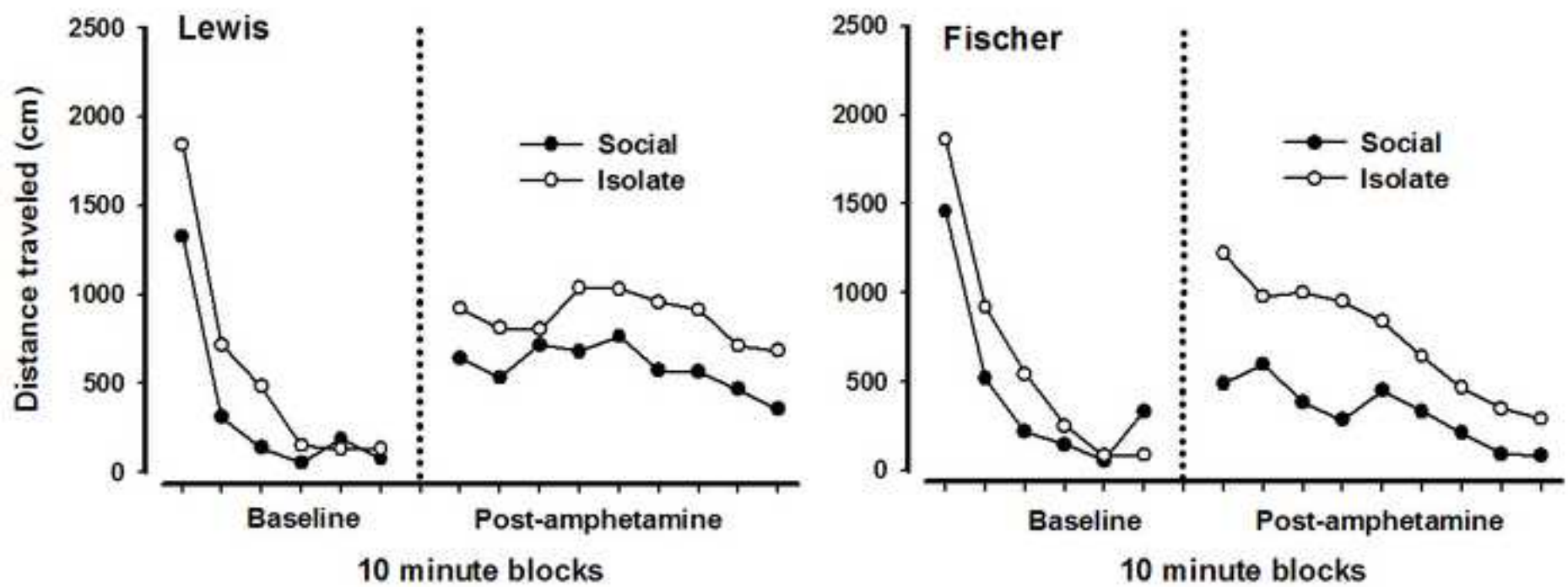


Figure 2
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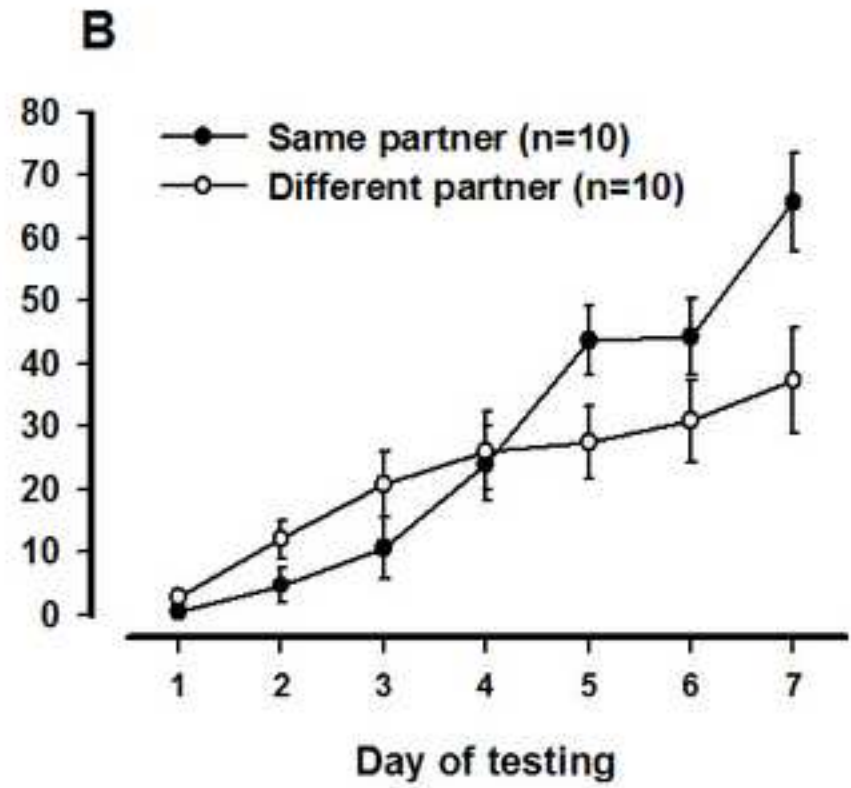
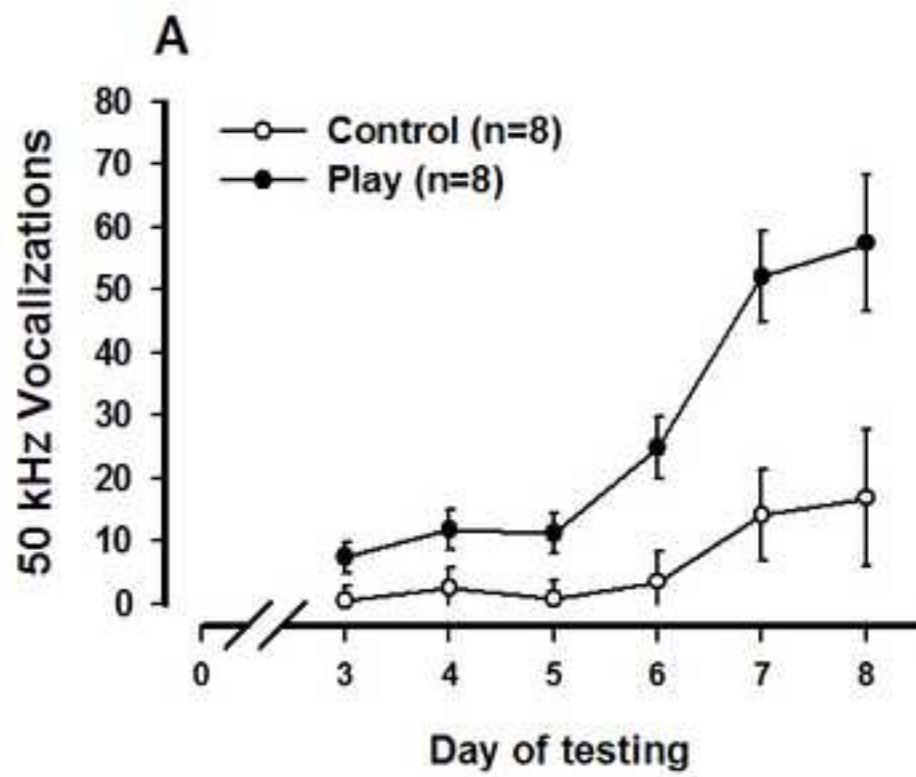


Figure 3
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