How the Brain Makes Play Fun

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In this article, the author describes the empirical studies that have investigated whether play (mostly social play) is rewarding. He then discusses the brain circuits and neurotransmitters that underlie the pleasurable aspects of play. He concludes that the pleasure of play has the ability to reinforce learning activities and that the brain's neurotransmitters and the brain regions that are deeply involved in motivation and pleasure also mediate the pleasures and motivations that social play produces.

Introduction

On an intuitive level, everybody understands that play is fun. Indeed, "playing" and "enjoying yourself" are almost synonymous. We have come increasingly to understand the mechanisms in the brain that make us enjoy activities such as eating something tasty, having sex, or spending time with loved ones. Research on the topic has grown more urgent with the rising costs and hardships caused by drug addiction and eating disorders. In these diseases, the function of brain pleasure mechanisms is altered, causing people to behave in ways destructive to themselves and others. Research has taught us a lot about brain reward mechanisms. This research has developed specific models to study mental subcomponents of the behaviors that constitute pleasure and fun, such as motivation and approach behavior. Clearly, knowing intuitively that play is fun may help us understand and conceptualize it, but in order to investigate how the brain makes such behavior fun, we need to conduct studies that specifically address the pleasurable properties of play. Here, then, I wish to review some of the studies that have already investigated the rewards of play, especially social play, and discuss the architecture of the brain that underlies the pleasure such play produces.

Play Is Fun: Empirical Demonstrations

One of the first experimental demonstrations to show that social interaction has reinforcing properties comes from Falk (1958). The study used a chimpanzee, one which Falk had noticed would grab his arm and groom whenever the animal had the opportunity. The experiment employed a discrimination setup. Falk showed the chimpanzee a Plexiglas panel with images of a cross and a square. If the chimp pointed at the square, Falk moved his own arm to allow the chimpanzee to groom it. When the chimp pointed at the cross, Falk did not allow it to groom his arm. The chimpanzee quickly learned to discriminate (i.e. to point at the square, not at the cross) and also easily managed a so-called reversal task, during which it learned that pointing at the cross instead of the square earned it the opportunity to groom the experimenter's arm. The experiment demonstrated that the chimpanzee was willing and able to perform an arbitrary act (i.e. to point at a square, which for a chimpanzee in the wild would be meaningless behavior) to earn the chance to groom the experimenter. According to experimental psychological definitions, the behavior indicates that for this particular animal, grooming could function as a reinforcer: if the consequences of a given act (usually a neutral and arbitrary one such as pressing a lever, pulling a chain, or, in this case, pointing at a square) are such that the probability of the behavior occurring in the future increases—that is, the behavior will be repeated—the consequences (in this case, being allowed to groom an experimenter, but it could as easily be gaining access to food, drugs, or sex) are said to be reinforcing. Strictly speaking, reinforcement only implies repetition of behavior, and in itself does not demonstrate that the reinforcer is pleasurable. After all, we cannot ask the chimpanzee directly whether it enjoys grooming the experimenter. However, its willingness to learn a particular task in exchange for the opportunity to groom another shows it finds grooming worth working for, which indicates that there must be something pleasurable about it. Indeed, by and large, stimuli that act as reinforcers are those we humans enjoy too, such as food, drugs, and sex.

The Falk study showed that grooming can be a reinforcer, but it did not assess whether this was also true for play. The reinforcing properties of social play were demonstrated in a study where chimpanzees could press two different levers (Mason, Saxon, and Sharpe 1963). Pressing one lever earned the reward of social interaction, which consisted of petting (stroking face, hands, and trunk) or play (vigorous tickling, pulling, and pushing). Pressing a different lever earned a reward of food. In the first experiment, the chimps

could choose between social interaction and a highly preferred food like a grape or an apple. They were tested either before their daily morning meal (in other words, they were hungry when tested) or one hour after their meal. If the social activity on offer was play, the chimps chose social interaction more often than if the social activity on offer was petting, which indicates that play is more reinforcing than petting. Furthermore, when hungry chimps were tested, they chose food more often than social activity unlike the chimps tested after the morning meal. However, most interestingly, even when hungry chimpanzees were tested, they still chose play 40 percent of the time. If they were tested when their appetites were sated, they preferred play over food almost 70 percent of the time.

In the second experiment, sated animals were tested, and their options were either social activity (play or petting) or foods of high, moderate, or low preferences (fruit, dried apricot, or chow). Again, they chose the social activity on offer more often when it was play than when it was petting. The chimps increasingly preferred play as the food alternative grew less appetizing. Remarkably, preference for play instead of highly preferred food was 50 percent, and it increased to 80 percent when the choice fell to play or just chow. Together, these experiments demonstrate that play is a strong reinforcer for chimps comparable to tasty fruit and much more attractive than regular food.

The positive properties of social play have also been investigated in rats using methods such as discrimination in a T-maze and place conditioning. In one study, rats were tested in a simple maze shaped like a T, and they were placed in the corridor at the far end. When they arrived at the point of intersection, they had the choice of proceeding left or right. In the earliest experiment that used this setup (Humphreys and Einon 1981), rats of approximately three-weeks-old (an age at which rats show a great deal of social play) were first trained hungry on a food/no food discrimination. Each rat could always find food at one end of the T but not at the other end. The animals learned to discriminate between the two ends easily, choosing the food side of the maze around 90 percent of the time within a few days of testing. When food was then suddenly offered at the other end of the T, the rats quickly changed their preference.

In the next experiment, rats were given the choice between two social partners at the respective ends of the maze: one that was unconfined and that they could freely interact with, and another one that was confined under a wire mesh container. In this experiment, the rats chose the free partner around 80 percent of the time.

In two following experiments, the rats were offered the choice between a normal social partner or one that had been treated with amphetamine or chlorpromazine. These treatments drastically change the social behavior of rats: they will no longer play, but they remain otherwise socially amicable. The choice in these experiments was between a playful social interaction and a nonplayful social interaction. The rats chose the side of the T where they could find a playful partner between 60 and 80 percent of the time.

These experiments show that young, playful rats can learn to discriminate between two sides of a T when the options are playful or nonplayful partners as easily as when the options are food or no food. Like the experiments with chimpanzees, these indicate that social play in young rats is as strong a reinforcer as food.

A study that used a similar T-maze setup produced similar results. In it, young (and therefore playful) rats could choose between food and social interaction (Ikemoto and Panksepp 1992), while they were hungry and socially isolated and therefore highly motivated to seek out both food and social interaction. In this experiment, the rats preferred social interaction slightly over food. But in later experiments, rats that had been housed in isolation since they were fifteen-days-old clearly preferred social interaction. Again, these data show that under conditions of deprivation from both food and social contact, food and social interaction (presumably, the social interaction consists, for the most part, of playful social behaviors) are equally strong reinforcers. Given the indispensable value of food for survival, this is a remarkable finding.

It is no surprise, then, that a high preference in a T-maze for social play over no social interaction was observed in another study, one that investigated the role of opioid neurotransmission at work (Normansell and Panksepp 1990). One interesting finding in the study, however, was that T-maze discrimination did not depend on how much the animals played during the learning process. At first glance, this seems counterintuitive. More play would probably mean more pleasure, which would make the play-associated part of the T-maze more appealing. Hence, animals that play more should learn the discrimination faster. However, other experiments (Douglas, Varlinskaya, and Spear 2004) have shown that maximal levels of social play are not necessary to realize its rewards. For an interaction to be pleasurable, it is more important that the rat encounters a partner with an equal level of sociability.

Social play has not only been shown to act as a reinforcer in lever-pressing and maze-learning setups, but also in the widely employed place-conditioning

experiments (Schechter and Calcagnetti 1993; Bardo and Bevins 2000; Tzschentke 1998; Tzschentke 2007). Place-conditioning experiments use an apparatus consisting of two chambers that look, feel, and smell different. Ideally, the animals should have no innate preference for either of the chambers before conditioning starts so that the environmental characteristics of the chambers are neutral cues to the animals. During conditioning, the animal is exposed to a behaviorally meaningful event (in other words, it is offered drugs, food, sex, or social interaction) in one chamber and receives a control treatment before being placed in the other chamber. In this way, the cues in one chamber gain meaning to the animal because they are paired with something behaviorally relevant and emotionally arousing. Note that this can be either a positive or a negative experience.

During testing, the animal can freely move around the two chambers, and the time it spends in either is recorded. If it spends more time in the chamber associated with some event, researchers say that the event evoked a conditioned place preference. Conversely, if the animal spends less time there, they say the event evoked a conditioned place aversion. Researchers have widely used this setup to investigate the brain mechanisms underlying the positive subjective properties of drug abuse. In general, drugs used and abused by humans—heroin, cocaine, nicotine, alcohol—as well as food and sex induce conditioned place preference. Therefore, if a stimulus, drug, or event induces conditioned place preference, we usually interpret that stimulus, drug, or event as having positive subjective or pleasurable effects.

The precise psychological interpretation of conditioned place preference can be difficult, because in most place-conditioning setups, it is hard to discern whether discrete or contextual cues attract the animal, or whether the spatial location of the conditioning chamber leads it to spend time there. In addition, it often remains unclear whether the animal spends time in the conditioning chamber because it wants to experience the event again (i.e. it seeks the food, the drugs, or the sex it had found there before) or because the reward-associated cues have gained meaning in themselves (i.e. it wants to spend time in a place where it had experienced something nice). In either case, the common denominator is this: for a conditioned place preference to develop, the conditioning event should have pleasurable properties. Indeed, research has shown that amphetamine evokes conditioned place preference in humans (Childs and de Wit 2009) and that the magnitude of place preference is proportional to the participants' enjoyment of the effects of the drug.

Calcagnetti and Schechter (1992) used a place-conditioning setup in which an animal in one chamber of the apparatus was paired with a partner that had been rendered nonplayful by treatment with scopolamine, and the other paired with a partner that had not been so treated and remained playful. They showed that conditioned place preference developed for the chamber associated with social play. These findings are consistent with a subsequent place-conditioning study (Crowder and Hutto 1992) that found conditioned place preference for social interaction among rats of a playful age (i.e., four- to eight-weeks-old) only when they had an explicit choice of entering the social interaction-paired chamber during conditioning. If they were forced to be there by just placing them in the conditioning chamber, they showed no such preference. In other words, the experiment suggests that rats perceived social play as more positive when they could choose to play rather than when they were forced to spend time with a partner, which researchers call a conspecific. Conditioned place preference for social play in four- to five-week-old rats was also observed in a study that assessed conditioned hyperactivity as a measure of anticipatory behavior (Van den Berg, Pijlman, Koning, Diergaarde, Van Ree, and Spruijt 1999). In this experiment, the rats got a light-plus-tone signal twenty minutes before they received access to a social partner for thirty minutes. Since the experimental rats were socially isolated throughout the study, their only social contact was this daily thirty-minute interaction, which, for the most part, consisted of playful social behaviors. These animals developed marked conditioned hyperactivity when they got the light-plus-tone signal. Such hyperactivity usually signifies anticipatory arousal for a forthcoming, positive event.

Interestingly, in all the experiments described, the experimental rats were socially isolated throughout the experiments to ensure that they were maximally motivated for social interactions during training and testing (Humphreys and Einon 1981; Ikemoto and Panksepp 1992; Normansell and Panksepp 1990; Calcagnetti and Schechter 1992; Crowder and Hutto 1992; Van den Berg, Pijlman, Koning, Diergaarde, Van Ree, and Spruijt 1999). Logically, the pleasurable value of a social interaction would be very high in an animal that is otherwise housed alone, and these setups are therefore well suited to investigate whether a social interaction, or social play, has any rewarding aspects.

To investigate the extent to which social isolation makes social play rewarding, Douglas, Varlinskaya, and Spear (2004) compared socially isolated rats to group-housed rats in a social place-conditioning setup. They also compared five-week-old rats to adult rats and males to females. Their data showed that

both group-housed and socially isolated rats developed social conditioned place preference of comparable magnitudes, despite the fact that the isolated animals played more during conditioning. Conditioned place preference did not develop in group-housed rats that were conditioned with an isolated partner, suggesting that being confronted by a conspecific with an exaggerated social motivation is not pleasurable. Indeed, group-housed rats conditioned with an isolated conspecific also showed elevated levels of social avoidance during conditioning.

Together, these experiments suggest that maximal levels of social motivation are not necessary for social play to be rewarding, but that it is important to encounter a conspecific with a comparable level of social motivation for a pleasurable interaction to happen. Only a partner comparably motivated seems to induce conditioned place preference. In this study, as in earlier ones (Van den Berg, Pijlman, Koning, Diergaarde, Van Ree, and Spruijt 1999), social conditioned place preference appeared in isolated (but not group-housed) adult rats. The adult rats tested still engaged in moderate social play during conditioning, but the amount of play did not differ between group-housed rats and isolates. This finding suggests that for adult rats, social motivation rather than the amount of social interaction determines how pleasurable they find social behavior. In addition, the results indicate that social interaction (albeit laced with play) is pleasurable under a greater variety of circumstances in young rats than in adults.

Several parameters of social conditioned place preference in rats of four- to five-weeks-old have been investigated in a recent study, which found that the development of social conditioned place preference largely depended on the social motivation of the rats and the number and length of their conditioning sessions (Trezza, Damsteegt, and Vanderschuren 2009). That is, the study found robust social conditioned place preference only in animals that were socially isolated during conditioning, which is not quite consistent with the Douglas, Varlinskaya, and Spear study (2004) described in the previous paragraph. This later study also found trends towards significant place preference in animals isolated for 3.5 hours before conditioning—which induces a half-maximal increase in the amount of social play behavior (Niesink and Van Ree 1989; Vanderschuren, Niesink, Spruijt, and Van Ree 1995; Vanderschuren, Trezza, Griffioen-Roose, Schiepers, Van Leeuwen, De Vries, and Schoffelmeer 2008)—but not in animals that were group housed or housed with an adult rat. In addition, the study observed that eight (but not four) conditioning sessions of thirty minutes (but not fifteen minutes) were needed to induce social place preference. Although the

study did not measure social behavior during conditioning, its data suggest that an optimal level of social motivation, as well as a minimum amount of social interaction and/or learning trials (to associate the pleasurable aspects of social interaction with the environmental cues of the conditioning chamber), is necessary for the positive properties of social interaction in young rats to become apparent as conditioned place preference.

The reasons for the discrepancy between this later study and the previous one are not clear. It may be that the optimal level of social motivation was already achieved in the group-housed rats in the study by Douglas and his colleagues. When the rats that showed conditioned place preference were subsequently tested every day, without further social experience in the testing apparatus, the place preference gradually waned. It did so probably because during non-rewarded exposure to the environment associated with a positive social interaction, a neutral association with these cues (i.e. cues-no social interaction) also develops, which competes with the positive (cues-social interaction) association. After extinction, the conditioned place preference could be reinstated with a single reconditioning session (Trezza, Damsteegt, and Vanderschuren 2009). This study found—as other studies have (Humphreys and Einon 1981)—no social place preference in animals that were conditioned with a partner that was treated with methylphenidate, a drug which selectively reduces social play, but leaves other social behaviors intact (Vanderschuren, Trezza, Griffioen-Roose, Schiepers, Van Leeuwen, De Vries, and Schoffelmeer 2008). This indicates that social play is the most pleasurable element of the rats' social repertoire. Thus, although how much social play they engage in during conditioning may not be critical (Douglas, Varlinskaya, and Spear 2004), its occurrence is necessary for the development of social conditioned place preference (Trezza, Damsteegt, and Vanderschuren 2009).

The parameters of social place conditioning were also investigated by Thiel, Okun, and Neisewander (2008), who tested for the involvement of the number of sessions per day, the length of conditioning sessions, and the total number of conditioning sessions. They found that only the last factor was important: animals that received four or eight social-conditioning sessions showed place preference, whereas one conditioning session was ineffective. The researchers also performed two important control experiments to show that the actual environmental characteristics of the social- conditioning chamber (white walls or black walls) did not affect the development of social conditioned place preference as long as there was social interaction in the chamber during conditioning.

This became evident when social conditioned place preference did not occur in an unpaired control group.

In a further set of experiments, Thiel and his colleagues investigated the interaction between a social and a drug reward. They found that in using a suboptimal conditioning protocol (i.e. two conditioning sessions), neither cocaine nor social interaction induced place preference, but the combination of the two did, suggesting that the positive properties of cocaine and social interaction can add up to a place preference. Remarkably, cocaine reduced (but did not abolish) social play. This is consistent with other findings showing that the amount of social play that occurs during conditioning is not critical for the development of conditioned place preference so long as it does occur (Humphreys and Einon 1981; Douglas, Varlinskaya, and Spear 2004; Trezza, Damsteegt, and Vanderschuren 2009). Dextromethorphan—which in itself has no rewarding properties—did not enhance social place conditioning. In a subsequent study by these investigators, nicotine was found to have a social reward-enhancing effect (Thiel, Sanabria, and Neisewander 2009). In this study, nicotine produced a marked reduction in social play as well, almost abolishing this behavior. This seems to contradict other recent studies showing that low doses of nicotine actually enhance social play (Trezza, Baarendse, and Vanderschuren 2009). Importantly, Thiel with others (Thiel, Okun, and Neisewander 2008; Thiel, Sanabria, and Neisewander 2000) measured social play only during the last conditioning session. Nicotine and cocaine may have qualitatively or quantitatively different effects on social play during earlier conditioning sessions, which cause the positive properties of play and drugs to add up.

In general, these studies convincingly show that social contact in young rats (as well as in chimpanzees) can be used as an incentive for lever pressing, maze learning, and place conditioning. The fact that three different paradigms widely employed to study the rewarding properties of a variety of drug and nondrug reinforcers yield positive data when social interaction is used as a stimulus clearly demonstrates that social behavior is pleasurable. Moreover, the observations that blocking playful behavior (either by drug treatment or by physical confinement) retards or reduces maze learning and place conditioning indicate that it is play, rather than interaction with a conspecific per se, that the animals find rewarding. Further empirical support for the notion that play is rewarding comes from the observations that during play, rats emit high-frequency, ultrasonic vocalizations (~50 kHz) (Burgdorf, Kroes, Moskal, Pfaus, Brudzynski, and Panksepp 2008; Knutson, Burgdorf, and Panksepp 1998). The number of high-frequency vocal-

izations correlated with the amount of play solicitation and with the magnitude of play-induced conditioned place preference (Burgdorf, Kroes, Moskal, Pfaus, Brudzynski, and Panksepp 2008; Knutson, Burgdorf, and Panksepp 1998). These vocalizations are also emitted during other events with positive value, such as sexual behavior, amphetamine ingestion, and expression of conditioned place preference for amphetamine and morphine (Burgdorf, Kroes, Moskal, Pfaus, Brudzynski, and Panksepp 2008; Burgdorf, Knutson, Panksepp, and Ikemoto 2001; Knutson, Burgdorf, Panksepp 1999). Rats will nose-poke for playback of these calls (Burgdorf, Kroes, Moskal, Pfaus, Brudzynski, and Panksepp 2008), and these calls evoke approach behavior (Wöhr and Schwarting 2007), demonstrating that their emission during positive events serves as a positive communication signal to conspecifics.

In short, these studies provide empirical support for the notion that playing with another individual is fun. However, it is likely so only (and this is also something that makes sense intuitively) when the other individual reciprocates the social initiative. Thus, when researchers investigated the invitation to play among animals, they found that those interacting with animals that were treated with haloperidol, scopolamine, or methylphenidate (drugs that eliminate playful behavior in rats) initiated play less often (Vanderschuren, Trezza, Griffioen-Roose, Schiepers, Van Leeuwen, De Vries, and Schoffelmeer 2008; Pellis and McKenna 1995). This suggests that the motivation to play decreases when the playmates do not respond. This mirrors the observation that being confronted with a conspecific that displays an exaggerated level of social motivation is not rewarding (Douglas, Varlinskaya, and Spear 2004).

Brain Mechanisms of Making Play Fun

Most knowledge about how brain mechanisms make us feel pleasure comes from studies in which the enjoyable properties of food, sex, or drugs have been investigated using setups just like those described in this article. These studies have shown that there are signaling substances in the brain called neurotransmitters that play a particular role in the mental processes of pleasure. The most prominent neurotransmitters are dopamine, endogenous opioids (often referred to as endorphins, although the endorphins are actually only one subclass of opioids), and endogenous cannabinoids (or endocannabinoids). These neurotransmitters also play an important role in social play (Vanderschuren, Niesink, and Van

Ree 1995; Siviy 1998), and this will be described in more detail. Dopamine, opioids, and endocannabinoids act in a distributed network of brain regions that generate and perceive emotions, including the ventral tegmental area, nucleus accumbens, pallidum, frontal cortex, and amygdala (Koob 1992; Schultz 2000; Cardinal, Parkinson, Hall, and Everitt 2002; Baxter and Murray 2002; Holland and Gallagher 2004; Kelley, Baldo, Pratt, and Will 2005; Balleine and Killcross 2006; Barbano and Cador 2007; Berridge 2007; Berridge and Kringelbach 2008; Salamone, Correa, Mingote, and Weber 2005; Smith, Tindell, Aldridge, and Berridge 2009). In recent years, the mental processes that create enjoyment have been subdivided into motivation (wanting) and hedonics (pleasure or liking) (Berridge and Robinson 2003; Berridge, Robinson, Aldridge 2009). Clearly, this distinction also pertains to play, but not many studies have been done that directly address which brain mechanisms underlie the separate motivational and hedonic properties of play. However, the studies on other rewarded behaviors have indicated that the dopaminergic pathway from the ventral tegmental area to the nucleus accumbens, also known as the mesolimbic dopamine pathway, mediates motivation rather than pleasure (Cardinal, Parkinson, Hall, and Everitt 2002; Kelley, Baldo, Pratt, and Will 2005; Barbano and Cador 2007; Berridge 2007; Berridge and Kringelbach 2008; Salamone, Correa, Mingote, and Weber 2005). On the other hand, locally secreted opioids and cannabinoids in the nucleus accumbens, ventral pallidum, and perhaps the amygdala likely mediate subjective hedonics (Kelley, Baldo, Pratt, and Will 2005; Barbano and Cador 2007; Berridge and Kringelbach 2008; Smith, Tindell, Aldridge, and Berridge 2009).

Neurotransmitters

It turns out that dopamine, which has long been thought to be the one crucial neurotransmitter underlying reward processes, only modulates social play. The studies that have established this fact have either looked at what happens to social play if animals are treated with drugs that mimic the effect of dopamine (i.e. dopamine-receptor agonists that bind to the signaling proteins on nerve cells that normally bind dopamine itself); with drugs that prohibit the normal action of dopamine (i.e. dopamine-receptor antagonists that bind to these signaling proteins but just prevent normal dopamine from binding without stimulating the protein themselves); or with drugs that prolong the normal action of dopamine (i.e. dopamine-reuptake inhibitors, that prevent released dopamine from being taken back up into the nerve cell that released it; this is a normal way for nerve cells to limit their chemical signals in space and time). The

effects of treatment with dopamine-receptor agonists are inconsistent across the literature, as both increases and decreases in play are reported (Niesink and Van Ree 1989; Vanderschuren, Trezza, Griffioen-Roose, Schiepers, Van Leeuwen, De Vries, and Schoffelmeer 2008; Beatty, Costello, and Berry 1984; Siviy, Fleischhauer, Kerrigan, and Kuhlman 1996). But the increases observed are usually quite modest. When animals are treated with dopamine-receptor antagonists, however, they do not play as much (Niesink and Van Ree 1989; Beatty, Costello, and Berry 1984; Siviy, Fleischhauer, Kerrigan, and Kuhlman 1996; Trezza and Vanderschuren 2009). Most remarkably, drugs that inhibit the reuptake of dopamine (which include psychostimulant drugs of abuse like cocaine and amphetamine, but also methylphenidate, which is used for the treatment of Attention Deficit Hyperactivity Disorder) also suppress play in animals (Humphreys and Einon 1981; Vanderschuren, Trezza, Griffioen-Roose, Schiepers, Van Leeuwen, De Vries, and Schoffelmeer 2008; Thiel, Okun, and Neisewander 2008; Beatty, Costello, and Berry 1984; Beatty, A. M. Dodge, L. J. Dodge, and Panksepp 1982).

Even so, though cocaine reduces the performance of play itself, it enhances the rewarding value of play in a place-conditioning setup (Thiel, Okun, and Neisewander 2008). Keep in mind that psychostimulant drugs are not selective for dopamine, because they also inhibit the reuptake of other neurotransmitters like noradrenaline and serotonin. Indeed, when rats were treated with drugs that are selective blockers of the reuptake of dopamine, noradrenaline, and serotonin, the blockers of noradrenaline and serotonin reuptake apparently inhibited play, but blockers of dopamine reuptake had no such effect (Vanderschuren, Trezza, Griffioen-Roose, Schiepers, Van Leeuwen, De Vries, and Schoffelmeer 2008; Homberg, Schiepers, Schoffelmeer, Cuppen, and Vanderschuren 2007). Therefore, the effects of cocaine, amphetamine, and methylphenidate on social play are not likely mediated by dopamine. Further, pretreatment with an antagonist for a subtype of noradrenaline receptor (the alpha-2 receptor), but not with a dopamine-receptor antagonist, prevented methylphenidate from suppressing play (Vanderschuren, Trezza, Griffioen-Roose, Schiepers, Van Leeuwen, De Vries, and Schoffelmeer 2008). Apparently, play is hard to stimulate by mimicking or enhancing the effect of dopamine in the brain, which suggests that when play occurs, it is accompanied by an optimal dopamine signal, and further stimulating this signal does not enhance play. On the other hand, when this dopamine signal is blocked, then play slacks off, likely because the blockage decreases an animal's motivation to play. As stated

above, dopamine plays a critical role in the motivational, but not the hedonic properties, of rewards (Cardinal, Parkinson, Hall, and Everitt 2002; Kelley, Baldo, Pratt, and Will 2005; Barbano and Cador 2007; Berridge 2007; Berridge and Kringelbach 2008; Salamone, Correa, Mingote, and Weber 2005).

Most experiments that observe and quantify the social behavior of two drug-treated animals will likely measure a mixture of both the motivational and hedonic properties of play in a way that prevents these properties of social play from being readily distinguished. Perhaps pleasure plays a more prominent role in the observed behavior because the presentation of a socially motivated conspecific may be enjoyable in itself and there is no need for more heightened motivation to engage in social play. These findings are comparable to studies on eating, which show that in a free-feeding situation, changes in dopamine neurotransmission do not alter food intake (even though changes in the motivation for food could, in theory, alter feeding). However, in a conditioning setting where animals have to work for food by pressing a lever, changes in dopamine neurotransmission determine whether food is perceived as attractive and how much work an animal is willing to perform to get the food (Cardinal, Parkinson, Hall, and Everitt 2002; Kelley, Baldo, Pratt, and Will. 2005; Barbano and Cador 2007; Berridge 2007; Berridge, and Kringelbach 2008; Salamone, Correa, Mingote, and Weber 2005). Dopamine, however, does modulate the effects of other drugs on social play, like endocannabinoids, nicotine, and alcohol, which I will discuss shortly.

Unlike dopamine, opioids can play a strong role in the performance of social play. For example, treatment of animals with drugs that mimic the effects of endogenous opioids such as morphine, methadone, or the endogenous opioid beta-endorphin potently enhances social play (Normansell and Panksepp 1990; Niesink and Van Ree 1989; Vanderschuren, Niesink, Spruijt, and Van Ree 1995; Vanderschuren, Niesink, and Van Ree 1997; Trezza and Vanderschuren 2008a; Trezza and Vanderschuren 2008b; Vanderschuren, Spruijt, Hol, Niesink, and Van Ree 1995; Panksepp, Jalowiec, Eskenazi, and Bishop 1985). Conversely, treatment with drugs that prevent endogenous opioids from having their effects (i.e. opioid-receptor antagonists such as naloxone and naltrexone) reduces social play (Normansell and Panksepp 1990; Niesink and Van Ree 1989; Panksepp, Jalowiec, Eskenazi, and Bishop 1985; Jalowiec, Calcagnetti, and Fanselow 1989; Siegel, Jensen, and Panksepp 1985; Siegel and Jensen 1986; Beatty and Costello 1982). We know of three opioid receptors, but the mu receptor is the one likely responsible for the effects of opioids on social play. Evidence for this comes

first, from the fact that the low doses of morphine that enhance play prefer to interact with mu-receptors. Second, drugs more selective for mu receptors than morphine, like fentanyl (an agonist) and beta-funaltrexamine (an antagonist), increase and reduce play, respectively, while agonists for other opioid receptors do not enhance (or even reduce) play (Vanderschuren, Niesink, Spruijt, and Van Ree 1995). Consistent with the notion that opioids play a more prominent role in hedonics, rather than motivation, Normansell and Panksepp (1990) reported that morphine and naloxone did not affect the acquisition of spatial discrimination rewarded with play in a T-maze, a task that measures the motivation to play. However, during the rewarded phase of the test, rats treated with morphine played more, and rats treated with naloxone played less than control rats. This suggests opioids control the performance of social play, likely through changes in its subjective pleasurable properties, rather than through motivation to play. Further support for the notion that opioids increase the hedonic properties of play comes from the observation that during social play there is an increase in opioid activity in the nucleus accumbens (Vanderschuren, Stein, Wiegant, and Van Ree 1995). Studies have reported that local opioid receptor stimulation in the nucleus accumbens increases the hedonic properties of food (Kelley, Baldo, Pratt, and Will 2005; Berridge and Kringelbach 2008), so most likely this mechanism enhances social reward as well.

The endogenous cannabinoids, or endocannabinoids, are a third neurotransmitter class that has been implicated in positive emotions and motivation (Mahler, Smith, and Berridge 2007; Solinas, Goldberg, and Piomelli 2008). Recent studies show that endocannabinoids also play an important role in the regulation of social play. Treating rats with drugs that enhance or prolong endocannabinoid signaling (by blocking either the enzymatic degradation or reuptake of the endocannabinoid anandamide) consistently also enhanced social play (Trezza and Vanderschuren 2009; Trezza and Vanderschuren 2008a; Trezza and Vanderschuren 2008b). Remarkably, drugs that directly mimic the action of endocannabinoids actually had a contrary effect and reduced social play (Trezza and Vanderschuren 2009; Trezza and Vanderschuren 2008a; Trezza and Vanderschuren 2008b). The explanation for this contradictory finding likely lies in the fact that the endocannabinoid system does not work like a conventional neurotransmitter system. Endocannabinoids are released into the synaptic cleft between nerve cells only on demand—whenever a postsynaptic cell changes its electrical activity. As a result, there is no—or hardly any—tonic endocannabinoid activity in the brain. The results obtained with the drugs that

enhance endocannabinoid signaling therefore suggest that during social play there is endocannabinoid activity in the brain regions mediating social play. Increasing this activity stimulates social play. However, since cannabinoid receptors are among the most abundant receptors in the brain, artificially inducing an endocannabinoid signal (by treatment with a direct cannabinoid-receptor agonist) in brain regions not directly involved in play may evoke a mental state in which the animals are less capable of performing the rather complex behavioral sequences involved in social play, perhaps because it disrupts higher cognitive function, which we know otherwise to be an effect of cannabinoid-receptor agonists (Arguello and Jentsch 2007; Hill, Froese, Morrish, Sun, and Floresco 2006).

Interestingly, other drugs that stimulate brain pathways involved in positive emotions and motivation, such as alcohol and nicotine, also enhanced social play (Trezza, Baarendse, and Vanderschuren 2009; Varlinskaya, L. P. Spear, and N. E. Spear 2001; Varlinskaya and L. P. Spear 2002; Varlinskaya and L. P. Spear 2006). Comparable to the effects of cocaine on social play (Thiel, Okun, and Neisewander 2008), nicotine also enhanced the rewarding properties of play in a place-conditioning setup (Thiel, Sanabria, and Neisewander 2009).

Recent studies have also investigated the interaction between these neurotransmitter systems in the regulation of social play. They have shown that the play-enhancing effects of morphine depend on stimulation of opioid and cannabinoid—but not of dopamine—receptors. These effects were reduced in animals pretreated with an opioid- or a cannabinoid-receptor antagonist—but not with a dopamine-receptor antagonist (Trezza and Vanderschuren 2008a). This fits with the notion that opioids do not enhance social play by affecting its motivational properties (supposedly mediated by dopamine signaling), but rather its hedonic, pleasurable characteristics. The effects of nicotine—and those of indirect cannabinoid agonists (i.e. drugs that enhance endocannabinoid signaling)—depend on the stimulation of opioid, cannabinoid, as well as dopamine receptors (Trezza, Baarendse, and Vanderschuren 2009; Trezza and Vanderschuren 2009; Trezza and Vanderschuren 2008a). Stimulation of social play by alcohol was blocked by antagonists of cannabinoid and dopamine, but not opioid receptors (Trezza, Baarendse, and Vanderschuren 2009). However, another recent study did find that the effects of alcohol on social play were attenuated by pretreatment with an opioid-receptor antagonist (Varlinskaya and L. P. Spear 2009), which suggests that ethanol can stimulate social behavior in young rats through opioid-dependent as well as opioid-independent mecha-

nisms. Together, these findings imply that endocannabinoids and nicotine may affect both the pleasure (opioid-mediated) and the motivations (dopamine-mediated) of social play, whereas alcohol is inclined to affect the motivations of play. On the other hand, blocking endocannabinoid receptors reduces the effects of morphine, nicotine, alcohol, and indirect cannabinoid agonists on social play, indicating that endocannabinoids are a very important neurochemical modulator of social play behavior.

Brain areas

There are three areas of the brain closely implicated in motivation and hedonics that have been investigated for their involvement in social play—the nucleus accumbens, the amygdala, and the frontal cortex. However, unlike some of the quite detailed pharmacological analyses of social play, this is an area of research that is relatively unexplored.

The involvement of the nucleus accumbens in social play has been documented in two studies that also addressed the neurotransmitters involved. In the first study, neonatal treatment with 6-hydroxydopamine into the cerebral ventricles—which led to reductions of dopamine and noradrenaline content and increased serotonin content in the nucleus accumbens, as well as the more dorsally located caudate putamen—markedly disrupted the sequential structure of social play (Pellis, Castañeda, McKenna, Tran-Nguyen, and Whishaw 1993). The animals in this experiment showed less initiative to play and responded in ways to play solicitation that was more likely to shorten the play episode. However, since the study altered the activity of three neurotransmitters in two brain regions, the exact mechanism underlying the altered play patterns is difficult to pinpoint. A second study investigated endogenous-opioid signaling during social play by measuring the binding of an exogenously applied radioactive tracer to opioid receptors after play. The researchers reasoned that enhanced opioid activity during a given behavior should lead to more competition for opioid activity at the receptor for an exogenous ligand and, therefore, to less ligand binding. This experiment showed that social play caused increased endogenous-opioid activity in a number of brain regions, including the nucleus accumbens (Vanderschuren, Stein, Wiegant, and Van Ree 1995).

The effects of lesions in the amygdala on social play have been inconsistent. An early study found that lesions in the amygdala only abolished the difference in levels of play between male and female rats, which suggests that mechanisms

in the amygdala are responsible for the sex differences in patterns and/or levels of social play (Meaney, Dodge, and Beatty 1981). However, a more recent study found that lesions in the amygdala, in neonatal rats and in three-week-old rats, reduced social play (Daenen, Wolterink, Gerrits, and Van Ree 2002).

Pellis and colleagues have investigated the effects of lesions in parts of the frontal cortex (i.e. the medial prefrontal and orbitofrontal cortex) on social play (Bell, McCaffrey, Forgie, Kolb, and Pellis 2009; Pellis, Hastings, Shimizu, Kamitakahara, Komorowska, Forgie, and Kolb 2006). These regions have been implicated in motivation and hedonics, most prominently in some of the higher cognitive aspects of these processes, such as attention, decision making, and coding the expected values of planned behavior (Robbins and Arnsten 2009; Miller 2000; Schoenbaum, Roesch, Stalnaker, and Takahashi 2009).

Young rats with neonatal lesions in the orbitofrontal cortex showed less age-appropriate responses (i.e. less rotating to supine) to playful solicitations, which caused their playful interactions to be shorter. Rats with adult orbitofrontal lesions showed less flexibility in adapting their playful tactics when confronted with different play partners. By and large, however, general play patterns were relatively unaffected (Pellis, Hastings, Shimizu, Kamitakahara, Komorowska, Forgie, and Kolb 2006).

Rats with medial prefrontal lesions—made either when they were neonates or after they became adults—also responded to playful initiation in ways that shortened the interactions such as more evasions of the partner and fewer rotations to supine. Interestingly, however, animals with neonatal lesions showed higher levels of playful solicitation. Again, patterns of playful behavior were largely intact (Bell, McCaffrey, Forgie, Kolb, and Pellis 2009).

Indeed, another study that investigated the role of the medial prefrontal cortex in social play found that lesions in this region in seven-day-old rats later on lead to somewhat reduced levels of play, often because of altered responsiveness to playful solicitation (Schneider and Koch 2005). These findings are consistent with earlier observations that neonatal decortication of rats—or neonatal ablation of the frontal cortex—has no major disruptive effects on social play (Panksepp, Normansell, Cox, and Siviy 1994). Together, these studies suggest that the medial prefrontal and orbitofrontal cortex do not play a primary role in the mediation of play itself, but rather in the ability of animals to respond appropriately and flexibly to changeable social conditions.

Conclusion

The studies reviewed here demonstrate three important points about the rewarding properties of social play. First, there is ample empirical evidence that social play has positive subjective, reinforcing effects. It can be used as an incentive for maze learning, lever pressing, and place conditioning—three setups that have been extensively used to study the rewarding properties (and brain mechanisms) of food, drugs, and sex. Indeed, some of these studies have shown that social play can have a rewarding value that is as strong as tasty food. Second, neurotransmitter systems that are intimately implicated in the motivational and pleasurable properties of food, drugs, and sex—such as endogenous opioids, endogenous cannabinoids, and dopamine—modulate social play to an important extent. Third, the regions of the brain where positive emotions and motivation originate—such as the nucleus accumbens, amygdala, and frontal cortex—also mediate social play. Together, these studies demonstrate that play is fun and that there are pathways in the brain that make it so.

However, important questions remain. Our experiments may have distinguished between the motivations and pleasures of play, but the brain mechanisms that underlie these separate properties of play remain to be discovered. In fact, apart from a few notable expections (Normansell and Panksepp 1990; Thiel, Okun, and Neisewander 2008; Thiel, Sanabria, and Neisewander 2009), there have been no studies that directly address which neurotransmitters or brain regions mediate the motivational and the hedonic properties of play. Future studies should be directed at elucidating the neural substrates of these separate aspects of social play.

References

Arguello, P. Alexander, and J. David Jentsch. 2007. Cannabinoid CB1 receptor-mediated impairment of visuospatial attention in the rat. *Psychopharmacology* 177:141–50.

Balleine, Bernard W., and Simon Killcross. 2006. Parallel incentive processing: An integrated view of amygdala function. *Trends in Neurosciences* 29:272–79.

Barbano, M. Flavia, and Martine Cador. 2007. Opioids for hedonic experience and dopamine to get ready for it. *Psychopharmacology* 191:497–506.

Bardo, M. T., and Rick A. Bevins. 2000. Conditioned place preference: What does it add to our preclinical understanding of drug reward? *Psychopharmacology* 153:31–43.

Baxter, Mark G., and Elisabeth A. Murray. 2002. The amygdala and reward. *Nature Reviews: Neuroscience* 3:563–73.

Bell, Heather C., David R. McCaffrey, Margaret L. Forgie, Bryan Kolb, and Sergio M. Pellis. 2009. The role of the medial prefrontal cortex in the play fighting of rats. *Behavioral Neuroscience* 123:1158–68.

Beatty, William W., and Kevin B. Costello. 1982. Naloxone and play fighting in juvenile rats. *Pharmacology, Biochemistry and Behavior* 17:905–7.

Beatty, William W., Kevin B. Costello, and Sharon L. Berry. 1984. Suppression of play fighting by amphetamine: Effects of catecholamine antagonists, agonists and synthesis inhibitors. *Pharmacology, Biochemistry and Behavior* 20:747–55.

Beatty, William W., Anthony M. Dodge, Laura J. Dodge, and Jaak Panksepp. 1982. Psychomotor stimulants, social deprivation and play in juvenile rats. *Pharmacology, Biochemistry and Behavior* 16:417–22.

Berridge, Kent C. 2007. The debate over dopamine's role in reward: The case for incentive salience. *Psychopharmacology* 191:391–431.

Berridge, Kent C., and Morten L. Kringelbach. 2008. Affective neuroscience of pleasure: Reward in humans and animals. *Psychopharmacology* 199:457–80.

Berridge, Kent C., and Terry E. Robinson. 2003. Parsing reward. *Trends in Neuroscience* 26:507–13.

Berridge, Kent C., Terry E. Robinson, and J. Wayne Aldridge. 2009. Dissecting components of reward: "Liking," "wanting," and learning. *Current Opinion in Pharmacology* 9:65–73.

Burgdorf, Jeffrey, Brian Knutson, Jaak Panksepp, and Satoshi Ikemoto. 2001. Nucleus accumbens amphetamine microinjections unconditionally elicit 50-kHz ultrasonic vocalizations in rats. *Behavioral Neuroscience* 115:940–44.

Burgdorf, Jeffrey, Roger A. Kroes, Joseph R. Moskal, James B. Pfaus, Stefan M. Brudzynski, and Jaak Panksepp. 2008. Ultrasonic vocalizations of rats (*Rattus norvegicus*) during mating, play, and aggression: Behavioral concomitants, relationship to reward, and self-administration of playback. *Journal of Comparative Psychology* 122:357–67.

Calcagnetti, Daniel J., and Martin D. Schechter. 1992. Place conditioning reveals the rewarding aspect of social interaction in juvenile rats. *Physiology & Behavior* 51:667–72.

Cardinal, Rudolf N., John A. Parkinson, Jeremy Hall, and Barry J. Everitt. 2002. Emotion and motivation: The role of the amygdala, ventral striatum, and prefrontal cortex. *Neuroscience & Biobehavioral Reviews* 26:321–52.

Childs, Emma, and Harriet de Wit. 2009. Amphetamine-induced place preference in humans. *Biological Psychiatry* 65:900–4.

Crowder, William F., and Cecil W. Hutto. 1992. Operant place conditioning measures examined using two nondrug reinforcers. *Pharmacology, Biochemistry and Behavior* 41:817–24.

Daenen, Elisabeth W. P. M., Gerrit Wolterink, Mirjam A. F. M. Gerrits, and Jan M. Van

Ree. 2002. The effects of neonatal lesions in the amygdala or ventral hippocampus on social behaviour later in life. *Behavioural Brain Research* 136:571–82.

Douglas, Lewis A., Elena I. Varlinskaya, and Linda P. Spear. 2004. Rewarding properties of social interactions in adolescent and adult male and female rats: Impact of social versus isolate housing of subjects and partners. *Developmental Psychobiology* 45:153–62.

Falk, John L. 1958. The grooming behavior of the chimpanzee as a reinforcer. *Journal of the Experimental Analysis of Behavior* 1:83–85.

Hill, Matthew N., Larissa M. Froese, Anna C. Morrish, Jane C. Sun, and Stan B. Floresco. 2006. Alterations in behavioral flexibility by cannabinoid CB(1) receptor agonists and antagonists. *Psychopharmacology* 187:245–59.

Holland, Peter C., and Michela Gallagher. 2004. Amygdala-frontal interactions and reward expectancy. *Current Opinion in Neurobiology* 14:148–55.

Homberg, Judith R., Olga J. G. Schiepers, Anton M. Schoffelmeer, Edwin Cuppen, and Louk J. M. J. Vanderschuren. 2007. Acute and constitutive increases in central serotonin levels reduce social play behaviour in peri-adolescent rats. *Psychopharmacology* 195:175–82.

Humphreys, Anne P., and Dorothy F. Einon. 1981. Play as a reinforcer for maze-learning in juvenile rats. *Animal Behaviour* 29:259–70.

Ikemoto, Satoshi, and Jaak Panksepp. 1992. The effects of early social isolation on the motivation for social play in juvenile rats. *Developmental Psychobiology* 25:261–74.

Jalowiec, John E., Daniel J. Calcagnetti, and Michael S. Fanselow. 1989. Suppression of juvenile social behavior requires antagonism of central opioid systems. *Pharmacology, Biochemistry and Behavior* 33:697–700.

Kelley, Ann E., Brian A. Baldo, Wayne E. Pratt, and Matthew J. Will. 2005. Corticostriatal-hypothalamic circuitry and food motivation: Integration of energy, action and reward. *Physiology & Behavior* 86:773–95.

Knutson, Brian, Jeffrey Burgdorf, and Jaak Panksepp. 1998. Anticipation of play elicits high-frequency ultrasonic vocalizations in young rats. *Journal of Comparative Psychology* 112:65–73.

———. 1999. High-frequency ultrasonic vocalizations index conditioned pharmacological reward in rats. *Physiology & Behavior* 66:639–43.

Koob, G. F. 1992. Drugs of abuse: Anatomy, pharmacology and function of reward pathways. *Trends in Pharmacological Sciences* 13:177–84.

Mahler, Stephen V., Kyle S. Smith, and Kent C. Berridge. 2007. Endocannabinoid hedonic hotspot for sensory pleasure: Anandamide in nucleus accumbens shell enhances "liking" of a sweet reward. *Neuropsychopharmacology* 32:2267–78.

Mason, William M., Sue V. Saxon, and Lawrence G. Sharpe. 1963. Preferential responses of young chimpanzees to food and social rewards. *Psychological Record* 13:341–45.

Meaney, Michael J., Anthony M. Dodge, and William W. Beatty. 1981. Sex-dependent effects of amygdaloid lesions on the social play of prepubertal rats. *Physiology & Behavior* 26:467–72.

Miller, Earl K. 2000. The prefrontal cortex and cognitive control. *Nature Reviews: Neuroscience* 1:59–65.

Niesink, Raymond J. M., and Jan Van Ree. 1989. Involvement of opioid and dopaminergic systems in isolation-induced pinning and social grooming of young rats. *Neuropharmacology* 28:411–18.

Normansell, Larry, and Jaak Panksepp. 1990. Effects of morphine and naloxone on play-rewarded spatial discrimination in juvenile rats. *Developmental Psychobiology* 23:75–83.

Panksepp, Jaak, John E. Jalowiec, Fatima G. De Eskenazi, and Paul Bishop. 1985. Opiates and play dominance in juvenile rats. *Behavioural Neuroscience* 99:441–53.

Panksepp, Jaak, Larry Normansell, James F. Cox, and Stephen M. Siviy. 1994. Effects of neonatal decortication on the social play of juvenile rats. *Physiology & Behavior* 56:429–43.

Pellis, Sergio M., Eddie Castañeda, Mario M. McKenna, Ly T. L. Tran-Nguyen, and Ian Q. Whishaw. 1993. The role of the striatum in organizing sequences of play fighting in neonatally dopamine-depleted rats. *Neuroscience Letters* 158:13–15.

Pellis, Sergio M., Erica Hastings, Takeshi Shimizu, Holly Kamitakahara, Joanna Komorowska, Margaret L. Forgie, and Bryan Kolb. 2006. The effects of orbital frontal cortex damage on the modulation of defensive responses by rats in playful and nonplayful social contexts. *Behavioral Neuroscience* 120:72–84.

Pellis, Sergio M., and Mario McKenna. 1995. What do rats find rewarding in play fighting? An analysis using drug-induced non-playful partners. *Behavioural Brain Research* 68:65–73.

Robbins, Trevor W., and Amy F. T. Arnsten. 2009. The neuropsychopharmacology of fronto-executive function: Monoaminergic modulation. *Annual Review of Neuroscience* 32:267–87.

Salamone, John D., Merce Correa, Susana M. Mingote, and Suzanne M. Weber. 2005. Beyond the reward hypothesis: Alternative functions of nucleus accumbens dopamine. *Current Opinion in Pharmacology* 5:34–41.

Schechter, Martin D., and Daniel Calcagnetti. 1993. Trends in place preference conditioning with a cross-indexed bibliography: 1957–1991. *Neuroscience & Biobehavioral Reviews* 17:21–41.

Schneider, Miriam, and Michael Koch. 2005. Deficient social and play behavior in juvenile and adult rats after neonatal cortical lesion: Effects of chronic pubertal cannabinoid treatment. *Neuropsychopharmacology* 30:944–57.

Schoenbaum, Geoffrey, Matthew R. Roesch, Thomas A. Stalnaker, and Yuji K. Takahashi. 2009. A new perspective on the role of the orbitofrontal cortex in adaptive behaviour. *Nature Reviews: Neuroscience* 10:885–92.

Schultz, Wolfram. 2000. Multiple reward signals in the brain. *Nature Reviews: Neuroscience* 1:199–207.

Siegel, Michael A., and Robert A. Jensen. 1986. The effects of naloxone and cage size on social play and activity in isolated young rats. *Behavioral and Neural Biology* 45:155–68.

Siegel, Michael A., Robert A. Jensen, and Jaak Panksepp. 1985. The prolonged effects of naloxone on play behavior and feeding in the rat. *Behavioral and Neural Biology* 44:509–14.

Siviy, Stephen M. 1998. Neurobiological substrates of play behavior: Glimpses into the structure and function of mammalian playfulness. In *Animal play: Evolutionary, comparative, and ecological perspectives*, ed. Marc Bekoff and John A. Byers, 221–42.

Siviy, Stephen M., Anne E. Fleischhauer, Lisa A. Kerrigan, and Sandra J. Kuhlman. 1996. D2 dopamine receptor involvement in the rough-and-tumble play behavior of juvenile rats. *Behavioral Neuroscience* 110:1168–76.

Smith, Kyle S., Amy J. Tindell, J. Wayne Aldridge, and Kent C. Berridge. 2009. Ventral pallidum roles in reward and motivation. *Behavioural Brain Research* 196:155–67.

Solinas, Marcello, Steven R. Goldberg, and Daniele Piomelli. 2008. The endocannabinoid system in brain reward processes. *British Journal of Pharmacology* 154:369–83.

Thiel, Kenneth J., Alec C. Okun, and Janet L. Neisewander. 2008. Social reward-conditioned place preference: A model revealing an interaction between cocaine and social context rewards in rats. *Drug and Alcohol Dependence* 96:202–12.

Thiel, Kenneth J., Federico Sanabria, and Janet L. Neisewander. 2009. Synergistic interaction between nicotine and social rewards in adolescent male rats. *Psychopharmacology* 204:391–402.

Trezza, Viviana, Petra J. J. Baarendse, and Louk J. M. J. Vanderschuren. 2009. Prosocial effects of nicotine and ethanol in adolescent rats through partially dissociable neurobehavioral mechanisms. *Neuropsychopharmacology* 34:2560–73.

Trezza, Viviana, Ruth Damsteegt, and Louk J. M. J. Vanderschuren. 2009. Conditioned place preference induced by social play behavior: Parametrics, extinction, reinstatement and disruption by methylphenidate. *European Neuropsychopharmacology* 19:659–69.

Trezza, Viviana, and Louk J. M. J. Vanderschuren. 2008a. Bidirectional cannabinoid modulation of social behavior in adolescent rats. *Psychopharmacology* 197:217–27.

———. 2008b. Cannabinoid and opioid modulation of social play behavior in adolescent rats: Differential behavioral mechanisms. *European Neuropsychopharmacology* 18:519–30.

———. 2009. Divergent effects of anandamide transporter inhibitors with different target selectivity on social play behavior in adolescent rats. *Journal of Pharmacology and Experimental Therapeutics* 328:343–50.

Tzschentke, Thomas M. 1998. Measuring reward with the conditioned place preference paradigm: A comprehensive review of drug effects, recent progress and new issues. *Progress in Neurobiology* 56:613–72.

———. 2007. Measuring reward with the conditioned place preference (CPP) paradigm: Update of the last decade. *Addiction Biology* 12:227–462.

Van den Berg, Caroline, Femke T. A. Pijlman, Hilde A. M. Koning, Leontien Diergaarde, Jan M. Van Ree, and Berry M. Spruijt. 1999. Isolation changes the incentive value of sucrose and social behaviour in juvenile and adult rats. *Behavioural Brain Research* 106:133–42.

Vanderschuren, Louk J. M. J., Raymond J. M. Niesink, Berry M. Spruijt, and Jan Van Ree. 1995a. Effects of morphine on different aspects of social play in juvenile rats. *Psychopharmacology* 117:225–31.

———. 1995b. m- and k-opioid receptor-mediated opioid effects on social play in juvenile rats. *European Journal of Pharmacology* 276:257–66.

Vanderschuren, Louk J. M. J., Raymond J. M. Niesink, and Jan Van Ree. 1997. The neurobiology of social play behavior in rats. *Neuroscience & Biobehavioral Reviews* 21:309–26.

Vanderschuren, Louk J. M. J., Berry M. Spruijt, Thorwald Hol, Raymond Niesink, and Jan M. Van Ree. 1995. Sequential analysis of social play behavior in juvenile rats: Effects of morphine. *Behavioural Brain Research* 72:89–95.

Vanderschuren, Louk J. M. J., Elliot A. Stein, Victor M. Wiegant, and Jan M. Van Ree. 1995. Social play alters regional brain opioid receptor binding in juvenile rats. *Brain Research* 680:148–56.

Vanderschuren, Louk J. M. J., Viviana Trezza, Sanne Griffioen-Roose, Olga J. G. Schiepers, Natascha Van Leeuwen, Taco J. De Vries, and Anton N. M. Schoffelmeer. 2008. Methylphenidate disrupts social play behavior in adolescent rats. *Neuropsychopharmacology* 33:2946–56.

Varlinskaya, Elena I., and Linda P. Spear. 2002. Acute effects of ethanol on social behavior of adolescent and adult rats: Role of familiarity of the test situation. *Alcoholism: Clinical and Experimental Research* 26:1502–11.

———. 2006. Differences in the social consequences of ethanol emerge during the course of adolescence in rats: Social facilitation, social inhibition, and anxiolysis. *Developmental Psychobiology* 48:146–61.

———. 2009. Ethanol-induced social facilitation in adolescent rats: Role of endogenous activity at mu opioid receptors. *Alcoholism: Clinical and Experimental Research* 33:991–1000.

Varlinskaya, Elena I., Linda P. Spear, and Norman E. Spear. 2001. Acute effects of ethanol on behavior of adolescent rats: Role of social context. *Alcoholism: Clinical and Experimental Research* 25:377–85.

Wöhr, Marcus, and Rainer K. W. Schwarting. 2007. Ultrasonic communication in rats: Can playback of 50-kHz calls induce approach behavior? *PLoS ONE* 2:e1365.