



# Adolescent social rejection alters pain processing in a CB1 receptor dependent manner



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## Abstract

Experiences of social rejection represent a major source of distress and in particular peer rejection during adolescence has been implicated in various psychiatric disorders. Moreover, experimentally induced acute social rejection alters pain perception in humans, implicating overlapping neurocircuits for social and physical pains. We recently demonstrated that rearing of adolescent Wistar rats with inadequate, less playful play partners (Fischer 344) persistently decreases pain sensitivity, although the detailed mechanisms mediating the aversiveness during the social encounter remained unsettled. With the present study we examined the behavioral performance during acute interaction of female adolescent Wistar rats with either age-matched same-strain partners or rats from the Fischer 344 strain. We here identify the low responsiveness upon playful attacks, which appears to be characteristic for social play in the Fischer 344 strain, as one of the main aversive components for adolescent Wistar animals during cross-strain encounters, which subsequently diminishes thermal pain reactivity. A detailed behavioral analysis further revealed increased ultrasonic vocalization at 50 kHz and an increased frequency of playful attacks for adolescent Wistar animals paired with a Fischer 344 rat compared to same-strain control pairs. Finally, an acute injection of a subthreshold dose of the cannabinoid type 1 receptor inverse agonist/antagonist SR141716 before the social encounter abolished enhanced play-soliciting behavior in Wistar/Fischer 344 pairs as well as the behavioral consequences of the rejection experience in adolescent Wistar rats, further

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emphasizing an important modulatory role of the endocannabinoid system in mediating the effects of social behavior and social pain.

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## 1. Introduction

In social animals, including humans, the need to belong has been found to be equally fundamental to survival as the need for food, sleep and reproduction (Baumeister and Leary, 1995). Being rejected from a social group therefore poses a threat to this basic need and has been recognized as a major risk factor for the emotional wellbeing in humans (Williams, 2006). Acute rejection experiences were found to alter pain sensitivity in test subjects (Bernstein and Claypool, 2012; DeWall and Baumeister, 2006). Together with earlier work in animals on separation distress (Panksepp, 1980), these findings eventually led to the hypothesis that the aversive experience of social rejection and physical pain share, at least partially, underlying neuronal substrates and mechanisms (reviewed in Eisenberger, 2015). This hypothesis is further supported by studies reporting on the ability of physical pain relievers to reduce feelings of social pain (DeWall et al., 2010; Vangelisti et al., 2014). However, the neurochemical substrates underlying acute social rejection experiences are not known.

Experimental studies in humans are limited to the acute induction of social rejection through a number of established paradigms which are often based on the exclusion from play and playful activities, such as on-line ball tossing (Cyberball) or children receiving a video message from other children declining to play with them (Sandstrom et al., 2003; Williams and Jarvis, 2006). Adolescent social play is a common denominator in a variety of species (Fagen, 1981; Pellis and Iwaniuk, 2004), thought to enable and train appropriate social responses required in adulthood (Spinka et al., 2001). Rats are highly social animals with a wide repertoire of social skills, including the well-studied complex patterns of social play behavior which peaks during early adolescence (postnatal day (pd) 30-40) (Pellis and Pellis, 1998; Vanderschuren et al., 1997). These peer-directed social activities are crucial for the development of intraspecific communication and appropriate social behavioral patterns (Vanderschuren et al., 1997) and have a considerable incentive value during adolescence (Douglas et al., 2004; Trezza et al., 2011). Specifically, the reciprocity during a play fight, i.e. the active engagement of the play partner, has been identified as the main rewarding component of these social interactions (Pellis and McKenna, 1995). Recently, we demonstrated that either acute encounters or chronic social rearing of adolescent Wistar rats with a play partner from the relatively less playful Fischer 344 strain (Siviy et al., 2003), decreases pain sensitivity in Wistar animals (Schneider et al., 2014). These findings indicated Fischer 344 animals as inadequate play partners for Wistar rats, although the main aversive component of these interactions had not been analyzed in detail before. Hence, the present study was aiming to increase the translational value of our previous peer-rejection model by

a more detailed analysis of acute playful interactions and play-related vocalization between the different rat strains, the consequences of these encounters on thermal pain sensitivity, as well as underlying neurochemical substrates.

Peer-acceptance gains increasing importance during adolescence, with girls being particularly sensitive to the perception of peer-rejection (Sebastian et al., 2010). As in our previous work we therefore used adolescent female rats from the Wistar strain for the present study. A first experiment was designed to determine if acute alterations in pain sensitivity in our model derive specifically from the inability to engage in reciprocal adequate playful interactions during an acute social encounter with animals from the Fischer 344 strain. Therefore, adolescent Wistar animals were subjected to short-term social encounters with Fischer 344 animals, during which sequences of social play behavior were analyzed in detail and thermal pain sensitivity was assessed subsequently on a hot plate. In order to determine whether consequences of these encounters are related specifically to the peculiar social play of Fischer 344 animals, Wistar rats were also subjected to social encounters with the more playful Sprague Dawley rat strain and subsequently tested for pain sensitivity. In addition, ultrasonic vocalizations (USVs), which may serve as a measure for the emotional state (Brudzynski, 2013), were recorded during social encounters with Fischer 344 animals. In a second experiment we further analyzed naturally occurring strain differences in home cage play behavior in same-strain groups of Wistar and Fischer 344 animals that would account for inadequate social play in cross-strain encounters. Since lasting changes in pain sensitivity after prolonged pairing with a Fischer 344 animal were found to coincide with region-specific alterations in expression of the cannabinoid type 1 receptor (CB1R) in our previous work (Schneider et al., 2014), and the endocannabinoid (eCB) system is well known to play an important modulatory role in pain processing (Guindon and Hohmann, 2009), we finally tested in a third experiment the ability of the CB1R inverse agonist/antagonist SR141716 to acutely reverse behavioral consequences of the rejection experience in adolescent Wistar rats.

## 2. Experimental procedures

### 2.1. Subjects

The female rats used for the present study arrived at our institute at postnatal day (pd) 24, Wistar HanRcc (Wistar; W) from Harlan Laboratories GmbH (AN Vanray, Netherlands), whereas Fischer 344 (F) and Sprague Dawley (SD) rats were purchased from Charles River (Sulzfeld, Germany). Experiments were conducted at age pd 30/32, the start of the peri-pubertal period in female animals culminating with the first ovulation (around pd 38) (Schneider, 2013), since high occurrence of social play has been reported around this age (Pellis and Pellis, 1997). Animals were housed under standard conditions on a 12 h light-dark cycle (lights on 0600-1800) with free access to tap water and standard lab chow.

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