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Review article

Towards an animal model of callousness

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ABSTRACT

Callous-unemotional traits – the insensitivity to other's welfare and well-being – are characterized by a lack of empathy. They are characteristic of psychopathy and can be found in other anti-social disorders, such as conduct disorder. Because of the increasing prevalence of anti-social disorders and the rising societal costs of violence and aggression, it is of great importance to elucidate the psychological and physiological mechanisms underlying callousness in the search for pharmacological treatments. One promising avenue is to create a relevant animal model to explore the neural bases of callousness. Here, we review recent advances in rodent models of pro-social choice that could be applied to probe the absence of pro-sociality as a proxy of callous behavior, and provide future directions for the exploration of the neural substrates of callousness.

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Contents

1. Introduction

Most of us feel the joy of a friend's success as if it would be our own happiness. Similarly, we regularly share the physical and psychological pain and distress of others, illustrated by our consoling gestures towards people in sorrow. However, while the ability to share other people's feelings (*i.e.*, empathy) is extensively found in humans, not every human has empathy. *Callousness* (*i.e.*, the

Abbreviations: CU, callous-unemotional; CD, conduct disorder; PCT, pro-social choice task; *f*MRI, functional Magnetic Resonance Imaging; ACC, anterior cingulate cortex; TPJ, Temporo-Parietal Junction; mPFC, medial Prefrontal Cortex; TMS, Transcranial Magnetic Stimulation; tDCS, transcranial Direct Current Stimulation.

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absence of empathy; Blair, 2013), or callous-unemotional traits (CU-traits), are often found in individuals who engage in anti-social behavior to reach a goal. For instance, callousness can be observed in conduct disorder (CD), a particular form of social impairment characterized by patterns of social norm violation and anti-social behaviors such as bullying, fighting, defiance and destruction of property (Moffitt, 1993; Offord and Bennett, 1994). Although a distinctive symptom, callousness is neither necessary nor sufficient for a CD diagnosis, as only a subset of individuals with CD show CU-traits. The revised DSM-5 diagnostic criteria for CD (Reynolds and Kamphaus, 2013) includes a specifier for 'limited prosocial emotions' that targets CU-traits found in a subgroup of CD individuals (Frick and Ellis, 1999; Barry et al., 2000). Additionally, callousness is one of the hallmarks of psychopathy (Barry et al., 2000), a disorder characterized, among others, by a lack of guilt and a general disinterest in the welfare of others (Quay, 1993; Frick et al., 1994; Anderson and Kiehl, 2012).

High CU-trait scores often go along with high aggressiveness and deficits in decision-making. A distinction can be made between reactive ("hot", hostile) and proactive ("cold", instrumental) aggression found in CD and psychopathy (Dodge and Coie, 1987; Dodge et al., 1997). While both types of aggression correlate highly in children (Kempes et al., 2005; Fite et al., 2009), CU-traits are often associated with proactive, but less so with reactive aggression (Kerig and Stellwagen, 2010). Furthermore, reactive and proactive aggression have different neural response signatures in brain regions associated with empathy and emotional awareness such as the anterior insula, the cingulate cortex and the amygdala (Carré et al., 2013; Michalska et al., 2016; Yoder et al., 2016). Finally, deficits in decision-making found in children scoring high on CU-traits are non-specific and shared with a wider range of personality disorders.

The prevalence rate of CD has increased in the last decades (Wittchen and Jacobi, 2005, but see also Canino et al., 2010), provoking incremental societal costs caused by the material and psychological impact of aggression, violence and bullying. A better understanding of the neurobiological roots of callousness could aid the development of more effective psychopharmacological treatments for anti-social disorders as well as, perhaps, guide cognitive-behavioral therapeutic strategies aimed at reducing callous tendencies (*e.g.* empathy promotion programs against bullying in schools).

While, over the last years, progress has been made to uncover the neurobiological correlates and genetic determinants of callousness in humans (Blair, 2013; Kuteykin-Teplyakov and Maldonado, 2014), animal models of CU-traits remain scarce in comparison with other types of anti-social behaviors, which might stem from the difficulty to model this particular and complex phenotype. While for reactive aggression, standardized animal models have been used extensively and its neurobiological determinants are becoming increasingly delineated (Lukas and de Jong, 2016), for callousness, however, a suitable animal model is lacking. Defined as the *absence* of emotional empathy, a promising approach to develop putative animal models of callousness is to capture experimentally-induced abolishment of an empathic reaction or other-regarding concern in a task in which behavior is normally modulated by the affective state of a conspecific.

There is considerable debate about the extent of social cognitive abilities of animals (Panksepp and Lahvis, 2011; Keum and Shin, 2016; Keysers and Gazzola, 2016; Sivaselvachandran et al., 2016) that could lead to disagreement on the construct validity of any animal model targeting empathy (Balter, 2012; Vasconcelos et al., 2012; Silberberg et al., 2014). To circumvent such a discussion here, we focus on reviewing the face validity of novel animal models in capturing callous behavior. With this scope in mind, we start by delineating the operational definition of empathy, review how this trait is affected in CU individuals on cognitive and neurobiological levels, and finally discuss the translational potential of animal models.

2. Callousness as dysfunctional empathy

Adam Smith, the Scottish philosopher and economist considered by many as the father of modern economics, believed that we are motivated to help a person in pain when we *"place ourselves in his situation,* [and] *conceive ourselves enduring all the same torments, we enter as it were into his body"* (Smith, 1759). This idea, which puts empathy at the core of pro-social interactions, (*i.e.*, actions that increase the well-being of another individual) hypothesizes that the vicarious emotion we experience when observing other's distress could trigger prosociality (Batson et al., 1983).

As pointed out by Blair (2013), we can distinguish between *cognitive* empathy (imagining that another individual has thoughts and feelings separate from our own), a skill set that relies on a mentalizing network involving medial prefrontal cortex (mPFC) and the temporo-parietal junction (TPJ), amongst others, and *emotional* empathy, or the ability to recognize affective displays in others and emulate the underlying emotion, a process recruiting the anterior cingulate cortex (ACC), the amygdala and the insula, amongst others (de Vignemont and Singer, 2006; Bernhardt and Singer, 2012). While the former relies on simulation of mental states (Frith and Frith, 2012), the latter is thought to be supported by low-level emotional contagion/mimicry and direct perception (Gallagher, 2008; McGann and De Jaegher, 2009), though of course both systems interact (Bohl and van den Bos, 2012) and could recruit overlapping neural resources such as mirror neurons (Gallese et al., 2004; Bastiaansen et al., 2009a; Caramazza et al., 2014; Ferrari and Rizzolatti, 2014). Here, we focus primarily on emotional empathy and its neural substrates.

Pioneering studies using functional Magnetic Resonance Imaging (*f*MRI) explored whether the neural activity triggered by witnessing the emotions of others resembles that of experiencing similar emotions firsthand. These experimental paradigms, well established in humans (Wicker et al., 2003; Keysers et al., 2004), typically quantify vicarious emotions (*i.e.*, the behavioral, emotional and/or cognitive effects on an observer witnessing an event that affects a fellow individual), thought to be a prerequisite of emotional empathy. By reverse inference, similarity in neural patterns associated with the experience of self- and other-sensations would be considered as an indication that witnessing the feeling of others triggers similar affective states in the observer – a potential neural substrate of vicarious emotions. In support of this idea, a seminal study showed that the somatosensory cortex was activated not only when the legs of scanned participants were caressed but also while they observed another person's leg being caressed (Keysers et al., 2004). Additionally, experiencing own, and witnessing disgust in others has been shown to trigger the activation of several common structures such as anterior insula (Wicker et al., 2003) and the gustatory cortex (Jabbi et al., 2007). Similarly, observing someone else receive a painful stimulation and experiencing this stimulation oneself activates overlapping subfields of the anterior insula and the cingulate cortex (Singer et al., 2004), suggesting that these structures participate in the experience of another individual's emotional (negative) state. Altogether, a large body of evidence supports the notion of shared neural activity related to experiencing own, and witnessing others' sensations and emotions in humans (Bastiaansen et al., 2009b; Lamm et al., 2011; Cui et al., 2015).

Interestingly, individuals with high CU-traits are unimpaired on measures of cognitive empathy, but show substantial deficiency in emotional empathy (Blair, 2012, 2013). High CU-traits often go

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along with deficits in the recognition of fear-related social signals (Marsch and Blair, 2008) in different modalities, such as fearful facial expressions or vocal affect (Blair et al., 2005; Muñoz, 2009), while emotional responses to unconditioned stimuli (Birbaumer et al., 2005). In line with this observation, individuals scoring high on CU-traits are thus especially impaired in detecting distress in others (with limited impairment in detecting happiness; Dolan and Fullam, 2006), and in showing a congruent empathic response to these emotional displays in facial expressions and vocalizations (Marsh and Blair, 2008; Dawel et al., 2012). Accordingly, several explanations have been proposed to account for callousness, such as deficits in stimulus-reinforcement learning (Blair, 2007), attention (Moul et al., 2012) or spontaneous vicarious perception (Meffert et al., 2013).

Here, neurobiological studies provide valuable insights by suggesting that callous individuals typically show dysfunctions in several neural networks devoted to social cognition, in particular the ventral frontal cortices and the amygdala (Blair, 2007). Because of the well-documented involvement of the amygdala in human and animal social behavior and its conspicuous association with the CU component of psychopathy (see below), we will devote special attention to this brain region in the remainder of this review (for exhaustive reviews of other brain regions involved in CU-traits, See Blair, 2007, 2012, 2013; Anderson and Kiehl, 2012).

3. The role of the amygdala in callousness

The amygdala is an interconnected set of nuclei located in the mammalian temporal lobe involved in emotional processing, fear and reward learning (Amaral, 2006). In humans, the amygdala has reciprocal connections with many thalamic and sensory cortical brain regions as well as other limbic areas (McDonald and Mascagni, 1996; Janak and Tye, 2015), and is strongly interconnected with other neural components of the social brain, such as the vmPFC, the temporo-parietal junction, the superior temporal sulcus, the ACC and the orbitofrontal cortex (Barbas and De Olmos, 1990; Schoenbaum et al., 2000; Ruff and Fehr, 2014). The amygdala is involved in, amongst others, social cognition, vigilance and affect (Bickart et al., 2014). Amygdala volume is correlated with social network size in humans (Bickart et al., 2011) and macaques (Sallet et al., 2011) as well as with social status in macaques (Noonan et al., 2014), and activation in this area correlates with a wide range of social tasks, skills and perceptions, including responding to eye gaze (Spezio et al., 2007; Mosher et al., 2014) and social network management (Kennedy et al., 2009; Bickart et al., 2011). Moreover, neurons in the macaque amygdala track the value of rewards delivered to both self and others in a social choice task (Chang et al., 2015).

Damage or atrophy of amygdala tissue is associated with selective deficits in affiliation and social signal processing (Adolphs et al., 1994, 1998; Adolphs, 1999). Individuals scoring high on CU-traits typically exhibit decreased amygdala reactivity to emotional stimuli (Kiehl et al., 2001; Birbaumer et al., 2005; Blair, 2012; Decety et al., 2013) and reduced amygdala volume (Sterzer et al., 2007; Yang et al., 2009). The amygdala is involved in the decoding of facial expressions (Breiter et al., 1996; Morris et al., 1996), and recent studies have reported a link between the inability to recognize fearful faces, reduced amygdala reactivity and the severity of psychopathic traits (Marsch and Blair, 2008; Jones et al., 2009). As put forward by Blair (2013), the role of the amygdala in emotional empathy could be facilitatory: in drawing or increasing attention to stimuli associated with emotions (such as the eye region, especially in distress), these stimuli could be processed faster and deeper and subsequently boost representation of emotional states in other brain regions. Of particular relevance is recent evidence suggesting that explicitly instructing individuals high on CU-traits to focus attention on others' emotions can remediate their deficit in emotion recognition (Dadds et al., 2006), suggesting that emotional empathy networks are not absent, but rather that these individuals show deficits in *spontaneous* vicarious perception (Meffert et al., 2013). As such, this impairment is shared between individuals with CU individuals and some individuals with autism spectrum disorder (Lockwood, 2016), though the anatomical substrate might differ (Birmingham et al., 2011).

4. The amygdala hypothesis of social reinforcement learning

The amygdala is also a key player in associative learning, as documented by decades of animal (see Gründemann and Lüthi, 2015; Sharpe and Schoenbaum, 2016 for recent reviews) and human research (Chase et al., 2015). Of particular interest here is social reinforcement learning, a type of model of associative learning used to explain adaptive changes in behavior induced by a social context or social feedback (Isbell et al., 2000; Chang et al., 2010; Ruff and Fehr, 2014). According to the social reinforcement learning hypothesis (Hernandez-Lallement et al., 2016a), and in line with the proposal of learning deficits in callous individuals (Blair, 2007), the likelihood of showing a particular behavior is increased or decreased, contingent on the type of *social* signals following the behavior. Within this framework, social signals, though different from primary hedonic reinforcers, such as of food or sex, have similar reinforcing power by means of carrying intrinsic positive or negative valence. In humans, examples include a smile of a recipient of help that is perceived as rewarding by the help provider (positive social reinforcement), or an angry face in response to a social norm transgression that is perceived as aversive by the wrongdoer (negative social reinforcement). In animals, candidates for putatively reinforcing social signals include, among others, vocal communications in macaques (so-called "coo calls", Furuyama et al., 2016) or facial expressions (Waller et al., 2016), and in rodents, ultrasonic vocalizations (Seffer et al., 2014; Willuhn et al., 2014) as well as behavioral (Márquez et al., 2015) and olfactory cues (Wang et al., 2006).

Social reinforcement learning requires the ability to experience the affective salience or value associated with social stimuli – a process likely mediated by the amygdala, given its prominent role in emotional processing and reinforcement learning. According to the social reinforcement hypothesis, if the affective salience or value of social stimuli is inadequately processed, for example due to impaired amygdala function, it follows that these stimuli would subsequently be less effective in driving learning. As such, they would fail to drive future behavior, leading to an unemotional or callous decision maker unable to properly weigh and integrate the value of emotional social feedback. In support of this hypothesis, human individuals high in CU-traits and reduced amygdala reactivity show impaired reinforcement learning in social contexts (Birbaumer et al., 2005; Blair, 2007). Taken together, these results hint towards a deficit in emotional empathy and social reinforcement learning in individuals high on CU traits, presumably related to a reduction in amygdala function. Consequently, a successful animal model of callous-like behavior could incorporate modulation of amygdala activity in tasks where social reinforcement learning normally takes place.

5. Towards a rodent model of callousness

Despite the promising advances in the neuroimaging field, we are still far from fully understanding the mechanism of callousness. While human neuroimaging approaches can explore neural corre-

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lates of emotional empathy, they allow only very limited insights into the causal links between brain function, empathy and callousness. Additionally, neuroimaging techniques cannot resolve individual neurons nor can they identify the cell-types involved in a task, limiting our mechanistic and pharmacological insights into empathy and callousness. Finally, one of the core regions of interest, the amygdala is relatively inaccessible to current non-invasive neuromodulation tools available for humans (primarily Transcranial Magnetic Stimulation –TMS- and transcranial direct current stimulation -tDCS-), restricting the therapeutic potential of these non-invasive approaches in CU individuals.

Consequently, we propose that progress in understanding the mechanism of callous behavior could be made using appropriate animal models. In addition to yielding direct between-species comparisons of neural structures' functional and anatomical organization, animal models offer a wide range of pharmacological, genetic, electrophysiological and optogenetic intervention possibilities as well as a panel of procedures to assess behavior in standardized contexts. What is needed are animal models for callousness (i) with high face validity, (ii) established in species that exhibit a high degree of similarity with humans in terms of brain architecture to make a case for construct validity, and (iii) for which high spatial resolution neuroscientific recording methods are readily available. We propose that recent advances in rodent models of social behavior could be adapted to study callousness, as a readily accessible complement to models emerging in non-human primates (Latzman et al., 2015). Rodents offer a cheap, convenient and ethically less controversial alternative to non-human primate in the study of social cognition. Laboratory rats in particular, but also mice, voles and other rodents, are widely available social mammals characterized by strong between-individual interactions (Schuster, 2002), helping behavior (Hernandez-Lallement et al., 2016a), conformity (Galef and Whiskin, 2008), inequity aversion (Oberliessen et al., 2016), reciprocity (Rutte and Taborsky, 2007, 2008), and precursors of empathy (Langford et al., 2006; Ben-Ami Bartal et al., 2011; Mogil, 2012; Langford and Williams, 2014; Dolivo and Taborsky, 2015; Sivaselvachandran et al., 2016). As a result, several researchers have argued that rodent models are a sensible long-term investment in comparative and translational neuroscience (Kalenscher and van Wingerden, 2011; Panksepp and Panksepp, 2013; Keysers and Gazzola, 2016).

Ideally, to bolster construct validity, these animal models of social behavior, if they are to be used to study callousness, should be sensitive to modulations of the (re)activity of brain regions involved in CU-traits in humans, most notably, the amygdala, the insula and ventral cortices. We will proceed to discuss a range of behavioral paradigms that we believe can track emotional empathy-like cognitions in animals, and conclude with a discussion of the application of amygdala lesions in one of these models.

6. What should a rodent model of callousness look like?

In order to explore callousness and its neural substrates in rodents, of particular interest are experimental paradigms in which the behavior of target animals are influenced by events affecting other conspecifics. We propose that, in order to establish a rodent model of callousness, we should be able to (i) track a baseline tendency towards emotional empathy, (ii) perform behavioral and pharmacological manipulations of this baseline behavior aimed at reducing the tendency towards emotional empathy, and (iii) assess repeated social interactions. The first point provides a proof-of-principle that animals are able to attach motivational value to the outcome of others. The second point allows exploring physiological manipulation that might induce a shift of baseline behavior towards callousness. The last point provides valuable methodological strength given that both neural recording techniques and associated statistical analyses of the data usually require multiple trials.

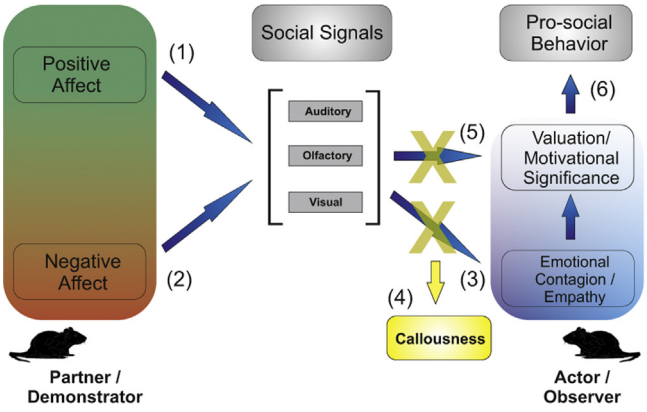

Fig. 1. A framework of pro-social behavior and callousness. Partner/demonstrator animals express their affective states (positive or negative; left bubble) as social signals (auditory, olfactory, visual) that are received by an actor/observer animal (right bubble). The perception of these social stimuli can trigger similar affective states in the actor/observer (emotional contagion), and/or possibly also empathy. These affective states are associated with motivational significance, motivating the actor/observer to make a pro-social response. Additionally, social signals may also be valued directly by the actor/observer, *i.e.*, social signals may have proper reinforcing power, leading to pro-social output independent of the induction of a particular affective state in the actor/observer. The crosses in the figure indicate that a disruption of the respective pathway is expected to induce callous-like behaviors. For example, callousness would be caused by any behavioral or neurophysiological manipulation that interferes with the causal link between social stimulus and empathy induction, leading to diminished pro-social response tendencies.
Numbers denote references supporting the suggested mechanisms. (1) Popik et al. (2012), Knutson et al. (1999) (2) Knapska et al. (2006), Atsak et al. (2011), Pereira et al. (2012), Kavaliers et al. (2001) (3) Atsak et al. (2011), Sanders et al. (2013), Carrillo et al. (2015), Kim et al. (2010) (4) Hernandez-Lallement et al. (2016b), Ben-Ami Bartal et al. (2016) (5) Kashtelyan et al. (2014), Willuhn et al. (2014), Hernandez-Lallement et al. (2016a) (6) Ben-Ami Bartal et al. (2011), Sato et al. (2015), Márquez et al. (2015), Hernandez-Lallement et al. (2015).

If we are to model emotional empathy in rodents, we should first establish that rodents can vicariously experience emotional states of others; that is, we need to show that the social signals generated by conspecifics (demonstrator/partner; Fig. 1; left) affect the behavioral and possibly also emotional state of an observer/actor animal (Fig. 1; right). Subsequently, we can investigate the behavior of the observer/actor in relation to the state of conspecifics, assuming that these states will feed into the decision-making process of the animal (Fig. 1; up). Hence, in the remainder of this article, we will first review evidence in favor of the existence of emotional contagion and empathy-like behavior in rats, and then discuss how these social processes might translate into pro-social decision-making as their observable read-out. We will conclude with a discussion of physiological manipulations aimed at reducing the normal level of pro-social behavior as a putative animal model for callousness.

6.1. Emotional contagion

Early work already suggested that rats show an emotional response to conspecifics in distress (Church, 1958; Rice and Gainer, 1962; Evans and Braud, 1969; See Sivaselvachandran et al., 2016 for overview). Freezing, the observable hallmark of distress (Whishaw and Kolb, 2004; Sharp and Villano, 2012) carries informational value for conspecifics (Pereira et al., 2012). Freezing occurs not only when a target animal is exposed to looming threat, but also when it observes other conspecifics in distress (Atsak et al., 2011), and it can induce consolation behavior in rats (Knapska et al., 2006) and voles (Burkett et al., 2016). Such putative emotional contagion of others' distress seems to depend in part on self-experience with

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the event eliciting distress (Atsak et al., 2011; Parsana et al., 2012b; Sanders et al., 2013; but see Kavaliers et al., 2001). Social transmission of fear to a naive observer is mediated by the rodent amygdala (Knapska et al., 2006) and its connectivity with prefrontal structures (Jeon et al., 2010; Ito et al., 2015). The opposite of distress contagion, *i.e.*, transfer of positive affect, can be observed in rats, too: observing a conspecific gaining access to food, or experiencing ultrasonic vocalizations associated with appetitive situations (Knutson et al., 1999; Popik et al., 2012), resulted in dopamine release in the nucleus accumbens (Kashtelyan et al., 2014; Willuhn et al., 2014). These results support the principle assumption that rats are able to vicariously experience emotions based on the affective display of a conspecific.

6.2. Emotional empathy: helping a conspecific in distress

Recently, a novel rat model for empathy was proposed on helping behavior in a controlled laboratory environment (Ben-Ami Bartal et al., 2011). In this experiment, a partner rat was trapped in a transparent restrainer that could be opened by an actor. The actor had the choice between either eating an appetitive reward or freeing the entrapped partner. Results showed that actors preferred to free the entrapped partner over eating the reward. This result was interpreted as evidence for the existence of emotional empathy with the distress of the trapped rat. The authors implemented a series of control experiments where the restrainer was empty, contained an object or where the partner was not restrained but located across a perforated divider, providing more evidence for pro-social motives in rats. Although the choice set in this experiment still conflates self- and other-oriented motives (Silberberg et al., 2014), the fact that door opening was motivated by help towards a conspecific is supported by recent evidence suggesting that rats help distressed partners but not non-distressed partners (Ben-Ami Bartal et al., 2014; Sato et al., 2015). It was further shown that helping behavior was modulated by social experience, that is, actor rats helped partners they have previously been in contact with (Ben-Ami Bartal et al., 2014).

The absence of this helping behavior, ignoring a conspecific in distress, could be classified as callous behavior, reflecting an insensitivity to putative negative social reinforcement. Interestingly, supplying benzodiazepine anxiolytics to rats in this paradigm reduces helping behavior (Ben-Ami Bartal et al., 2016), suggesting that emotional contagion of the actor could have motivated helping behavior in order for the actor to alleviate its vicariously experienced distressed state.

This raises the interesting possibility that neural mechanisms relying on GABAergic action, such as the amygdala, are essential for the expression of this type of helping behavior. As of yet, a mediating role for the amygdala has not yet been established in this paradigm. In addition, the action resulting from the putative empathic concern in this paradigm takes place entirely in the negative domain, by restoring a negative vicarious emotional state back to neutral. However, a full model of callousness should also include absence of a empathically motivated behavior taking place in the positive domain, *i.e.* insensitivity to putative positive social reinforcement.

6.3. Pro-social choice

Social choice-based paradigms, *i.e.*, experiments that track the choice allocation of an animal whose decisions affect the reinforcer state of a conspecific, are a strong suit to establish a rodent model of emotional empathy. Indeed, while empathy does not require a behavioral output *per se* (which would rather belong to the realm of sympathy), social decision making paradigms are a powerful approach to detect empathy-driven behaviors, and the experimentally-induced absence of them.

In choice-based experiments, an animal is trained to make decisions that determine the outcome received by a second partner animal. Typically, the outcome can be modulated by several attributes (magnitude, valence, modality, etc.) and these experiments generally involve multiple interaction rounds, often across days and weeks, and are therefore well suited to (i) capture enduring manifestations of emotional empathy beyond volatile disinterest or transient insensitivity in one-shot or time-based measurements, and (ii) track these processes using neuroscientific approaches. These paradigms probe an animal's willingness to act to aid a conspecific, and can vary regarding the payoff layout inherent to the action, *i.e.*, helping a conspecific can be either costly or non-costly for the decision maker. Both non-costly (Taylor, 1975; Hernandez-Lallement et al., 2015; Márquez et al., 2015; Oberliessen et al., 2016) and costly helping behavior (Ben-Ami Bartal et al., 2011; Sato et al., 2015) is observed in rodents, although costly behavior generally imply a physical effort rather than actual resource sharing.

We have recently shown in a rodent Prosocial Choice Task (PCT) that rats prefer options that yield mutual rewards for themselves and another conspecific over alternatives yielding reward only to themselves (Hernandez-Lallement et al., 2015). Pairs of rats, an actor and a partner rat, perform the PCT in a double T-maze. The actor rat decides to enter one of two compartments in the maze, either choice leading to identical food rewards to the actor. However, entering one compartment yields an additional reward for the partner rat, whereas entering the other compartment leaves the partner empty-handed. Our results showed that actor rats preferred to enter compartments associated with partner reinforcement, but only when the partners were real rats, not when they were inanimate toy rats. Interestingly, another study using a similar design replicated these results only when the partner showed food-seeking behavior (Márquez et al., 2015), but not when the actor moved first. Mutual reward preferences in the PCT may be possibly due to vicarious reinforcement resulting from watching a conspecific eat (Kashtelyan et al., 2014), from appetitive social ultrasonic vocalizations emitted by a rewarded partner rat (Seffer et al., 2014; Willuhn et al., 2014), or from aversive social vocalizations (Parsana et al., 2012a) emitted by a duped partner missing out on reward. As argued above, a manipulation that abolishes this normally occurring pro-social behavior might serve as an effective model of callousness in rats.

6.4. The role of rat amygdala in pro-social choice: a model for callousness?

In light of the evidence reviewed above, a prime candidate target region to induce callousness is the amygdala. Amygdala functions and circuitry are phylogenetically old and well conserved across vertebrates (McDonald, 1998). Accordingly, evolutionary homologues of major amygdala clusters are found in most mammals including primates and rodents but also in birds, reptiles and fish (Scalia and Winans, 1975; Jarvis et al., 2005; Janak and Tye, 2015). In rats, strong projections from sensory areas (McDonald, 1998) such as insular (gustatory and proprioceptive areas) and parietal structures (somatosensory) as well as occipito-temporal (visual information; McDonald and Mascagni, 1996) and temporal networks (auditive pathways; Herbert et al., 1991) innervate the amygdala. Moreover, the amygdala receives robust afferents from the auditory and visual thalamus (see LeDoux and Farb, 1991 and Vaudano et al., 1991 for auditory and visual thalamic projections, respectively). Similarly to humans, the rat amygdala shares robust reciprocal connections with frontal cortices, mainly with the insu-

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lar (Allen et al., 1991), infralimbic (Hurley et al., 1991) and lateral orbital cortices (Krettek and Price, 1977; Ongür and Price, 2000).

We have recently provided evidence that the basolateral amygdala is essential for the expression of mutual-reward preferences in the PCT (Hernandez-Lallement et al., 2016b). Specifically, we found that while sham-operated animals developed pro-social preferences for the both-reward option in the partner- but not toy-condition, as reported before (Hernandez-Lallement et al., 2015), rats with bilateral lesions of their basolateral amygdala (BLA) failed to acquire mutual-reward preferences. Importantly, BLA-lesioned rats showed intact reward magnitude discrimination, motivation, food-intake, and movement times to enter the compartments, suggesting that the lesion effects reflected a deficit selective to the social domain of the task. Thus, the BLA-lesion effects were characterized by the *absence* of pro-social tendencies, suggesting a disruption of the cognitive, emotional or motivational mechanisms underlying pro-social behavior. As mutual-reward preferences in the PCT in BLA-intact animals are thought to be driven by social reinforcement learning (Hernandez-Lallement et al., 2016a), the lack of mutual-reward preferences in BLA-lesioned animals implies that they became insensitive to the affective value of social feedback signals, either in the emotional processing stage or in the learning/updating stage.

It is presently unclear what type of social reinforcement may be responsible for producing pro-social choices in the PCT. One likely candidate signal type is ultrasonic vocalization. Given the importance of the amygdala in the neural and behavioral response to ultrasonic vocalizations, it is tempting to speculate that damaging amygdala led to the presumed failure to attach motivational and affective value to these putative social signals, positive or negative. However, whether other sensorial modalities are involved in shaping behavior in the PCT remains to be investigated. In sum, we propose that amygdala lesions in animals performing the PCT task produces a deficit in pro-social motivation, and thus meets the face and construct validity criteria to qualify as animal model of callousness.

Like every new animal model, however, the present paradigm has limitations. The computational mechanisms underlying pro-social choices, or the absence thereof after amygdala lesions, are still elusive. For instance, the USV-hypothesis of rodent pro-social choice awaits confirmation and substantiation (Willuhn et al., 2014), and it remains to be determined if other modalities, such as olfaction (Wang et al., 2006) and others (Pereira et al., 2012), are important, too. Furthermore, in this review, we have repeatedly highlighted the lack of emotional empathy as a central symptom in CU-traits. But, even though the ability for empathy-like behavior has been demonstrated in rats, in light of the social reinforcement learning framework proposed in this article, it is not strictly necessary to suppose empathy in rats to explain pro-social behavior in the PCT. Hence, the absence of mutual-reward preferences following amygdala lesions does not inevitably imply lack of emotional empathy. Nevertheless, even the most conservative account of amygdala lesion effects on mutual-reward preferences in the PCT has to account for the observed reduction in sensitivity to a conspecific's outcome – a hallmark of callousness. We thus maintain that the animal model of callousness proposed in this article provides a good starting point for future research.

7. Conclusions

In this article, we have argued that callousness can be understood as a lack of emotional empathy. Even though a distributed network of brain regions is implicated in emotional empathy, vicarious affect and related social cognitions in humans, or lack thereof, we have paid particular attention to the role of amygdala in these faculties as dysfunction of this brain region is especially implicated in callousness in humans. We contended that an animal model for callousness should, in order to meet sufficient face and construct validity criteria, (i) be –dependent on the neural networks implied in empathy and pro-sociality, including amygdala, (ii) allow for the measurement of pro-social behavior, and, most notably, (iii) permit the quantification of the *absence* of the emotional and/or motivational mechanisms prompting pro-social behavior, as a proxy for the lack of empathy. While other paradigms could prove suitable as well, we propose that the effects of lesions of the amygdala in the rodent PCT already meets these criteria. This paradigm is, in particular, suitable for quantifying, tracking and manipulating the emotional and motivational mechanisms underlying social valuation. Hence, we propose that amygdala lesions in animals performing the PCT task produce a deficit in pro-social motivation, and thus meet the face and construct validity criteria to qualify as animal model of callousness. It therefore provides a first step towards the development of a viable animal model of callousness.

We are only at the beginning of the endeavor to develop animal models of callousness, and additional research is needed in order to explore the underpinnings of callous-like traits in rodents. Variants of the designs proposed here, such as modifying the pay-off matrix so that animals can decide to punish a conspecific without affecting their own payoff (*e.g.* make an active choice to deliver a foot-shock or prevent access to food) would allow more detailed testing of the behavioral dynamics of social choice in rodents. Finally, investigating inter-individual differences in behavior in order to identify genetic or developmental markers conductive to anti-social preferences (Kuteykin-Teplyakov and Maldonado, 2014) could be useful for comparisons with factors influencing callousness, and other psychological disorders that feature anti-social behavior in humans.

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References

Adolphs, R., Tranel, D., Damasio, H., Damasio, A., 1994. Impaired recognition of emotion in facial expressions following bilateral damage to the human amygdala. Nature 372, 669–672.
Adolphs, R., Tranel, D., Damasio a, R., 1998. The human amygdala in social judgment. Nature 393, 470–474.
Adolphs, R., 1999. Social cognition and the human brain. Trends Cogn. Sci. 3, 469–479, Available at: http://linkinghub.elsevier.com/retrieve/pii/S1364661399013996.
Allen, G.V., Saper, C.B., Hurley, K.M., Cechetto, D.F., 1991. Organization of visceral and limbic connections in the insular cortex of the rat. J. Comp. Neurol. 311, 1–16.
Amaral, D.G., 2006. The amygdala, social behavior, and danger detection. Ann. N. Y. Acad. Sci. 1000, 337–347, http://dx.doi.org/10.1196/annals.1280.015 (Accessed 12 January 2015).
Anderson, N.E., K.A, Kiehl, 2012. The psychopath magnetized: insights from brain imaging. Trends Cogn. Sci. 16, 52–60.
Atsak, P., Orre, M., Bakker, P., Cerliani, L., Roozendaal, B., Gazzola, V., Moita, M., Keysers, C., 2011. Experience modulates vicarious freezing in rats: a model for empathy. PLoS One 6, e21855, Available at: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3135600&tool=pmcentrez&rendertype=abstract (Accessed 29 May 2013).
Balter, M., 2012. Killjoys challenge claims of clever animals. Science 335, 1036–1037.
Barbas, H., De Olmos, J., 1990. Projections from the amygdala to basoventral and mediodorsal prefrontal regions in the rhesus monkey. J. Comp. Neurol. 300, 549–571.
Barry, C.T., Frick, P.J., DeShazo, T.M., McCoy, M.G., Ellis, M., Loney, B.R., 2000. The importance of callous-unemotional traits for extending the concept of psychopathy to children. J. Abnorm. Psychol. 109, 335–340.
Bastiaansen, J.A.C.J., Thioux, M., Keysers, C., 2009a. Evidence for mirror systems in emotions. Philos. Trans. R. Soc. Lond. B: Biol. Sci. 364, 2391–2404.

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Bastiaansen, J.A.C.J., Thioux, M., Keysers, C., 2009b. Evidence for mirror systems in emotions. Philos. Trans. R. Soc. B: Biol. Sci. 364, 2391–2404, http://dx.doi.org/10.1098/rstb.2009.0058.
Batson, C.D., O'Quin, K., Fultz, J., Vanderplas, M., Isen, A.M., 1983. Influence of self-reported distress and empathy on egoistic versus altruistic motivation to help. J. Pers. Soc. Psychol. 45, 706–718.
Ben-Ami Bartal, I., Decety, J., Mason, P., 2011. Empathy and pro-social – behavior in rats. Science 334, 1427–1430, http://dx.doi.org/10.1126/science.1210789 (Accessed 08 December 2011).
Ben-Ami Bartal, I., Rodgers, D.A., Bernardez Sarria, M.S., Decety, J., Mason, P., 2014. Pro-social behavior in rats is modulated by social experience. Elife 3, e01385, Available at: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3884117&tool=pmcentrez&rendertype=abstract (Accessed 20 January 2014).
Ben-Ami Bartal, I., Shan, H., Molasky, N.M.R., Murray, T.M., Williams, J.Z., Decety, J., Mason, P., 2016. Anxiolytic treatment impairs helping behavior in rats. Front. Psychol. 7, 1–14, Available at: http://journal.frontiersin.org/article/10.3389/fpsyg.2016.00850.
Bernhardt, B.C., Singer, T., 2012. The neural basis of empathy. Annu. Rev. Neurosci. 35, 1–23, Available at: http://www.ncbi.nlm.nih.gov/pubmed/22715878 (Accessed 20 Setember 2013).
Bickart, K.C., Wright, C.I., Dautoff, R.J., Dickerson, B.C., Barrett, L.F., 2011. Amygdala volume and social network size in humans. Nat. Neurosci. 14, 163–164, Available at: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3079404&tool=pmcentrez&rendertype=abstract (Accessed 12 January 2015).
Bickart, K.C., Dickerson, B.C., Feldman Barrett, L., 2014. The amygdala as a Hub inbrain networks that support social life. Neuropsychologia 14, 235–248.
Birbaumer, N., Veit, R., Lotze, M., Erb, M., Hermann, C., Grodd, W., Flor, H., 2005. Deficient fear conditioning in psychopathy. Arch. Gen. Psychiatry 62, 799–805.
Birmingham, E., Cerf, M., Adolphs, R., 2011. Comparing social attention in autism and amygdala lesions: effects of stimulus and task condition. Soc. Neurosci. 6, 420–435.
Blair, R.J.R., Budhani, S., Colledge, E., Scott, S., 2005. Deafness to fear in boys with psychopathic tendencies. J. Child Psychol. Psychiatry Allied Discip. 46, 327–336.
Blair, R.J.R., 2007. The amygdala and ventromedial prefrontal cortex in morality and psychopathy. Trends Cogn. Sci. 11, 387–392.
Blair, R.J.R., 2012. Neurobiological basis of psychopathy. Br. J. Psychiatry 182, 5–7.
Blair, R.J.R., 2013. The neurobiology of psychopathic traits in youths. Nat. Rev. Neurosci. 14, 786–799, Available at: http://www.ncbi.nlm.nih.gov/pubmed/24105343.
Bohl, V., van den Bos, W., 2012. Toward an integrative account of social cognition: marrying theory of mind and interactionism to study the interplay of Type 1 and Type 2 processes. Front. Hum. Neurosci. 6, 274.
Breiter, H.C., Etcoff n, L., Whalen p, J., Kennedy w a Rauch s, L., Buckner r, L., Strauss m, M., Hyman s, E., Rosen b, R., 1996. Response and habituation of the human amygdala during visual processing offacial expression. Neuron 17, 875–887.
Burkett, J.P., Andari, E., Johnson, Z.V., Curry, D.C., de Waal, F.B.M., Young, L.J., de Waal, F.B.M., Young, L.J., 2016. Oxytocin-dependent consolation behavior in rodents. Science 351, 375–378.
Canino, G., Polanczyk, G., Bauermeister, J.J., Rohde, L.A., Frick, P.J., 2010. Does the prevalence of CD and ODD vary across cultures? Soc. Psychiatry Psychiatr. Epidemiol. 45, 695–704.
Caramazza, A., Anzellotti, S., Strnad, L., Lingnau, A., 2014. Embodied cognition and mirror neurons: a critical assessment. Annu. Rev. Neurosci. 37, 1–15.
Carré, J.M., Murphy, K.R., Hariri, A.R., 2013. What lies beneath the face of aggression? Soc. Cogn. Affect. Neurosci. 8, 224–229.
Carrillo, M., Migliorati, F., Bruls, R., Han, Y., Heinemans, M., Pruis, I., Gazzola, V., Keysers, C., 2015. Repeated witnessing of conspecifics in pain: Effects on emotional contagion. PLoS One 10, 1–11.
Chang, L.J., Doll, B.B., van 't Wout, M., Frank, M.J., Sanfey, A.G., 2010. Seeing is believing: trustworthiness as a dynamic belief. Cogn. Psychol. 61, 87–105.
Chang, S.W.C., Fagan, N.A., Toda, K., Utevsky A, V., Pearson, J.M., 2015. Neural mechanisms of social decision-making in the primate amygdala. PNAS 112 (52), 1–6.
Chase, H.W., Kumar, P., Eickhoff, S.B., Dombrovski, A.Y., 2015. Reinforcement learning models and their neural correlates: an activation likelihood estimation meta-analysis. Cogn. Affect Behav. Neurosci. 15, 435–459.
Church, R.M., 1958. Emotional reactions of rats to the pain of others. J. Comp. Physiol. Psychol. 52, 132–134.
Cui, F., Abdelgabar, A., Keysers, C., Gazzola, V., 2015. Responsibility modulates pain-matrix activation elicited by the expressions of others in pain. Neuroimage 114, 371–378, Available at: http://www.sciencedirect.com/science/article/pii/S1053811915002165.
Dadds, M.R., Perry, Y., Hawes, D.J., Merz, S., Riddell, A.C., Haines, D.J., Solak, E., Abeygunawardane, A.I., 2006. Attention to the eyes and fear-recognition deficits in child psychopathy. Br. J. Psychiatry 189, 280–281.
Dawel, A., O'Kearney, R., McKone, E., Palermo, R., 2012. Not just fear and sadness: meta-analytic evidence of pervasive emotion recognition deficits for facial and vocal expressions in psychopathy. Neurosci. Biobehav. Rev. 36, 2288–2304, http://dx.doi.org/10.1016/j.neubiorev.2012.08.006.
Decety, J., Chen, C., Harenski, C., Kiehl, K.A., 2013. An fMRI study of affective perspective taking in individuals with psychopathy: imagining another in pain does not evoke empathy. Front. Hum. Neurosci. 7, 489, Available at: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3782696&tool=pmcentrez&rendertype=abstract.
de Vignemont, F., Singer, T., 2006. The empathic brain: how, when and why? Trends Cogn. Sci. 10, 435–441, Available at: http://www.ncbi.nlm.nih.gov/ubmed/16949331 (Accessed 29 February 2012).
Dodge, K.A., Coie, J.D., 1987. Social-information-processing factors in reactive and proactive aggression in children's peer groups. J. Pers. Soc. Psychol. 53, 1146–1158.
Dodge, K.A., Lochman, J., Harnish, J., Bates, J., Pettit, G., 1997. Reactive and proactive aggression in school children and psychiatrically impaired chronically assaultive youth. J. Abnorm. Psychol. 106, 37–51, Available at: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=ovftc&NEWS=N&AN=00004468-199702000-00004.
Dolan, M., Fullam, R., 2006. Face affect recognition deficits in personality-disordered offenders: association with psychopathy. Psychol. Med. 36, 1563–1569.
Dolivo, V., Taborsky, M., 2015. Norway rats reciprocate help according to the quality of help they received. Biol. Lett. 11, 20140959.
Evans, V.E., Braud, W.G., 1969. Avoidance of a distressed conspeclflc. Psychon. Sci., 166.
Ferrari, P.F., Rizzolatti, G., 2014. Mirror neuron research: the past and the future. Philos. Trans. R. Soc. Lond. B: Biol. Sci. 369, 20130169.
Fite, P.J., Stoppelbein, L., Greening, L., 2009. Proactive and reactive aggression in a child psychiatric inpatient population. J. Clin. Child Adolesc. Psychol. 38, 199–205, Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2664256/.
Frick, P.J., Ellis, M., 1999. Callous-unemotional traits and subtypes of conduct disorder. Clin. Child Fam. Psychol. Rev. 2, 149–168.
Frick, P.J., Brien, B.S.O., Wootton, J.M., Mcburnett, K., 1994. Psychopathy and conduct problems in children. J. Abnorm. Psychol. 103, 700–707.
Frith, C.D., Frith, U., 2012. Mechanisms of social cognition. Annu. Rev. Psychol. 63, 287–313.
Furuyama, T., Kobayasi, K.I., Riquimaroux, H., 2016. Role of vocal tract characteristics in individual discrimination by Japanese macaques (Macaca fuscata). Nat. Publ. Gr., 1–8, http://dx.doi.org/10.1038/srep32042.
Galef, B., Whiskin, E., 2008. Conformity in Norway rats? Anim. Behav. 75, 2035–2039, Available at: http://linkinghub.elsevier.com/retrieve/pii/S0003347208001000 (Accessed 21 July 2011).
Gallagher, S., 2008. Direct perception in the intersubjective context. Conscious. Cogn. 17, 535–543.
Gallese, V., Keysers, C., Rizzolatti, G., 2004. A unifying view of the basis of social cognition. Trends Cogn. Sci. 8, 396–403.
Gründemann, J., Lüthi, A., 2015. Ensemble coding in amygdala circuits for associative learning. Curr. Opin. Neurobiol. 35, 200–206.
Herbert, H., Aschoff, A., Ostwald, J., 1991. Topography of projections from the auditory cortex to the inferior colliculus in the rat. J. Comp. Neurol. 304, 103–122.
Hernandez-Lallement, J., van Wingerden, M., Marx, C., Srejic, M., Kalenscher, T., 2015. Rats prefer mutual rewards in a prosocial choice task. Front. Neurosci. 8, 1–9, Available at: http://www.frontiersin.org/Decision_Neuroscience/10.3389/fnins.2014.00443/abstract(Accessed January 16, 2015).
Hernandez-Lallement, J., van Wingerden, M., Kalenscher, T., 2016a. A social reinforcement learning hypothesis of mutual reward preferences in rats. Curr. Top. Behav. Neurosci.
Hernandez-Lallement, J., van Wingerden, M., Schäble, S., Kalenscher, T., 2016b. Basolateral amygdala lesions abolish mutual reward preferences in rats. Neurobiol. Learn Mem. 127, 1–9, Available at: http://linkinghub.elsevier.com/retrieve/pii/S1074742715002063.
Hurley, K.M., Herbert, H., Moga, M.M., Saper, C.B., 1991. Efferent projections of the infralimbic cortex of the rat. J. Comp. Neurol. 308, 249–276.
Isbell, C.L., Shelton, C.R., Kearns, M., Singh, S., Stone, P., Avenue, P., Park, F., 2000. A social reinforcement learning agent. Fifth International Conference on Autonomous Agents.
Ito, W., Erisir, A., Morozov, A., 2015. Observation of distressed conspecific as a model of emotional trauma generates silent synapses in the prefrontal-amygdala pathway and enhances fear learning, but ketamine abolishes those effects. Neuropsychopharmacology 40, 1–32, Available at: http://www.ncbi.nlm.nih.gov/ubmed/25865929.
Jabbi, M., Swart, M., Keysers, C., 2007. Empathy for positive and negative emotions in the gustatory cortex. Neuroimage 34, 1744–1753, Available at: http://linkinghub.elsevier.com/retrieve/ii/S1053811906010780.
Janak, P.H., Tye, K.M., 2015. From circuits to behaviour in the amygdala. Nature 517, 284–292.
Jarvis, E.D., et al., 2005. Avian brains and a new understanding of vertebrate brain evolution. Nat. Rev. Neurosci. 6, 151–159.
Jeon, D., Kim, S., Chetana, M., Jo, D., Ruley, H.E., Lin, S.-Y., Rabah, D., Kinet, J.-P., Shin, H.-S., 2010. Observational fear learning involves affective pain system and Cav1.2 Ca2+ channels in ACC. Nat. Neurosci. 13, 482–488.
Jones, A.P., Laurens, K.R., Herba, C.M., Barker, G.J., Viding, E., 2009. Amygdala hypoactivity to fearful faces in boys with conduct problems and callous-unemotional traits. Am. J. Psychiatry 166, 95–102.
Kalenscher, T., van Wingerden, M., 2011. Why we should use animals to study economic decision making – a perspective. Front. Neurosci. 5, 82, Available at: http://www.pubmedcentral.nih.gov/articlerender.

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fcgi?artid=3118901&tool=pmcentrez&rendertype=abstract (Accessed 21 July 2011).
Kashtelyan, V., Lichtenberg, N.T., Chen, M.L., Cheer, J.F., Roesch, M.R., 2014. Observation of reward delivery to a conspecific modulates dopamine release in ventral striatum. Curr. Biol. 24, 2564–2568.
Kavaliers, M., Choleris, E., Colwell, D.D., 2001. Learning from others to cope with biting flies: social learning of fear-induced conditioned analgesia and active avoidance. Behav. Neurosci. 115, 661–674.
Kempes, M., Matthys, W., De Vries, H., Van Engeland, H., 2005. Reactive and proactive aggression in children. A review of theory, findings and the relevance for child and adolescent psychiatry. Eur. Child Adolesc. Psychiatry 14, 11–19.
Kennedy, D.P., Gläscher, J., Tyszka, J.M., Adolphs, R., 2009. Personal space regulation by the human amygdala. Nat. Neurosci. 12, 1226–1227, http://dx.doi.org/10.1038/nn.2381.
Kerig, P.K., Stellwagen, K.K., 2010. Roles of callous-unemotional traits, narcissism, and machiavellianism in childhood aggression. J. Psychopathol. Behav. Assess. 32, 343–352.
Keum, S., Shin, H.-S., 2016. Rodent models for studying empathy. Neurobiol. Learn Mem., Available at: http://linkinghub.elsevier.com/retrieve/pii/S1074742716301198.
Keysers, C., Gazzola, V., 2016. A plea for cross-species social neuroscience. Curr. Top. Behav. Neurosci., 1–13.
Keysers, C., Wicker, B., Gazzola, V., Anton, J.-L., Fogassi, L., Gallese, V., 2004. A touching sight: SII/PV activation during the observation and experience of touch. Neuron 42, 335–346.
K.A, Kiehl, Smith, A.M., Hare, R.D., Mendrek, A., Forster, B.B., Brink, J., Liddle, P.F., 2001. Limbic abnormalities in affective processing by criminal psychopaths as revealed by functional magnetic resonance imaging. Biol. Psychiatry 50, 677–684.
Kim, E.J., Kim, E.S., Covey, E., Kim, J.J., 2010. Social transmission of fear in rats: The role of 22-kHz ultrasonic distress vocalization. PLoS One 5.
Knapska, E., Nikolaev, E., Boguszewski, P., Walasek, G., Blaszczyk, J., Kaczmarek, L., Werka, T., 2006. Between-subject transfer of emotional information evokes specific pattern of amygdala activation. Proc. Natl. Acad. Sci. U. S. A. 103, 3858–3862.
Knutson, B., Burgdorf, J., Panksepp, J., 1999. High-frequency ultrasonic vocalizations index conditioned pharmacological reward in rats. Physiol. Behav. 66, 639–643, Available at: http://www.ncbi.nlm.nih.gov/ubmed/10386908.
Krettek, J.E., Price, J.L., 1977. Projections from the amygdaloid complex to the cerebral cortex and thalamus in the rat and cat. J. Comp. Neurol. 172, 687–722.
Kuteykin-Teplyakov, K., Maldonado, R., 2014. Looking for prosocial genes: ITRAQ analysis of proteins involved in MDMA-induced sociability in mice. Eur. Neuropsychopharmacol. 24, 1773–1783, http://dx.doi.org/10.1016/j.euroneuro.2014.08.007.
Lamm, C., Decety, J., Singer, T., 2011. Meta-analytic evidence for common and distinct neural networks associated with directly experienced pain and empathy for pain. Neuroimage 54, 2492–2502, Available at: http://www.sciencedirect.com/science/article/ii/S1053811910013066.
Langford, D.J., Williams, A.C., 2014. The caring, sharing rat? Pain 155, 1183–1184, http://dx.doi.org/10.1016/j.pain.2014.03.026.
Langford, D.J., Crager, S.E., Shehzad, Z., Smith, S.B., Sotocinal, S.G., Levenstadt, J.S., Chanda, M.L., Levitin, D.J., Mogil, J.S., 2006. Social modulation of pain as evidence for empathy in mice. Science 312, 1967–1970, Available at: http://www.ncbi.nlm.nih.gov/ubmed/16809545 (Accessed 05 March 2013).
Latzman, R.D., Drislane, L.E., Hecht, L.K., Brislin, S.J., Patrick, C.J., Lilienfeld, S.O., Freeman, H.J., Schapiro, S.J., Hopkins, W.D., 2015. A chimpanzee (Pan troglodytes) model of triarchic psychopathy constructs: development and initial validation. Clin. Psychol. Sci., http://dx.doi.org/10.1177/2167702615568989.
LeDoux, J.E., Farb, C.R., 1991. Neurons of the acoustic thalamus that project to the amygdala contain glutamate. Neurosci. Lett. 134, 145–149.
Lockwood, P.L., 2016. The anatomy of empathy: vicarious experience and disorders of social cognition. Behav. Brain Res. 311, 255–266.
Lukas, M., de Jong, T.R., 2016. Conspecific interactions in adult laboratory rodents: friends or foes? Curr. Top. Behav. Neurosci. (May), 1–22.
Márquez, C., Rennie, S.M., Costa, D.F., Moita, M.A., 2015. Prosocial choice in rats depends on food-Seeking behavior displayed by recipients. Curr. Biol., 1–10, Available at: http://linkinghub.elsevier.com/retrieve/pii/S0960982215005928.
Marsch, A.A., Blair, R.J.R., 2008. Deficits in facial affect recognition among antisocial populations. Neurosci. Biobehav. Rev. 32, 454–465.
Marsh, A.A., Blair, R.J.R., 2008. Deficits in facial affect recognition among antisocial populations: a meta-analysis. Neurosci. Biobehav. Rev. 32, 454–465.
McDonald, A.J., Mascagni, F., 1996. Cortico-cortical and cortico-amygdaloid projections of the rat occipital cortex: a Phaseolus vulgaris leucoagglutinin study. Neuroscience 71, 37–54.
McDonald, A.J., 1998. Cortical pathway to the mammalian amygdala. Prog. Neurobiol. 55, 257–332.
McGann, M., De Jaegher, H., 2009. Self-other contingencies: enacting social perception. Phenomenol. Cogn. Sci. 8, 417–437.
Meffert, H., Gazzola, V., Den Boer, J.A., Bartels, A.A.J., Keysers, C., 2013. Reduced spontaneous but relatively normal deliberate vicarious representations in psychopathy. Brain 136, 2550–2562.
Michalska, K.J., Zeffiro, T.A., Decety, J., 2016. Brain response to viewing others being harmed in children with conduct disorder symptoms. J. Child. Psychol. Psychiatry Allied Discip. 57, 510–519.
Moffitt, T.E., 1993. The neuropsychology of conduct disorder. Dev. Psychopathol. 5, 135.
Mogil, J.S., 2012. The surprising empathic abilities of rodents. Trends Cogn. Sci. 16, 143–144, Available at: http://www.ncbi.nlm.nih.gov/ubmed/22206750 (Accessed 01 October 2013).
Morris, J.S., Frith, C.D., Perrett, D.I., Rowland, D., Yound, A.W., Calder, A.L., Dolan, R.J., 1996. A differential neural response in the human amygdala to fearful and happy facial expressions. Nature 383, 812–815.
Mosher, C.P., Zimmerman, P.E., Gothard, K.M., 2014. Neurons in the monkey amygdala detect eye contact during naturalistic social interactions. Curr. Biol. 24, 2459–2464, Available at: http://linkinghub.elsevier.com/retrieve/ii/S0960982214011270.
Moul, C., Killcross, S., Dadds, M.R., 2012. A model of differential amygdala activation in psychopathy. Psychol. Rev. 119, 789–806, http://dx.doi.org/10.1037/a0029342.
Muñoz, L.C., 2009. Callous-unemotional traits are related to combined deficits in recognizing afraid faces and body poses. J. Am. Acad. Child Adolesc. Psychiatry 48, 554–562.
Noonan, M.A.P., Sallet, J., Mars, R.B., Neubert, F.X., O'Reilly, J.X., Andersson, J.L., Mitchell, A.S., Bell, A.H., Miller, K.L., Rushworth, M.F.S., 2014. A neural circuit covarying with social hierarchy in macaques. PLoS Biol. 12.
Oberliessen, L., Hernandez-Lallement, J., Schäble, S., van Wingerden, M., Seinstra, M., Kalenscher, T., 2016. Inequity aversion in rats, Rattus norvegicus. Anim. Behav. 115, 157–166, Available at: http://linkinghub.elsevier.com/retrieve/ii/S0003347216000828.
Offord, D., Bennett, K.J., 1994. Conduct disorder: long-term outcomes and intervention effectiveness. J. Am. Acad. Child Adolesc. Psychiatry 33, 1069–1078, Available at: http://www.jaacap.com/article/S0890-8567(09)64110-1/abstract.
Ongür, D., Price, J.L., 2000. The organization of networks within the orbital and medial prefrontal cortex of rats, monkeys and humans. Cereb. Cortex 10, 206–219, Available at: http://www.ncbi.nlm.nih.gov/ubmed/10731217.
Panksepp, J.B., Lahvis, G.P., 2011. Rodent empathy and affective neuroscience. Neurosci. Biobehav. Rev. 35, 1864–1875, Available at: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3183383&tool=pmcentrez&rendertype=abstract (Accessed 26 September 2013).
Panksepp, J., Panksepp, J.B., 2013. Toward a cross-species understanding of empathy. Trends Neurosci. 36, 489–496, Available at: http://linkinghub.elsevier.com/retrieve/ii/S0166223613000830.
Parsana, A.J., Li, N., Brown, T.H., 2012a. Positive and negative ultrasonic social signals elicit opposing firing patterns in rat amygdala. Behav. Brain Res. 226, 77–86, http://dx.doi.org/10.1016/j.bbr.2011.08.040.
Parsana, A.J., Moran, E.E., Brown, T.H., 2012b. Rats learn to freeze to 22-kHz ultrasonic vocalizations through autoconditioning. Behav. Brain Res. 232, 395–399, http://dx.doi.org/10.1016/j.bbr.2012.03.031.
Pereira, A.G., Cruz, A., Lima, S.Q., Moita, M.A., 2012. Silence resulting from the cessation of movement signals danger. Curr. Biol. 22, R627–R628, Available at: http://www.ncbi.nlm.nih.gov/pubmed/22917506 (Accessed 01 October 2013).
Popik, P., Potasiewicz, A., Pluta, H., Zieniewicz, A., 2012. High-frequency ultrasonic vocalizations in rats in response to tickling: the effects of restraint stress. Behav. Brain Res. 234, 223–227, Available at: http://www.ncbi.nlm.nih.gov/ubmed/22766213 (Accessed 18 March 2013).
Quay, H.C., 1993. The psychobiology of undersocialized aggressive conduct disorder: a theoretical perspective. Dev. Psychopathol. 5, 165–180, Available at: http://www.journals.cambridge.org/abstract_S0954579400004326.
Reynolds, C.R., Kamphaus, R.W., 2013. Conduct disorder. DSM-5, 1–2.
Rice, G.E., Gainer, P., 1962. Altruism in the albino rat. J. Comp. Physiol. Psychol. 55, 123–125, Available at: http://www.ncbi.nlm.nih.gov/pubmed/14491896.
Ruff, C.C., Fehr, E., 2014. The neurobiology of rewards and values in social decision making. Nat. Rev. Neurosci. 15, 549–562, Available at: http://www.ncbi.nlm.nih.gov/ubmed/24986556 (Accessed 09 July 2014).
Rutte, C., Taborsky, M., 2007. Generalized reciprocity in rats. PLoS Biol. 5, e196, Available at: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1914408&tool=pmcentrez&rendertype=abstract.
Rutte, C., Taborsky, M., 2008. The influence of social experience on cooperative behaviour of rats (Rattus norvegicus): direct vs generalised reciprocity. Behav. Ecol. Sociobiol. 62, 499–505, http://dx.doi.org/10.1007/s00265-007-0474-3 (Accessed 05 July 2011).
Sallet, J., Mars, R.B., Noonan, M.P., Andersson, J.L., O'Reilly, J.X., Jbabdi, S., Croxson, P.L., Jenkinson, M., Miller, K.L., Rushworth, M.F.S., 2011. Social network size affects neural circuits in macaques. Science 334, 697–700, Available at: http://www.ncbi.nlm.nih.gov/pubmed/22053054 (Accessed 29 September 2013).
Sanders, J., Mayford, M., Jeste, D., 2013. Empathic fear responses in mice are triggered by recognition of a shared experience. PLoS One 8, 1–7.
Sato, N., Tan, L., Tate, K., Okada, M., 2015. Rats demonstrate helping behavior toward a soaked conspecific. Anim. Cogn., 1039–1047, http://dx.doi.org/10.1007/s10071-015-0872-2.
Scalia, F., Winans, S.S., 1975. The differential projections of the olfactory bulb and accessory olfactory bulb in mammals. J. Comp. Neurol. 161, 31–55.
Schoenbaum, G., Chiba, A.A., Gallagher, M., 2000. Changes in functional connectivity in orbitofrontal cortex and basolateral amygdala during learning and reversal training. J. Neurosci. 20, 5179–5189.
Schuster, R., 2002. Cooperative coordination as a social behavior. Hum. Nat. 13, 47–83.

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Seffer, D., Schwarting, R.K.W., Wöhr, M., 2014. Pro-social ultrasonic communication in rats: insights from playback studies. J. Neurosci. Methods, 1–9, Available at: http://www.ncbi.nlm.nih.gov/pubmed/24508146 (Accessed 03 April 2014).
Sharp, P., Villano, J., 2012. The Laboratory Rat (Press C, ed). Boca Raton.
Sharpe, M.J., Schoenbaum, G., 2016. Back to basics: making predictions in the orbitofrontal–amygdala circuit. Neurobiol. Learn Mem. 131, 201–206.
Silberberg, A., Allouch, C., Sandfort, S., Kearns, D., Karpel, H., Burton, S., 2014. Desire for social contact, not empathy, may explain rescue behavior in rats. Anim. Cogn. 17, 609–618, Available at: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2674118&tool=pmcentrez&rendertype=abstract (Accessed 13 March 2012).
Singer, T., Seymour, B., Doherty, J.O., Kaube, H., Dolan, R.J., Frith, C.D., 2004. Empathy for pain involves the affective but not sensory components of pain. Science 303, 1157–1162.
Sivaselvachandran, S., Acland, E.L., Abdallah, S., Martin, L.J., 2016. Behavioral and mechanistic insight into rodent empathy. Neurosci. Biobehav. Rev., 1–8, http://dx.doi.org/10.1016/j.neubiorev.2016.06.007.
Smith, A., 1759. Theory of Moral Sentiments, Cambridge.
Spezio, M.L., Huang, P.-Y.S., Castelli, F., Adolphs, R., 2007. Amygdala damage impairs eye contact during conversations with real people. J. Neurosci. 27, 3994–3997.
Sterzer, P., Stadler, C., Poustka, F., Kleinschmidt, A., 2007. A structural neural deficit in adolescents with conduct disorder and its association with lack of empathy. Neuroimage 37, 335–342, http://dx.doi.org/10.1016/j.neuroimage.2007.04.043.
Taylor, C.J., 1975. Study of altruism in rats in an appetitive situation. Psychol. Rep. 36, 571–574, http://dx.doi.org/10.2466/pr0.1975.36.2.571.
Vasconcelos, M., Hollis, K., Nowbahari, E., Kacelnik, A., 2012. Pro-sociality without empathy. Biol. Lett. 8, 910–912, Available at: http://www.ncbi.nlm.nih.gov/ubmed/22859561 (Accessed 02 March 2013).
Vaudano, E., Legg, C.R., Glickstein, M., 1991. Afferent and efferent connections of temporal association cortex in the rat: a horseradish peroxidase study. Eur. J. Neurosci. 3, 317–330, Available at: http://www.ncbi.nlm.nih.gov/ubmed/12106189.
Waller, B.M., Whitehouse, J., Micheletta, J., 2016. Macaques can predict social outcomes from facial expressions. Anim. Cogn. 19, 1031–1036.
Wang, Y., Fontanini, A., Katz, D.B., 2006. Temporary basolateral amygdala lesions disrupt acquisition of socially transmitted food preferences in rats. Learn. Mem. 13, 794–800.
Whishaw, I.Q., Kolb, B., 2004. The Behavior of the Laboratory Rat: A Handbook with Tests. Oxford University Press.
Wicker, B., Keysers, C., Plailly, J., Royet, J.P., Gallese, V., Rizzolatti, G., 2003. Both of us disgusted in My insula: the common neural basis of seeing and feeling disgust. Neuron 40, 655–664.
Willuhn, I., Tose, A., Wanat, M.J., Hart, A.S., Hollon, N.G., Phillips, P.E.M., Schwarting, R.K.W., Wöhr, M., 2014. Phasic dopamine release in the nucleus accumbens in response to pro-social 50ökHz ultrasonic vocalizations in rats. J. Neurosci. 34, 10616–10623, Available at: http://www.ncbi.nlm.nih.gov/pubmed/25100595 (Accessed 07 November 2014).
Wittchen, H., Jacobi, F., 2005. Size and burden of mental disorders in Europe – A critical review and appraisal of 27 studies. Eur. Neuropsychopharmacol. 15, 357–376.
Yang, Y., Raine, A., Narr, K.L., Colletti, P., Toga, A.W., 2009. Localization of deformations within the amygdala in individuals with psychopathy. Arch. Gen. Psychiatry 66, 986–994.
Yoder, K.J., Lahey, B.B., Decety, J., 2016. Callous traits in children with and without conduct problems predict reduced connectivity when viewing harm to others. Sci. Rep. 6, Article number: 20216, Available at: http://www.nature.com/articles/srep20216.

Please cite this article in press as: Hernandez-Lallement, J., et al., Towards an animal model of callousness. Neurosci. Biobehav. Rev. (2016), http://dx.doi.org/10.1016/j.neubiorev.2016.12.029