A Plea for Cross-species Social Neuroscience

Christian Keysers and Valeria Gazzola

Abstract Over the past two decades, the question of how our brain makes us sensitive to the state of conspecifics and how that affects our behaviour has undergone a profound change. Twenty years ago what would now be called social neuroscience was focused on the visual processing of facial expressions and body movements in temporal lobe structures of primates (Puce and Perrett 2003). With the discovery of mirror neurons, this changed rapidly towards the modern field of social neuroscience, in which high-level vision is but one of many focuses of interest. In this essay, we will argue that for the further progress of the field, the integration of animal neuroscience and human neuroscience is paramount. We will do so, by focusing on the field of embodied social cognition. We will first show how the combination of animal and human neuroscience was critical in how the discovery of mirror neurons placed the motor system on the map of social cognition. We will then argue why an integrated cross-species approach will be pivotal to our understanding of the neural basis of emotional empathy and its link to prosocial behaviour.

Keywords Empathy · fMRI · Single cell · Animal physiology · Neuroimaging · Emotional contagion · Mirror neuron

Contents

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1 The Importance of Animal Neuroscience for Our Understanding of Action Observation

The discovery of mirror neurons in monkeys (di Pellegrino et al. 1992; Gallese et al. 1996; Keysers et al. 2003; Kohler et al. 2002) was a game-changer for how neuroscientists conceived of social perception (Keysers 2009). That neurons in the motor system could contain highly reliable information about complex visual and auditory stimuli such as the sight and sound of someone performing an action was unorthodox. It forced the field to rethink how semantic meaning is associated with visual and auditory input, by introducing the possibility of embodied cognition.

Embodied cognition is a term that has been used with slightly different meanings, but here we will use it to refer to information that is not in an abstract format, or in that of the input modality (e.g. visual in the case of visual stimuli), but that involves representations that are specific to the body of the perceiver (Goldman and de Vignemont 2009). Core examples are motor formats, i.e. commands that normally aim to move the body, and somatosensory formats, i.e. normally triggered by afferent input from the somatosensory receptors.

What mirror neurons showed was that witnessing the actions of others triggered in addition to the well-known high-level visual representations of regions in the temporal lobe (Puce and Perrett 2003), also embodied information in premotor cortices, that would permit the observer to replicate the observed action. The observer mirrored the observed action in its own motor cortex, hence the name ‘mirror neuron’ (Keysers 2009).

The acceptance that social perception involved embodied cognition was a true paradigm shift that only occurred because single cell recordings demonstrating that the very same neurons are involved in performing an action and in perceiving it (via vision or sound) were *direct* evidence that neural substrates involved in motor planning are recruited during perception. Had the data permitted any alternative explanation, it is unlikely that this paradigm shift would have occurred. That one could classify what action the animal itself had done, or what action someone else had performed, from the activity of the same neuron with >90 % accuracy was important to determine just how reliable embodied information can be (Keysers et al. 2003). These data were available from invasive single cell recordings in monkeys. In addition, a key element of the animal literature on mirror neurons was the description of what mirror neurons responded to exactly (Gallese et al. 1996;

Keysers et al. 2003; Kohler et al. 2002; Umilta et al. 2001). By comparing the execution and observation of numerous actions, and by exploiting the very high signal to noise of single cell measurements, it became clear that individual neurons sometimes have very sharp preferences for a particular action (e.g. tearing apart) that is shared between action observation and execution in what is called strictly congruent mirror neurons (Gallese et al. 1996). However, neurons with different preferences (e.g. grasping) are often found in the exact same penetration, less than 100 μm away.

Human neuroscience was used rapidly to verify whether a similar system might exist in humans. Initially, positron emission tomography confirmed that regions in the frontal lobe associated with action execution were recruited during action observation in humans too (Rizzolatti et al. 1996). Later, more refined fMRI studies showed that the exact same voxels are involved in performing, hearing and seeing actions (Gazzola et al. 2006; Gazzola and Keysers 2009) and that pattern classifiers could discriminate which of two actions were performed across action execution and perception (Etzel et al. 2008). We can vouch from our own experience that sceptics consistently argue that finding that a voxel is involved in action observation and execution is not strong evidence for the involvement of mirror neurons (Gazzola and Keysers 2009). Some argue that a voxel contains so many neurons that it can be activated in both cases without any of the neurons being involved in both cases. Others argue that even if neurons are involved in both cases, it does not show that they encode action-specific information: action observation and execution both require attention and executive resources that can be the source of the common activation. An additional constraint of neuroimaging in this field is the limited ability to unravel what neurons actually represent in these brain regions. Neurons in the premotor cortex, as mentioned above, have exquisitely specific response profiles, responding for instance to precision but not whole hand prehension during both observation and execution (Gallese et al. 1996), which support classification accuracies above 90 % (Keysers et al. 2003) between different hand actions. However, neurons with different selectivity occur so close to one another that averaging signals over the volume of a typical fMRI voxel would lead to very unspecific signals. Indeed, pattern classification from fMRI BOLD signals drops to levels typically below 60 % even when hand and mouth actions are compared (Etzel et al. 2008), which is thus a gross underestimate of the selectivity of the actual neurons. Such unspecific signals make it difficult to unravel what information such processes could contribute to perception.

It is fair to say that social neuroscience would never have embraced embodied cognition if neuroimaging evidence of overlapping voxels during action observation and execution would have been the only source of information. The animal single cell data were absolutely instrumental in shaping our understanding of this new component of social perception. Neuroimaging on the other hand has also been important. The whole-brain field of view of typical fMRI studies is in stark contrast to the very focal field of view of single cell recordings that is typically confined to a very specific cortical area. While the original mirror neuron work was confined to the ventral premotor cortex (Gallese et al. 1996), neuroimaging naturally expanded

the search to the entire brain, with careful studies revealing that inferior parietal, somatosensory, dorsal premotor, supplementary motor and cerebellar cortices all consistently were activated both during the observation and execution of actions (Caspers et al. 2010; Gazzola and Keysers 2009; Keysers and Gazzola 2009). This has guided single cell recordings in animals and humans towards similar brain regions, and there is now evidence from single cell recordings for the existence of mirror neurons in most of these regions (Cisek and Kalaska 2004; Hihara et al. 2015; Rozzi et al. 2008; Mukamel et al. 2010).

In summary, the realization that the motor cortices are part of the network of brain regions involved in action observation has significantly reshaped social neuroscience by introducing embodied cognition into the mainstream. A combination of invasive animal physiology and non-invasive human neuroimaging has been key to the success of this endeavour.

2 The Discovery of Vicarious Emotional Activations and the Limits of Human Neuroscience

A decade after the discovery of mirror neurons in the motor domain, the time was right to explore whether the same basic principle, namely using embodied neural substrates involved in representing states of the self are also used to represent similar states in others, would also apply outside of the motor system (Gallese et al. 2004). In 2003 and 2004, two independent groups showed that experiencing an emotion such as disgust (Wicker et al. 2003) or pain (Singer et al. 2004) triggered activity in the anterior insula (aIns) and in the rostral cingulate cortex (rCC) that overlapped with the activity triggered while experiencing disgust and pain. Simply seeing someone else being touched on a body part also triggered activity in the secondary somatosensory cortex in a region overlapping with activity triggered by the experience of a similar touch (Keysers et al. 2004). Somehow, we vicariously activate our aIns, rCC and somatosensory cortices when we witness the emotions and sensations of others (Keysers and Gazzola 2006). These neuroimaging findings have since been replicated numerous times, with meta-analyses confirming how reliably these regions are recruited during both the experience and perception of emotional and tactile states (Keysers et al. 2010; Lamm et al. 2011).

Individual differences between people who report experiencing more or less empathy have been leveraged to explore the functional significance of these activations (Jabbi et al. 2007; Singer et al. 2004). This correlational approach has been expanded to explore individuals on the extreme of the empathic continuum. So for instance, psychopathic criminals recruit these regions less when witnessing the pain of others (Meffert et al. 2013). It has also been expanded to see whether people more willing to help have stronger activations in these regions (Hein et al. 2010). This has led many to propose that vicarious activations in these regions, the aIns and rCC in particular, are what causes us to share the emotions of others (Engen and Singer 2013). More or less implicit to this line of thinking is the notion that the

same neural substrate within the voxels common to observing and experiencing emotions and sensations is recruited in the two conditions. If it were different neurons triggered by the observation and experience of an emotion, the notion that we experience our own emotions in response to the emotions of others makes little sense.

Since 2003, hundreds of studies have investigated vicarious activations in the emotional domain using fMRI, and even just the initial 3 studies have attracted over 2500 citations. However, the core hypotheses of the initial studies, namely that vicarious activations cause us to share the emotions of others and that the same neurons are involved in the experience and observation of emotions, remain untested. This is because these experiments are conducted in humans, in which it is difficult to test either of them. The aIns and rCC are relatively deep structures. To test whether they cause us to share the emotions of others, one would need to modulate their activity and show that this would modulate our ability to share the emotions of others. This is difficult to do, because state-of-the-art methods for non-invasive brain manipulation in humans, including TMS or tDCS, are currently unable to modulate brain activity so deep without having larger effects on the cortices that are closer to the surface. Also, the assumption that the same neurons are active during the observation and experience of emotions in these regions cannot be systematically tested in humans. Although surgical procedures for the treatment of epilepsy offer occasional opportunities to record from single neurons in these regions in humans (Hutchison et al. 1999), they seldom offer the opportunity to carefully characterize the response pattern of neurons over multiple hours of testing, making it difficult to ascertain that neurons truly selectively represent a particular emotional experience (e.g. pain) during the observation and experience of an emotion. It is thus unlikely that human neuroscience will be able, any time soon, to test the hypotheses that seminal neuroimaging studies have helped generate.

3 Behavioural Evidence for Affect Sharing in Rodents

We therefore argue that it is essential that the field now starts to supplement the non-invasive human work with invasive animal neuroscience. Rodents seem a natural model to undertake that work. In this section, we will review behavioural evidence that rodents show affective responses to the distress of others. In the next section, we will review evidence that the neural substrates for pain experience and for affect sharing might be similar enough to humans to make them a powerful model.

In 1959, Church showed that a rat shows signs of distress when witnessing another receive shocks (Church 1959). In 1962, Rice and Gainer showed that a rat would work to help free another rat from an uncomfortable situation (Rice and Gainer 1962), and in 1969, Greene showed that most rats would forgo an easy reward if that meant delivering a shock to another rat (Greene 1969). This initial evidence that rodents find the pain of others aversive and show signs of a

motivation to avoid pain to others been supplemented by a second, more recent, series of studies. Langford et al. (2006) injected acetic acid into the abdomen of mice to induce abdominal writhing. Writhing was increased in the mice if they witnessed another suffering similar pain—as if they had shared the pain of the other. Knapska et al. (2010) have shown that rats will start licking rats that had previously been electroshocked, showing that they sense and care about the distress of other rats. Finally, several teams, including us, showed that rats and mice can show 'vicarious freezing' (Atsak et al. 2011; Kim et al. 2010; Jeon et al. 2010; Wohr and Schwarting 2008) in response to the distress of others. In our paradigm, two rats were separated only by a perforated Plexiglas divider. One of the rats was exposed to a series of moderate but startling electroshocks. The other, that either had or had not experienced electroshocks in the past, was made to witness this event through the divider. We found that shock-experienced, but not shock-naïve, rats freeze in response to the other's pain as if they had been shocked themselves, a phenomenon we call 'vicarious freezing' (Carrillo et al. 2015; Atsak et al. 2011). Playing back the sound of the interaction also caused freezing (only in shock-experienced listeners), but playing back the 22 kHz ultrasonic vocalizations alone did not, suggesting that the effect was not mediated by species-specific vocalizations alone but at least partially by a recognition of the situation. The silence caused by the freezing of the demonstrator appears to play an important role in this process (Pereira et al. 2012). Other teams have observed that the amount of 22 kHz vocalizations emitted by the demonstrators can predict the degree of vicarious freezing in the observers (Wohr and Schwarting 2008), a finding compatible with the fact that listening to 22 kHz vocalizations can trigger activity in limbic structures of the listener (Wohr and Schwarting 2010). This suggests that multiple channels of auditory communication can be at play during social fear transmission. Kim and colleagues (Kim et al. 2010) used a fear conditioning paradigm to trigger freezing in the demonstrator rat during the social exchange and arrived at similar conclusions: experienced but not naïve witnesses show vicarious freezing to the distress of a fellow rat. Finally, Jeon et al. (2010) conducted an experiment similar to ours in mice and also observed vicarious freezing in witness mice. However, they also varied how long the demonstrator and witness mice had been housed together previously and found that animals that had spent more time together before the experiment showed more vicarious freezing—an effect reminiscent of the stronger vicarious emotional activations in humans to the pain of in-group members (Avenanti et al. 2010; Hein et al. 2010; Martin et al. 2015; Xu et al. 2009).

Together, these independent rodent experiments converge to show two important findings. First, rats and mice evidence (through vicarious freezing) signs of distress to the distress of others, suggesting that they may provide a valuable animal model for empathy. Second, vicarious freezing is modulated by social factors (familiarity with the demonstrator) and is therefore potentially a valid model for similar factors in humans. It should be noted that in humans, different forms of reactions to another's distress have been distinguished (Preston and de Waal 2002). *Emotional contagion* occurs when the witness experiences an emotion similar to that of the demonstrator. *Empathy* occurs if the witness is additionally aware of the fact that

the vicarious emotional state is not his/her own, but a reflection of the demonstrators' state. *Sympathy*, finally, occurs when the witness no longer only experiences vicarious pain in response to the pain of the demonstrator, but transforms this into a motivation to help the other. It is generally assumed that emotional contagion is a prerequisite for empathy, which is in turn a prerequisite for sympathy. How far along this hierarchy of empathy rodents might be remains entirely unclear, but even if vicarious freezing were only a reflection of emotional contagion, understanding its neural basis would illuminate the neural basis of a constituent part of empathy and sympathy (Panksepp and Panksepp 2013).

An additional feature of social fear transmission in rodents is that it shows interesting individual variability associated with genetic background (Chen et al. 2009) and chemically induced disorders (Jung et al. 2013).

4 Anatomical Considerations Towards the Validity of a Rodent Model

For rodents to enable us to attain a better understanding of the neural basis of affect sharing, it is important to explore whether the neural basis of the behavioural signs of affect sharing is homologous to that in humans. As in humans, affect sharing has been linked to the vicarious activation of regions involved in emotional experiences, and we will start by exploring whether the neural basis of emotional experiences is similar across rodents and primates. We will do so in particular, for the regions involved in the experience of pain. We will then review the limited evidence for the role of these regions in affect sharing.

The central representation of pain in rodents is not identical to that in humans (Tracey 2008), but similar enough to be considered a valuable model (Mogil 2009). Like humans, their pain system is composed of a lateral and a medial pain system (Gauriau and Bernard 2002). In the lateral pain system, nociceptive information is sent via lateral nuclei of the thalamus (VPL, VPM, Po) to nociceptive neurons in SI and SII. In the medial pain system, nociceptive information travels through parabrachial and medial nuclei of the thalamus (MD in particular) to the rCC and the rostral agranular insula (Gauriau and Bernard 2002; Iwata et al. 2011). Stimulation of nociceptive fibres in the rats paw triggers activity in $\sim$30 % of neurons in the rCC and SI, with stronger stimulation triggering more spikes per neuron and activating more neurons in both structures (Zhang et al. 2011). fMRI and deoxyglucose mapping in rats have confirmed that nociceptive stimulation consistently triggers activation in SI, SII and rCC (Shih et al. 2008; Zhao et al. 2011; Porro et al. 1999), much as it does in human (Lanz et al. 2011). While the rCC is therefore very similar in rodents and humans, the similarity of the aIns is notable but potentially less profound. First, as in humans, the insula of rodents receives nociceptive information as revealed by anatomical (Gauriau and Bernard 2002), electrical (Ito 1998; Rodgers et al. 2008), fMRI (Shih et al. 2008) (but see Zhao

et al. 2011) and deoxyglucose mapping (Porro et al. 1999) data. However, it receives that input via a thalamic nucleus (PoT) differs from that in primates (VMpo). Second, the human insula has a primary pain representation in the posterior insula and a higher-level representation in the anterior insula, with the latter related to feelings (Craig 2009). This meta-representation may be lacking in rats (Craig 2009). Overall, the organization of the pain matrix in mice is less studied but generally considered similar to that in rats (Mogil 2009).

At present, relatively little is still known about which regions of the pain matrix in rodents show vicarious activation that could trigger vicarious freezing. However, there is increasing evidence that the rCC is involved—a region central to vicarious emotional for pain in humans as we have seen above. Chemical deactivation of the rCC reduces the social transmission of fear in mice (Jeon et al. 2010; Kim et al. 2012) and the electrical stimulation of this region increases social transmission of fear (Kim et al. 2012). Both of these effects are stronger in the right hemisphere (Kim et al. 2012). Also, oscillations in the theta band are increased in this region, while observers witness the distress of another (Jeon et al. 2010; Kim et al. 2012). Much as in humans, this finding does not show that the rCC contains single cells involved in both the experience and observation of pain, but suggests that the rodent rCC may be a good model of the human rCC in relation to empathy for pain.

In summary, rodents show behaviour compatible with vicarious emotions and possess a central pain representation resembling that of humans in many ways, and one of the regions involved in human vicarious emotions (rCCs) is vicariously activated in rodents; its deactivation reduces and its activation increases vicarious freezing.

5 Why We Should Use Rodents to Advance Our Understanding of Empathy

Human neuroscience has powerful methods to map what brain regions are associated with a particular task. This mapping enterprise has very successfully identified that the aIns and rCC are hot spots in the human brain when it comes to sharing the affect of others. Whether this activity causes us to share the affect of others, however, remains difficult to test. It also remains unclear what it is that activity in these brain regions represents (and hence could make us share) about the state of the self and of the other. Both regions are activated by a wide array of tasks, ranging from the experience of negative and positive emotions to a variety of other cognitive tasks (Yarkoni et al. 2011). This makes it impossible to determine with any level of certainty, what neurons in these regions really encode about emotions of the self and other. Do they represent individual emotions, such as disgust or pain, and do they represent emotions in more dimensional fashion (e.g. its level of arousal or valence). Or do they represent even more abstract properties such as salience or uncertainty? It is difficult to imagine how this question can be rigorously

addressed without systematically measuring the response of individual neurons over a wide range of emotions and visual stimuli.

What makes rodents a particularly powerful model to shed more light on the neural basis of empathy is the rapidly expanding pallet of techniques neuroscientists have at their disposal to address the very questions that are most difficult to address in humans. This involves both sophisticated ways to modulate and to measure brain activity at the neural level. In terms of modulation, neuroscientists have tools at their disposal that vary from relatively classic chemical deactivations using local anaesthetics such as lidocaine or GABA agonists such as muscimol that powerfully deactivate most neurons in a well-controlled volume (Martin 1991), to highly sophisticated genetically encoded methods, most notably optogenetics, that permit the silencing or stimulation of neurons in a time-resolved fashion (Bernstein and Boyden 2011). These methods have already shown that chemically deactivating the rCC in mice reduces and activating the rCC electrically increases signs of sharing the distress of others (Jeon et al. 2010; Kim et al. 2012), offering what might be argued to be the first powerful experimental demonstration of a link between vicarious rCC activation and affect sharing. More selective modulations of activity in specific cell types, in the aIns, and time-resolved modulations promise to provide valuable insights into this system in the near future.

Methods to measure brain activity in rodents have also made tremendous progress. With the development of silicon-based probes (Buzsaki et al. 2015) that track the activity of dozens of neurons at a time in freely moving animals over days, we have the potential to characterize neurons, while rodents undergo a large pallet of experiences, thereby providing us with the opportunity to characterize the code through which neurons encode emotional states with unprecedented precision. With the development of hybrid devices that combine silicon probe electrodes for recording with miniature LED to stimulate neurons that have photosensitive ion channels will make it possible to combine the identification of local neural codes with the selective activation of these codes to study their impact on the affective state of the animal and behaviour. The possibilities for brain activity recording have been further expanded using genetically encoded calcium indicators (Scanziani and Hausser 2009). This involves the expression of proteins that alter their fluorescence when neurons are active [e.g. GCaMP6 (Chen et al. 2013)], which can then be visualized using two-photon microscopy in vivo. Using such methods, scientists can monitor the activity of hundreds of neurons at a time, while rodents undergo behavioural paradigms. Most importantly, the method can be combined with the staining of different cell types in different colours to enable experimenters to identify which cell types are involved in particular tasks. For the case of mirror neurons for actions, only about 10 % of neurons in the premotor cortex have the ability to respond to the observation of the actions of others. To this day, we do not know what makes these 10 % of mirror neurons any different from the 90 % that do not have mirror properties. Methods available in rodents, such as calcium imaging, would enable us to tackle such questions for the very first time and bring our level of understanding of emotion sharing to an entirely new, cellular level.

6 Summary

Over the past decades, social neuroscience has made great advances. With regard to our understanding of how we perceive the actions of others, the discovery of mirror neurons, and the combination of animal and human neuroscience, has been seminal in revealing the presence of embodied cognition. Animal neuroscience contributed the proof of the overlap at single cell levels of actions of the self and others and a thorough understanding of what it is about actions that is represented in these neurons. Human neuroimaging has contributed a system-level understanding of the brain regions involved and has confirmed striking homologies between the macaque and human brain with regard to action processing. With regard to the neural basis of empathy, we are still in the beginning of our understanding. Human neuroscience has so far not been seconded by systematic animal neuroscience experiments. We have evidenced that regions involved in our own emotions are recruited while witnessing the emotions of others, and correlational evidence suggests a link between these vicarious activations and empathy. However, we still lack an understanding of the properties of neurons in these regions and the causal link between activity of these neurons and sharing the emotions of others. We argue that rodents show signs of emotional contagion and afford a powerful pallet of methods to measure and alter brain activity and that the neuroscience of empathy would now be well advised to combine human experiments with rodent experiments to bring our understanding of empathy to a cellular and causal level that will otherwise remain evasive.

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References

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

Avenanti A, Sirigu A, Aglioti SM (2010) Racial bias reduces empathic sensorimotor resonance with other-race pain. Curr Biol 20:1018–1022

Bernstein JG, Boyden ES (2011) Optogenetic tools for analyzing the neural circuits of behavior. Trends Cogn Sci 15:592–600

Buzsaki G, Stark E, Berenyi A, Khodagholy D, Kipke DR, Yoon E, Wise KD (2015) Tools for probing local circuits: high-density silicon probes combined with optogenetics. Neuron 86:92–105

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: e0136979

Caspers S, Zilles K, Laird AR, Eickhoff SB (2010) ALE meta-analysis of action observation and imitation in the human brain. Neuroimage 50:1148–1167

Chen Q, Panksepp JB, Lahvis GP (2009) Empathy is moderated by genetic background in mice. PLoS ONE 4:e4387

Chen TW, Wardill TJ, Sun Y, Pulver SR, Renninger SL, Baohan A, Schreiter ER, Kerr RA, Orger MB, Jayaraman V, Looger LL, Svoboda K, Kim DS (2013) Ultrasensitive fluorescent proteins for imaging neuronal activity. Nature 499:295–300

Church RM (1959) Emotional reactions of rats to the pain of others. J Comp Physiol Psychol 52:132–134

Cisek P, Kalaska JF (2004) Neural correlates of mental rehearsal in dorsal premotor cortex. Nature 431:993–996

Craig AD (2009) A rat is not a monkey is not a human: comment on Mogil (Nature Rev Neurosci 10:283–294 (2009)). Nat Rev Neurosci 10:466–466

di Pellegrino G, Fadiga L, Fogassi L, Gallese V, Rizzolatti G (1992) Understanding motor events: a neurophysiological study. Exp Brain Res 91:176–180

Engen HG, Singer T (2013) Empathy circuits. Curr Opin Neurobiol 23:275–282

Etzel JA, Gazzola V, Keysers C (2008) Testing simulation theory with cross-modal multivariate classification of fMRI data. PLoS ONE 3:e3690

Gallese V, Fadiga L, Fogassi L, Rizzolatti G (1996) Action recognition in the premotor cortex. Brain 119(Pt 2):593–609

Gallese V, Keysers C, Rizzolatti G (2004) A unifying view of the basis of social cognition. Trends Cogn Sci 8:396–403

Gauriau C, Bernard JF (2002) Pain pathways and parabrachial circuits in the rat. Exp Physiol 87:251–258

Gazzola V, Keysers C (2009) The observation and execution of actions share motor and somatosensory voxels in all tested subjects: single-subject analyses of unsmoothed fMRI data. Cereb Cortex 19:1239–1255

Gazzola V, Aziz-Zadeh L, Keysers C (2006) Empathy and the somatotopic auditory mirror system in humans. Curr Biol 16:1824–1829

Goldman A, de Vignemont F (2009) Is social cognition embodied? Trends Cogn Sci 13:154–159

Greene JT (1969) Altruistic behavior in albino rat. Psychon Sci 14:47

Hein G, Silani G, Preuschoff K, Batson CD, Singer T (2010) Neural responses to ingroup and outgroup members' suffering predict individual differences in costly helping. Neuron 68:149–160

Hihara S, Taoka M, Tanaka M, Iriki A (2015) Visual responsiveness of neurons in the secondary somatosensory area and its surrounding parietal operculum regions in awake macaque monkeys. Cereb Cortex 25:4535–4550

Hutchison WD, Davis KD, Lozano AM, Tasker RR, Dostrovsky JO (1999) Pain-related neurons in the human cingulate cortex. Nat Neurosci 2:403–405

Ito SI (1998) Possible representation of somatic pain in the rat insular visceral sensory cortex: a field potential study. Neurosci Lett 241:171–174

Iwata K, Miyachi S, Imanishi M, Tsuboi Y, Kitagawa J, Teramoto K, Hitomi S, Shinoda M, Kondo M, Takada M (2011) Ascending multisynaptic pathways from the trigeminal ganglion to the anterior cingulate cortex. Exp Neurol 227:69–78

Jabbi M, Swart M, Keysers C (2007) Empathy for positive and negative emotions in the gustatory cortex. Neuroimage 34:1744–1753

Jeon D, Kim S, Chetana M, Jo D, Ruley HE, Lin SY, Rabah D, Kinet JP, Shin HS (2010) Observational fear learning involves affective pain system and $Ca_v1.2$ Ca^{2+} channels in ACC. Nat Neurosci 13:482–488

Jung S, Seo JS, Kim BS, Lee D, Jung KH, Chu K, Lee SK, Jeon D (2013) Social deficits in the AY-9944 mouse model of atypical absence epilepsy. Behav Brain Res 236:23–29

Keysers C (2009) Mirror neurons. Curr Biol 19:R971–R973

Keysers C, Gazzola V (2006) Towards a unifying neural theory of social cognition. Prog Brain Res 156:379–401

Keysers C, Gazzola V (2009) Expanding the mirror: vicarious activity for actions, emotions, and sensations. Curr Opin Neurobiol 19:666–671

Keysers C, Kohler E, Umilta MA, Nanetti L, Fogassi L, Gallese V (2003) Audiovisual mirror neurons and action recognition. Exp Brain Res 153:628–636
Keysers C, Wicker B, Gazzola V, Anton JL, Fogassi L, Gallese V (2004) A touching sight: SII/PV activation during the observation and experience of touch. Neuron 42:335–346
Keysers C, Kaas JH, Gazzola V (2010) Somatosensation in social perception. Nat Rev Neurosci 11:417–428
Kim EJ, Kim ES, Covey E, Kim JJ (2010) Social transmission of fear in rats: the role of 22-kHz ultrasonic distress vocalization. PLoS ONE 5:e15077
Kim S, Matyas F, Lee S, Acsady L, Shin HS (2012) Lateralization of observational fear learning at the cortical but not thalamic level in mice. Proc Natl Acad Sci USA 109:15497–15501
Knapska E, Mikosz M, Werka T, Maren S (2010) Social modulation of learning in rats. Learn Mem 17:35–42
Kohler E, Keysers C, Umilta MA, Fogassi L, Gallese V, Rizzolatti G (2002) Hearing sounds, understanding actions: action representation in mirror neurons. Science 297:846–848
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
Langford DJ, Crager SE, Shehzad Z, Smith SB, Sotocinal SG, Levenstadt JS, Chanda ML, Levitin DJ, Mogil JS (2006) Social modulation of pain as evidence for empathy in mice. Science 312:1967–1970
Lanz S, Seifert F, Maihofner C (2011) Brain activity associated with pain, hyperalgesia and allodynia: an ALE meta-analysis. J Neural Transm 118:1139–1154
Martin JH (1991) Autoradiographic estimation of the extent of reversible inactivation produced by microinjection of lidocaine and muscimol in the rat. Neurosci Lett 127:160–164
Martin LJ, Hathaway G, Isbester K, Mirali S, Acland EL, Niederstrasser N, Slepian PM, Trost Z, Bartz JA, Sapolsky RM, Sternberg WF, Levitin DJ, Mogil JS (2015) Reducing social stress elicits emotional contagion of pain in mouse and human strangers. Curr Biol 25:326–332
Meffert H, Gazzola V, den Boer JA, Bartels AA, Keysers C (2013) Reduced spontaneous but relatively normal deliberate vicarious representations in psychopathy. Brain 136:2550–2562
Mogil JS (2009) Animal models of pain: progress and challenges. Nat Rev Neurosci 10:283–294
Mukamel R, Ekstrom AD, Kaplan J, Iacoboni M, Fried I (2010) Single-neuron responses in humans during execution and observation of actions. Curr Biol 20:750–756
Panksepp J, Panksepp JB (2013) Toward a cross-species understanding of empathy. Trends Neurosci 36:489–496
Pereira AG, Cruz A, Lima SQ, Moita MA (2012) Silence resulting from the cessation of movement signals danger. Curr Biol 22:R627–R628
Porro CA, Cavazzuti M, Baraldi P, Giuliani D, Panerai AE, Corazza R (1999) CNS pattern of metabolic activity during tonic pain: evidence for modulation by beta-endorphin. Eur J Neurosci 11:874–888
Preston SD, De Waal FB (2002) Empathy: its ultimate and proximate bases. Behav Brain Sci 25:1–20; discussion 20–71
Puce A, Perrett D (2003) Electrophysiology and brain imaging of biological motion. Philos Trans R Soc Lond B Biol Sci 358:435–445
Rice GE, Gainer P (1962) "Altruism" in the albino rat. J Comp Physiol Psychol 55:123–125
Rizzolatti G, Fadiga L, Matelli M, Bettinardi V, Paulesu E, Perani D, Fazio F (1996) Localization of grasp representations in humans by PET: 1. Observation versus execution. Exp Brain Res 111:246–252
Rodgers KM, Benison AM, Klein A, Barth DS (2008) Auditory, somatosensory, and multisensory insular cortex in the rat. Cereb Cortex 18:2941–2951
Rozzi S, Ferrari PF, Bonini L, Rizzolatti G, Fogassi L (2008) Functional organization of inferior parietal lobule convexity in the macaque monkey: electrophysiological characterization of motor, sensory and mirror responses and their correlation with cytoarchitectonic areas. Eur J Neurosci 28:1569–1588
Scanziani M, Hausser M (2009) Electrophysiology in the age of light. Nature 461:930–939

Shih YY, Chen YY, Chen CC, Chen JC, Chang C, Jaw FS (2008) Whole-brain functional magnetic resonance imaging mapping of acute nociceptive responses induced by formalin in rats using atlas registration-based event-related analysis. J Neurosci Res 86:1801–1811

Singer T, Seymour B, O'Doherty J, Kaube H, Dolan RJ, Frith CD (2004) Empathy for pain involves the affective but not sensory components of pain. Science 303:1157–1162

Tracey I (2008) Imaging pain. Br J Anaesth 101:32–39

Umilta MA, Kohler E, Gallese V, Fogassi L, Fadiga L, Keysers C, Rizzolatti G (2001) I know what you are doing. A neurophysiological study. Neuron 31:155–165

Wicker B, Keysers C, Plailly J, Royet JP, 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

Wohr M, Schwarting RKW (2008) Ultrasonic calling during fear conditioning in the rat: no evidence for an audience effect. Anim Behav 76:749–760

Wohr M, Schwarting RKW (2010) Activation of limbic system structures by replay of ultrasonic vocalization in rats. In: Brudzynski SM (ed) Handbook of Mammalian vocalization. An integrative neuroscience approach. Elsevier, Amsterdam

Xu X, Zuo X, Wang X, Han S (2009) Do you feel my pain? Racial group membership modulates empathic neural responses. J Neurosci 29:8525–8529

Yarkoni T, Poldrack RA, Nichols TE, van Essen DC, Wager TD (2011) Large-scale automated synthesis of human functional neuroimaging data. Nat Methods 8:665–670

Zhang Y, Wang N, Wang JY, Chang JY, Woodward DJ, Luo F (2011) Ensemble encoding of nociceptive stimulus intensity in the rat medial and lateral pain systems. Mol Pain 7:64

Zhao F, Welsh D, Williams M, Coimbra A, Urban MO, Hargreaves R, Evelhoch J, Williams DS (2011) fMRI of pain processing in the brain: a within-animal comparative study of BOLD vs. CBV and noxious electrical vs. noxious mechanical stimulation in rat. Neuroimage