The function of the medial prefrontal cortex in emotions and empathy

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Review

Several approaches divide empathy into emotional and cognitive subparts. The emotional reactions are strongly related to the mirror neuron system and interact with cognitive processes as the theory of mind. The aim of this review is to investigate the relationship between empathy and emotions. For this reason the review focuses on the medial prefrontal cortex (mPFC), because it is involved in empathy, emotion regulation, and self-conscious emotions. Overall, it can be concluded that mPFC distinguishes between self-generated emotions and empathy-generated emotions based on a self-other distinction. These findings suggest a shared network of empathy, emotion regulation and self-conscious emotions in cortical regions.

Keywords: medial prefrontal cortex; empathy; emotion regulation; self-other distinction; theory of mind

INTRODUCTION

Social affective cognitive neuroscience is a relatively new branch of neuroscience with growing interest to the public. It focuses on the role of emotions in a social context. However, brain functions in social situations are also influenced by cognitive processes. It remains to be specified how these cognitive processes are connected to emotional reactions during social events. Concerning empathy, several theories suggest a two stream model divided into emotional and cognitive routes (de Waal, 2008; Rizzolatti & Sinigaglia, 2008; Decety, 2011). During emotional empathy, the emotion of another person is simulated automatically in the observer by activating limbic structures responsible for the given emotion. Considering that emotional
empathy and emotions recruit the same macro-anatomical regions it is an ongoing
discussion whether these processes share neural populations or even single neurons
(Decety, 2011; Rizzolatti & Sinigaglia, 2008; Csibra, 2007). In general, single neurons
which are similarly active in observing and performing an action are known as
mirror neurons. This creates the possibility of understanding the movements of
others automatically because the observed action directly activates the equivalent
motor response in the observer.

Although it is well documented that mirror neurons exist for motor behavior
(Rizzolatti & Sinigaglia, 2008) it remains to be specified in how far mirror neurons
contribute to the understanding of emotions in empathy.

Nevertheless, empathy is not a pure mirroring mechanism. For example,
if two persons collaborate in a card game and a frowning face is presented, an
empathic reaction will be evoked, signaled by a medial frontal negativity (MFN). By
contrast, if the two persons have a competing relation, the same facial expression
evokes a much stronger MFN, demonstrating a different evaluation of the affective
state (Yamada, Lamm, & Decety, 2011). This example illustrates how cognitive
processes change automatic reactions to other peoples’ emotions. Still, it remains to
be analyzed which cognitive processes are the basis of these phenomena.

Regarding cognitive processes in empathy, the main theories have focused
on the interaction between the Theory of Mind (TOM), perspective taking and
emotional empathy (de Waal, 2008; Decety, 2011). Nevertheless, empathy is not the
only mechanism in which emotions and cognition interact. Other processes such
as emotion regulation or self-conscious emotions also depend on emotional and
cognitive information. So far, there exists no coherent overview on how empathy is
related to other cognitive-emotional processes.

To extend the existing theories, the current review will examine cognition-
emotion interactions in empathy, self-conscious emotions and emotion regulation.
Furthermore, it will discuss the possibility of an emotional mirror neuron system
(MNS) and its connection to cognition. To restrict the amount of information this
review will focus on one region of interest, namely the medial prefrontal cortex
(mPFC) as it contributes to facial perception (Mattavelli, Cattaneo, & Papagno,
2011), emotion regulation (Kim & Hamann, 2007), empathy and the TOM (Decety
& Jackson, 2004; Keysers & Gazzola, 2007, Völlm et al., 2006; Mitchell, Banaji, &
Macrae, 2005).

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Affective and cognitive information are strongly interconnected, especially in
empathy. Empathic processes use information of emotional states, as well as
cognitive information as the TOM (Decety, 2011). Considering their similar functions
and their interdependence it seems likely that emotion and TOM processing share
functional regions which will be described in this review.
The mPFC controls basic emotions

Although it has been repeatedly shown that the mPFC seems to play a role in higher cognitive functions as the TOM (see for example Fletcher et al., 1995; Frith & Frith, 1999; Castelli, Happe, Frith, & Frith, 2000; Völlm et al, 2006) and response selection when several choices are possible (Rushworth, 2008), it is also strongly involved in controlling basic emotional reactions.

Previous animal research suggested that the mPFC is functionally connected to the limbic system (Diorio, Viau, and Meaney, 1993; Milad, Vidal-Gonzalez & Quirk, 2004). This was confirmed for humans by a study on fear regulation using fMRi (Ochsner, Brunge, Graff & Gabrieli, 2002). In this experiment, aversive pictures were presented while subjects should increase, maintain or decrease their emotional reaction to the pictures. To modulate their emotional reaction, subjects reappraised the emotional relevance of the stimulus. As reappraisal requires attention, a control condition was included in which subjects attended to the stimulus without altering their emotional reaction. Strong aversive pictures showed an increase in amygdala and insula activation. Amygdala activation was significantly higher during the control condition compared to reappraisal. Interestingly, the dorsal mPFC was the most active region for high emotional pictures using a reappraisal > attention contrast. Similarly, a study by Zotev at al. (2011) revealed functional connectivity between the mPFC and the amygdala. Subjects had to decrease their amygdala activation by retrieving positive autobiographical memories while receiving real-time fMRI biofeedback of their amygdala. Post-processing showed a negative correlation between amygdala and mPFC activity which became stronger over training trials.

As the mPFC is important for emotion regulation it may also have a function in regulating emotional empathy which also recruits limbic areas. This assumption is supported by an fMRi experiment of Peelen, Atkinson, and Vuilleumier (2010) which demonstrated abstract emotional processing in the mPFC in response to social stimuli. They observed brain activity in response to the perception of basic emotions across different modalities, including face movements, body movements and vocal intonations. Emotional categories included anger, disgust, fear, happiness and sadness and subjects rated the emotional intensity of each stimulus. Multivoxel pattern analysis revealed a differential activation of voxels in the mPFC between emotional categories. However, there was no difference between modalities. The perceived intensity of emotional stimuli was also not correlated to mPFC activation. Peelens’ (2010) experiment reveals important insight into the functional properties of the mPFC, namely that the mPFC is also active in perceiving other people’s emotions, based on a cognitive level as its activation is not influenced by the modality or emotional intensity.

The mPFC in self-conscious emotions

The emotional content of primary emotions is mainly focused on the own mental state and does not require an understanding of others or the self (Lewis & Haviland-Jones, 2000). During ontogeny, children have to develop a concept of the self to reach the next level of emotional development. Once achieved, the self-conscious
emotions develop, which are empathy, envy, embarrassment, pride, shame and guilt (see for example Slater & Lewis, 2002). Additionally to empathy, the mPFC seems to play a role in many of these emotions. In an fMRI study of Takahashi, Yahata, Koeda, Matsuda, and Asai (2004) subjects were instructed to read sentences with neutral, guilty or embarrassing content. The mPFC showed significantly higher activation in the guilt and embarrassment conditions compared to neutral sentences.

However, in a following study of Takahashi and colleagues subjects had to read sentences with joy or pride evoking contents (Takahashi, Matsuura, Koeda, Yahata, & Suhara, 2008). In contrast to the expectations, no activation of the mPFC was observed in both conditions. Concerning the joy condition it is reasonable that no mPFC activation was found because no social cognition, empathy or emotion regulation was required in this task and joy is no self-conscious emotion.

Contrasting to Takahashi et al.’s (2008) results on pride, an fMRI study by Zahn et al. (2009) found mPFC activation in response to pride by using a more pronounced paradigm. In this study, subjects viewed sentences containing both the subject’s name and their best friend’s name. The sentences described either a behavior of the subject towards the friend (self-agency) or vice versa (other-agency). During scanning subjects rated sentences on how pleasant the depicted events were. After this, subjects labeled each sentence according to four possibilities: Self-agency in accordance with social values, other-agency in accordance with social values, self-agency counter to social values and other-agency counter to social values. Pride was defined as self-agency in accordance with social values and guilt as self-agency counter social values. The conditions used for analysis were therefore individual for each subject, depending on the subjects’ moral sentiments. Thereby, it was controlled for interindividual differences in moral evaluation of the situations. Results showed significant activation of the ventromedial PFC in pride vs. fixation and guilt vs. fixation. The disagreement between Takahashi’s (2008) and Zahn’s (2009) study may be caused by the fact that Takashi and colleagues predefined which sentences stimulate pride. This definition may deviate from the subject’s own evaluation of the stimulus.

The mPFC and cognitive control of affective and empathic reactions

This section will describe the relationship between empathy and emotions concerning the function of the mPFC. The similarities of empathy-regulation and emotion-regulation will be related to the cognitive processes which are responsible for coordinating both.

The relationship between mPFC functioning in empathy and emotions

To investigate the role of the mPFC in empathy it seems valuable to compare emotion processing to empathy because the mPFC shows the following functions in both processes. First, the mPFC is a central structure in a network responsible for combining affective and cognitive information during emotions and empathy (Keysers & Gazzola, 2007; Decety, 2011; Kim & Hamann, 2007). Second, the mPFC is strongly connected to the emotional regions which are not only involved in affect production but also in empathy such as the amygdala and the insula (Milad et al.,
2004; Chiba et al., 2001; Kim & Hamann, 2007; Preston & de Waal, 2002). Thirdly, the mPFC is directly involved in the processing of facial expressions (e.g. Mattavelli et al., 2011) and the TOM (Völlm et al., 2006) which is important for empathy and self-conscious emotions. Fourthly, several independent approaches to empathy suggest a controlling function of higher cognitive regions including the mPFC on emotion sharing in empathy (Preston & de Waal, 2002; Decety, 2011, Rizzolatti & Sinigaglia 2008). Similarly, during emotion regulation the mPFC is responsible for controlling emotional reactions (Ochsner et al., 2002; Zotev et al, 2010; Kim & Hamann, 2007; Decety & Jackson, 2004). Fifth, during social fear learning in rats a combination of emotional-motivational and empathic information produces a shared mPFC activation (Olsson & Phelps, 2007).

**Differentiating between empathy and emotions: The self-other distinction**

Although empathy and emotions share several functional similarities they remain distinct processes. The distinction between empathy and emotions is of special importance for emotional empathy in which the emotional state of another person is simulated in the observer (de Waal, 2008). The question arises why this simulation is not confused with own emotions as in both processes the same regions are activated (see for example Singer et al., 2004). This question was addressed in a theoretical approach on empathy by Decety (2011) and Decety and Jackson (2004). Decety proposes three main mechanisms as bases for empathy, namely self regulation, emotion understanding and affective arousal/sharing of emotions. In this model, cognitive understanding of emotions includes perspective taking and TOM processes and is strongly related to the mPFC. Affective arousal describes automatic affective reactions to simple emotional stimuli and it is mainly performed by the limbic system. Sharing of these automatic reactions describes the taking over of another person’s emotion comparable to a mirroring mechanism. During self regulation the emotional reactions are regulated by cognitive processes in the mPFC to fit empathic response to the social context (Decety, 2011). However, it remains to be investigated which cognitive processes are involved in self regulation during empathy. An important cognitive mechanism in this context is the distinction between the self and others because it ensures that empathic emotions are not confused with own emotions (Decety and Jackson, 2004).

Interestingly, recent studies have suggested that the mPFC is important in distinguishing between the own mental state and the mental state of others. For example, in an fMRI experiment by Ochsner et al. (2004) subjects had to evaluate social-emotional pictures on three aspects. First, they had to judge their own emotional reaction to the picture. Second, they had to evaluate the emotional state of the central person of the picture. Third, they had to indicate whether the picture was taken inside or outside as baseline measurement. The results showed that the first and the second conditions activated the mPFC compared to the baseline. In condition one, sub-regions of the mPFC and the left temporal cortex were active, compared to condition two. In contrast, the left lateral prefrontal cortex (including Broca’s area), the medial frontal gyrus and the medial occipital cortex were activated in condition two. These findings suggest that the cognitive representations of the own and someone else’s emotional state rely on two distinct networks and that the
mPFC contributes to both. However, it remains unclear what the exact function of the mPFC is in this context (Ochsner et al., 2004).

**Connections between the mPFC and the affective MNS**

Interpreting Ochsner et al.’s (2004) findings with Decety and Jackson’s (2004) approach, the mPFC activation would discriminate between emotions and empathic reactions based on the self-other distinction. By this, the mPFC would influence the activation of emotional core regions involved in empathy and emotions.

However, not only macro-anatomical structures but even the same neurons may be active during emotions and empathy. These neurons are defined as affective mirror neurons. Potentially, affective mirror neurons could be found in every region that is active in empathy and emotions. It remains to be investigated whether affective mirror neurons exist and how the mPFC is connected to them.

This topic was addressed by an fMRI study by Schulte-Ruther and colleagues (2007) which indicates that the mirror neuron system (MNS) is related to the self-other distinction in the mPFC. In this study, subjects performed two different tasks with faces (either directed towards the observer or adverted by 45⁰) expressing anger, fear, sadness, disgust, happiness or no expression. In the other-task subjects indicated the emotional state of the person. In the self-task subjects indicated their own emotional reaction to the facial expression. An additional high level baseline condition included a gender and age decision task of neutral faces. Before scanning general empathy scores of the subjects were assessed by using the Balanced Emotional Empathy Scale (BEES) and the Empathic Concern Scale (ECS). There was no difference in activation across face emotions and the authors concluded that their paradigm only tested a general mechanism for face perception, not specific enough to activate different emotional representations. The results also showed that the left lateral orbito-frontal cortex, the mPFC, bilateral inferior frontal cortices, superior temporal sulci, temporal poles, and the right cerebellum were involved in both the “self” and the “other” task compared to baseline. The “self” compared to the “other” task differentially activated the mPFC (see also Heatherton et al., 2006). Significant activation differences between the self vs. other task were also found in the inferior frontal gyrus (see also Ochsner et al., 2004). Remarkably, the iFG activity correlated with empathy scores. Importantly related to these findings, Kilner and colleagues found evidence for motor mirror neurons in the inferior frontal gyrus (Kilner, Neal, Weiskopf, Friston, & Frith 2009). Taken together these studies reveal functional connectivity during empathy between the mPFC and regions related to the MNS based on the self-other distinction.

Furthermore, the activation of the mPFC in TOM tasks (Völlm et al., 2006) and its functional connectivity to other regions associated with the TOM (especially the STS and the temporal parietal junction) suggests a contribution of the self-other distinctions to the TOM (Saxe & Kanwisher, 2003; Mitchell et al., 2005; Schulte-Rüther et al., 2007). Therefore it seems plausible that the TOM influences the MNS based on the self-other distinction (Schulte-Rüther et al., 2007). Other examples for connections between MNS related regions and the mPFC are reflected by projections from the mPFC to the insula and the anterior cingulate cortex (Chiba et al., 2001). Remarkably, Hutchison, Davis, Lozano, Tasker, and Dostrovsky (1999)
found evidence for affective mirror neurons in the human ACC using single cell recording. During surgery in epileptic patients they delivered pain stimuli to the patients. A class of neurons was selective for pinprick stimuli and responded when the patient received the stimulus and also when they viewed the experimenter receiving the stimulus. Furthermore, evidence for mirror neuron activity in the insula is based on fMRi studies by Wicker et al. (2003) and Singer et al. (2004).

**Self-other distinction based regulation of emotions and empathy**

To summarize the findings presented in this paper, the author proposes the following model (see Figure 1). Most fundamentally, the mPFC is involved in controlling emotional reactions (Davidson, Putnam, & Larson, 2000; Diorio et al. 1993) which are produced in emotional core regions such as the amygdala, insula and the cingulate cortex (Olsson & Phelps, 2007). Similarly, the mPFC regulates emotional empathy and possibly the affective MNS (Hutchison et al., 1999; Singer et al., 2004) based on the self-other distinction (Decety, 2011). The mPFC controls affective and empathic responses by distinguishing between the self and others. In accordance with this, various theories have suggested that the self-other distinction controls affect processing by signalling whether an emotional response is internally or externally generated (i.e. the self-other distinction reflects whether the current emotional reaction is produced by empathy or whether it is an own emotional reaction) (Schulte-Rüther et al., 2007; Keysers & Gazzola, 2007; Decety & Jackson, 2004).

The main function of the mPFC in the TOM is to compare self and other related information (Mitchell et al., 2005; Schulte-Rüther et al., 2007; Keysers & Gazzola, 2007). Evaluating the self in relation to others is crucial in self-conscious emotions and depends on the TOM (Takahashi et al., 2004; Takahashi et al., 2008). By evaluating the self in relation to others the mPFC activates emotional core regions such as the amygdala and the cingulate cortex during self-conscious emotions (Ruby & Decety, 2003). The self-other distinction is therefore a crucial functional connection between cognitive and emotional information in empathy and emotions. This is in accordance with de Waals (2008) evolutionary approach to empathy, which states that the self-other distinction characterizes social cognition but also influences emotional empathy.

![Figure 1](image-url)
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CONCLUSION

Two distinct neural circuits form the neural basis of empathy (de Waal, 2008). The first pathway is used for fast reactions to social-emotional stimuli and contains the medial prefrontal cortex and basic emotional structures such as the amygdala and the insula. The second pathway contains prefrontal (including the medial prefrontal cortex) and cingulate cortex regions. The cortical pathway controls the automatic reactions of the first pathway based on cognitive processes (Olsson & Phelps, 2007). The mPFC is embodied in both pathways, suggesting that it is an important structure for connecting emotions and cognition.

In this review the relationship between affective and cognitive information processing in the mPFC was analyzed. Cognitive processes in the mPFC seem to be fundamental for making self-other distinctions (Mitchell et al., 2005). Distinguishing between the self and others is crucial in the TOM, empathy and perspective taking (Mitchell et al., 2005; de Waal, 2008). It is further suggested, that the self-other distinction is crucial for controlling automatic subparts of empathy (Keysers & Gazzola, 2007). More precisely, recent studies suggest that the mPFC may control parts of the affective mirror neuron system (e.g. Schulte-Rüther et al., 2007). This seems necessary, because the affective response has to differ if an emotional reaction is one’s own emotion compared to a simulation based on mirror neuron activity (Decety & Jackson, 2004). Besides reactions to emotions of others, the mPFC also is active in regulating one’s own emotions and basic affective responses of sadness, disgust, fear and happiness (Milad et al., 2004; Kim & Hamann, 2007). Additionally, the mPFC and connected regions (especially the STS) are involved in self-conscious emotions by evaluating the self in relation to others based on the TOM (Takahashi et al., 2004; Takahashi et al., 2008). Summarizing, the presented studies suggest a similar function of the mPFC and related subcortical regions in empathy/TOM and in emotions.

To verify the implementations of these conclusions further, mPFC activation should be compared between empathy/TOM and emotion regulation tasks. The influence of the mPFC on the human mirror neuron system should furthermore be observed in more detail, as there is much debate on the function of mirror neurons in empathy.

In general, there is still much need for further research and finer theoretical differentiations. Firstly, the mPFC can be subdivided in several functional subparts. Differences between ventral and dorsal sections of the mPFC seem crucial (Decety, 2011) but also other differentiations should be taken into account. Secondly, the cognitive level on which the mPFC operates remains undefined. For example a meta-analysis by Wager, Jonides, and Reading (2004) demonstrated the activation of the mPFC in different task-switching studies. Wager et al.’s meta-analysis compared task switching paradigms that used different types of task switching (e.g. switching attention between the shape vs. colour of an object or switching between two earlier learned rules which both applied to one object). mPFC activation was found in nearly all task switching types. Thus, the findings of Wager et al. suggest that the mPFC contributes to the switching between abstract mental sets in general. However, it remains to be specified how these content independent processes are...
related to emotion processing.

Thirdly, the studies presented in this review mainly focus on the mPFC. Although the mPFC seems to be the crucial structure in this context, probably many other regions are involved. As the STS is strongly connected to the mPFC and involved in the TOM and self-conscious emotions it could be another structure of interest (Takahashi et al., 2004). Furthermore, the iFG remains a region of special interest as it is related to the MNS (Kilner et al., 2009) but also active during self-conscious-emotions (Simon-Tomas et al., 2011).

Fourthly, it remains unclear to what extent empathy is based on affective-mirroring systems or motor-mirroring systems. Therefore, the research on the human mirror neuron system should be interpreted more carefully. For example, many studies claim to demonstrate mirror neurons but only find a common activation of one region. However, a common activation of a region does not imply that the same neurons are active although several studies interpret it that way (Schulter-Rüther, 2007). This is mainly due to the fact that fMRI lacks the spatial resolution to investigate mirror neurons directly. As single cell recording can only rarely be used in humans, inferences on human mirror neurons are indirect by using TMS, fMRI with adaption paradigms (Kilner et al., 2009) or multivariate pattern analysis (Schulte-Rüther et al., 2007) which is in state to reveal sub-voxel activation (Mur, Bandettini & Kriegeskorte, 2009). Remarkably, the study mentioned by Hutchison demonstrated affective mirroring activity by using single cell recording in humans (Hutchison et al., 1999). It also has to be mentioned that the concept of mirror neurons is not necessary for self-other distinction based regulation of empathy as the distinction may control different neural populations within a functional area. Furthermore, it remains to be analyzed in how far single neuron activity is informative to investigate complex social processes as they probably recruit a huge amount of distributed neural populations. Nevertheless, it is crucial to clarify the existence of affective mirror neurons to understand the neural basis of empathy.

Finally it has to be mentioned that the content of this review describes a fundamental problem for every topic in neuroscience that deals with emotion; that the influence of cognitive information on affective information is widely undefined (Lemerise & Arsenio, 2000). This review presents potential regions and cognitive processes which could contribute to this issue.

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