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Social Cognitive Neuroscience of Empathy: Concepts, Circuits, and Genes

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Abstract

This article reviews concepts of, as well as neurocognitive and genetic studies on, empathy. Whereas cognitive empathy can be equated with affective theory of mind, that is, with mentalizing the emotions of others, affective empathy is about sharing emotions with others. The neural circuits underlying different forms of empathy do overlap but also involve rather specific brain areas for cognitive (ventromedial prefrontal cortex) and affective (anterior insula, midcingulate cortex, and possibly inferior frontal gyrus) empathy. Furthermore, behavioral and imaging genetic studies provide evidence for a genetic basis for empathy, indicating a possible role for oxytocin and dopamine as well as for a genetic risk variant for schizophrenia near the gene ZNF804A.

Keywords
empathy, genetics, imaging genetics, theory of mind

Empathy, the ability to share another's internal world of thoughts and feelings, has become an increasingly popular subject in science and culture. People may vary considerably with respect to their empathic abilities. Psychotherapists, for example, usually are quite good empathizers—or at least they should be. Also, there are some extraordinary individuals with an apparently almost unlimited capacity for empathy, such as the Dalai Lama. On the other hand, subjects with psychopathy are able to perform unbelievable cruelties without any empathy for their victims. A reduced capacity for empathy or the ability to control feelings of empathy might be advantageous in certain professional contexts, for example for soldiers or surgeons. Apart from the extremes mentioned, the capacity for empathy is a trait that we all share in a more or less comparable manner. It is found in different cultures worldwide and thus may qualify very well as a human transcultural universal.

Recently, social cognitive neuroscience has begun to investigate the neural mechanisms of empathy (Decety & Ickes, 2009; Lamm, Decety, & Singer, 2011). If empathy is a biologically based human universal we should be able to delineate specific neural circuits or even its genetic basis. In this paper I will do three things: First, I will map the conceptual territory of empathy and related terms. Then I will give an overview of neurocognitive approaches investigating the neural basis of empathy, focusing on three areas of research: mirror neurons, empathy for pain, and affective theory of mind. Finally, I will present recent data about the possible neurogenetic basis of empathy.

Mapping the Conceptual Territory of Empathy

There are multiple research traditions with a corresponding variety of empathy concepts. For example, Batson (2009) distinguishes eight different concepts of empathy. But what is empathy really? Philosophers tend to think that this is a good and relevant question. I do not think so. There is no definite answer to the question of what "true" empathy "really" is, because the meaning of words is greatly influenced by their usage and can change over time. For example, although empathy often is used as the general capacity to understand thoughts and feelings of others, most cognitive neuroscientists understand it today as an affective reaction to the affective state of someone else (Singer & Lamm, 2009). Instead of defining empathy in general, or to distinguish too many empathy concepts, I therefore propose along with many others to distinguish between two main concepts of empathy: affective empathy and related affective phenomena on the one hand and cognitive empathy on the other hand (cf. Table 1).

According to this suggestion, a rich concept of *affective empathy* is characterized by the following features. It is (a) an

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Table 1. Essential components of empathy and related concepts

	Affective behavior	Affective experience	Affective isomorphy	Perspective taking	Self–other distinction	Other orientation	Prosocial motivation
Emotional mimicry	+						
Emotional contagion	(+)	+	+				
Personal distress	(+)	+			+		
Affective empathy	(+)	+	+	+	+	+	
Cognitive empathy	(+)			+	+		
Sympathy	(+)	+		+	+	+	+

Note. The figure shows a suggestion for the decomposition of empathy and related concepts into their constituting subcomponents.

affective state that is (b) elicited by the perceived, imagined, or inferred state of the affective state of another; (c) is similar (isomorphic) to the other's affective state; (d) is oriented towards the other; and (e) includes at least some cognitive appreciation of the other's affective state comprising perspective taking, self–other distinction, and knowledge of the causal relation between the self and the other's affective state. Note that according to this definition, affective empathy includes some meta-knowledge about self and the other that distinguishes it from emotional contagion. Also note that affective isomorphism has been made a defining criterion of empathy. Not all empathy concepts require isomorphism, only some kind of appropriate affective resonance (e.g., Dziobek et al., 2008). For example, you may see someone suffering from a bad situation, such as having lost his job and feeling despair, and you yourself do not feel despair but pity or love. Maybe leaving out affective isomorphism would be closer to real life in that it would match better the kind of real-world cases that we call empathy. However, including isomorphism in the definition of affective empathy is consistent with current use in cognitive neuroscience. Note that the question of isomorphism might have an empirical rather than a conceptual answer, namely if it turned out that most cases of affective empathy that seem not to depend on isomorphism show isomorphism, for example, on a neural level.

Sometimes empathy is more or less equated with *compassion* or the old philosophical notion of *sympathy*. However, neither of these two phenomena requires affective isomorphism. Moreover, both terms are essentially characterized by prosocial motivation, that is, by a motivation to help or relieve the suffering of the other. Although there is indeed a certain association between empathy and prosocial behavior, there can be affective empathy with no prosocial or even antisocial behavior, for example, in a torturer who uses his empathic abilities in order to get more information out of his victim. Therefore, these concepts should not be confused with affective empathy as defined before.

As most empathy experts stress, there are other, more simple affective reactions to the affective state of others. The most basic is *emotional mimicry*, which can be defined as automatic synchronization of emotional behavior, for example, affective expressions, vocalizations, postures, and movements with those of another person. *Emotional contagion* occurs when people experience emotions similar as those of others by mere association, for example, when you feel happy because others around you feel happy, or when you are panicking because you are in a crowd of people feeling panic. Emotional contagion requires neither perspective taking nor an explicit self–other distinction. It can be observed already in infants, when they imitate a smile or cry when other infants around them do so. Arguably, in the case of infants, it is not always easy to know whether they only show emotional behavior (emotional mimicry) or really are in an affective state (emotional contagion). Besides, this might also be uncertain in social interactions of adults.

Another important concept is *personal distress*. This is defined as a negative affective state that can be elicited by affective states of others, but is rather self-centred than other-oriented. For example, when you see other people suffering you might react with a negative affective state motivating you to turn away in order to feel better.

Most importantly, taking into account the mentioned criteria, affective empathy can be distinguished from the other important form of empathy, that is, cognitive empathy. *Cognitive empathy* refers to the ability to *understand* the feelings of others without necessarily implying that the empathizer is in an affective state himself. For example, there can be purely cognitive understanding that someone is sad, without any emotional effect on the observer. Cognitive empathy is very closely related to *theory of mind* (ToM) or *mentalizing*. Theory of mind refers to the ability to represent and understand the mental states of others in general. Mental states include beliefs, desires, or intentions but also emotions and affective states. Mentalizing about affective states of others is therefore called *affective theory of mind*—which is more or less synonymous with cognitive empathy. Thus empathy and ToM overlap as follows: (a) cognitive theory of mind = mentalizing about cognitive states, (b) affective theory of mind = mentalizing about affective states = cognitive empathy; (c) affective empathy (as already defined).

However, in the literature there is no consistent use of these terms. Indeed, the general term "empathy" is often used in a very wide sense, so that mentalizing about beliefs and intentions

(and not only about emotions) is subsumed under this concept. Actually, I used empathy in this wide sense in the first sentence of this article. Papers on empathy often contrast only cognitive ToM and affective empathy and ignore mentalizing about emotions. At this point, I would like to stress that working definitions are only meant to conceptually distinguish between different phenomena in order to be able improve the discussion and to empirically investigate them. In real life and in phenomenal experience, there will be blends and co-occurrences. For example, apart from extremes such as psychopaths it is possible that mentalizing the emotions of others (affective ToM = cognitive empathy) might more or less automatically lead to experience of similar affective states in oneself (i.e., affective empathy). Vice versa, affective empathy that is elicited automatically by visual signals (facial expressions, crying) will normally lead to mentalizing about the emotions of the other. Therefore, cognitive and affective empathy will most often co-occur in real life. Also, it might be that feeling empathy usually leads to a motivation to help in many people, so that a mixture of empathy and sympathy emerges. Naturally, it is also possible to draw the lines between different terms differently. For example, it is possible to say that affective empathy does not require isomorphism but only (a hot) affective reaction in contrast to (cold) inferences. A flexible way is to define empathy as a multidimensional ability and then to distinguish more than two forms of empathy. Whatever route is taken, researchers carrying out empirical investigations should try to make clear what definitions of empathy their research refers to.

Two more remarks: The first concerns *perspective taking*. Perspective taking means to take over the mental perspective of the observed other, or as it is often said, to put oneself mentally in the shoes of the other. However, perspective taking itself is neutral to the question whether an (isomorphic or nonisomorphic) affective state is elicited in the observer. Rather, perspective taking can be understood as a cognitive mechanism which is important in both, cognitive and affective empathy, as well as in traditional mentalizing about perceptions (e.g., in visuospatial perspective taking), beliefs, and intentions. Note that the requirement to make an explicit self–other distinction requires, to a certain extent, taking over the perspective of the other. The second remark pertains to the ways by which empathy is induced. Similar to approaches to visual perception of affective stimuli (LeDoux, 1996), a *low and a high road to empathy* can be distinguished (see Figure 1). By this, I mean that for the low road certain basic features indicating affective states or suffering (facial expressions, bodily movements, highly salient features like blood or injuries) might lead to more or less automatic empathic responding in a bottom–up fashion. The high road to empathy means that empathic processes are induced top–down by higher cognitive processes, like inferences on thoughts based on logical relations or contextual and situational information, for example knowing that someone lost his job or has received an adverse diagnosis. This cognitive understanding will often lead to affective empathy as well.

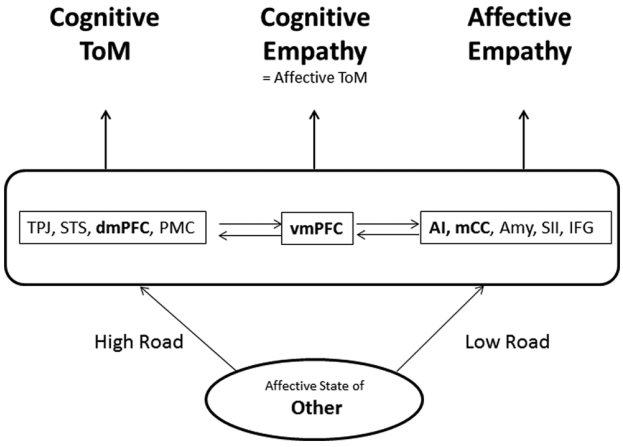

Figure 1. Brain circuits for empathy and theory of mind (ToM). The affective state of another can elicit activations in the observer either by bottom–up affective signals ("low road") or by top–down cognitive information on content and context ("high road"). The large rectangle depicts schematically the brain of the observing self and the small rectangles depict neural networks that have some specificity for the types of mental processes in the upper part. However, as indicated by the arrows between the small rectangles, these systems can be coactivated, as, for example, shown by the recruitment of the cognitive ToM system in cue-based elicitation of empathy for pain.
Note. TPJ: temporo-parietal junction; STS: superior temporal sulcus; dmPFC: dorsomedial prefrontal cortex; PMC: posteromedial cortex (i.e., precuneus, posterior cingulated, and medial superior parietal cortex); vmPFC: ventromedial prefrontal cortex; AI: anterior insula; mCC: midcingulate cortex; AMY: amygdala; SII: secondary somatosensory cortex; IFG: inferior frontal gyrus.

The Social Neuroscience of Empathy

One of the starting points of the social neuroscience of empathy was a seminal review by the psychologist Stephanie Preston and the primatologist Frans de Waal (Preston & de Waal, 2002). The authors argue that there are a variety of views and concepts of empathy used in the literature. Then they identified five main cross-species findings on empathy, namely that it increases with familiarity (previous experience of the self with the other), similarity (perceived overlap between self and the other, e.g., species, personality, age, gender), learning (explicit or implicit teaching), past experience (with situations of distress), and salience (strength of perceptual signals, e.g., louder, closer, more realistic, etc.). They suggested a *perception–action model* to explain these findings and integrate the different views on empathy. According to their model the attended perception of the other's state automatically activates the observer's representations of the state and these automatically generate autonomic and somatic responses that are associated with that state. In other words, observing an emotion in someone else automatically generates (parts of) that emotion in the observer. This idea of a shared network between observer and observed is one of the uniting features of neurocognitive approaches to empathy.

This perception–action model finds support from the so-called *simulation theory* of other minds, the idea that our

ability to understand mental states (including emotions) and their expression by others relies on internally simulating the same psychological state in ourselves (Goldman, 2006). The opponent theory to simulation theory is the so-called *theory-theory* (Carruthers, 1996). This approach suggests that we understand others by way of inference, that is, that we have an internal model of what mental states are and infer the mental states of others on the basis of a ToM. The discussion of these opposed philosophical theories was boosted by the discovery of the so-called mirror neurons in the mid- 1990s. Mirror neurons seemed to provide the perfect neurobiological mechanisms for simulation and very quickly the idea of simulation theory and mirror neuron theory joined forces (Gallese, 2001). Nowadays they are often treated as if they were one and the same theory, which is not the case. Thus, what are mirror neurons?

Empathy and the Human Mirror Neuron System

Mirror neurons are a unique class of neurons that were discovered about 15 years ago in the premotor cortex (area F5) in monkeys by single-cell recordings (Gallese, Fadiga, Fogassi, & Rizzolatti, 1996; Rizzolatti & Craighero, 2004). They show unique response properties by firing both when a monkey executes a particular action (e.g., grasping, placing, or manipulating an object) and when the monkey observes someone else performing that same action. Neurons with similar mirror properties in the visuo-motor domain were also discovered in the anterior intraparietal area and in the primary motor cortex in monkeys. Subsequently, many functions have been attributed to mirror neurons, including action understanding, imitation, empathy, and mentalizing.

Evidence for the existence of mirror neurons in humans relies on functional neuroimaging studies that demonstrate an overlap in activation between observation and performance of actions in regions homologous to the areas of the monkey brain where mirror neurons have been found. These regions include the inferior frontal gyrus, the ventral premotor cortex, and the anterior and posterior intraparietal sulcus (e.g., Dinstein, Hasson, Rubin, & Heeger, 2007), as well as the somatosensory cortex in the case of sensations. Basically, these studies have investigated motor phenomena similar to the original studies done in monkeys. It should be noted though, that it is more appropriate to speak of the human mirror neuron *system* since the existence of mirror *neurons* has not yet been proven. This would require single-cell recordings in humans (see Decety, 2010; also Hickok, 2009, for a critical view on mirror neurons; and Rizzolatti & Sinigaglia, 2010, for a reply).

One of the first neuroimaging studies of empathy actually was done on the emotion of disgust (Wicker et al., 2003). In this fMRI study it was found that the insular cortex and the frontal opercular taste cortex were activated when experiencing odor-induced disgust, as well as when subjects observed another person showing facial signs of experiencing disgust induced by odors. A recent review on the evidence for mirror systems in emotion, including studies on pain, disgust, and touch, concluded that there is evidence for emotional mirror systems in humans, although there does not seem to be a reliable mapping of particular emotions onto particular brain regions (Bastiaansen, Thioux, & Keysers, 2009). The experimental evidence rather suggests that motor simulation may be a trigger for the simulation of associated feeling states. So the assumed mirror systems for action may be involved in emotional mimicry or contagion which can then trigger emotional experiences. In our terminology they may be involved in particular in the low road to empathy.

Neural Correlates of Affective Empathy for Pain

A straightforward strategy to look for neural correlates of affective empathy based on the idea of affect sharing is to look for common activations (a shared network) during the observation of someone being in an affective state ("other condition") versus being in the same affective state ("self condition"). By far the most frequently investigated affective state is pain, on which I will focus here, whereas emotions such as disgust (see previous lines) or happiness have been investigated only rarely. Two main empathy-for-pain paradigms have been used. The first is cue-based (e.g., Hein, Silani, Preuschoff, Batson, & Singer, 2010; Singer et al., 2004), where an abstract cue indicates whether oneself or a person in the scanner room (e.g., a partner) receives an electrical shock. The second is picture-based (Jackson, Meltzoff, & Decety, 2005; Lamm, Meltzoff, & Decety, 2010), where pictures of body parts are shown in painful and nonpainful situations.

A recent meta-analysis analysed nine studies (four picture-based, five cue-based; $N = 168$) on the basis of comparing contrast images of brain activation (image based) and additionally 39 studies on a coordinate base from the literature (Lamm et al., 2011). Across all nine studies two regions were consistently activated during pain experience as well as during empathy for pain of the other: the anterior insula (AI) and the midcingulate cortex (mCC). The anterior insula also was found in another recent coordinate-based meta-analysis as consistently activated during empathy irrespective of the emotion empathized with and the induction method (Fan, Duncan, de Greck, & Northoff, 2011). Both the mCC and the AI have been linked to the affective-motivational aspect of nociception. An influential view holds that both regions are part of a network that is engaged in interoceptive awareness and metarepresentations of emotional moments (Craig, 2009). Whereas the ventral division of the AI might be more related to affective aspects due to its connection with the amygdala and medial orbitofrontal cortex, the dorsal part might be more relevant for motor aspects of empathy due to its connections to the motor system. Consistent with its role in empathy, it was found that activation in the AI and mCC correlated with self-reported empathy scores in some studies (Lamm, Batson, & Decety, 2007; Singer et al., 2004), but not in all (e.g., Jackson et al., 2005). Note, however, that strictly speaking, isomorphism was not found between psychological states but rather between neural correlates in the observer and the observed.

Although these findings can easily be related to empathy, a more simple explanation holds that AI and mCC activations merely reflect a general aversive response coupled with motor preparation for defensive actions, which may not be specific to nociception (Yamada & Decety, 2009). In other words, the shared affective empathy network may only reflect personal distress. Consistent with this alternative interpretation, patients with the rare condition of congenital insensitivity to pain show activation of the anterior cingulate cortex and the insula, although they never experienced pain in their lives (Danziger, Faillenot, & Peyron, 2008). Also, physicians show no activation of these two regions when seeing body parts being pricked by a needle, which may be explained by the fact that needle pricking is not aversive to them (Cheng et al., 2007). Therefore, appealing as the shared-network hypothesis for empathy in pain studies is, it is not clear if this network really is the specific neural correlate for affective empathy for pain.

Apart from the shared network, the meta-analysis by Lamm et al. (2011) also showed evidence for activation of other networks when comparing picture- and cue-based studies that speak in favor of different routes to empathy. Picture-based paradigms elicited more activation in regions like anterior inferior parietal cortex and ventral premotor areas. Note that these regions are thought to constitute the human mirror neuron system. In contrast, the cue-based studies elicited more activation in a network comprising the ventromedial prefrontal cortex (vmPFC), the posteromedial cortex (PMC, i.e., precuneus, posterior cingulate, and medial superior parietal cortex), the bilateral temporo-parietal junction (TPJ), and the bilateral superior temporal sulcus (STS). This network is associated with mentalizing (ToM) (e.g., Walter et al., 2004; for reviews, cf. Carrington & Bailey, 2009; Gallagher & Frith, 2003). Moreover, the mentalizing network shows strong overlap with the default-mode network (Schilbach, Eickhoff, Rotarska-Jagiela, Fink, & Vogeley, 2008) which has been related to processing of social representations, that is, representations of the self and others (Ciaramidaro et al., 2007). Therefore, there is some neural evidence that mentalizing and affective empathy are co-occurring as explained before, at least in cue-based paradigms of empathy for pain.

Neural Correlates of Cognitive Empathy

Cognitive empathy (or affective theory of mind or mentalizing about emotions) does not require that one actually shares, but only that one understands the affective states of others. Although there are now several neuroimaging studies investigating cognitive empathy (see following text) most studies have investigated cognitive ToM (Carrrington & Bailey, 2009). These studies usually show activation of the PMC, the TPJ, the STS, the anterior temporal poles, and the dorsomedial prefrontal cortex (dmPFC) (Carrington & Bailey, 2009). There is some controversy in the literature over which region is the most specific for mentalizing in general. While according to one view it is the dmPFC (Amodio & Frith, 2006), others have found quite convincing evidence that the right TPJ is the most specific region for representing the mental state of others (Saxe & Wexler, 2005). These authors have argued that the role of the medial prefrontal cortex (MPFC) in ToM is more general, namely that it is involved in presenting triadic relations, for instance, an observer, an observed and an object (Saxe, 2006). Another suggestion is that the TPJ and the dmPFC are differentially involved in the aspect of self–other distinction (Brass, Ruby, & Spengler, 2009) in mentalizing situations. Whereas the TPJ is important for agency attribution, that is, in attributing an observed action to the other and not the self, the dmPFC is thought to be required to enforce one's own motor intention against an externally triggered response tendency. This idea also links mirror system theory and mentalizing.

There are now several imaging studies investigating cognitive empathy (Hynes, Baird, & Grafton, 2006; Preston et al., 2007; Schnell, Bluschke, Konradt, & Walter, 2011; Völlm et al., 2006; Walter et al., 2011). In general these studies find activation of the ToM network when mentalizing about emotions plus activation of areas that are related to affective processing, for example, the amygdala or the vmPFC. In our own work we have used a cartoon paradigm in which the characters depicted had no mouth and showed no affective eye signals (Schnell et al., 2011; Walter et al., 2011). This ensured that subjects had to use the high road to cognitive empathy. The stories consisted of three consecutive pictures developing a story around a protagonist. After the second and third pictures, a question was asked about the change of either the number of living beings or the affective state from either one's own perspective or the perspective of the cartoon's protagonist. Thus, basically the study had a 2×2 design with self/other and cognitive/affective as factors. The results were as follows: Mentalizing about the emotions of the other compared to mentalizing about cognitions of the other showed higher activation in the anterior part of the mentalizing network (dmPFC, bilateral STS, bilateral temporal poles) as well as in limbic areas like the left amygdala, the left hippocampus, and the left posterior cingulate gyrus. In posterior regions of the mentalizing network only one small cluster in the left TPJ showed higher activation for affective mentalizing content. Higher activation was also observed in bilateral inferior frontal gyri and left ventromedial prefrontal cortex. Note that the inferior frontal gyrus (IFG) is part of the human mirror neuron system. The vmPFC is an important relay station between cognitive and affective processing.

The role of both the IFG and vmPFC for empathy has recently been investigated in two lesion studies. Shamay-Tsoory and Aharon-Peretz (2007) investigated 49 patients with different types of brain lesions (ventromedial PFC, dorsolateral PFC, mixed, posterior cortex) for cognitive ToM and affective ToM (in our terminology: cognitive empathy) using two different tasks. The first was a false-belief task in a cognitive and an affective (irony) version. In the other task, subjects had to judge by eye gaze and facial expression of "Yoni" (a cartoon picture of a face) what Yoni was either thinking of or feeling about objects and people around her. They found subjects with lesions in the vmPFC to be specifically impaired in affective ToM

(= cognitive empathy) but not in cognitive ToM tasks. This role for the vmPFC for cognitive empathy is consistent with the findings in our own study.

In a second study the same group investigated the effect of brain lesions in 30 patients with various lesions (vmPFC, inferior frontal cortex, posterior cortex) with respect to cognitive and affective empathy (Shamay-Tsoory, Aharon-Peretz, & Perry, 2009). They calculated an emotional and cognitive empathy index from an empathy questionnaire and two experimental tasks. Consistent with the earlier study, vmPFC patients had a lower cognitive empathy index, whereas IFG patients had a lower affective empathy index. As the patients were not impaired in the respective other index, the findings were interpreted as evidence for a double dissociation of cognitive and affective empathy. Concerning the role of the inferior frontal cortex it should be noted that the left inferior frontal cortex was also found to be activated in picture-based paradigms of affective empathy.

Figure 1 summarizes the findings described so far in a simplified schema relating neural structures to the concepts of cognitive ToM, cognitive empathy (= affective ToM), and affective empathy.

Empathy and the Genetics of Human Social Cognition

So far, we have considered the neural correlates of empathy and related phenomena as indexed by brain activation or brain lesions. In this last section I want to go a step further and consider the evidence for a genetic basis for human empathy. In order to elucidate genetic factors for social cognition (Ebstein, Israel, Chew, Zhong, & Knafo, 2010; Robinson, Fernald, & Clayton, 2010) there are basically two routes in human research. First, twin studies are performed to establish the heritability of social phenotypes. Second, genetic association studies seek to identify specific genes and polymorphisms contributing to individual differences in social phenotypes. Recently, a third, intermediate approach has been developed called imaging genetics. Imaging genetics investigates effects of genetic variants on brain activation in circuits that are known to be involved in specific psychological functions (Esslinger et al., 2009; Meyer-Lindenberg & Weinberger, 2006). A prototypical social neurogenetic study then would look like this: First, a social phenotype is established and characterized by questionnaires, psychological tests, laboratory models, or natural experiments. Once the phenotype is defined, twin studies are used comparing the phenotype in mono- and dizygotic twins to estimate the contribution of heredity and shared or nonshared environment. Then, candidate genes are studied as established either by animal evidence or informed hypotheses that suggest neural mechanisms molding specific social behaviors. Ideally, these neural mechanisms refer directly to specific molecules like neurotransmitters, neuropeptides, receptors, or molecular pathways relevant for brain function or development.

Two prime examples of target molecules in social neurogenetics are the evolutionary old neuropeptides, oxytocin and vasopressin (Donaldson & Young, 2008; Insel, 2010). Their expression and receptor density drastically influences social behavior in voles with respect to maternal behavior, affiliative behavior, and pair bonding. In humans, it has been shown that the intranasal application of oxytocin can increase cognitive empathy abilities (Domes, Heinrichs, Michel, Berger, & Herpertz, 2007). Another study demonstrated that intranasal oxytocin improved social but not nonsocial learning and increased affective but not cognitive empathy in the Movie for the Assessment for Social Cognition (MASC) (Hurleman et al., 2010). Interestingly, after oxytocin treatment, emotional empathy responses in men were raised to levels similar to those found in untreated women. In accordance with this finding another study found oxytocin to increase empathic accuracy only in less socially proficient individuals (Bartz et al., 2010).

Is there any direct evidence for a genetic foundation of empathy, that is, evidence for a behavioral phenotype? In a recent review, Knafo and Uzefovsky (in press) reviewed all twin studies looking for the heritability of individual differences in empathy (seven studies, 1,655 subjects: three studies were on young children between 1.1 and 3.5 years; four studies in adults, ranging from 17 to 48 years). Only one of the studies was longitudinal (Knafo, Zahn-Waxler, van Hulle, Robinson, & Rhee, 2008), testing 222 children at the age of 1.2 years, and most of them later at 1.8, 2, and 3 years. Four studies tested emotional as well as cognitive empathy, and three of these four used behavioral tests, whereas the others used questionnaires. In six out of the seven studies, evidence for a genetic contribution explaining individual differences in empathy was found at least in one age group. In the meta-analysis, genetic factors accounted for 35% of the variance in empathy in general. In the six studies investigating cognitive as well as affective empathy, genetic factors accounted for 30% and 26% of the variance, respectively. More detailed analyses revealed further interesting findings: First, the presence of low economic status or medical risks reduced the genetic influence. In other words, only an advantageous environment allowed children to fully develop their genetic potential for empathy, whereas in an adverse environment, environmental factors dominated the development of empathic abilities. This is consistent with similar results in the field of the genetics of intelligence. Second, genetic effects increased with age. Similar age effects had been found in the longitudinal study on genetics of empathy. Third, the authors found heritability of empathy to be much higher in twins who showed high degrees of emotional symptoms (Knafo et al., 2009).

Do we know anything about specific genes contributing to the heritability of empathy? The first natural candidate to look for is oxytocin. And indeed, in a study with 192 young, racially mixed male participants, Rodrigues, Saslow, Garcia, John, and Keltner (2009) found an influence of a genetic variant (rs53576) within intron 3 of the oxytocin receptor gene on chromosome 3 on empathy and stress reactivity. Individuals with at least one copy of the A-allele exhibited lower behavioral and dispositional empathy, as measured by the Reading the Mind in the

Eyes Test (cognitive empathy) and the Interpersonal Reactivity Index (IRI) questionnaire (cognitive and affective empathy elements). Furthermore, they displayed higher physiological and dispositional stress reactivity. This is consistent with the fact that A-allele carriers have been found to have a statistically increased likelihood of an autism diagnosis and display less parental sensitivity. These findings support the already cited studies arguing for a role of oxytocin in empathy.

Another candidate gene for a genetic foundation of empathy is a 7-repeat polymorphism in the dopamine receptor gene (DRD4-III), as this has been shown to be strongly associated with parenting influences and child outcome (Belsky & Pluess, 2009). Although a direct effect on empathy could not be demonstrated, Knafo and Uzefovsky (in press) found a gene by environment interaction of the 7-repeat polymorphism. Only in 7-repeat carriers (but not in 4-repeat carriers) was empathic concern lower in children when their mothers showed a higher degree of negativity.

Finally, the first imaging genetic study on cognitive empathy (= affective theory of mind) was published recently (Walter et al., 2011), using the two most opposite conditions of the described cartoon task (mentalizing about the affective state of the other versus self-counting number of living objects). In this study, 109 young, healthy, adult subjects were investigated for an effect of a genetic variant (rs1344706) near the gene ZNF804A on chromosome 2 on brain activation. This variant was the first that was shown to have a genome-wide significant association with schizophrenia and bipolar disorder (O'Donovan et al., 2008), a finding that has now been replicated several times (Steinberg et al., 2011). ToM dysfunction has been shown to be a robust endophenotype in schizophrenia (Bora, Murat, & Pantelis, 2009; Sprong, Schothorst, Vos, Hox, & van Engeland, 2007), and aberrant activation in two important nodes of the general ToM network, the dmPFC and bilateral STS/TPJ, was shown in a recent fMRI study in patients with schizophrenia (Walter et al., 2009). Because this finding of reduced activation was due to an absence of differential activation in mentalizing and judging physical causality, it was speculated that the results could be due to an increased tendency in patients with schizophrenia to infer intentionality in a purely physical context.

The schizophrenia study motivated us to test the hypothesis that there is an effect of the schizophrenia risk variant ZNF804A and the activation of the affective mentalizing network. Indeed, consistent with the schizophrenia study, risk carriers of this variant showed less activation in the dmPFC and left posterior STS/TPJ. Additionally, less activation in risk carriers was found in the left inferior frontal cortex (implicated in the mirror neuron system and affective empathy) and the left inferior parietal cortex (part of the human mirror neuron system). Although the function of the ZNF804A gene is not yet known—possibly it is involved in gene regulation—imaging genetics was thus able to link large association studies and the endophenotype of ToM dysfunction using a cognitive-empathy task. With regard to the previously mentioned oxytocin studies one might be tempted to look for an effect of the risk variant near ZNF804A on neuropeptide metabolism, although this hypothesis is mere speculation at the moment.

Taken together, the behavioral genetic and neurogenetic studies discussed can be seen as first evidence for a genetic foundation of empathy. However, at this early time, further conclusions about the relevance are not warranted because replication is essential in genetic studies and has not yet been demonstrated. Nevertheless, the studies show a principal way in which we can approach the question of a neurogenetic foundation for empathy.

General Conclusion

Empathy has become a hot topic in social cognitive neuroscience over the last decade. We have seen that different concepts of empathy can be defined and have to be differentiated from other affective phenomena like emotional contagion or compassion. A widely used distinction is made between affective and cognitive empathy with the latter being identical with mentalizing about emotions, that is, affective theory of mind. From a neurobiological point of view three neural systems play a major role in empathy: the mirror neuron system, an affective empathy system centered on the anterior insula and midcingulate cortex, and the mentalizing system. A link between cognitive and affective empathy is provided by the ventromedial prefrontal cortex. First neurogenetic studies suggest an involvement of some candidate genes in the genetic foundations of empathy, related to oxytocin and dopamine and a gene of unknown function associated with schizophrenia, ZNF804A. Although some core regions can be associated more strongly with affective and cognitive empathy, respectively, it seems that the natural blend of different types of empathy is reflected in partially overlapping networks.

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