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Neurobiological Correlates of the Attitude Toward Human Empathy

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Abstract Over the last decade, integrated philosophical and neuroscientific studies of empathy have been steadily growing, because of the pivotal role that empathy plays in social cognition and ethics, as well as in the understanding of human behavior both under physiological conditions and in the presence of mental disorders. The umbrella concept of empathy embraces multi-faceted characteristics, including affective and cognitive processes, such as so-called emotional contagion and concern and perspective-taking. In this paper, we review the state-of-the-art of knowledge about the neurobiology of empathy. Specifically, we examine studies regarding empathy for pain, emotional imitation and expression and their alterations in psychopathological conditions. We also consider studies on the theory of mind (ToM) and the mirror neuron system (MNS). Finally, we propose measures of brain resting state activity as a potential neurobiological marker of proneness to be empathic.
KEYWORDS: Empathy; Mirror Neurons; Theory of Mind; Mental Disorders; Psychopathy.

Riassunto *Correlati neurobiologici della disposizione all'empatia umana* – Nell'ultimo decennio è cresciuto il numero delle indagini sull'empatia condotte integrando la prospettiva filosofica e quella neuroscientifica, in ragione del ruolo cardine svolto dall'empatia nella cognizione sociale e nell'etica, come pure nella comprensione del comportamento umano dal punto di vista delle condizioni fisiologiche e in presenza di disturbi mentali. La nozione di empatia funge da ombrello concettuale sotto cui ricadono caratteristiche multiformi, compresi i processi affettivi e cognitivi, come il cosiddetto contagio emotivo e l'assunzione di ruolo e di prospettiva. In questo lavoro intendiamo offrire una rassegna dello stato dell'arte delle conoscenze sulla neurobiologia dell'empatia. In particolare prenderemo in esame gli studi che vertono sull'empatia per il dolore, l'imitazione emotiva e dell'espressione e le loro alterazioni in condizioni psicopatologiche. Considereremo inoltre studi sulla teoria della mente (ToM) e sul sistema dei neuroni specchio (MNS). In sede conclusiva intendiamo proporre delle misure dell'attività cerebrale in condizioni di riposo come potenziale marcatore neurobiologico della propensione a empatizzare.
PAROLE CHIAVE: Empatia; Neuroni specchio; Teoria della mente; Disturbi mentali; Psicopatia.

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A brief introduction for a broad issue

EMPATHY HAS MANY DIFFERENT DEFINITIONS, which are related to its multi-faceted characteristics. In fact, under the umbrella concept of empathy one can consider a variety of distinct affective and cognitive processes: the feeling of caring for other people and desiring to help them (often defined as "emotional concern"); emotional contagion, meaning the experience of emotions that match those of another individual; understanding what another person is thinking or feeling; feeling discomfort related to the observation of others' suffering (often defined as "personal distress") and the ability to portray oneself in the shoes of a fictional character (often defined as "fantasy").[1]

Several psychological scales have been adopted to measure the various aspects of empathy. Among them, the *Interpersonal Reactivity Index* (IRI)[2] tried to address the composite nature of empathy by including four dimensions: emphatic concern; perspective taking; personal distress and fantasy. While the last one does not seem to be so closely related to the experience of empathy as we typically define it, the other three dimensions are widely used and studied in the psychological assessment of empathy.

Given these premises, is not surprising that empathy is of great interest not only in social psychology and in ethics, because it is one of the components in the human proneness to bond, but also in clinical psychology and psychopathology, because it is considered that disturbances of empathic abilities are present in different mental disorders, including autism, alexithymia, dementias, social anxiety and psychopathic personality disorder.[3]

Over the last decade or so, studies of empathy have generated a wide interest in neuroscience research because empathy has implications relevant not only for neuroethics, but also for the affective neuroscience of physiological and pathological conditions. By combining modern neuroimaging methodologies, such as functional magnetic resonance imaging (fMRI), with sophisticated psychological paradigms, scientists now have an unprecedented tool to dissect the neural correlates of human behavior and emotion.[4] The aim of the present review is to provide a critical examination of the existent knowledge on the neurobiology of empathy. In this sense, we do not aim to provide a complete inventory of the studies conducted, but rather a synthetic summary of research that may contribute to a neurobiological model of empathy that is supported by data and not by mere speculations.

Empathy in action: The study of empathic concern in studies on pain and emotional recognition

One of the most used paradigms in research on empathic concern is the study of empathy for somebody else's pain. This paradigm is considered optimal for several reasons. First of all, brain mechanisms involved in the perception of pain are very well-known. Pain perception has been decomposed into its more basic components. The thalamus and somatosensory cortex account for the physical representation of pain (localization, intensity, qualitative characteristics), while the limbic structures (including amygdala, insula and anterior cingulate cortex) account for the emotional value of the nociceptive experience.[5] Also, recognition of and empathy for someone else's pain have been well-described in the literature.

The most frequently used paradigms for studying empathy for pain involve exposure to pictures of subjects with pain expressions or of body parts with wounds.[6] Despite the methodological differences among the protocols, these studies have consistently highlighted that pain perception and pain observation both lead to neural responses in the same cerebral regions. Among these areas, the anterior cingulate cortex plays a relevant role. Anterior cingulate activity appears to be related to the subjective experience of pain.

For instance, the discharge of this region

correlates with the level of subjective intensity of pain perception, but not with the physical intensity of the painful stimulation. In the pivotal study by Coghill and colleagues, subjects were asked to rate their subjective perception of a painful stimulation on a visual analogue scale. Despite the fact that the physical stimulation was the same for all the volunteers (a 49° Celsius degrees hot patch on their non-dominant ventral forearm), subjects rated their painful experiences on a wide spectrum of intensities, ranging from mildly to extremely painful. The most relevant difference in brain activation was a higher discharge of the anterior cingulate in those subjects who reported a more painful experience.[7]

Consistent results were obtained by Rainville and colleagues, using a different experimental approach.[8] To evaluate the role of different cortical areas involved in pain perception, hypnotic suggestion was used to modulate the unpleasantness of a noxious stimulus (induced with hand immersion in ice-cold water), without changing the perceived intensity. During hypnotic modulation of pain, neural activity within the anterior cingulate cortex, but not in the primary somatosensory cortex, changed as a function of the degree of unpleasantness.[9]

Neural activation in the anterior cingulate cortex has also been consistently found during the perception of and empathy for pain in others. For instance, Singer and colleagues demonstrated a similar pattern of discharge in the anterior cingulate cortex of women both during direct pain stimulation and its observation: identical activity was recorded when subjects underwent a painful stimulation and when they saw the same pain conveyed to their beloved one.[10] However, anterior cingulate cortex is activated not only by physical pain or its observation, but also during "emotional" and "social" pain, as well as in frustration.[11]

Moreover, the role of the anterior cingulate in frustration and in social pain is even wider, due to its involvement in coping with emotionally hurtful situations. In a recent study by our group,[12] subjects who had been exposed to imagined hurtful scenarios, were asked to forgive the offender or to meditate and plan revenge. As compared to the hurtful scenario, the imagination of a way to cope with the situation (both forgiving or not forgiving) increased neural activity in the anterior cingulate cortex.[13]

Therefore, in line with the available literature, we consider the anterior cingulate cortex a relevant area in the empathy for pain, but we argue that more than being a mirror region (see below), this region may represent the neurobiological counterpart of the personal distress triggered by the recognition of others' suffering.

Empathy for pain also appears to recruit other regions involved in emotional processing, in general, and in the emotional evaluation of pain, in particular.[14] It is crucial to underline that one's own pain perception and the perception of someone else's pain shared several brain area activations. However, it must be noted that a distinctive network of areas is active during our own pain perception and is not recruited during observation of pain in others. This network includes portions of the anterior cingulate and of the anterior insula, the posterior insula and the somatosensory cortex.[15] These differences between the perception of pain in oneself and in others are crucial since they represent, at the neurobiological level, our ability to discriminate between self and other experiences.

Although pain perception is a very powerful stimulus for studying the neural mechanisms of empathy, other emotional stimuli have been used as well, and this is important for the validation of results. We highlighted above how perceiving pain in others activates a network of brain areas that widely overlaps with those involved in the perception of one's own pain. Can this finding be extended to other emotions?

As a matter of fact, a similar overlap between the feeling of an emotion and its observation has been shown. For instance, it has been shown how specific areas within the

anterior insula respond similarly both while subjects are experiencing disgust and when they are watching somebody else experiencing the same emotion.[16]

As also pointed out in the case of pain, however, self-perception of disgust and recognition of disgust in others' faces result also in distinct brain activations. In fact, while activation in the insula is shared in the two conditions, the authors also found that being disgusted activated a wider part of the anterior insula, while recognizing disgust in somebody else activated visual and dorsal prefrontal cortical areas.

Consequently, the available literature suggests that empathy for a given emotion requires the recruitment of brain areas that include but are not limited to those involved in the subjective experience of the same emotion.

Understanding Intentions: The "Theory of Mind" Brain System

In the previous section, we considered the neurobiological underpinnings of empathic concern. In the present and in the next ones, we will describe the role of other neural systems, which are supposed to be involved in the perspective-taking component of empathy, namely, the theory of mind (ToM) network and the mirror neuron system (MNS). Although, as stated before, perspective-taking, personal distress and empathic concern are three separate dimensions, it makes sense to hypothesize that in order to develop empathic concern, one needs to understand other's behaviors, intentions and feelings.

The term "Theory of Mind" was introduced by Premack and Woodruff in 1978. Often used as a synonym for mentalizing, ToM is defined as the ability to understand mental states, including beliefs, intents, desires and knowledge, to attribute such mental states to oneself and/or others and to understand that others have mental states that may differ from one's own.[17] In fact, having a ToM seems a necessary prerequisite not only for being empathic, but also for developing any social cognition ability.

The identification of the neurobiological underpinnings of ToM is very complex: ToM includes several features and abilities with distinct neural representations. In a seminal review of the literature, Frith and Frith[18] identified three ToM areas: temporal poles, posterior temporal sulcus and middle prefrontal cortex. Each of these areas seem to be specialized for some of the abilities comprised in the concept of ToM, for instance middle prefrontal cortex activity may be related to the ability to distinguish mental from physical state representations. However, the activation of these components in concert appears to be critical to mentalizing and therefore activity in each of these regions is often shared across different ToM tasks.[19]

The problem is that ToM is a compact and parsimonious definition which gathers under the same umbrella everything that is involved in social cognition and understanding but includes a larger set of abilities than one realizes at a first glance. In our opinion, this contributes to explaining why, only a few years after the work by Frith and Frith, a new review of the literature pointed out that over twelve regions are recruited during ToM tasks.[20] Therefore, more than a single ability, ToM seems to include a series of mind faculties with the same general scope. With regard to its neural correlates, ToM tasks present patterns of brain activation which are in part shared across different mental faculties and in part are distinctive for each one. Empathy, and more precisely the *perspective-taking* component of empathy, has been considered one of these faculties. In the review cited above, only one study focused on empathy.[21]

The comparative analysis of the neuronal pattern obtained in this study with those from the other studies included in the review, once more highlighted that several ToM regions are active during almost all the ToM tasks, while a certain degree of specialization in single areas for perspective-taking emerged as well: although not distinctive, precuneus/posterior cingulate gyrus and the cerebellum seemed to

be more specifically recruited during empathic perspective-taking. The neural response in precuneus/posterior cingulate is of particular interest, since this region seems to be related to the ability to switch the attention from inner thoughts and sensations to the external world and others.[22]

Consequently, we can hypothesize that in order to understand someone else's thoughts and eventually engage in empathic feelings, it is necessary to reduce one's own self-focused attention and redirect own cognitive resources toward others.

Is empathy for others looking at oneself in the mirror?

In the last decade, the role of the mirror neuron system (MNS) in empathy has stirred up a lot of interest. The MNS has been defined as a group of regions where neurons discharge in an identical way both while an individual performs an action and while they observe the same action being performed by somebody else.[23] Initially discovered in the monkey,[24] later fMRI studies identified a similar mirror system in humans as well.[25] Furthermore, a study by our group showed that the mirror neuron system develops and functions also in the absence of any visual experience, for instance, in congenitally blind individuals, underscoring the relevance of this system from an evolutionary perspective.[26]

Scientists have claimed that the mirror neuron system may explain imitation and mimicry both in primates and humans[27] and be involved in learning from imitation[28] as well as in social interaction.[29] Based on this evidence, it was proposed that MNS may be the neurobiological underpinning of the association between mimicry and imitation on one side and empathy on the other.[30] A fundamental element in this link is the concept of emotional contagion.

Emotional contagion is not only mediated by imitation and mirror-like phenomena, but also involves the diffusion of an emotion from one individual to another (which is part of the properties of the above-mentioned concepts of emotional contagion, empathic concern and of affective empathy).[31] The MNS would therefore trigger emotional contagion through imitation.

One of the most valid paradigms for studying emotional contagion is yawning. Yawning can be observed in different species with (affective) empathic abilities;[32] although yawning is a reflex stereotype motor action, its contagion seems to be modulated by emotional and social bonding (i.e., the contagion is more frequent when two individuals are bonded).[33] Finally, some studies highlighted how yawning observation and imitation activates the MNS,[34] although contrasting results exist and others researches failed to find a specific recruitment of this system in yawning.[35]

Despite the relatively inconsistent evidence for a relationships between yawing, mirror neurons and empathy, the relationship between empathy and imitation is strong and sustained by several other works, showing for instance how a higher ability to imitate facial expression is correlated to empathy.[36]

According to Ferrari, mirror neurons may be involved in empathy and in emotional contagion in two possible ways.[37] The first way implies a very strong and fundamental participation of the MNS: since these neurons discharge in an identical way while performing or while observing an action, their activity alone would be enough to evoke the emotional contagion reaction. In our opinion, this hypothesis, although intriguing, is insufficiently supported and even contradicted by the data. In fact, suggesting that the mirror neurons themselves are responsible for empathic emotional contagion is in conflict with several observations. Despite the fact that mirror neurons "do not make a difference" between observation and execution of an action, the emotions evoked by empathic contagion are not exactly identical to the ones experienced by the individual with whom one empathizes. Moreover, action recognition and emotional contagion can be independent: one can still be able to recogni-

ze an action or a feeling in someone else's face without undergoing the contagion.

As ingeniously exemplified by Aragon and colleagues:

> How could a boxer mirror a losing opponent's expressions of fatigue, feeling his weariness, precisely when strength is required?[38]

The necessity to this disconnection brings about, in our opinion, the necessity that the MNS in itself is not what generates empathy and empathic contagion.

However, an alternative possibility exists: in the other hypothesis proposed by Ferrari, mirror neurons, while creating a neural code for the observed action and producing its simulated copy, would also interact with the limbic system and other emotional brain areas. Such a communication would eventually trigger the emotional reaction.[39] This hypothesis seems to be more corroborated by empirical research. Several fMRI studies have shown that during both observation and imitation of emotional facial expressions, regions not belonging to the MNS display increased activations.[40] For instance, Van der Gaag and colleagues showed an increased activity in the insular cortex, anterior cingulate and amygdala during both observation and imitation of emotional faces.[41]

Therefore, either these regions have mirror properties (an assertion for which an empirical basis is still lacking) or their activity is triggered by the brain representations of the emotional face created also through the activation of the MNS.[42] Interestingly, significant correlations have also been shown between the activity of both the MNS and emotional areas and measures not just of empathy, but also of interpersonal abilities.[43] This indicates that recognizing and imitating emotional faces are in strict relationship not only with empathic abilities, but also with social cognition skills. In this sense social cognition may represent the necessary antecedent on which empathy can develop.

To conclude, we agree with a recent critical review of the literature evaluating the relationships among empathy, imitation and MNS which stated that:

> MNS are deeply involved in empathy but given the various forms of imitation, encompassing emotional and non-emotional, automatic, and voluntary actions such a relationship may vary. Moreover, these different forms of imitation may involve the MNS to different extents.[44]

When empathy is missing: The study of psychopathology to understand empathy

A widely used approach to understand empathy and its biological bases is through the study of those psychopathological disorders characterized by altered empathic abilities, from a subtle reduction of these skills all the way to their complete lack. Among psychopathological models, the one that seems best suited for this purpose is *Psychopathic Personality*.

Psychopathy is in fact a personality disorder characterized by lack of empathy and of guilt, superficial affect, manipulation of other people, and severe, premeditated and violent antisocial behavior.[45] Callous, unemotional and detached personality traits observed in adolescents and children (the so-called callous-unemotional personality) are also considered as antecedents or risk factors for the development of psychopathic personality in adulthood.[46]

From a behavioral point of view, lack of empathy in these individuals has been studied in many different ways, providing scientific support to early clinical observations. For instance, it was shown that psychopathic subjects have a reduced ability to recognize emotional expressions. More precisely, recognition of fearful, sad, and happy expressions is reduced, while disgusted and angry expressions are normally detected[47] (for a detailed summary of the other cognitive, emotional and behavioral alterations reported in this condition please refer to a recent narrative review by Blair).[48]

Neurobiological alterations were shown as well, both at a structural-morphological and a functional brain level. Studies on morphological abnormalities consistently pointed out a reduced volume of the two amygdalae in individuals with psychopathic traits.[49] The severity of psychopathic traits were also correlated with the severity of grey matter loss.[50] Functional data also supported the importance of amygdala alterations in psychopathic subjects during empathic situations.

For instance, Glenn and colleagues found reduced amygdala activity while psychopathic subjects coped with moral judgments.[51] Reduction in amygdala responses were shown during several other types of tasks involving empathy, which include face perception and the perception of others' pain, both in psychopathic subjects and in adolescent with callous-unemotional traits.[52]

As a matter of fact, pain perception deserves a more extended consideration in this review, since it has been widely used as an experimental paradigm to study empathy in *psychopaths*. In adolescents, reduced activation in amygdala and anterior cingulate cortex correlates with psychopathic traits as measured by clinical rating scales.[53] These results are strongly consistent across studies.

For instance, in another study on adolescents with callous traits, the perception of others' pain evoked reduced brain activity (as compared to not-callous adolescents) in bilateral anterior insula, anterior cingulate cortex, and inferior frontal gyrus, regions associated with empathy for pain in previous studies (see below).[54] Therefore, studies on empathy for pain in psychopathic individuals confirm results from those conducted with healthy individuals and suggest that similar regions are involved in perceiving our own pain and others' suffering.

Finally, it is also interesting to note that the Default Mode Network (DMN) is altered in individuals with psychopathic traits.[55] The DMN is a group of regions that show higher activity during resting states and internally, as opposed to externally, directed mental activity. The DMN remains more active in psychopaths during an externally directed task, namely a Go-no Go task, suggesting that failure to properly deactivate this network may be a characteristic of these personality alterations. Particularly, the posteromedial cortical region of the DMN seems to be specifically affected, as suggested also by a multiple regression analysis, showing how the changes in brain activity of this region, during the Go-no Go task, were associated with psychopathic traits.[56]

Another psychopathological condition that seems to be correlated with a lack of empathy is *alexithymia*. Alexithymic patients are unable to display emotions, to describe, recognize and label them. As a matter of fact, lack of empathy, in this condition, may be related to a primary difficulty in understanding their own emotions. In this sense, the lack of what we would call semantic categories, may also prevent these individuals from recognizing emotions in others. A few studies evaluated empathic alterations in alexithymic patients, though their results are not completely consistent. In particular, patients with alexithymia show reduced activity in regions related to empathic process. For instance, reduced activity in the dorsolateral prefrontal and anterior cingulate cortex while processing others' pain has been found.[57]

Furthermore, a reduced response in the amygdala has been found in alexithymic patients also while they watched emotional faces. This reduction was also statistically correlated with the severity of their alexithymia as measured by clinical rating scales.[58] These reduced activations can be considered related to the alterations of the cognitive components of the emotional processing, particularly the executive and regulatory aspects.

The last psychopathological example of altered empathic ability is the one involving disorders of the *autistic spectrum*. Autism is not a unique clinical entity and the autistic spectrum also includes, for instance, conditions characterized by mild to severe mental retardation.[59] Therefore, since patients with

autistic spectrum disorders not only have empathic deficits, but also cognitive, intellective and behavioral alterations, trying to define whether an altered brain response is in fact related to a given, distinctive clinical manifestation – in our case impaired empathic skills – exposes us to a high risk of oversimplification.

As such, the lack of empathy in these patients should be considered not as a detached condition but in the framework of the general pattern of alterations. For instance, it is well-known that one of the most common alterations in autism is the lack of ability to understand others' facial expressions.[60] This deficit is often related to altered ToM and perspective-taking mechanisms. However, it is well-known that these patients also show alterations in early face perception mechanisms, including an abnormal response in the face-selective fusiform gyrus and an altered eye scan-path while exploring picture of faces, as demonstrated with the use of eye-tracking techniques which can follow gaze movements and fixations.[61]

Thus, the alterations in face emotional perception and response may be explained, at least in part, by some more basic perceptual abnormalities. If this is true, autistic patients may not be capable of emotional recognition primarily because they are capable of gathering only incomplete, biased or incorrect information about faces.

In line with this hypothesis, some studies do not support the view that altered ToM mechanisms play a role in reduced empathic abilities in autistic patients. For instance, Peterson showed that children with autism were less empathic, according to their teachers, than normal children. However, ToM competencies were unrelated to the alterations in empathic abilities.[62] In this study autistic children and normally developed ones were evaluated using a test for ToM abilities (particularly the false beliefs test). Moreover school teachers assessed their empathic behavior on a scale from 0 (complete lack of empathy) to 5 (almost always empathic). Although autistic children had lower ToM and empathic scores as compared to normally developed children there was no significant statistical correlation between ToM and empathic ability impairments. On the contrary, a relationship between ToM and empathy was found in normally developed controls.[63]

Given these fundamental premises, a few studies have tried to evaluate the neurobiological counterparts of the altered social skills found in autistic patients.[64] As far as empathic concern for pain is concerned, a recent study failed to identify differences in autistic patients as compared to controls. Autistic patients and controls showed overlapping neural activity in several areas involved in pain perception and emotional reaction (including amygdala, orbitofrontal cortex, insula and anterior cingulate cortex) while looking at painful faces as compared to non-painful ones.

The only difference was that the score of empathic concern as measured by the Empathic Quotient questionnaire predicted the magnitude of the activations in patients but not in controls. This suggests a subtle difference in the neurobiology of the pain empathic concern, but not a deficit as previously sustained.[65] Nonetheless, other studies did not provide consistent findings. For instance, Fan and colleagues were able to highlight differences in autistic patients as compared to healthy controls while viewing body parts being accidentally injured or a person intentionally hurting another.

In the first case, autistic patients recruited significantly more somatosensory cortex, but showed less activity in the anterior midcingulate and anterior insula. In the second case, a reduced neural response in the medial prefrontal cortex was observed in the patient group. The authors suggested that autistic patients exhibited heightened empathic arousal, but impaired social understanding when perceiving others' distress.[66] In another study on moral reasoning, autistic patients showed decreased activity in amygdala and other limbic regions, as well as increased ac-

tivation in the anterior and posterior cingulate gyri. The reduced activity may be related to a decrease in empathic abilities, while the hyper-activations of anterior and posterior cingulates – regions that also belong to the DMN – were explained in terms of biased social information processing.[67]

Empathy in autistic patients was also evaluated with tasks based on face perception, in which patients and controls were instructed either to evaluate the emotional state observed in a face or to identify their own emotional response to that face. Despite the lack of differences in behavioral performance, different pattern of activations were highlighted between the two groups.

For instance, autistic patients activated the dorsal middle prefrontal cortex while controls activated the ventral prefrontal cortex. Moreover, during the identification of their own emotional response, autistic subjects activated additional frontal and inferior temporal areas that were not recruited in the control group. On the other hand, both groups showed areas (specifically, the subgenual anterior cingulate cortex and the precuneus, both belonging to the DMN) in which the brain response during the task was parametrically correlated with empathic scores, as measured by the Empathic Questionnaire.[68] Such differential patterns of activation may suggest that patients used different strategies to identify their emotional response to others' emotions and to evaluate others' face expressions.

It is interesting to note that the cited studies did not find any specific alterations within the mirror neuron system of autistic as compared to healthy individuals. While there are several possible explanations for this lack of differences, the most relevant in our opinion is the fact that, at least to our knowledge, no study has specifically assessed the role of the MNS in relation to empathic alterations in autistic patients.

As a matter of fact, several studies in autistic patients showed alterations in the mirror neuron system during observation/imitation tasks that did not involve empathy. For instance, during action observation and imitation, autistic patients showed reduced activity in the MNS (namely, the inferior parietal lobule) and in ToM areas (including the temporo-parietal junction).[69] Therefore, these results supported the idea that altered MNS may be responsible for dysfunction in social cognition. In particular, the so-called "broken mirror" hypothesis suggested that altered mirror neuron system activity might be responsible for a self-other matching impairment, altering the *Embodied Cognition* of this type of patients.[70]

However, the broken mirror hypothesis was recently criticized, by maintaining that alterations in the MNS were not responsible for the alteration of embodied cognition and social skills in autism.[71] In this sense, as previously stated, the MNS may be more strictly related to the basic function of recognizing and giving sense to others' actions that may eventually trigger also an emotional/empa-thic/reaction.[72]

Future studies, therefore, should not only clarify to what extent this system is altered in autistic spectrum disorders, but also whether this alteration is directly linked to alterations in empathy in these patients or rather if it affects some more basic function which, in turn, may be relevant for empathic reaction.

Finally, in autistic spectrum disorders, resting state activity was also examined in search of alterations that may be related to dysfunctional empathic abilities. In a study on global functional resting state connectivity, participants with autism showed a complex pattern of alterations.[73] Specifically, increased connectivity was detected between mirror neuron system areas and ToM areas. This increased connectivity was positively correlated with difficulties in social cognition and communication.[74]

Would one be empathic in the desert? Resting state activity and empathy as a trait psychological characteristic

In the previous section, we reported how alterations in the DMN and resting state activi-

ty may be among the neurobiological correlates of psychopathic personality or alterations of empathic abilities in patients with autism. Such results may have implications that are deeper than one can get at the first glance. In particular, an alteration of the DMN may mean that the baseline spontaneous activity of the brain could also be affected by psychopathological traits, that is, the alterations seen during an emotional or empathic task are already present in the *resting* brain.

Thus, if psychopathic and autistic brains have a different morphological and functional architecture than healthy brains, they may respond differently to empathic triggering situations because of a different information processing system. Can we extend such an idea to normal personality traits? Is it an empathic brain someway different from a less empathic one in the absence of any stimulus?

It is undoubtedly true that empathy rises as a behavior or a thought in the presence of a situation in which we have to consider others. Compassion, understanding and even pity cannot exist without an object. However, the proneness to be more or less empathic, to understand better or worse others' feelings or their intentions and states of mind, represents a trait characteristic, like all the other personality traits. Specifically, a trait characteristic is clearly related to the predictability and the reproducibility of our behavior. For instance, a shy person will be consistently shy within different contexts. In the same way, a person with high levels of empathic concern will constantly show greater participation in the feelings of meaningful others.

To put it differently, an empathic person will be empathic under the most diverse situations. In this sense, cognitive psychology has hypothesized that the way in which we react to a given situation largely depends on the *state of mind* that precedes that situation. The idea that how we cope with situations is deeply influenced by our "mind disposition" is indeed an old one:[75] from Plato to William James and cognitive psychology. In this sense, the way in which we react to relevant situations, which may trigger empathy, is somewhat determined *a priori* and derives from our personality and psychological characteristics.

According to cognitive models, therefore, the development of the empathic reaction is also related to information processing. If empathy is a state of the mind, a trait characteristic of our personality, it is plausible that neural activity would be modulated by its degree, not only when individuals are exposed to engaging situations, but also *at rest.* An empathic mind is such because it is shaped in advance to process information and react emphatically. Over the last decade, these considerations, among many others, have prompted the study of resting-state brain activity and its correlations with defined psychological or psychopathological traits.

As compared to activation studies, however, resting-state studies present a different difficulty – the fact that there are different ways to measure and to assess neuronal fMRI signal. This is not a trivial issue since each method conveys different, often complementary, information on spontaneous brain activity. For instance, functional connectivity is supposed to provide a measure of the functional relationship among distinct brain regions, as an expression of the degree of coherence of their neural discharge. Other indices, like the *Hurst Exponent*, are measures of complexity that reflect the mutual interaction between segregated and integrated brain activity of a given region. The *Hurst Exponent*, in particular, is an index that describes the predictability of a time series. The *Hurst Exponent* has a range between -1 and 1. The closer to the extremes the Hurst exponent is, the more the time-series is regular and predictable, namely, the past and long term dynamics have a stronger influence on future responses. On the other hand, a Hurst exponent closer to 0.5 describes a chaotic and less predictable time-series. The *Hurst Exponent* of an fMRI time-series is increased in the hippocampus with aging but decreases with cholinergic transmission enhancement.[76] Nonetheless, this does not warrant the con-

clusion that a higher *Hurst Exponent* is related to a worsening in brain functioning. For instance, a reduction of HE has been observed in autistic and schizophrenic patients.[77] Therefore, it seems more plausible that the *Hurst Exponent* reflects some inherent pattern of spontaneous discharge and that it can be modulated by psychological or psychopathological variables. Furthermore, the *Hurst Exponent* has been linked to personality traits involving extraversion and impulsivity.[78]

In a preliminary research from our laboratory presented at the 2014 Annual Congress of the Italian Society of Neuroethics,[79] we calculated the *Hurst Exponent* in twenty subjects with different degrees of emotional concern as measured by the Interpersonal Reactivity Index and showed that emotional concern was related to the activity of emotionally related regions (figure 1). In particular, we found that the Hurst Exponent in the amygdala was correlated with the score of this empathic dimension: the higher the emotional concern, the more predictable the neural discharge in the amygdala. Thus, it seems that a coordinated discharge of this structure is fundamental for entering in emotional resonance with others. As the data were acquired at rest, they may reflect the predisposition, the proneness to react in an emphatic (or not empathic) way.

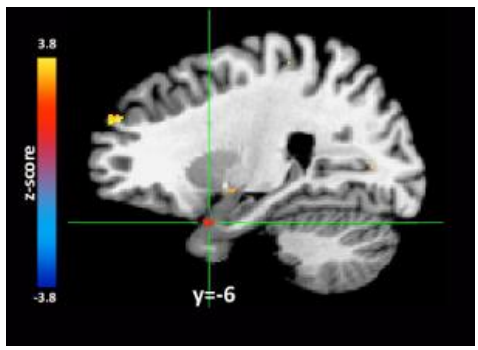

Figure 1. Hurst exponent in the amygdala increases with the increase of empathic concern measured by the Interpersonal Reactivity Index, in a group of twenty healthy volunteers

Other studies have tried to describe the relationship between brain resting state activity and empathy. Most of them were conducted using functional connectivity measures, the most widely used metric in resting state analysis. A recent review examined the role of the DMN in understanding others' thoughts and emotions.[80] Consistently, these different studies showed that the medial prefrontal cortex may be involved in the social understanding of others. In particular, as far as empathy is concerned, the ventral portion of this cortical region, along with the medial temporal lobe, is mainly associated with emotional engagement during social interactions, while its dorsal part, through its connection with the tempo-ro-parietal junction, is related to the understanding of mental states.[81] These results confirm the hypothesis that the DMN plays a fundamental role in empathy and social cognition, as clearly summarized by Mitchell who claimed that «when left to its own devices, the human brain appears naturally to engage in social-cognitive thought».[82]

Would one be

In this review we discussed how a widespread neural system supporting empathy is present in our brain. Although descriptive psychology has defined different forms of empathy, in neuroscience these distinctions have not been as sharply drawn. This makes a systematic review of the literature is more difficult, given that researchers most often refer generally to the neurobiological correlates of empathy without making any distinction among emotional understanding, perspective-taking, emotional contagion and distress for others' suffering.

Regarding the emotional sharing and contagion components of empathy, the literature has consistently pointed out that regions related to emotional perception and regulation, like the anterior cingulate cortex, insula and amygdala, seem to be recruited both during the subjective experience of a given emotion

and in the understanding and sharing others' emotions. Due to the type of analysis and the limitations of the functional exploration of the brain techniques, which cannot image single neurons, it is not possible to understand whether an identical pattern of neural discharge is involved in both inner emotional experience and in empathy. However, what can be said is that a large common recruitment of these brain areas is present during both experiences.

Of course, despite the commonalities, experiencing an emotion and observing or being empathic with it also recruit specific and different brain areas. Empathy studies are not generally interested in these differences, since they are more focused in assessing commonalities between subjective emotional experience and empathy. However, differences do count. Too focused on highlighting, showing and demonstrating that feeling sorrow for others' pain is just like experiencing our own, sometimes researchers seem to forget that if this were the case, we would not be able to distinguish ourselves from others: we would be in a condition where the boundaries of the self would be lacking, as happens in some psychotic conditions.[83]

Also, understanding differences between feeling one's own emotions and empathy for others' emotions is the basis for the understanding of a third person perspective, which is fundamental in detaching from emotions which may otherwise become unbearable.[84] Detaching from emotions is a necessary operation, for instance, in the psychological and psychiatric professions: being too absorbed by patients' suffering may lead to negative effects, like emotional exhaustion and burn-out.[85]

As far as the perspective-taking dimension of empathy is concerned, several studies have shown that a wide and complex network of areas is involved. Specifically, the ToM and mirror neuron networks were systematically evaluated. The ToM network has been extensively studied over the last years: its functional neuroanatomy now includes several different areas. Each area seems to serve distinct functions and abilities gathered under the umbrella definition of ToM.

On the other hand, despite the increasing interest in the mirror neuron system, the findings that confirm a direct role of MNS in empathy and perspective-taking are relatively weak. For both ToM and MNS we would suggest that rather than being the neurobiological counterparts of empathy, they are systems that may trigger affective empathy. In particular, we believe that the two systems, allowing the interaction and the comprehension of others, may help to trigger emotional contagion and perspective tacking, but they are not sufficient and may not even be necessary.

It is interesting to note that emotional concern and perspective-taking are the two most studied dimensions of empathy. Despite the fact that the multidimensional construct of empathy proposed by Davis[86] also included the personal distress and the fantasy scale, there is no concluding evidence on their neurobiological underpinnings.

Finally, although the number of studies is still small, an interesting approach to studying empathy and, more generally, psychological dimensions, entails the study of brain resting state activity which could shed light on the processes that trigger the empathic reaction while we cope with others' feelings.

To summarize, the available literature on the neurobiology of empathy portrayed in this short narrative review suggests a few conclusive points that may be a base on which to develop future research:

(a) Neurobiological research confirmed the position of descriptive psychology that empathy is not a unitary concept but rather a constellation of behaviors, thoughts and feelings consistently and constantly present when we deal with other human beings;

(b) Since there is no evidence for a shared system for all of the forms of empathy defined, the very concept of empathy

and the possibility of defining its neurobiological underpinnings have to be reconsidered. We can no longer speak of this concept without specifying which definition, part or dimension we are referring to;

(c) In line with this complexity, each dimension of empathy seems to be linked to a different neurobiological correlate;

(d) The proposed distinction between cognitive empathy and emotional empathy may also be traced at a neurobiological level. Specifically, the activity of the Theory of Mind network and the mirror neuron system may play a role in cognitive empathy, while the limbic and paralimbic areas seem to play a role in emotive empathy.

To conclude, it is our opinion that recent achievements in cognitive neuroscience have provided a novel and deeper comprehension of how we interact, understand and eventually empathize with others. However, several aspects still remain to be dissected, including the neurobiological underpinnings of the distinct forms of empathy already described in clinical and behavioral research.

Future research and theoretical speculation should start from these consistent pieces of knowledge to develop a more inclusive and comprehensive theory of the way we feel about others.

Notes

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