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The multi-layered structure of empathy: from theoretical to neuroscientific perspectives

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Alla memoria di Gianluca

Fermo sulla frontiera da cui osservi
quel che sei stato, quel che già non sei
- F. Scarabicchi

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Introduction

Before beginning, three years ago, my PhD course at the University of Camerino, in the research group of Professor Roberto Ciccocioppo, I didn't know anything about Neurosciences. In my mind, it was the field of reductionism, where every phenomenon is explained through the principle of "this is how it works". But let me be clearer: before starting my PhD course, I had always been studying Philosophy. Of course, during my philosophical studies I had met, now and then, some neuroscientific contributions, but nothing that could give me solid basis for understanding the field.

The breakthrough happened while attending a first level Master course in *Narrative Medicine, Communication and Ethics of Care*, right before applying for the PhD program. During those classes I could open myself to a more scientific approach and understand that the problem is not the reductionism. As Luca Grion[1] stresses, indeed, although an *ontological reductionism* is to be avoided in order not to miss the whole complexity and *eccentricity*[2] of our experience, there is a healthy reductionism, which is the *methodological reductionism*. To methodologically reduce the analysis to the mechanisms that inhabit the complexity is the duty and the vocation of the Science (and thus also Neurosciences). On the other hand, Philosophy, and Human Sciences in general, must take care of keeping together the complexity itself.

Pavel Florenskij, the Russian philosopher I wrote about in my masters' thesis, says that every discipline is a different language through which we approach reality. Given the high number of languages (that is of disciplines) we use to study the phenomena of reality, reality seems to us extremely fragmented. But it is only a perspectival error: reality is one, although methodologically reducible to many layers.

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[1] Grion, L., *Persi nel labirinto. Etica e antropologia alla prova del naturalismo*, Mimesis, Milano-Udine 2012.

[2] The reference is at Plessner, H., *Levels of Organic Life and the Human: An Introduction to Philosophical Anthropology*, Fordham University Press, 2019.

Keeping this awareness, I began my PhD course with the intent of building my research activity on a multi-layered approach that could take into account different languages and establish a dialogue between them. So I started addressing and studying the topic of consciousness. It has been always fascinating to me, since without consciousness, I would not even be here, asking myself what it means to be conscious. As the months passed, I realized that what I loved about consciousness was exactly what made its study so complicated. I refer to the fact that the only way we can analyze consciousness, is through consciousness itself. This makes things really hard. So to escape this loop, I thought it would be better to dissect this complexity by focusing on a different phenomenon, however related to consciousness.

And thus I met empathy, one of the most discussed topics in both philosophy and neuroscience. I decided, together with my supervisors, Professor Ciccocioppo and Professor Donatella Pagliacci from the University of Macerata, to elaborate a novel model to study empathy, building my research on a multi-disciplinary approach that keeps together both the theoretical and the experimental perspectives.

In particular, I first focus my investigations on revisiting the traditional approaches on empathy, such as the aesthetic, the phenomenological and the anthropological ones. I then elaborate a theoretical paradigm to read empathy as a multi-layered phenomenon. It involves bodily, emotional and cognitive dimensions and leads to particular kind of experiential knowledge, through which the self can access, although in a non-original way, the emotional state of another self and also come to a better knowledge of itself.

During the six months I spent in the research group of Georg Northoff, at the Royal Ottawa Mental Health Center, in Ottawa (Canada), I developed the idea of self and empathy being highly intertwined. I test this hypothesis by performing an ALE meta-analysis on studies about empathy and comparing the results with an already published analysis[3], to look for overlapping brain regions between the empathic

[3] Qin, P., Wang, M., & Northoff, G. (2020). Linking bodily, environmental and mental states in the self-A three-level model based on a meta-analysis. *Neuroscience and biobehavioral reviews*, *115*, 77–95.

process and the self-processing. After that I analyze, from a neuroscientific point of view, the phenomenon of synchronization, that has been found to be at the basis of different inter-personal phenomena, among which empathy. This focus made me understand better the natural roots of the phenomenon I was addressing and, in general, the fact that we are nature.

For this reason, I worked on the elaboration of an animal model of empathic-like behaviors that could help in the study of the molecular and biochemical mechanisms that underlie empathy. So in the fourth Chapter of this work, I propose a rodent paradigm to observe and evaluate intra-specific and inter-specific behaviors in response to different emotive states. Lastly, I analyze the case study of the public perception of laboratory animal testing, to warn against the biases and prejudices that can come from relying too much on what an unbalanced empathic experience could suggest.

These are the things that you will find while reading my work. The things that you won't find are all the ones that lie outside and yet surround my work. Without the latter, the former would never come to life.

Chapter I

THE THEORETICAL FRAMEWORK

1. Traditional approaches

1.1. The aesthetic approach

The history of empathy is first and foremost the history of a word. *Empathy* indeed is not the original term associated to this complex and intriguing phenomenon. In order to track down its earliest conceptualization we need to go back to the Aesthetic Theory. Before becoming the field of art and beauty, Aesthetics was the «domain of sensory or perceptual experience in contrast to that of conceptual thought or reason» (Lanzoni, 2018). Into this context, authors adopted the German word *Einfühlung* to describe the ability of "feeling-into" the observed objects. The term is composed of *Fühlung*, that comes from the verb *fühlen* which means "to feel", and the prefix *ein*, through which it is expressed the movement of a subject "going into" something else. In 1909 E. Titchener translated *Einfühlung* into the English term *empathy* to indicate the «natural tendency to feel ourselves into what we perceive or imagine» (Titchener, 1915).

Before Titchener's translation, the first author who used the concept of *Einfühlung* was Friedrich T. Vischer who composed a phenomenology of the aesthetic experience. In his *On the optical sense of form* (Vischer, 1873), he linked this experience to an imaginary bodily reaction to what is seen: the aesthetic pleasure passes through an activation of the muscles and, in general, through physical processes, among which the mechanism of *Versetzung* (Vischer, 1873). This term was coined by the German philosopher a Johann Gottfried Herder (Herder, 1778, 2002 (Plastik, 1778)) and refers to a sort of one's own "displacement" into the outer body or object. So the aesthetic contemplation of something is seen as a process through which the observer, thanks to her sensitive experience, introduces her feeling into the observed object, making that object "alive" and, at the same time, receiving some sensations and feelings from it and thus becoming one with it.

In this way, perception is always an embodied experience. In particular, according to Vischer, the perceptual experience is composed of different affective responses, among which also *Einfühlung* is found. Starting from the most basic one, the

aesthetic experience is characterized by a *sensation* (*Empfindung*), that is an unconscious and intuitive bodily response to the stimulus. At the second level, we can find the more complex experience of a *feeling* (*Fühlung*), that is an emotional response to an observed object in which a familiar vital sense is recognized or, otherwise, projected. The act of projecting one's own interiority into an exterior object is put into play most of all at the third level, that is the proper experience of *feeling-into* (*Einfühlung*), through which the subject projects her own vital sense into an observed form and experiences a unification with it. Beyond these further conceptualizations, at the basis of Vischer's analysis of the aesthetic experience there is the belief that what is fundamental for perceiving and enjoying an observed object is our body. As Silvia Scasserra points out in her master's thesis *Un altro me? Dall'Einfühlung alla empathy machine* (Scasserra, 2021), corporeity is the *medium* that allows for experience.

In the analysis that Vischer elaborates around the phenomenon of *Einfühlung*, we can find a twofold commitment: on one hand, he is careful to join the romantic tendency of considering art as a form of spiritual enjoyment[4]; on the other hand, he wants to bring an innovation in the field of aesthetic perception and enjoyment. In order to meet both these two needs, he structures *Einfühlung* as an act in which both the spiritual component is present, in the form of the inner "feeling" that the observer person projects into what he/she is observing, and a more scientific component, in the form of the psychological mechanism of projecting that builds the perceptive act.

After these philosophical conceptualizations, another author focused his attention to the phenomenon of *Einfühlung*, making it very popular among the researchers. This author was the psychologist Theodor Lipps, who extended the analysis of the phenomenon to the psychological field[5]. Lipps wanted to approach the study of the

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[4] According to the romantic theory, nature is the perfect mirror of human feelings and humans can inspire the natural things with their inner feelings (see, for example, Novalis. (1798). *Die Lehrlinge zu Sais*.).

[5] T. Lipps was taught philosophy in Monaco, were he founded a Psychologisches Institut in 1913. He distinguished two psychological fields: psychology as analysis of inner consciousness and psychology as experimental analysis of nervous phenomena. He stressed the importance of recognizing the autonomy of both these two fields' methodologies.

aesthetic acts from the perspective of psychology, without cutting off the point of view of a spiritual understanding of art, in accordance with the romantic needs. As well as Vischer, Lipps investigated the experience of *feeling-into*, of "projecting" one's own inner feeling into the external observed object and considers this experience as a form of knowledge. In particular, it is one of the three distinct domains of knowledge: the knowledge of external objects is called *perception*, the self-knowledge is called *introspection*, and the knowledge of others is called *empathy* (Lipps, 1903).

According to Lipps, we possess an *instinct of empathy* that involves both the capability of *expressing* a certain feeling when we experience it, and that of *imitating* the expression that comes from someone else's feeling (Lipps, 1907). When observing someone else, our system is unconsciously activated in response to the stimuli, in the form of an instinctual kinesthetic resonance. This resonance leads the empathizer to experience a sort of "fusion" with the empathized. From this feeling of fusion felt by the empathizer, it derives an automatic expression of experiences that are similar to the ones that the empathizer experiences when first-personally performing the same action performed by the empathized. This is possible because of the empathizer's capability of an inner *imitation* of what is outside.

The introduction, into the psychological field, of the concept of empathy, intended as this form of imitative process, substitutes the one of *inference by analogy*[6]. According to this hypothesis,

> the only mind I have direct access to is my own. My access to the mind of another is always mediated by his bodily behavior. But how can the perception of another person's body provide me with information about his mind? Starting from my own mind and linking it to the way in which my body is given to me, I then pass to the other's body and by noticing the analogy that exists between this body and my own body, I *infer* that the foreign body is probably also linked in a similar manner to a foreign mind (Zahavi, 2001).

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[6] One of the most important proposers of the argument was J.S. Mill (Milll, J. S. (1865). *An examination of sir William Hamilton's philosophy*. Longmans.).

On the contrary, Lipps' hypothesis bases the possibility of reading others' minds on an instinctual and automatic mechanism of *imitation* in which no mental inference occurs. In this way, this basic form of empathy is not a mental act, but an immediate experience, a complete "emotive participation" to the nature of what is observed[7].

So, at the basis of Lipps' concept of empathy there is an *inner imitation* (*innere Nachahmung*) (Lipps, 1903-1906), that is an innate and instinctual ability of mirroring others' experiences. In order to understand better this ability, we want to make an example proposed by Lipps himself, the one about observing an acrobat's performance. When observing an acrobat who is performing a difficult and possibly dangerous stunt, our instinctual imitative mechanism is provoked and it makes us feel as if we were performing that stunt.

But what is different between the process described by Lipps and the one described in the hypothesis of the inference by analogy is the source of our empathic process. Indeed, while in the other hypothesis we make some inferences on the basis of what we see, that is the acrobat's external movements and expressions, in Lipps' theory we internally imitate something that is not properly visible, that is the acrobat's effort and tension towards action. This is why we feel as we were one and the same with the acrobat while she is performing her stunt. We experience a sort of "fusion" with the acrobat.

We have to notice that the imitation that Lipps refers to is not the imitation of a model. We do not simply imitate someone else, but we originate, we *express*[8] an experience of participation to someone else's experience. So when we are in front of some stimuli, we instinctually express ourselves according to a sort of resonance, of fusion to what we perceive. This expression in response to the other is an original experience for us and then we "project" it into the other person, through a sort of "doubling" (*Verdoppelung*) (Lipps, 1903-1906). So we can say that the real source of

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[7] The mental and cognitive component, in Lipps' analysis of empathy, is secondary to the instinctual and automatic one, which is the most basic one.

[8] The instinct of expression is quoted by Lipps together with the instinct of imitation.

our empathic process is our own experience that derives from our moment of fusion with the empathized individual and that then we project into him/her.

Of course, our internal "imitation" of the acrobat's experience is always contextualized and nested in our own personal life experience. Using Georg Northoff's terminology, it seems to us that this process of imitation is *self-related* (Northoff, 2011). Being self-related and, at a more cognitive level, also *self-referential*[9], the empathic process tells something not only about the empathized but also, and most of all, about one's self. When empathizing with someone, indeed, we experience them through our own experience and, as a consequence, we can say that we experience them as an expansion of ourselves. This means that, in some way, when experiencing others, we experience ourselves.

This happens because of what Lipps calls *apperception* (Lipps, 1903/06). By apperception, it is intended a spiritual and mental form of act that "adds something" to the actual perceived object. In addition to the example of the acrobat, there is another example elaborated by Lipps that is useful to understand better the apperceptive movement. It is the example of observing a column. When we observe a column, we can say that it "stands up" even if this descriptive sentence does not make any sense, since the column is inanimate and thus it is not able to perform any action or movement. Although we describe the column as standing up. The reason for such a phenomenon is that we mentally *apperceive* a movement at the basis of the form of the column, a movement that is endowed with a precise direction, that is from the basis of the column to its highest point[10].

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[9] The self-referentiality of the act refers to the fact that the act is reflexive, meaning that it leads to an experience that is recognized as belonging to one's own self (Northoff, G., Heinzel, A., de Greck, M., Bermpohl, F., Dobrowolny, H., & Panksepp, J. (2006). Self-referential processing in our brain--a meta-analysis of imaging studies on the self. *Neuroimage, 31*, 440–457.).

[10] It is important to notice that for Lipps every kind of form refers to a particular emotive value ad that there is a deep connection between forms and inner spiritual states. This is because of the conformation of the forms and the human anatomy and experience. This means, for example, that a vertical line (such as the one present in a column) represents the concretization of the upright posture that contrasts the gravity force. So for Lipps a vertical line is the symbol of the standing up against gravity (Lipps, 1903/06). On the basis of these considerations, Lipps elaborates also an analysis of the optical illusions (Lipps, 1897a).

In both the cases, as we already noticed, the source of the empathic act is the empathizer's inner life and emotions. However, in the case of empathizing with another person, the apperceptive act is based on the actual experience of the empathized, that is internally "imitated" and expressed by the empathizer. On the contrary, when empathizing with an inanimate object, there is no such an experience coming from that object. So in this case, the apperception is totally based on a mental movement of *representation*[11] (Lipps, 1903-1906). Our apperception of the external object comes in the form of a representation of that object as experiencing a particular emotive experience, in accordance with our personal experience. This representation is then transferred, projected into the actual external object that, in this way, appears to us as alive and endowed with an inner world.

So, as well as the empathic experience of someone else's emotive states, also the aesthetic enjoyment is based upon an expansion of one's own interior movements. In particular, according to Lipps, we perceive as beautiful those objects that intensify or confirm our interior reality and vital sense and, on the contrary, we perceive as ugly those objects that deny our interior life. These opposite movements lead to what Lipps refers to as "positive empathy" or "sympathy" in the first case and, on the other hand, as "negative empathy" or "antipathy" in the second case. So for example, in order to be beautiful, the column must stand up in a harmonic way, with all its energies, without dedicating any effort to any other purposes than the one of standing and contrasting the gravity force (Lipps, 1897a).

It is worth highlight that, differently from Vischer, for Lipps the reaction experienced when empathizing is not physical but mental or, better, "spiritual": when observing something, we can project our self's inner vital sense, our psychic "soul", into it, as if we could feel spiritually absorbed into the observed object (Lipps, 1897b). It is my "aesthetically contemplating I", that does not belong to the physical reality, which is engaged in the act of enjoying . So it seems that for Lipps it is through a sort of "self-objectification" that we can experience empathy towards an observed object.

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[11] We will deepen the concept of *representation* in the next chapter of our work.

Despite the fact that Lipps' theory of the empathic knowledge received some criticisms from the phenomenologists[12] that elaborated the concept of empathy after him, the importance of his position into the context of the research must be recognized. For the first time, instead, Lipps started to use the concept of empathy not only for addressing the aesthetic experience of contemplating something, but also for describing a form of knowledge linked to expressions and, by consequence, to emotions (Lipps, 1903). In this way, empathy is for the first time also a phenomenon of intersubjectivity and, in particular, of social cognition.

In addition, we insist that Lipps' contribution to the analysis of the empathic capability is fundamental also for another reason: it grounds the phenomenon of experiencing, and thus knowing, the world in an always ongoing process of instinctively and immediately resonating with the environment and of a following projecting our own inner experience into it. We will examine this process in depth in one of the next chapters, but for now we want to notice that this process could be seen as being in line with some hypothesis coming from the discovery of the *mirror* neurons, happened at the end of the last century, by an Italian research team of the University of Parma. They accidentally noticed that there are some neurons that are activated in conjunction with a specific movement of the body, but also when watching (mirroring) someone else making the same movement (di Pellegrino et al., 1992). It has been hypothesized that mirror neurons are not only essential to mimic somebody else's movement but, putting a subject in contact with others, also to experience the sense of empathy (Rajmohan & Mohandas, 2007)(Rizzolatti & Craighero, 2004). Even if we do not have evidence for this theory, it is interesting to notice that it is possible to hypothesize the existence of a neural substrate that describes the phenomenon defined by Lipps.

Other authors, that seem to us as important as Lipps, contributed to the investigation on empathy and offered a slightly different, but somehow complementary approach.

[12] We will focus on the positions elaborated by Husserl, Steins, Scheler and Merleau-Ponty.

1.2. The phenomenological approach

Around the first decade of the 20th century the concept of empathy was introduced in the field of Philosophy and, into this perspective, it became to be addressed as an important concept for the study of the intersubjective and relational field, but also as a phenomenon involved in the human knowledge. In particular, as we will observe, the authors who brought this approach considered empathy itself as a knowing capability, the one that we put into play when in contact with other individuals.

Into this new field of research, the investigations of Edmund Husserl and those of his student Edith Stein were probably the most popular ones at that time. Both Husserl and Stein share the use of an innovative method for addressing the topic of the empathic knowledge. This method is *phenomenology*. It was elaborated by Husserl in his work *Ideen I* (Husserl, 1913) and it aimed at exploring each phenomenon in the way it is, meaning "in itself". This method is thought by Husserl as the only way for reaching an objective knowledge of reality, a knowledge that is based on a direct perception of the "given" phenomena. This "givenness" of the phenomena we are in front of is what allows for grasping the "essence" of the phenomenon itself[13].

This introduction about the functioning of the human knowledge as it is analyzed by the phenomenological approach is useful to understand not only Husserl's perspective, but also Stein's one about empathy. Indeed, in her 1917 doctoral dissertation *Zum Problem der Einfühlung* (Stein, 1989) she describes empathy as an act that aims at reaching some kind of knowledge of another individual. Following the phenomenological method, Stein stresses that the empathic knowledge is based on the fact that the other individual is "given" to us in the form of a phenomenon. Before explaining this idea in depth, we think that it is important to disambiguate the terminology and thus the conceptual meaning of what we are talking about. In order

[13] The most important instrument that phenomenology uses for reaching a knowledge of phenomena's essence is the *epoché*. It consists in the act of suspending the judgment upon what is in front of us. After having suspended every "ontical" aspect (meaning everything that concerns its existence), the only data that remains to consciousness's awareness is consciousness itself, as a "phenomenological residual" (Husserl, 1913). These acts of *suspension* and *reduction* lead consciousness to understand not only the essence of the phenomena that it takes into account, but also its own transcendental structure, in order to understand how the process of knowledge works and, at the same time, in order to know reality.

to do this, we must observe that Stein's idea of empathic knowledge has nothing to do with a purely cognitive and rational act. Indeed, its meaning is linked to the concept of *experience*: to empathize with someone means to experience, in a *non-original* way, an emotion that belongs, in an *original* way, to the empathized (Stein, 1989).

In the opposition between what is "original" and what is "non-original", we can find Stein's innovative interpretation of the phenomenon of empathy. She indeed criticized Lipps' hypothesis according to which when observing for example an acrobat we experience what he/she experiences. According to Stein, if this was the case, it would be impossible to distinguish one's self body (and thus experience) and the body of the other individual (and thus his/her experience). The solution proposed by Stein - and by Husserl before her (Husserl, 1962a) - is the idea of reading empathy as a form of *intentionality.* With this term, used in the context of Husserl's phenomenological method, it is described the fact that consciousness is always consciousness of something, that it has always a content. An *intentional* act is thus an act of consciousness that is always directed towards something (Husserl, 1900–1901, 1913).

So, for Stein, empathy is an intentional act that is directed towards another subject who has his/her own experiences and who, in the context of the encounter, is always given to us as a phenomenon. In particular, as we already noticed, it is an intentional act that aims at reaching a knowledge about the other.

At this point, we have all the elements to define better this intentional act of knowledge that Stein calls empathy. Through her analysis, she intends to describe it first and foremost as the *basic* and *primitive* capability of immediately *experiencing* (though in a non-original way) someone else's experience. Of course, this does not mean that empathy is an irrational and unconscious process. We can realize this by following the development of empathy through the three steps that for Stein constitute its mechanism: at first, the other's experience is given to us in the exact moment in which we are in front of him/her; then we have an experience of the other's emotive state through her expressions and behaviors; finally the other's

experience becomes a content of our own consciousness and we can live it as it was our own experience (Stein, 1989).

In this three-step structure of the empathic process we can recognize, on one hand, a sort of naturalization of the empathic phenomenon, that is useful to fight against way too cognitive approaches, and, on the other hand, the awareness that empathy is an act of consciousness that, by its nature, is a complex and multi-layered phenomenon involving *also* the cognitive component. So empathy itself is a complex phenomenon and it involves both the basic instinctual layers and the cognitive and mental ones. To stress the importance of considering this multi-layered structure, though, does not mean to say that empathy is not a unique process. For Stein, indeed, others' mindedness and psyche is immediately and intuitively present in their gestures, intonation and facial expressions. Following this hypothesis, we can say that through empathy, the behavior of every other individual is for us immediately endowed with a psychological meaning.

The possibility to have experience of the other individuals is given by the fact that every individual is always immersed in an intersubjective reality. Thanks to this contraposition and relationship among subjects, every subject can experience him/ herself as a *self*, that is a unity that emerges from the flow of experiences in which it is immersed and that is distinguished from this flow. The unity that constitutes the self is built through a process through which every lived experience is recalled by the memory and assigned to one's self (**Figure 1**).

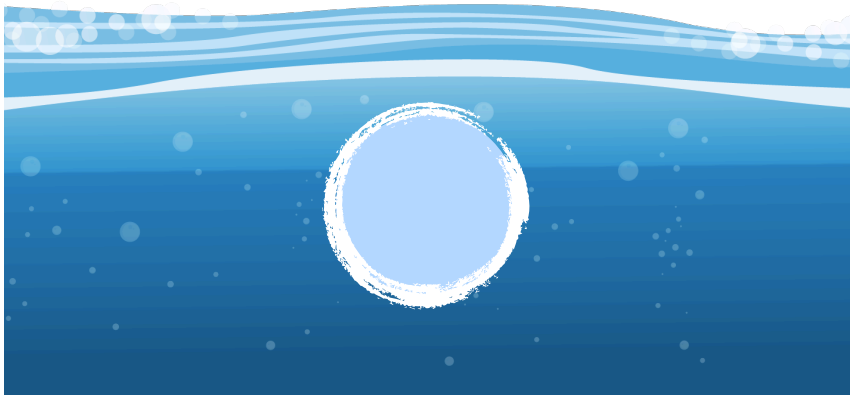

Figure 1. A representation of Stein's idea of the construction of the self. The sea represents all the experiences and, in general, the whole reality in which the self is always immersed. The flow represents the self that, on one hand, is made of the same water that composes the see, but, on the other hand, is individuated as a unity with a coherent form and direction. The process of integrating and centralizing all the experiences in the experience of being a self is made by the Default Mode Network (DMN) (Scalabrini et al., 2022). The DMN is a network of brain regions (including the medial prefrontal cortex, posterior cingulate cortex, the precuneus, and the inferior parietal lobule) that are active when the brain is not focused on any specific task or stimulus, but rather is engaged in internal thoughts, such as self-reflection, daydreaming, or mind-wandering and, in general, during tasks that require self-referential thinking, autobiographical memory retrieval, mental imagery, introspection, theory of mind and social cognition (Mak et al., 2017; Raichle, 2015). Its activity is thought to be fundamental for experiencing the world as a self (Qin, 2011).

Into this context, empathy is not an instrument that the consciousness uses for knowing a reality that is considered as its own product, as it seems to be in Husserl's formulation of the problem of consciousness and identity[14]. For Stein, empathy is

[14] Among the critiques that were raised against Husserl's theory, we can find the one of solipsism (see Kassis, R. (2001). *De la phénoménologie à la métaphisique: difficultés de l'intersubjectivité et ressources de l'intopathie chez Husserl*.), according to which for Husserl empathy is an instrument used by the self to build the reality, intended as a product of the self. Into this context, through empathy, the self reaches a more objective knowledge of reality, because it can count on different points of view. The other is for Husserl always an "alter ego" that is posed by the self, he/she is not seen as another individual with his/her own lived experience.

instead an experience that anyone can have to grasp others' consciousness and experience, that is always embedded and "concrete". Into this concrete world the self lives in an intersubjective space, where also other selves live and interact to each other in an autonomous but relational way (**Figure 2**).

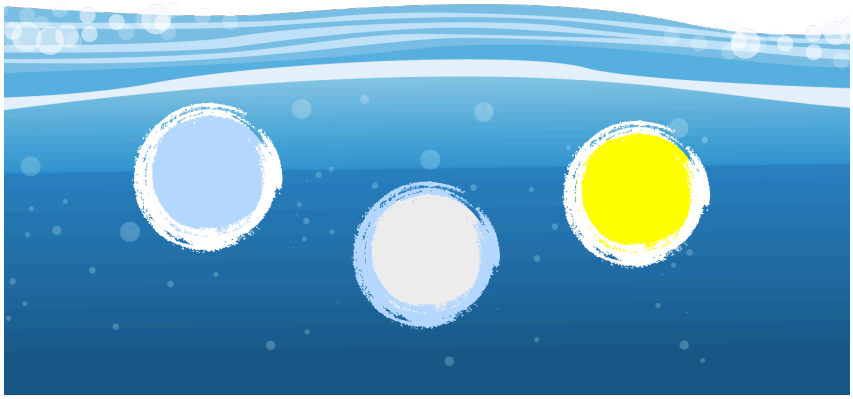

Figure 2. The intersubjective context, in which every self is in contact with other selves, that it can recognize as being similar in structure and functions, but qualitatively different in lived experiences.

In order to deepen the importance of these phenomenological considerations, we want to present now the element that Stein puts at the basis of the empathic process and that makes us understand what it means for her that empathy is an embedded experience. What allows for our embedded life is our living *body*. Through our body we can be in front of the other person and we can experience him/her in a direct, although non original way.

Husserl's phenomenological analysis read the body both as *Körper*, that is the physical body, and as *Leib*[15], that is the living body (Husserl, 1950). Thanks to this twofold meaning, the body is both an "object" that we can observe as a content of our intentional acts of consciousness and something that we can experience as

[15] The distinction between these two concepts was elaborated by Husserl in his *Cartesianische Meditationen* (Husserl, 1950). In particular, it is in the *Fifth Meditation*, where the author investigates the topic of intersubjectivity.

completely ours and, even more deeply, as properly ourselves. We are body. Through our body we have sensations and perceptions and we can count on a *medium* that allows for an experience of the inner world of another person.

Through what Stein calls "sensual empathy" (Stein, 1989), we can perceive the outer body as a living body as well as our own one, even if it is different from ours. So for example, if I am in front of a another person's hand, I am able to perceive it as belonging to someone who is alive and who has her own inner world,

> for my physical body and its members are not given as a fixed type but as an accidental realization of a type that is variable within definite limits. On the other hand, I must retain this type. I can only empathize with physical bodies of this type; only them can I interpret as living bodies (Stein, 1989).

The concept of *type* that Stein puts into play is useful to understand even better the organization of the empathic process. As we said, this organization originates first of all from an immediate and direct mechanism of coupling through which the outer body can be experienced by me in a non-original way as a living body. This recognition is possible because the outer body belongs to the same *type* as my own one, which I experience in an original way. This clarification fixes the empathic phenomenon to the interpersonal context, differently from the Aesthetic Theory's perspective, according to which I can empathize with an inanimate object as well as with another person. In the phenomenological perspective, indeed, the more the other individual belongs to a *type* that I recognize as similar to *my own type*, the more I can truly empathize with him/her. This primitive level of similarity between individuals, that precedes any form of cognitive intentionality and recognition, is the costitutive basis of the empathic process.

Stein's concept of type is useful also in the context of two other elements that we will deepen in the next chapters. The first one is the temporo-spatial constitution of conscious phenomena like empathy (Northoff & Zilio, 2022b); the second one is the well known phenomenon of empathizing more with familiar individuals than with unknown ones (Gonzalez-Liencres et al., 2014; Kawamichi et al., 2013; Rogers-Carter et al., 2018).

These considerations are also useful to approach what Zahavi (Zahavi, 2014a, 2014b) addresses as Husserl and Stein's preoccupation of describing the intentional structure of empathy and, in particular, of deciding whether empathy itself is a form of perception or not. In Husserl's investigation, indeed, only *perception* leads us to grasp the experienced object in a direct modality[16]. So can we conceptualize empathy as a form of perception? Husserl and Stein's answer is very interesting, as it is able to consider both the intentional element and the adherence of this intentional knowing act to some external environmental cues.

They both insist on the fact that empathy is different from perception as it does not allow for an original experience of the empathized's experience:

> there will always, and by necessity, remain a difference in givenness between that which I am aware of when I empathize with the other, and that which the other is experiencing. To experience, say, the emotion of the other consequently differs from the way you would experience the emotion if it were your own (Zahavi, 2014b).

In this way, Husserl and Stein's hypothesis has twofold relevance: on one hand the process of perceiving the cues coming from others ensures a direct and basic connection with their experiences and, on the other hand, the clarification about the non-originality of the intentional act ensures the self-relatedness of the empathic knowledge, that we anticipated earlier and that we will deepen further in the next chapters.

For now, we want to stress that through this phenomenological approach we can talk about a subject who is capable of directly experiencing others' emotions and, at the same time, of understanding that those emotions belong to someone else who has his/her own experience. According to this view, thanks to my empathic capability, I can perceive the other person as a foreign subject, that is a human being and that can

[16] Other kinds of intentional acts, such as the *signitive* one and the *pictorial* one, are less capable of making the object directly and bodily present to our experience.

experience as well as I can experience (Husserl, 1937), and not just as a mere body with her own expression.

In order to deepen the perspective according to which empathy is a particular kind of perception, Husserl notices that every kind of perception, and not just the empathic one, acts in the same way. The perceived object, indeed, is never experienced in its totality, as there is always some of its parts that are hidden from vision: «our perceptual consciousness is consequently characterized by the fact that we persistently transcend the intuitively given profile in order to grasp the object itself. That is, perception furnishes us with a full object-consciousness, even though only part of the perceived object is intuitively given» (Zahavi, 2014b). Perception is thus anticipatory and it involves the act of transcending what is given and co-intending what is absent. In this way, perception always requires interpretation (Husserl, 1962b) and every perception is always *apperception* (Zahavi, 2014b). So on one hand, empathy seems to be thought here as an immediate way of experiencing others' inner life but, on the other hand, both Husserl and Stein stress that others' psychical life is never completely accessible to direct perception (Husserl, 1966a). The other always remains the other, since his/her experience is directly but non-originally given to my perception (Stein, 1989).

This phenomenological approach to the empathic knowledge is useful to prevent a perspective that would consider it as a form of cognitive comprehension of others' mind. Thanks to Husserl and Stein's elaboration, indeed, we can refer to the empathic knowledge as an act that is based upon immediate mechanisms and that, for this reason, does not exclude important dimensions of the human experience, such as the direct bodily and emotional experience. So it is true that the empathic knowledge involves a cognitive act that requires a mature capability of having a Theory of Mind, but it is not entirely a cognitive process.

1.3. The anthropological-emotional approach

Both the aesthetic approach and the phenomenological one are useful for the investigation of the phenomenon of empathy, since they offer slightly different perspectives that, if taken together, can be complementary to each other.

At this point we want to introduce another interesting approach that has been adopted to investigate the empathic phenomenon. This third approach is the one that we could call anthropological-emotional one. The author that foremost contributed to this approach is Max Scheler.

Scheler's investigation is important because it digs deeply towards the heart of the intersubjective problem and thus of the relationship between individuals. In his work *Wesen und Formen der Sympathie* (Scheler, 1923)[17] we can find Scheler's phenomenological approach to some topics of the emotional life and, in general, of intersubjectivity and social cognition. According to the author, the phenomenon of understanding others' minds must be investigated in its whole complexity, since the human being is a complexity itself. This intention makes Scheler a phenomenologist but also one of the founders of the contemporaneous anthropology. In fact, he wants to pull the phenomenological approach out from the mere field of intentionality and consciousness, by bringing it into the study of emotions and thus values.

In particular, there is not a unique term that Scheler uses for addressing the phenomenon that he intends to analyze. In fact, he uses different terms, such as, for example, fellow-feeling (*Mitgefühlen*), feeling affectively and emotionally unified (*Einsfühlung*), reproduction of feeling (*Nachfühlen*), but also many others. *Nachfühlen* is used by Scheler in opposition to the term *Einfühlung*. They have similar meanings but Scheler's one does not present the reference to a sort of instinctual imitation/projection of one's own inner state into another one. In fact, this imitation/projection mechanism is what Scheler intends to fight as, according to him, inappropriate to indicate the phenomenon of understanding others' minds. In general, we can notice that in Scheler's terminological choice there is the will to contrast the study of *Einfühlung* as it was conducted by other authors before him. In addition, we can also notice the will to address a much richer phenomenon that anyone can

[17] The first edition of the book was published in 1913, under the title *Zur Phänomenologie und Theorie der Sympathiegegühle und von Liebe und Hass*.

experience and that we can trace at the basis of social cognition. We can call this general phenomenon *sympathy*.

By *sympathy* Scheler intends to denotate the disposition of "being together" that we can experience when in front of someone else's emotive state. This being together makes us resonate with the emotions of the other, thus generating a shared feeling. Although linked to and based on bodily and physical elements, the phenomena that concern the emotional field, such as feelings of sympathy, love and hate, must be considered as dominated by autonomous laws that it is possible to investigate through the phenomenological method. These emotional intentional acts do not depend upon the causal mechanisms of the physical reality, but they are independent from them. Scheler's will is to phenomenologically study and understand these intentional laws. This is why he puts into play different terms and concepts, with the idea that only one term does not explain the complexity of this field.

According to Scheler, we could find ourselves in many different situations, in which we can either feel emotionally involved in front of someone else's emotions or not. The case in which we emotionally share other's emotion and we feel concerned about him/her is a case in which we experience *sympathy*. It seems to be the same perspective that also Lipps and Stein adopted, but actually there is a difference between them. Scheler seems to reverse the perspective: in order to sympathize with someone, we first need to realize and understand that he/she is suffering. It is interesting to notice that the phenomenon that Scheler puts at the basis of this kind of sympathy is the one that he addresses, among other terms, with the term *Nachfühlen* which, as we said, is used instead of *Einfühlung*. This means that for Scheler, we need a prior understanding, given by what we could call *empathy*, in order to experience *sympathy*.

> Whereas empathy has to do with a basic perceptually understanding of others, sympathy adds an emotional response. Now, apart from stressing the difference between empathy and sympathy, the point that Scheler's examples is also to remind us that it is possible to empathize with somebody while being indifferent to his plight (Zahavi, 2014b).

So according to the author, we could describe empathy (intended as what Scheler calls *Nachfühlen*, that is "reproducing") as the capability of perceptually recognizing and understanding that another person is in a certain emotive state, without being affected by that state. Following these considerations, we could also say that empathy is the basis also for acts of cruelty, in which one can perceive someone else's emotion and use that knowledge to hurt him/her. But how can we come to such a perceptual knowledge about others' inner states?

Of course, Scheler's vision, as well as Lipps' and Stein's ones, is not cognitive. This means that we do not come to an understanding of others through, for example, an inference by analogy or an active cognitive mechanism. But Scheler's vision is innovative also for another reason: he stresses that others' feelings are directly accessible for an observer who implicitly and directly comes to know what a certain expression means for the one he/she is observing. We do not need any first-person experience of an emotion, in order to recognize it when lived by someone else. Instead, because of the characteristics of our body (that can be considered both as *Körper* but also as *Leib*), other psychic states are directly manifested in their bodily expressions.

In order to understand better the dynamics that Scheler describes, we intend to analyze some phenomena that he takes into account when talking about the experience of fellow-feeling. In particular we will describe the four following phenomena: the "immediate fellow-feeling" (*Mitgefühl*); the "fellow-feeling about something" (*Mitleid*); the "emotional contagion or infection" (*Gefühlsansteckung*) and the "emotional identification" (*Einsfühlung*) (Scheler, 1923).

With the first term it is intended the experience that can be phenomenologically addressed as "being one and the same". To make an example, two parents who face the death of their child share the same pain but none of their pains becomes "objective" for the other person. They just feel the same thing.

The second phenomenon is based on a proper intentional act: my emotive state is activated as a reaction to someone else's emotive state, which I can share and which becomes the object of my feeling. In this kind of fellow-feeling, the distance between the two selves is maintained.

The third term refers to the proper experience of being affected by someone else's emotion. In this case, both the intentionality of the act and the distance between the selves are lost and I can feel as if I was lost in the other's feelings.

The last phenomenon is the one that has been addressed as *unipathy*, meaning a form of complete identification with someone else. In this case, a complete identification with the other self occurs[18], as in the case of the sexual union between two partners in love. Another example that Scheler uses to describe this phenomenon is the mother-child relationship. When life begins, the infant shares his/her embodiment with her mother and only through a gradual process towards separation and thus individualization, he/she becomes a self who is distinct from the mother and thus from the environment and the other selves. So this process of differentiation, that goes from a moment of self-other total bonding in which only a sort of "vital sphere" is present, to a moment of self-other distinction in which also the bodily and intellectual spheres are active, leads to the formation of individuals who can experience others.

So empathy itself is based on this shared field in which we are all immersed and that precedes individual consciousness and experience (both bodily and intellectual). This does not happen despite the body, but exactly because of the body that offers the possibility to have experiences but also to immediately recognize others' experiences. So the experience of oneness that Scheler calls *Einsfülung* and that is present during the first moments of life is what allows for our perceptual empathic understanding of others, but also for our sympathetic being concerned by them.

1.4. The anthropological-perceptual approach

This developmental perspective is carried on by another important author that belongs both to the phenomenological tradition and to the anthropological one and that brings into the investigation some fundamental elements. This author is Maurice Merleau-Ponty.

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[18] Scheler stresses that there are kinds of identification: an *idiopathic* one and a *heteropathic* one. The first one describes the phenomenon of an alter self is completely absorbed by one's self; while the second one describes the phenomenon of a substitution of one's self with the alter self (Scheler, 1923).

> Merleau-Ponty develops a genetic phenomenology and is therefore close to developmental psychology and its later expressions in for example Daniel Stern (1985) or Donald Winnicott (1964) (Bornemark, 2014).

His contribution is important as it grasps perfectly the origin of our capability of having an access to others' mind. This does not happen through a decontextualized ability that humans possess and that derives from comparison or projection, but it is possible thanks to our being in relation with the world in which we are embedded. Our being in relation with the world, as parts of the world itself, is precisely what allows for our consciousness. It precedes every other event and experience. When we first come to life, we are not endowed with developed projecting or inferring capabilities: according to Merleau-Ponty, instead,

> the first phase of experience includes an anonymous collectivity, an undifferentiated group-life from which distinct individuals emerge. In the early phase empathy is constituted through an ignorance of oneself, and not through a perception of others (Merleau-Ponty, 1964) (Bornemark, 2014).

So Merleau-Ponty theorizes an initial period in which the infant's perception is not yet organized, but is characterized by the experience of a "system" that

> should here be understood as an organic whole, a continuum with different parts that belong together, and without sharp limits. this system includes, among other things, motility, perceptions, and feelings, which are intimately connected, a connection that is explored and through which an organized world can grow forth. […] Empathy grows out of this overlapping of perception and motility, "the other" lives in "one's own" bodily movements and "I" am totally present in, for example, the emotion present in the other's face (Merleau-Ponty, 1964) (Bornemark, 2014).

The child is not aware of being part of the system, although he/she is, because his/her attention is always moving around the system itself. The consequence is that the child identifies with the whole and not with his/her own individualized self. To live

the continuum without distinction is what precedes, prepares and builds the distinction itself: «One's individuality can only grow out of a non-individualistic motility within a syncretistic sociability» (Bornemark, 2014).

Despite considering this moment of anonymity in which the child is immersed, Merleau-Ponty is careful not to end up in a form of panpsychism that dissolves any relationship between self and other. Indeed, from this moment of "anonymity", empathy develops as the capability of, we could say, "giving discrete names" that break the continuum. With Bornemark (Bornemark, 2014), we could hypothesize that as we go back to the very first stages of the life of the fetus before birth, the continuum itself is constituted by a "stream of perceptions" and of *rhythms*[19] that the fetus experiences without integrating those experiences into an experience of his/her own self in contrast to another. Into this experience, there is no space for empathy, as it requires an encounter of selves and of experiences. This state seems to be similar to Scheler's conceptualization of *unipathy*.

Anyways, empathy arrives later, when the child begins to experience the world (both internal and external) in a self-related way. And yet empathy is possible because of that moment of continuum, since it is grounded in what we could define a "stream of experiences" that continuously flows.

This primitive and basic form of experience is explicit when the experience is experience of the continuum and becomes implicit but foundational when the experience becomes experience of a system in which both a self and an alterity move. From an experiential perspective, we could interpret this ground-experience, that both Scheler[20] and Merleau-Ponty thematize, as "consciousness as such" or "non-dual awareness" (Josipovic, 2021); as "pure experience" (James, 1967; Nishida, 1987/1989); or as "minimal phenomenological experience" (Metzinger, 2020). It is present, in an implicit way, in every kind of daily dual experience and

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[19] The concept of alignment to a certain *rhythm* seems to be fundamental both for a reconsideration of cognition (Vara Sánchez, C. (2020). Raw Cognition. Rhythms as Dynamic Constraints. *JoLMA, 1*.) and for a proper neuroscientific understanding of the intersubjective relationship, as we will observe when we will talk about synchronization.

[20] That is called *Einsfülung* by Scheler (Scheler, 2008), as we wrote previously.

becomes explicit only in rare particular experiences that follow meditative practices (**Figure 3**) or, as we noticed, in the pre-relational experience that occurs before birth.

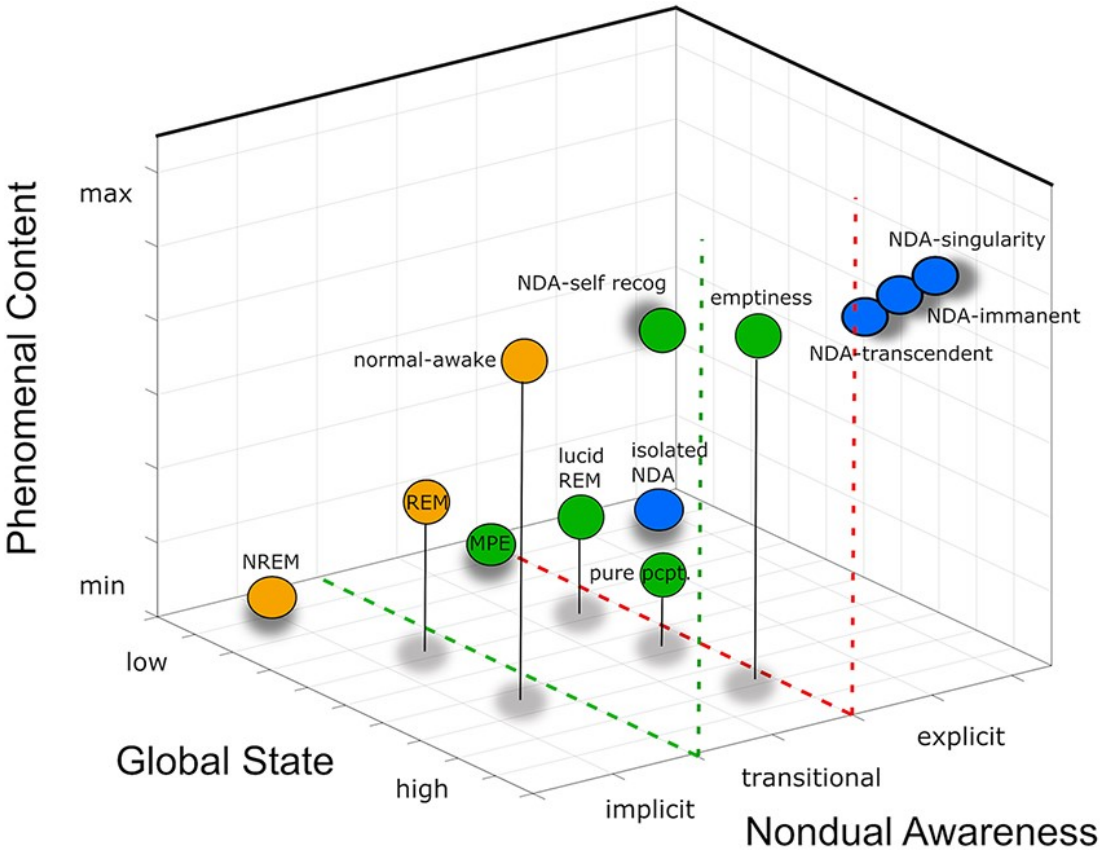

Figure 3. «Implicit–explicit gradient of consciousness as such (nondual awareness) on z-axis. Two axes of the standard map, the global state on x-axis and phenomenal content of y-axis, with the gradient of consciousness as such or nondual awareness represented on z-axis. Three main zones of the gradient: implicit—orange, transitional—green, and explicit—blue. Specific experiences are represented as colored circles with gray shadows indicating their approximate locations on the gradient, for illustration purposes only» (Josipovic, 2021).

During these experiences (meditation and living in the womb), we could say that consciousness loses what Husserl (Husserl, 1966b) calls "transverse intentionality" and reaches the "longitudinal intentionality", that

> forms the consciousness of the continuity of the movement itself, instead of the continuity of the objects. Through this intentionality consciousness is aware of

> its own unit. […] it is an immediate consciousness that is always present in the background (Bornemark, 2014).

In order to come back to Merleau-Ponty's analysis, we need to focus on an aspect that is crucial in his philosophy. This aspect is the *perceptive* experience of the human being. What does it mean to perceive something? In this embodied perspective, in which our body has a fundamental role for intersubjectivity, perception is thought as something different from an intentional act. We do not intention other's body as a content of consciousness; instead, it is our own body that is "touched" by the presence of the other. This being touched by the other's presence is a costitutive of perception itself which can be described, by consequence, as what allows for grasping what is identical in what is different, meaning the other self.

To consider the body as the foundation for the empathic perception means to stress that we need to take seriously the problem of the right *distance* to keep in order to be beside someone, as Donatella Pagliacci notices through her work *L'io nella distanza* (Pagliacci, 2019). If we are body and if our perceptive experience does not derive from an intentional act of consciousness, then empathy is a matter of being neither too distant nor too close to the other in order to perceive him/her. Only if we keep the right distance, we can experience the other's body through our own body.

So Merleau-Ponty's corporeity, as Pasquinucci observes (Pasquinucci, 2022), is not the intentional corporeity that Husserl put into play when talking about the *Leib*. Instead, it is the "place of a bond", in which it is possible to experience a contact that precedes consciousness (Merleau-Ponty, 1960). In this way, we can say that for Merleau-Ponty the bodily experience is at the basis of every other intentional experience, such as knowing, hypothesizing, verifying and so forth. Perception is what shapes our own being in the world and among other individuals. Through perception, indeed, we experience new informative bodily patterns that precede intentionality as we already stressed and that generate a question about the other person. Answering that question means to recognize a meaningful expression in a meaningless gesture.

2. *Neuroscientific theories of reference*

After having presented the theoretical background in which the analysis of the empathic phenomenon developed and was approached from different perspectives, from the aesthetic one, through the phenomenological one, to the anthropological, we want not to contextualize it into two neuroscientific theories that we think appropriate for our own theoretical and empirical investigation.

2.1. The 4E Cognition approach

At the end of the 20th century, indeed, the phenomenon of empathy started to be addressed from an experimental perspective and it landed in the field of the neuroscience. The event that signed the beginning of the neuroscientific investigation of empathy was the discovery of the *mirror neurons*, that we briefly introduced in one of the previous paragraphs. So after this discovery, empathy was approached not only from a theoretical perspective, but also from an experimental one. For this reason, we want now to present two neuroscientific approach that can be useful for our own investigation.

The first one is the so called "4E cognition approach". We think that it can shade light to our analysis, since it aims at considering the human experience as a whole, without cutting off any important dimension that seems to be neglected in some traditional cognitive approaches. Indeed, the traditional cognitive science, elaborated on the basis of different approaches offered by different disciplines such as psychology (Miller, 1956), linguistic (Chomsky, 1975), computer science (Newell, 1956), have elaborated models that consider cognition as a sort of information processing consisting in the syntactically driven manipulation of representational mental structures.

According to these perspectives, the mind is understandable as a software that works inside a physical hardware represented by the brain. To have a mind means to have something that is abstract and a-modal; that processes information and that mediates between modality-specific sensory inputs (perception) and motor and behavioral outputs (action). The mind performs computations over mental representations that

are either symbolic (e.g., concepts in a "language of thought"; (Fodor, 1975)) or sub-symbolic (e.g., activations in neural networks; (Rumelhart, 1986)). Into this context, it becomes very important to discover where cognition takes place, and for this purpose some kind of "contingent intracranialism" (Adams, 2008) has been elaborated. Indeed, this kind of cognition thinks of human cognitive processes as deriving only from brain processes that are internal and that are not in relation to anything external. So cognition is understandable and explainable by focusing only on these internal and abstract processes.

Later, thanks to the advent of innovative technologies and methods, such as the implementation of neural network models in the informatics and the neuroimaging techniques in the neuroscientific field, and thanks to their application to the study of the cognitive phenomena, traditional cognition have started to focus no more on the mind as an abstract program, but on the observation of the brain and its neurobiological functioning. In addition, it has also started to be elaborated the idea of the brain being situated in the body and thus in the world. To quote an image used by Alva Noë (Noë, 2010), consciousness occurs in the form of a dance that does not come from our brain in its isolation, but from the interaction between our brain, our body and the world.

These new ways of thinking consciousness and thus experience can be grouped into a unique definition that includes different but similar epistemological approaches. This definition is the "embodied, embedded, enacted and extended cognition", or "4E cognition".

According to 4E approach, cognitive phenomena such as spatial navigation, action, perception, and understanding other's emotions cannot be thought as abstract and isolated, but they depend on the morphological, biological, and physiological features of an agent's body, an appropriately structured natural, technological, or social environment, and the active and embodied interaction between the agent and the environment.

> Even most of the phenomena studied by traditional cognitive science - such as language processing (Glenberg & Kaschak, 2002), memory (Casasanto & Dijkstra, 2010), visual-motor recalibration (Bhalla & Proffitt, 1999) and perception-based distance estimation (Witt & Proffitt, 2008) - are not abstract, modality-unspecific processes in a central processing area either, but essentially rely on the system's body and its dynamical and reciprocal real-time interaction with its environment (Gallagher, 2018).

So the 4E cognition approach focuses its attention on the brain-body-environment relationship and its dynamics instead of considering only what happens in the head.
Coming to a terminological explanation, the first "E", the one that remands to the concept of an *embodiment* of the mind, derives its meaning from Merleau-Ponty's phenomenology (Merleau-Ponty, 1945) and that has been conceptualized, among others, by F. Varela, E. Thompson and E. Rosch in their 1991 *The Embodied Mind* (Varela, 2017). In addition to the importance of the coupling between brain and body (which is described by the use of the term "embodied"), 4E cognition also looks at the importance of the coupling between body and environment. From this second relationship, it derives the term *embedded*, which refers to the fact that the body is placed in an environment, that is physical, intersubjective and also cultural, involving also the technological features that define different possibilities for acting in it.
From this coupling between the brain, the body and the environment derives also the third concept, that is the *enactive* aspect of cognition, that has been elaborated with reference to Gibson's investigations (Gibson, 1950). By this term it is intended the fact that because of our being embodied and embedded we are always oriented towards action. This means that the sensorial and motor capabilities of our body determine out cognitive process. What we experience is not a product of mental representations of what we perceive, but it depends upon our own ability of moving and acting in the environment:

> It does not seem to us as if somewhere in our brain there is a complete, coherent representation of the scene. Perceptual experience is directed to the world, not to the brain. [...] We take ourselves to be situated in an environment, to have

> access to environmental detail as needed by turns of the eyes and the head and by repositioning of the body (Noë, 2004).

So according to the enactive theory, our bodily features shape our mind.

The fourth aspect is the idea of an *extended* mind. It refers to the fact that the mind is not delimited to the skull and to the brain, but it is extends beyond it. This formulation derives from Clark and Chalmers' 1998 work *The extended mind* (Clark, 1998), that elaborates a theory of "active externalism", according to which external factors actively interact with the subject and they influence her behavior as well as the internal parts. So brain, body and environment are thought as a unique system, for the study of which it is also considered the dynamical systems theory. In this way, the extended mind approach is the attempt to enlarge also the borders of neuroscience itself that in this way, according to this theory, cannot limit its observation to the brain, but must extend it to all the aspects of the individual and also of her interaction with the environment:

> The notion of the extended mind is nothing other than the notion of system-level cognitive (rather than neuro-) science. All it adds to that notion is some discussion, adverting to the details of biological-artifactual coupling, meant to make it plausible to treat some of these larger-scale systems as the local supervenience base for the knowledge and cognitive capacities of a specific agent (Clark, 2010).

Thanks to this provocative although interesting observation, we can stress the importance of a multidisciplinary approach, a "multifocal approach" that could address any topic from different perspectives and that could think at reality as a complex and interconnected network.

2.2. The temporo-spatial approach

The second approach that we consider important for our contextualization of the problem of empathy is the one we can call the temporo-spatial approach. Our decision to make this kind of reading is motivated by the fact that we think that in

order to talk about phenomena that are related to consciousness[21], such as the empathic process, we need to considerate that they happen according to some particular spatio-temporal dynamics. In fact, we should say that not only everything is "embedded" in this dynamical spatio-temporal fabric, but it is *made of* this fabric. We ourselves are made of this fabric. We *are* spatio-temporal dynamics.

If we look at the approaches that we analyzed in the previous paragraphs, we can notice that each one of the authors we talked about presents the empathic process in the context of some event that happen in a particular spatial context (especially if they involve a face-to-face encounter) and unfold through a particular period of time. For this reason, we think that a complete theoretical framework of the phenomenon cannot prescind from an investigation of these very primitive coordinates that are at the bases of its whole structure. In order to introduce this approach, we will present an analysis of the Temporo-spatial Theory of Consciousness (TTC), elaborated by Georg Northoff.

According to Northoff's approach, mental features, such as consciousness, self, free will and sense of the other (and thus also empathy) cannot be studied as phenomena that are isolated from the world as most of the philosophical and neuroscientific approaches tend to do:

> I argue that the need to include the world in our neuroscientific and philosophical investigation of mental features will change and shift our focus from brain and mind to world-brain relation as a necessary condition of mental features, specifically consciousness. We are then no longer confronted with the mind-body problem in our quest for the existence and reality of mental features. Instead, we may then need to shift our focus to what I describe as the "world-brain problem" - this requires nothing less than a Copernican revolution in neuroscience and philosophy (Northoff, 2018).

On the basis of this consideration, Northoff stresses that, in order to study the phenomena linked to consciousness, we should study the building blocks that are at

[21] From now on, we will take about consciousness in terms of our ability of experiencing, meaning of processing the stimuli coming from the environment (both internal and external).

the basis of the world-brain relationship. These structural and fundamental elements are, as we anticipated, time and space:

> Given that (1) time and space are most basic features of nature and (2) that the brain itself is part of nature, we here consider the brain in its neural activity in explicitly temporal and spatial terms. In other words, we conceive the brain's different forms of neural activity (spontaneous, prestimulus, early and late stimulus-induced activity) in primarily spatiotemporal terms rather then in informational, behavioral, cognitive, or affective terms. I postulate that such a spatiotemporal view of the brain's neural activity is central for understanding how the brain can generate consciousness with its different dimensions. In this sense, then, consciousness may be understood as a spatiotemporal phenomenon of the brain's neural activity (Northoff, 2018).

But which meanings of time and space this theory refers to? As Northoff stresses, we must consider the time and space that are constructed by the brain in its neural activity, that can be called the "intrinsic" time and space of the neural activity. The intrinsic time of the brain concerns the duration of neuronal activity, embedded in specific frequency ranges, while the intrinsic space of the brain concerns the extension of neural activity across different regions and networks in the brain. The temporal duration of the brain is related to the temporal ranges or circle durations of neural oscillations or fluctuation, including frequencies ranging from infraslow (0.0001-0.1 Hz), over slow (0.1-1 Hz), delta (1-4 Hz) and theta (5-8 Hz), to faster frequencies of alpha (8-12 Hz), beta (13-30 Hz) and broadband gamma (30-240 Hz) (Buzsaki, 2006, 2013; Buzsaki & Draguhn, 2004). These different frequencies show different functions and are associated with different physiological mechanisms. The intrinsic time of the brain is highly structured and finely organized and this temporal structure and organization is considered by the TTC crucial for the phenomenon of consciousness. Indeed, there seem to be some intrinsic "temporal receptive windows" (Northoff, 2018) that match with the physical features of the extrinsic stimuli.

The spatial extension of the neural activity is instead characterized by the fact that the brain is extensively connected and linked across neurons, regions and networks. This *structural connectivity* provides the hardware through which neurons can functionally communicate, that is for the *functional connectivity*[22].

Together, the temporal duration and the spatial extension of the brain's neural activity construct the brain's intrinsic time and space, that, although in a different context, we could define, following Immanuel Kant, the *transcendental* forms of our perception (Kant, 1781-1787). These two intrinsic elements are located in the extrinsic time and space encompassing both the body and the world (Park et al., 2014; Park, 2014). The alignment of the intrinsic time and space to the extrinsic time and space (i.e. *spatiotemporal alignment*[23]) constitute a world-brain relation that allows us to experience ourselves, including our body, within and also as part of the spatiotemporally more extended world. In this way, as Northoff writes,

> the spatiotemporal model of consciousness conceives both brain and consciousness in spatiotemporal terms - I propose that a specific way of constituting time and space by the brain's neural activity is central for transforming neural activity into phenomenal activity, what we call consciousness (Northoff, 2018).

According to the TTC, at the basis of this "transformation" of the neural activity into the phenomenal activity there are the following four mechanisms: *expansion*, *globalization*, *alignment*, *nestedness* (Northoff & Zilio, 2022b). By introducing these

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[22] Despite the fact that the functional connectivity strongly depends on the structural connectivity (Honey, C. J., Sporns, O., Cammoun, L., Gigandet, X., Thiran, J. P., Meuli, R., & Hagmann, P. (2009, Feb 10). Predicting human resting-state functional connectivity from structural connectivity. *Proc Natl Acad Sci U S A, 106*(6), 2035-2040. https://doi.org/10.1073/pnas.0811168106), the divergence between the two is relevant for consciousness, in a way that loss of consciousness is linked to a loss of divergence between structural and functional connectivity (Tagliazucchi, E. (2017, Oct). The signatures of conscious access and its phenomenology are consistent with large-scale brain communication at criticality. *Conscious Cogn, 55*, 136-147. https://doi.org/10.1016/j.concog.2017.08.008).

[23] The alignment of the brain rhythm to the body rhythm and thus to the rhythm of the world can be described as a sort of dance (Northoff, G. (2021). *Il codice del tempo. Cervello, mente e coscienza*. il Mulino.).

mechanisms, the TTC tries to investigates consciousness going beyond the study of the stimulus-related activity and focusing on how the external input/stimulus interact with the brain's spontaneous activity. In particular, the temporospatial *expansion* refers to a particular form of the interaction of pre-stimulus and post-stimulus activity that allows for assigning contents to consciousness (Northoff & Zilio, 2022b). During the pre-post stimulus interaction with the brain's neural activity, the original temporal duration and spatial location of the input/stimulus is integrated into the brain's neural activity and it is expanded by the brain's activity itself (**Figure 4**).

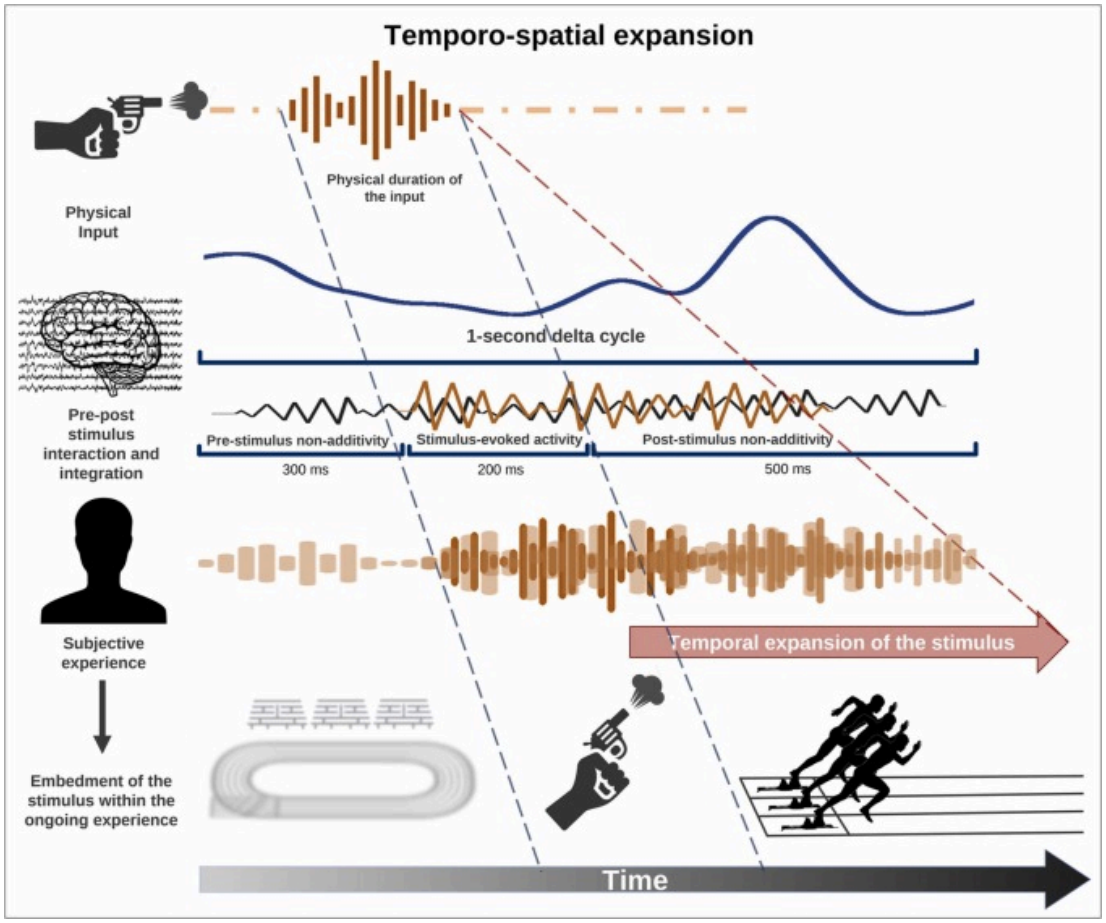

Figure 4. «Temporo-spatial expansion of the input/stimulus's original (physical) temporal duration and spatial location during the pre-post stimulus interaction of the brain's neural activity. The stimulus-related activity is non-additively integrated within an ongoing delta cycle of 1 Hz that spills over for another 500 ms into the post-stimulus period. Thus, the original temporal duration of the input is virtually expanded by the neural activity during the pre-post-stimulus interaction. The actual input or stimulus of a firing gun is embedded in the ongoing experience (during the pre-stimulus period) which, after the onset of the input/stimulus is expanded towards the post-stimulus experience. The actual input/stimulus, the firing gun, is thus

integrated and embedded within the ongoing experience of the pre-stimulus period, the stadium. Together, pre-stimulus experience (stadium) and the actual input/ stimulus (firing gun) amount to the experience of runners starting for a competitive run (as the firing gun in a stadium is usually associated semantically with the start of a run in a competition). If, in contrast, there was a different experience in the pre-stimulus period like a deer in a forest, the same input/stimulus, i.e., firing gun, would elicit a different conscious content, most likely the one of a hunter shooting the deer» (Northoff & Zilio, 2022b).

This neural expansion corresponds also to a phenomenal expansion:

> we perceive the external stimulus/input in our consciousness in a temporally and spatially more expanded way when compared to its actual physical duration and location. There is a discrepancy between physical and phenomenal locations/durations of the external input/stimulus - the TTC speaks of a "physical-neuronal-discrepancy" (Northoff & Zilio, 2022b).

The temporospatial *globalization* can be conceived as a continuation of the expansion and it provides a link to cognitive functions (**Figure 5**). It refers to a global recruitment of regions and frequencies that are linked to consciousness itself (Block, 1995).

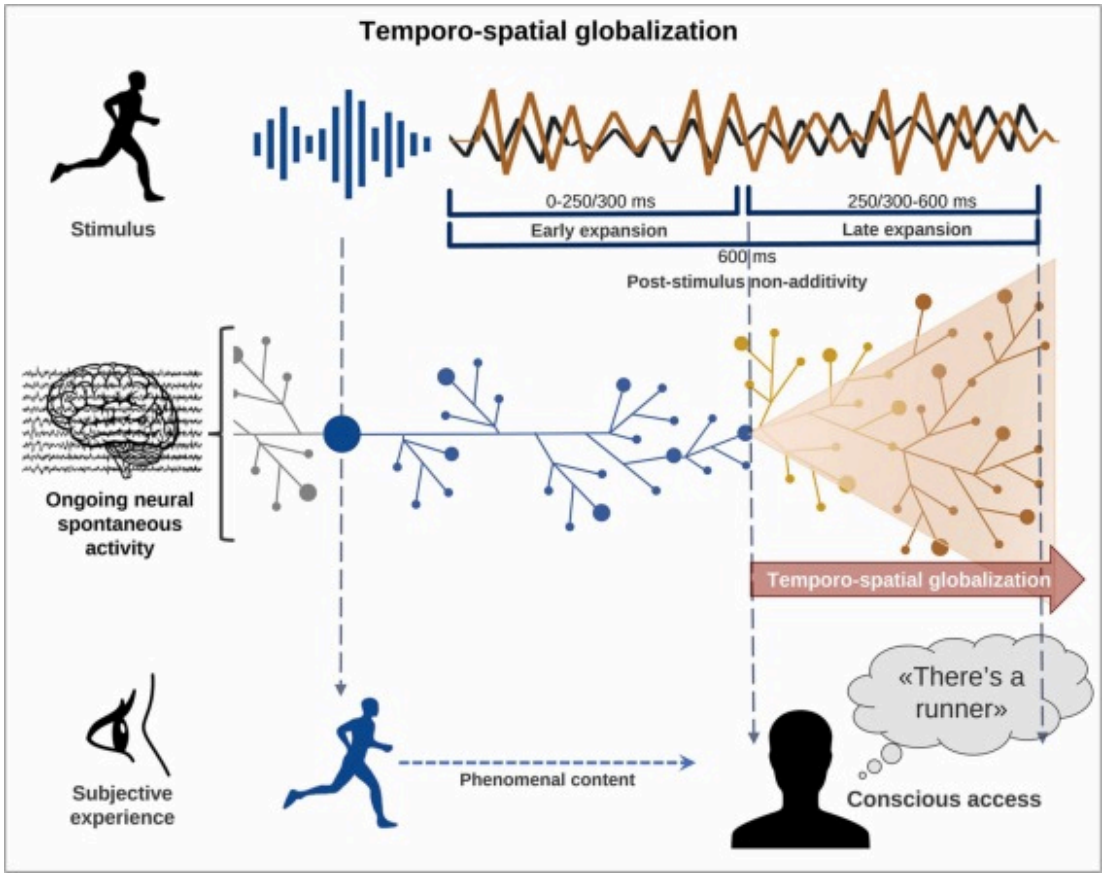

Figure 5. «Temporo-spatial globalization of an input/stimulus allows for accessing it through cognitive functions, i.e., access consciousness. The input/stimulus of the runner perceived through the eyes is encoded and its information is progressively distributed along the activations of multiple regions and their different time scales; this makes the content available for conscious cognitive access. Neurophenomenally speaking, after an immediate manifestation of an experience of the runner as phenomenal content, i.e., phenomenal consciousness, it is then made available to various cognitive facilities like reasoning, speech, report, behavior, and reflection, i.e., access consciousness» (Northoff & Zilio, 2022b).

The temporospatial *alignment* refers to bran's capability of encoding the environment by adapting (aligning) its neural activity to the context (**Figure 6**).

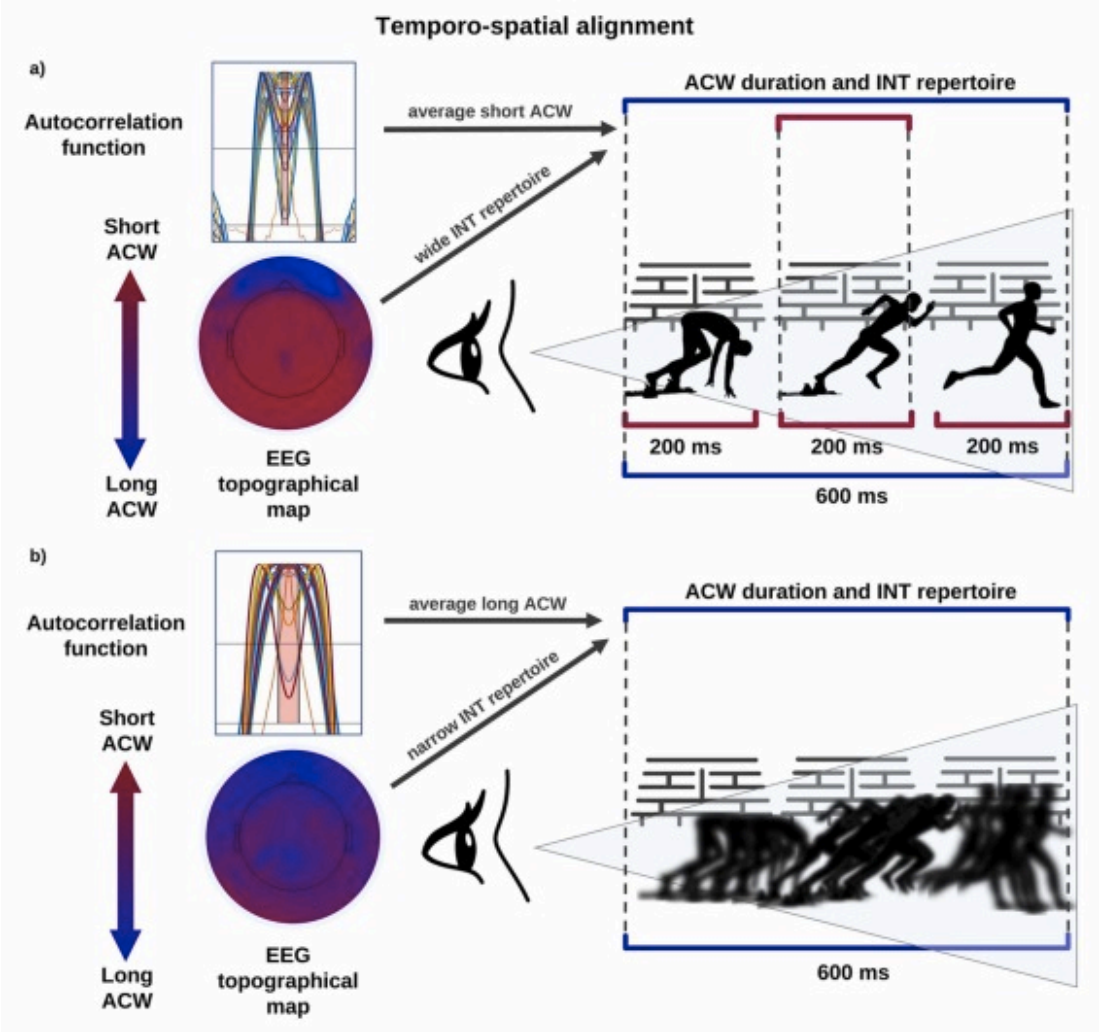

Figure 6. Temporo-spatial alignment of the brain's intrinsic activity to ongoing environmental stimuli. In the upper part of the figure (a), the autocorrelation window (ACW) of the subject shows the different lengths of the INT repertoire and its topographic distribution (EEG map). In particular, the temporal dynamic of the subject are sufficiently short to allow sampling the start of the runners in a fine-grained and temporally precise and differentiated way. Neurophenomenally speaking, every detail of the competition (figure-runner and background-bleachers) is well parsed across multiple levels of duration. On the contrary, in the lower part of figure (b), the mildly sedated subject has a reduced and generally longer INT repertoire. This corresponds to the loss of the ability to segment the input series in detail, resulting in the coarse-grained integration of all stimuli into long time windows. Instead of perceiving the input in a temporally precise way (as in the first case), the subject now perceives the same input in a temporally imprecise or smoothed way – the perceived image of the runner is blurred with the other inputs/ stimulus of the same scene or context.

The temporospatial *nestedness* refers to the organization of different spatial and temporal scales of neural activity. They do not operate in parallel, unconnected or causally connected, rather, they are contained or *nested* within each other. This nested organization concerns both the spatial and the temporal organization[24] (**Figure 7**).

[24] The spatial nestedness is evident by observing that the local activity of some regions is spatially nested within the global activity of the whole brain (Tanabe, S., Huang, Z., Zhang, J., Chen, Y., Fogel, S., Doyon, J., Wu, J., Xu, J., Zhang, J., Qin, P., Wu, X., Mao, Y., Mashour, G. A., Hudetz, A. G., & Northoff, G. (2020, Jun). Altered Global Brain Signal during Physiologic, Pharmacologic, and Pathologic States of Unconsciousness in Humans and Rats. *Anesthesiology, 132*(6), 1392-1406. https://doi.org/10.1097/ALN.0000000000003197). The temporal nestedness is instead evident by the fact that the short cycle duration of the less powerful faster frequencies like gamma and beta are contained, nested, within much longer cycle durations of more powerful slower frequencies, such as theta and delta (He, B. J., Zempel, J. M., Snyder, A. Z., & Raichle, M. E. (2010, May 13). The temporal structures and functional significance of scale-free brain activity. *Neuron, 66*(3), 353-369. https://doi.org/10.1016/j.neuron.2010.04.020) (He, B. J. (2014, Sep). Scale-free brain activity: past, present, and future. *Trends Cogn Sci, 18*(9), 480-487. https://doi.org/10.1016/j.tics.2014.04.003).

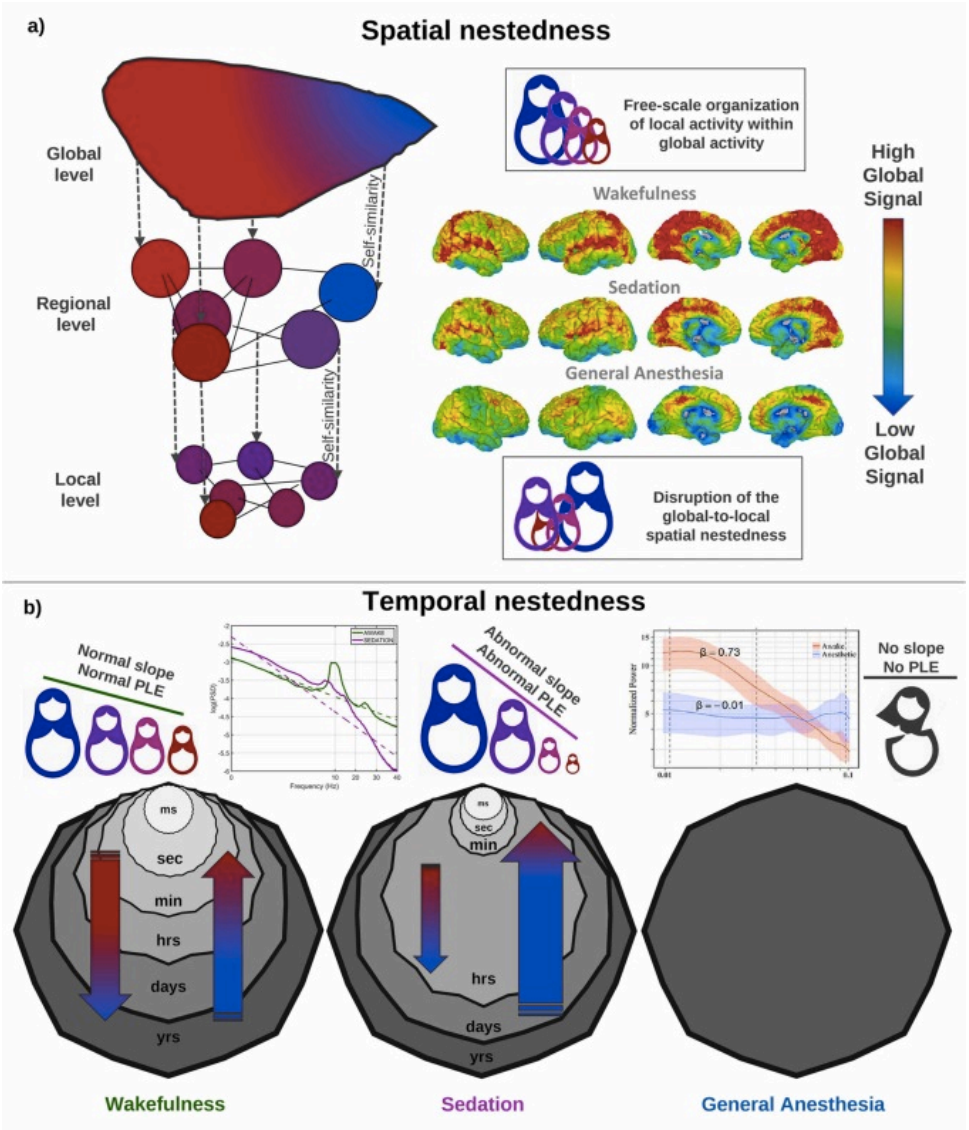

Figure 7. Visual illustration of spatial (a) and temporal (b) nestedness. The spatial nestedness represented by the brain's global cortical and subcortical signal shows how the various levels of activity (global, regional, and local) are spatially nested within each other in a scale-free way. Similarly, on the temporal level, the fastest frequencies are nested within the slowest frequencies following the power-law distribution (slow frequencies-high power; fast frequencies-low power). The disruption of the global-to-local spatial relationship and/or the unbalance of the relationship between slow-fast frequencies corresponds to the decline of the level/ state of consciousness, up to the complete loss of consciousness as in deep anaesthesia, which is related to the complete disruption of the nested structure of spontaneous brain activity.

Taken together, these mechanisms describe, in temporo-spatial terms, the process through which the brain-world interaction can generate consciousness. So, according to the TTC, both the neural activity and the phenomenal one can be described and analyzed through the analysis of their temporo-spatial dynamics that, in this way, constitute the *common currency* between the two elements (Northoff, 2020).

3. Conclusions

In this first Chapter we have presented different approaches that have been used or that we think could be used for addressing the topic of empathy. In **Table 1**, we summarize the theories that we took into account.

Approach	Description
Aesthetic Theory	*Einfühlung* is the term used for defining the empathic perception of the world. It is described as the human ability of perceiving a vital sense in what is observed. This perception (and thus also the aesthetic enjoyment) passes through an identification with the observed object, in which our emotions are reflected.
Phenomenological approach	Empathy is a form of knowledge that derives from the process of non-originally experiencing someone else's experience.
Anthropological-emotional approach	The empathic understanding of others is contextualized into the radical relatedness in which we are all immersed. Thanks to this connection, we are able to share and understand others' emotions.
Anthropological-perceptual approach	Our perception of the world is shaped by the fact that our body is the first thing that is "touched" by the world. So when in front of another person, we perceive, through our body, the body of that person and this perception builds our understanding of him/her.
4E Cognition Theory	Cognitive phenomena such as action, perception, understanding other's emotions cannot be thought as abstract and isolated, but as dependent on the brain-body-environment relationship. Following this theory, the mind is *embodied*, *embedded*, *enactive* and *extended*.

Approach	Description
Temporo-spatial Theory of Consciousness	Mental features, and thus empathy, depend on the alignment of the temporo-spatial patterns of the neural activity (the intrinsic time and space) to the temporo-spatial patterns of the environment (extrinsic time and space) and on four mechanisms: *expansion*, *globalization*, *alignment*, *nestedness*.

In particular, we first analyzed the traditional approaches that constitute the origin of a theoretical study of the empathic phenomenon. These traditional approaches are the aesthetic one, the phenomenological one, the anthropological-emotional one and the anthropological-perceptual one. In addition, we secondly presented two contemporaneous theories, the 4E cognition theory and the temporo-spatial theory of consciousness, that we found particularly efficient for offering a context to the study of our phenomenon.

In order to make some conclusive considerations, we intend to highlight the specificity of each one of these approach, to see how they can dialogate together and shade more light to the investigation of empathy, being it a very complex phenomenon. The first thing that we can observe in order to justify our choice regarding these particular theories (particularly the more recent two) is that all of them constitute a basis for investigating empathy from a non-reductive perspective. Indeed, we think that it is always very important to consider every aspect of reality, the study of which, according to the Russian philosopher Pavel Florenskij (Florenskij, 2004), cannot be reduced only to what is directly observable. Science must *encounter* reality, and this encounter must occur at every different layer reality is composed of. In order to encounter reality in such a multi-layered way, science itself must be a multi-layered instrument and it must involve many different sights and points of view, including the aesthetic, the philosophical and the anthropological ones. This does not mean, of course, that the scientific findings are not useful to understand reality. In fact, they are necessary. But they, alone, are not sufficient. They need to be integrated with different theoretical designs that can be used for interpreting the data from different perspectives.

Coming back to the study of empathy, we find it interesting that its investigation was born into the aesthetic field and that only in a second moment it was introduced into the psychological one. This fact tells us that empathy is first and foremost a modality through which we experience, and thus know, the world, as also Anna Donise notices (Donise, 2019). In particular, it tells us that we always experience the world through our own experience. At the same time, it tells us that we naturally experience the world as something that is not so different from us, since we are part of the nature and we share the same vital "breath"[25]. So, thanks to the aesthetic analysis, we can conceive empathy as the capability of perceiving reality in terms of a "living reality"[26]. On the basis of this capability, we are also able to perceive other individuals as individuals, who are, by nature, endowed with an inner vital sense.

The second approach that we took into account is the phenomenological one. We find it interesting since it considers empathy as a form of knowledge and as given through experience. In particular, the element that we want to highlight as a fundamental characteristic of the empathic experience of someone else, is the *non-originality* of such an experience. When empathizing with someone else, we know his/her original emotive state by experiencing it in a non-original way, meaning, once again, through our own personal experience.

Before coming to the other approaches, we want to clarify that to focus on the subjective element of our experience does not mean to say that empathy is absolutely subjective and self-centered. Lipps' aesthetic theory itself highlights the fact that our knowledge passes through an inner imitation of some outer shapes and movements, and not only through a projection of our inner world into the outer one. By saying that, he intends that there are some traits, in the outer world, that refer to and that

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[25] It is not by chance that the aesthetic theory was born in the 19th century, in which the Romanticism has a deep influence.

[26] Saying that reality is for us always a "living reality" means that it involves both life and death as constitutive elements of every interaction we have with reality itself.

evoke in us some inner inclinations[27]. Also Stein's considerations on the non-originality of the empathic experience highlights the same things: there is an original content outside us that we, although in a non-original way, can intention and then experience.

Using Florenskij's words, we can say that we, as humans, have the capability of encounter reality through the encounter of its *symbols*. A *symbol* is an element that is composed of a material physical substrate and a transcendent "spiritual" meaning. When encountering a symbol, we experience its physical component, which evokes a meaning that we can intention as what completes the physical part. Through this encounter, we have a deeper experience and understanding of reality (Florenskij, 2007). In this way, empathy itself can be considered as the process of physically and bodily encountering some other individuals and of recognizing that they are also made of a "spiritual" content, meaning an inner emotive world.

This process is possible because of the particular conformation of our psycho-physical structure and, at the same time, because of the fact that our experience of the world always occurs in an intersubjective space. These two elements are elaborated by the anthropological approaches that we took into account, namely the emotional and the perceptual ones. In particular, the anthropological-emotional approach is useful to contextualize the empathic capability into the developmental perspective and to see that the self-other differentiation experience (that is necessary for the empathic experience) comes from what we could call a "temporo-spatial expansion" of the self-other bonding experience that occurs during the first moments of life (**Figure 8**).

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[27] Vittorio Gallese talks about an "embodied simulation" to refer to a basic bodily and motor level of reaction to the stimuli (Gallese, V. (2007b). Embodied simulation: from mirror neuron systems to interpersonal relations. *Novartis Found Symp, 278*, 3-12; discussion 12-19, 89-96, 216-221. https://www.ncbi.nlm.nih.gov/pubmed/17214307 ; Gallese, V. (2007a, Apr 29). Before and below 'theory of mind': embodied simulation and the neural correlates of social cognition. *Philos Trans R Soc Lond B Biol Sci, 362*(1480), 659-669. https://doi.org/10.1098/rstb.2006.2002).

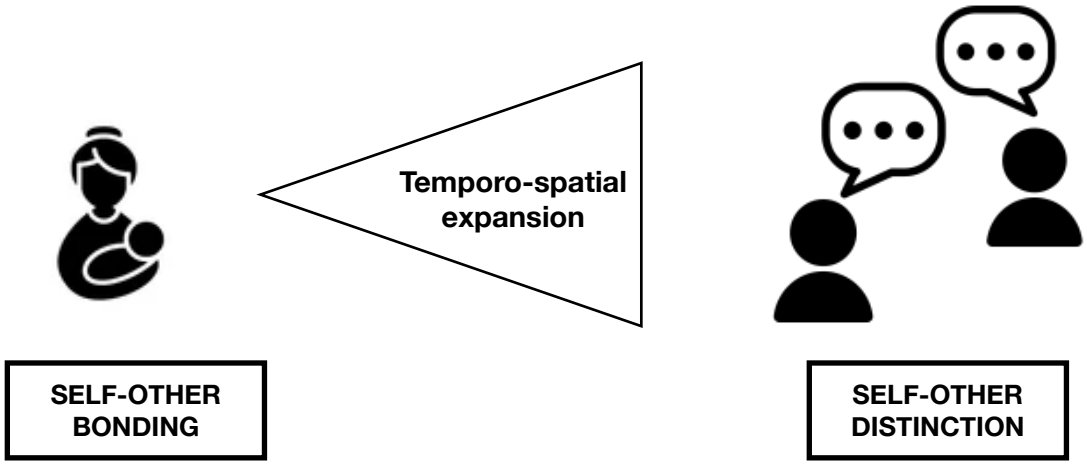

Figure 8. The self-other distinction that is the prerequisite for the empathic experience is the result of a temporo-spatial expansion of the self-other bonding. Both the self-other bonding and the self-other distinction are fundamental for being able to modulate the distance between self and other and thus for being able to empathize with others.

This is also what Patricia Churchland stresses, when she says that different species, including humans, have developed their social capabilities (and thus empathy) and moral capabilities on the basis of the experience of attachment between mother and child (Churchland, 2019). Without having felt one with everything, we cannot feel one among others in the intersubjective space in which we are always embedded.

Into this context, it is fundamental to recognize the element that connects these different experiences and that is the medium in every relationship we have. This element is our *body*. We analyzed its importance for the study of empathy through what we called the anthropological-perceptual approach. It focuses on the process of *perception* as the basis for every kind of knowledge and cognitive act, by stressing that perception is the way our bodily patterns are shaped by the different stimuli. According to this perspective, also empathy derives from our body's capability of being "touched" by the others. In this way, empathy is first and foremost a form of perception that leads to a multi-layered knowledge.

The last two approaches that we took into account in our analysis are not strictly connected to theories of empathy, but we think that can be integrated as theoretical references where to contextualize our own definition of this phenomenon. In

particular, through the 4E cognition approach and through the temporo-spatial approach, we intend to confirm the necessity of reading empathy as a phenomenon which concerns a consciousness that must not be considered only in cognitive terms, but that is always *embodied*, *embedded*, *enacted* and *extended*. These characteristics of our consciousness, can be described in temporo-spatial terms, being time and space the fundamental and basic coordinates of everything in nature.

In order to find a dialogue between these different approaches, we could try to define empathy as an experience that leads to know the others' inner experience on the basis of a *perceptive-hermeneutical process*. This process is based on what we could call an *imitative/projective*[28] mechanism that makes us, as *embodied* and *embedded* individuals, *encounter* the others. Through this encounter, the borders of our own bodily experience are "shaped"[29] by the others' presence and we develop new bodily patterns, in accordance to that presence. These patterns are the basis for the other step of the mechanism, that is the interpretative (projective) one, through which we process, in an *enacted* way, the patterns in the form of a *non-original experience* that we give back to its owner. The experience we feel on the basis of those patterns is non-original for us, but, through our cognitive capabilities, we are able to understand that it is original for the other person[30]. We will explain this process better in the next Chapter.

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[28] We will use a slightly different terminology (introjective/projective mechanism) in the next chapter for the description of the mechanism at the basis of the empathic process.

[29] The "imitative" step is not an active mechanism through which we consciously and voluntarily imitate the other, rather it is a sort of unconscious *resonance* of our body to the presence of someone else's body.

[30] It could also happen, sometimes, that the cognitive recognition comes before the resonance activation. In general, we must highlight that we do not want to consider the empathic process as merely the sum of different acts. Rather, it is a continuous cyclic process, in which both bottom-up and top-down mechanisms are always intertwined.

The list of the theories of empathy is not exhaustive. Indeed, other approaches from different fields have been used to investigate the topic. From the psychoanalytic field, we can quote the contribution of Sigmund Freud (Freud, 1905), that does not use the term "empathy", but refers to the process through which we understand others by putting ourselves in their place and through which the analyst can establish a relationship with the patient for a better interpretation; Carl Rogers (Rogers, 1978), who sees empathy as one of the most important instruments for the therapeutic relationship and defines it as the capability of synchronizing with the patient and of understanding his/her emotive and cognitive states; Hanz Kohout (Kohut, 1984) who analyzes empathy as an important therapeutic instrument.

Some example from the neuroscience are the Theory of Mind theory (Churchland, 1989; Gopnik, 1992; Ratcliffe, 2006; Stich, 1994), according to which we we have an innate naïve theory of psychology ("folk psychology") that we use to infer mental states of others; the Simulation theory (Goldman, 2006), according to which we understand others by mentally simulating what would produce the same behavior that another person is showing; the theory according to which empathy is related to the activity of mirror neurons (Bekkali et al., 2021; Iacoboni, 2009), the "Perception-Action Model" (PAM) (Preston, 2007), that reads empathy as the shared emotional experience occurring when one person (the subject) comes to feel a similar emotion to another (the object) as a result of perceiving the other's state.

We did not deepen the study of these approaches, since we focused on those that were functionally useful for contextualizing our own model of empathy.

References

Adams, F., & Aizawa, K. (2008). *The bounds of cognition*. Blackwell Publishing.

Bekkali, S., Youssef, G. J., Donaldson, P. H., Albein-Urios, N., Hyde, C., & Enticott, P. G. (2021, 2021/3//). Is the Putative Mirror Neuron System Associated with Empathy? A Systematic Review and Meta-Analysis. *Neuropsychology Review, 31*(1), 14-57. https://doi.org/10.1007/s11065-020-09452-6

Bhalla, M., & Proffitt, D. R. (1999, Aug). Visual-motor recalibration in geographical slant perception. *J Exp Psychol Hum Percept Perform, 25*(4), 1076-1096. https://doi.org/10.1037//0096-1523.25.4.1076

Block, N. (1995). On a confusion about a function of consciousness. *Behavioral and Brain Sciences, 18*.

Bornemark, J. (2014, May). The genesis of empathy in human development: a phenomenological reconstruction. *Med Health Care Philos, 17*(2), 259-268. https://doi.org/10.1007/s11019-013-9508-y

Buzsaki, G. (2006). *Rhythms of the brain*. Oxford University Press.

Buzsaki, G. (2013, May 30). Cognitive neuroscience: Time, space and memory. *Nature, 497*(7451), 568-569. https://doi.org/10.1038/497568a

Buzsaki, G., & Draguhn, A. (2004, Jun 25). Neuronal oscillations in cortical networks. *Science, 304*(5679), 1926-1929. https://doi.org/10.1126/science.1099745

Casasanto, D., & Dijkstra, K. (2010, Apr). Motor action and emotional memory. *Cognition, 115*(1), 179-185. https://doi.org/10.1016/j.cognition.2009.11.002

Chomsky, N. (1975). The Logical Structure of Linguistic Theory. Springer US.

Churchland, P. (2019). Conscience: The Origins of Moral Intuition. W W Norton & Co Inc.

Churchland, P. M. (1989). Folk Psychology and the Explanation of Human Behavior. *Philosophical Perspectives, 3*.

Clark, A. (2010). Memento's revenge: the extended mind, extended. In R. Menary (Ed.), *The extended mind*. MIT Press.

Clark, A. C., D. (1998). The extended mind. *Analysis, 58*, 7-19.

di Pellegrino, G., Fadiga, L., Fogassi, L., Gallese, V., & Rizzolatti, G. (1992). Understanding motor events: a neurophysiological study. *Exp Brain Res, 91*(1), 176-180. https://doi.org/10.1007/BF00230027

Donise, A. (2019). Critica della ragione empatica. Fenomenologia dell'altruismo e della crudeltà. il Mulino.

Florenskij, P. (2004). The Pillar and Ground of the Truth: An Essay in Orthodox Theodicy in Twelve Letters. Princeton University Press.

Florenskij, P. (2007). Il simbolo e la forma: scritti di filosofia della scienza. Bollati Boringhieri.

Fodor, J. A. (1975). *The language of thought*. Harvard university press.

Freud, S. (1905). Der Witz und seine Beziehung zum Unbewußten. F. Deuticke.

Gallagher, A. N. L. d. B. S. (2018). *The Oxford handbook of 4E cognition*. Oxford University Press.

Gallese, V. (2007a, Apr 29). Before and below 'theory of mind': embodied simulation and the neural correlates of social cognition. *Philos Trans R Soc Lond B Biol Sci, 362*(1480), 659-669. https://doi.org/10.1098/rstb.2006.2002

Gallese, V. (2007b). Embodied simulation: from mirror neuron systems to interpersonal relations. *Novartis Found Symp, 278*, 3-12; discussion 12-19, 89-96, 216-221. https://www.ncbi.nlm.nih.gov/pubmed/17214307

Gibson, J. J. (1950). The Perception of the Visual World. Houghton Mifflin.

Glenberg, A. M., & Kaschak, M. P. (2002, Sep). Grounding language in action. *Psychon Bull Rev, 9*(3), 558-565. https://doi.org/10.3758/bf03196313

Goldman, A. I. (2006). *Simulating Minds*. Oxford University Press.

Gonzalez-Liencres, C., Juckel, G., Tas, C., Friebe, A., & Brüne, M. (2014, 2014/4//). Emotional contagion in mice: The role of familiarity. *Behavioural Brain Research, 263*, 16-21. https://doi.org/10.1016/j.bbr.2014.01.020

Gopnik, A., Wellman, H.M. (1992). Why the Child's Theory of Mind Really Is a Theory. *Mind & Language, 7*.

He, B. J. (2014, Sep). Scale-free brain activity: past, present, and future. *Trends Cogn Sci, 18*(9), 480-487. https://doi.org/10.1016/j.tics.2014.04.003

He, B. J., Zempel, J. M., Snyder, A. Z., & Raichle, M. E. (2010, May 13). The temporal structures and functional significance of scale-free brain activity. *Neuron, 66*(3), 353-369. https://doi.org/10.1016/j.neuron.2010.04.020

Herder, J. G. v. (1778). On the Cognition and Sensation of the Human Soul. In M. N. Forster (Ed.), *Herder: Philosophical Writings, 2022* (pp. 187 - 244). Cambridge University Press.

Herder, J. G. v. (2002 (Plastik, 1778)). Sculpture: Some Observations on Shape and Form from Pygmalion's Creative Dream (J. Gaiger, Ed.). University of Chicago Press.

Honey, C. J., Sporns, O., Cammoun, L., Gigandet, X., Thiran, J. P., Meuli, R., & Hagmann, P. (2009, Feb 10). Predicting human resting-state functional connectivity from structural connectivity. *Proc Natl Acad Sci U S A, 106*(6), 2035-2040. https://doi.org/10.1073/pnas.0811168106

Husserl, E. (1900–1901). *Logische Untersuchungen*. M. Niemeyer.

Husserl, E. (1913). Ideen zu einer reinen Phänomenologie und phänomenologischen Philosophie.

Husserl, E. (1937). Zur Phänomenologie der Intersubjektivität: Texte aus dem Nachlass (Vol. II). Martinus Nijhoff.

Husserl, E. (1950). Cartesianische Meditationen und Praiser Vorträge (Vol. 1). Martinus Nijhoff.

Husserl, E. (1962a). Phänomenologische Psychologie. Martinus Nijhoff.

Husserl, E. (1962b). Phänomenologische Psychologie: Vorlesungen Sommersemester 1925. Martinus Nijhoff.

Husserl, E. (1966a). Analysen zur passiven Synthesis: Aus Vorlesungs und Forschungsmanuskripten, 1918-1926. Martinus Nijhoff.

Husserl, E. (1966b). Zur Phänomenologie des inneren Zeitbewusstseins. Martinus Nijhoff.

Iacoboni, M. (2009, 2009/1//). Imitation, Empathy, and Mirror Neurons. *Annual Review of Psychology, 60*(1), 653-670. https://doi.org/10.1146/annurev.psych.60.110707.163604

James, W. (1967). Essays in Radical Empiricism and a Pluralistic Universe. Peter Smith.

Josipovic, Z. (2021). Implicit–explicit gradient of nondual awareness or consciousness as such. *Neuroscience of Consciousness, 2021*(2).

Kant, I. (1781-1787). Kritik der reinen Vernunft.

Kassis, R. (2001). De la phénoménologie à la métaphisique: difficultés de l'intersubjectivité et ressources de l'intopathie chez Husserl.

Kawamichi, H., Tanabe, H. C., Takahashi, H. K., & Sadato, N. (2013, 2013/1//). Activation of the reward system during sympathetic concern is mediated by two types of empathy in a familiarity-dependent manner. *Social Neuroscience, 8*(1), 90-100. https://doi.org/10.1080/17470919.2012.744349

Kohut, H. (1984). *How Does Analysis Cure?* University of Chicago Press.

Lanzoni, S. (2018). *Empathy. A History*. Yale University Press.

Lipps, T. (1897a). Raumästhetik und geometrisch-optische Täuschungen.

Lipps, T. (1897b). Raumästhetik und geometrisch-optische Täuschungen [Aesthetics of space and geometrical optical illusions]. Leipzig: J. A. Barth.

Lipps, T. (1903). *Leitfaden der Psychologie*. Leipzig: Wilhelm Engelmann.

Lipps, T. (1903-1906). Ästhetik. Psychologie des Schönen und der Kunst (Vol. I).

Lipps, T. (1903/06). Ästhetik. Psychologie des Schönen und der Kunst. Voss.

Lipps, T. (1907). Das Wissen von fremden Ichen. In *Psychologische Untersuchungen*. Engelmann.

Mak, L. E., Minuzzi, L., MacQueen, G., Hall, G., Kennedy, S. H., & Milev, R. (2017, Feb). The Default Mode Network in Healthy Individuals: A Systematic Review and Meta-Analysis. *Brain Connect, 7*(1), 25-33. https://doi.org/10.1089/brain.2016.0438

Merleau-Ponty, M. (1945). Phénoménologie de la perception. Gallimard.

Merleau-Ponty, M. (1960). Le philosophe et son ombre. In *Signes*. Gallimard.

Merleau-Ponty, M. (1964). The child's relations with others. In *The primacy of perception*. Northwestern University Press.

Metzinger, T. (2020). Minimal phenomenal experience: Meditation, tonic alertness, and the phenomenology of “pure” consciousness. *Philosophy and the Mind Sciences*, 1-44.

Miller, G. A. (1956). The Magical Number Seven, Plus or Minus Two: Some Limits on Our Capacity for Processing Information. *Psychological Review*.

Milll, J. S. (1865). An examination of sir William Hamilton’s philosophy. Longmans.

Newell, H. A. S. C. S. A. (1956). *Logic Theorist.* In

Nishida, K. (1987/1989). Nishida Kitaro Zenshu (Collected Works). Iwanami Shoten.

Noë, A. (2004). Action in perception. MIT Press.

Northoff, G. (2011, May). Self and brain: what is self-related processing? *Trends Cogn Sci, 15*(5), 186-187; author reply 187-188. https://doi.org/10.1016/j.tics.2011.03.001

Northoff, G. (2018). The Spontaneous Brain. From the mind-body to the world-brain problem. The MIT Press.

Northoff, G. (2021). Il codice del tempo. Cervello, mente e coscienza. il Mulino.

Northoff, G., Heinzel, A., de Greck, M., Bermpohl, F., Dobrowolny, H., & Panksepp, J. (2006). Self-referential processing in our brain--a meta-analysis of imaging studies on the self. *Neuroimage, 31*, 440–457.

Northoff, G., Wainio-Theberge, S., & Evers, K. (2020). Is temporo-spatial dynamics the "common currency" of brain and mind? In Quest of "Spatiotemporal Neuroscience". *Physics of life reviews, 33*, 34–54. https://doi.org/https://doi.org/10.1016/j.plrev.2019.05.002

Northoff, G., & Zilio, F. (2022, Apr 29). Temporo-spatial Theory of Consciousness (TTC) - Bridging the gap of neuronal activity and phenomenal states. *Behav Brain Res, 424*, 113788. https://doi.org/10.1016/j.bbr.2022.113788

Novalis. (1798). Die Lehrlinge zu Sais.

Noë, A. (2010). Out of the head. Why you are not your brain. MIT Press.

Pagliacci, D. (2019). L’io nella distanza. Essere in relazione, oltre la prossimità. Mimesis.

Park, H. D., Correia, S., Ducorps, A., & Tallon-Baudry, C. (2014, Apr). Spontaneous fluctuations in neural responses to heartbeats predict visual detection. *Nat Neurosci, 17*(4), 612-618. https://doi.org/10.1038/nn.3671

Park, H. D., Tallon-Baudry, C. (2014). The neural subjective frame: from bodily signals to perceptual consciousness. *Philosophical Transactions of the Royal Society B: Biological Sciences, 369*.

Pasquinucci, P. (2022). L'empatia come rispecchiamento creativo. Merleau-Ponty e la tesi della reversibilità. *Bollettino Filosofico, 37*, 301-313.

Preston, S. D. (2007). A perception-action model for empathy. In T. F. P. W. (Eds.) (Ed.), *Empathy in mental illness*. Cambridge University Press.

Qin, P., and Georg Northoff. (2011). How is our self related to midline regions and the default-mode network? *Neuroimage, 57*.

Raichle, M. E. (2015, Jul 8). The brain's default mode network. *Annu Rev Neurosci, 38*, 433-447. https://doi.org/10.1146/annurev-neuro-071013-014030

Rajmohan, V., & Mohandas, E. (2007, Jan). Mirror neuron system. *Indian J Psychiatry, 49*(1), 66-69. https://doi.org/10.4103/0019-5545.31522

Ratcliffe, M. (2006). Folk Psychology is not folk psychology. *Phenomenology and the Cognitive Sciences, 5*.

Rizzolatti, G., & Craighero, L. (2004). The mirror-neuron system. *Annu Rev Neurosci, 27*, 169-192. https://doi.org/10.1146/annurev.neuro.27.070203.144230

Rogers, C. R. (1978). The formative tendency. *J. Hum. Psychol*.

Rogers-Carter, M. M., Djerdjaj, A., Culp, A. R., Elbaz, J. A., & Christianson, J. P. (2018, 2018/10//). Familiarity modulates social approach toward stressed conspecifics in female rats. *PLoS One, 13*(10), e0200971-e0200971. https://doi.org/10.1371/journal.pone.0200971

Rumelhart, D., Hinton, G. & Williams, R. (1986). Learning representations by back-propagating errors. *Nature, 323*, 533–536.

Scalabrini, A., Schimmenti, A., De Amicis, M., Porcelli, P., Benedetti, F., Mucci, C., & Northoff, G. (2022, Jan). The self and its internal thought: In search for a psychological baseline. *Conscious Cogn, 97*, 103244. https://doi.org/10.1016/j.concog.2021.103244

Scasserra, S. (2021). Un altro me? Dall'Einfühlung alla empathy machine Università Ca' Foscari, Venezia].

Scheler, M. (1923). Wesen und Formen der Sympathie (2. erw. u. umgearbeitete Auflage von Scheler 1913).

Stein, E. (1989). *On the Problem of Empathy* (W. Stein, Trans.). ICS Publications.

Stich, S., & Ravenscroft, I. (1994). What is folk psychology? *Cognition*.

Tagliazucchi, E. (2017, Oct). The signatures of conscious access and its phenomenology are consistent with large-scale brain communication at criticality. *Conscious Cogn, 55*, 136-147. https://doi.org/10.1016/j.concog.2017.08.008

Tanabe, S., Huang, Z., Zhang, J., Chen, Y., Fogel, S., Doyon, J., Wu, J., Xu, J., Zhang, J., Qin, P., Wu, X., Mao, Y., Mashour, G. A., Hudetz, A. G., & Northoff, G. (2020, Jun). Altered Global Brain Signal during Physiologic, Pharmacologic, and Pathologic States of Unconsciousness in Humans and Rats. *Anesthesiology, 132*(6), 1392-1406. https://doi.org/10.1097/ALN.0000000000003197

Titchener, E. B. (1915). *A Beginner's Psychology*. The Macmillan Company.

Vara Sánchez, C. (2020). Raw Cognition. Rhythms as Dynamic Constraints. *JoLMA, 1*.

Varela, E. R. E. T. F. (2017). The Embodied Mind: Cognitive Science and Human Experience. MIT Press Ltd.

Vischer, R. (1873). On the Optical Sense of Form: A Contribution to Aesthetics. In *Empathy, Form, and Space. Problems in German Aesthetics, 1873-1893*. Getty Center for the History of Art and the Humanities.

Witt, J. K., & Proffitt, D. R. (2008, Dec). Action-specific influences on distance perception: a role for motor simulation. *J Exp Psychol Hum Percept Perform, 34*(6), 1479-1492. https://doi.org/10.1037/a0010781

Zahavi, D. (2001). Beyond empathy: Phenomenological approaches to intersubjectivity. *Journal of consciousness studies, 8*, 151-167.

Zahavi, D. (2014a). Empathy and Other-Directed Intentionality. *Topoi*, 129-142.

Zahavi, D. (2014b). Self and Other: Exploring Subjectivity, Empathy, and Shame. Oxford University Press.

Chapter II

THE ONTOLOGICAL AND BIOLOGICAL ROOTS OF EMPATHY. AN INVESTIGATION THROUGH AN ALE META-ANALYSIS

1. Introduction

After having traced the theoretical framework in which we intend to contextualize our own model of empathy, we will now present our own approach, that will be also completed through an activation likelihood estimate (ALE) meta-analysis.

In particular, we aim to describe empathy as a multi-layered phenomenon through which we are able to experience other individuals and through which we also experience something more about ourselves. In order to do this, we will first offer an ontological view of our experience in general, namely our capability of processing the world. We will then consider this capability from a developmental perspective, in order to see how much it is linked to the relationship with others, in particular with the care givers. In doing this, we will stress the importance of conceptualizing an "Ontological Co-Emergence of 'Self and Other'" (Arisaka, 2001), through which we can read self-processing and the empathic process as two intertwined phenomena. Finally, we will perform an activation likelihood estimate (ALE) meta-analysis of previous functional imaging studies investigating empathy in their experimental paradigm in order to see whether the empathic process is actually linked to the phenomenon of self-processing. For this aim, we will compare the results of our meta-analysis with the ones obtained by Qin and colleagues (Qin et al., 2020), to look for overlaps between the self-processing regions and the ones linked to the empathic process.

2. The relational self

By referring to the concept of embodied cognition that we highlighted in the first Chapter, we intend to build our own model of empathy on the idea according to which

> embodied cognition emerges from the dynamic co-determination of self and other. […] the embodied mind is intersubjectively constituted at the most fundamental levels (Thompson, 2001).

Indeed, after the conceptualization according to which affect and emotion are at the basis of the mind (Damasio, 1994, 1999; Panksepp, 1998), we are now able to stress that

> the affective mind isn't in the head, but in the whole body; and affective states are emergent in the reciprocal, co-determination sense: they arise from neural and somatic activity that itself is conditioned by the ongoing embodied awareness and action of the whole animal or person (Thompson, 2001).

In this way, being cognition characterized by affective components and being the affective component an inter-individual event, we must stress that cognition itself can be thought as an inter-individual event. In particular, we can talk about cognition in the sense of a "lived experience".

Being such an inter-individual event, our lived experience is not built upon a solipsistic abstraction through which we think about ourselves as "I"s, as for example in Descartes' philosophy (Descartes, 1637). Rather, it is built upon a relation, namely the self-other relation. For this reason, our self can be thought as a "relational self" (Andersen, 2002; Gergen, 2011; Herring, 2019; Wallace, 2019) that arises from the interpersonal dynamic among individuals that Martin Hiedegger would call *Mitsein* ("being-with") (Heidegger, 1927) and that Tetsuro Watsuji calls *aidagara* ("betweenness"[31]) , which is the

> fundamental nature of what it means for one to be a "self". In this context, what is primary in human relation is not the atomically separate "individuals", but rather what is generate "in-between" such individuals as a result of interaction. The very dynamic of such interaction defines the way in which the self *is* for others (Arisaka, 2001).

In addition to Husserl and Stein's theory of intentionality that we described in the first Chapter, this view stresses that consciousness and experience are built in a

[31] Arisaka notices that the term *aidagara* is composed of two Chinese characters: "aida", which means "between", both in spatial and temporal terms; and "gara", which means "the quality of" (Arisaka, 2001).

reciprocal way, meaning that the determination of an intentional act is also determined by the fact that there are other individuals whose intentional acts are as well determined by our mutual interaction. In this context, we can see that empathy itself plays a fundamental role in the construction of consciousness, in a way that our self-experience is shaped by the empathic experience and vice-versa. In order to deepen this connection, we intend to begin our analysis from the self-side, by investigating the ontological and functional structure of our self-processing.

3. The point of view in/and the world

At the basis of our embodied self-experience, we can find what Northoff and Smith call the *point of view* (from now on POV) (Georg Northoff, 2022b). The authors define POV as what "allows the subjectivity of self to be constituted ontologically and temporo-spatially" (Georg Northoff, 2022b). In a word, POV is the ontological and temporo-spatial[32] basis for the emergent experience of being an "I", meaning a "self" in the world and thus among other selves.

Campos and Gutierrez (Campos, 2015) consider POV as determined by two main components: a *background ecological layer* and a *mental surface layer*. The *background ecological layer of POV* is its ultimate ontological background. Thanks to the intrinsic and necessary connection between every POV and its background, every POV itself is situated, embedded, within the world.

The *mental surface layer of POV*, instead, refers to the subject and its mental life, meaning its capability of experiencing the world. As we will explain in detail in the paragraphs "self-processing" and "predictions", the mental surface layer of POV can be intended as the continuous process of introjecting/projecting patterns of synchronization and desynchronization, that are experienced (consciously and unconsciously) in a certain interaction. We will refer to this mental surface layer also as *self-processing*.

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[32] By "ontological" and "temporo-spatial" we refer both to the notion of an "embedded cognition", addressed by the 4E Cognition approach and to Northoff's notion of a temporo-spatial nature of the world and thus of every event, including consciousness and also every interaction, occurring in the world.

The conceptual subdivision of POV in an ecological background component and a mental surface one is linked to the distinction made by Campos and Gutierrez between the *emplacement world* and the *perspectival world* (Campos, 2015; Georg Northoff, 2022a). The *emplacement world* is the world (both external and internal to the subject) within which every ecological background layer of POV is situated, that is embedded. We posit that through the ecological background layer of POV, the single individual is in the emplacement world as a *living body*. The living body is the ontological and biological condition for experience, since it itself is a part of the intrinsically relational and transindividual network (Simondon, 2020) which the emplacement world consists of. We stress that the emplacement world is "inhabited" and structured by what we called "pure consciousness" in the first Chapter. This minimal and unified experience precedes and founds every distinct integrated subjective experience. It is prior to and transcends every subject-object distinction and it could become both.

The *perspectival world*, instead, is the part of the world (both external and internal to the subject) that every POV, in its mental features (i.e., mental surface layer of POV), can process in virtue of the morphophysiological characteristics of its sense organs and its intrinsic neural timescales (i.e., every different POV is related to a different perspectival world that can range from slightly to completely different) (Golesorkhi et al., 2021; Nagel, 1974). The perspectival world is thus formed and experienced through a mechanism that we can define as *self-processing*. Through self-processing, each POV can *sense*, *perceive* and *cognize* the world (both external and internal to the subject), always in a self-related way, hence the expression *perspectival world*. Through the formation of the perspectival world, the undifferentiated and pure experience becomes and takes the form, from the POV perspective, of a subjective experience, distinct from any other objectively experienced reality.

Thanks to this capability, then, every POV can experience itself not only as a living body but also as a *lived body*. This means that not only it can experience the world (both internal and external) but it can also experience itself as a perceiving agent, meaning that it can have a "meta-perception" over its own perceptions (Vallortigara,

2021), an internal centered and integrated elaboration of the stimuli (both internal and external) (Tononi & Koch, 2015).

4. Processing the world

The mechanism through which we process the world can be functionally subdivided in three nested layers (Qin et al., 2020). In **Figure 1** we show the structure of self-processing, embedded in the emplacement world and involved in the process of *sensing*, *perceiving* and *cognizing* the perspectival world.

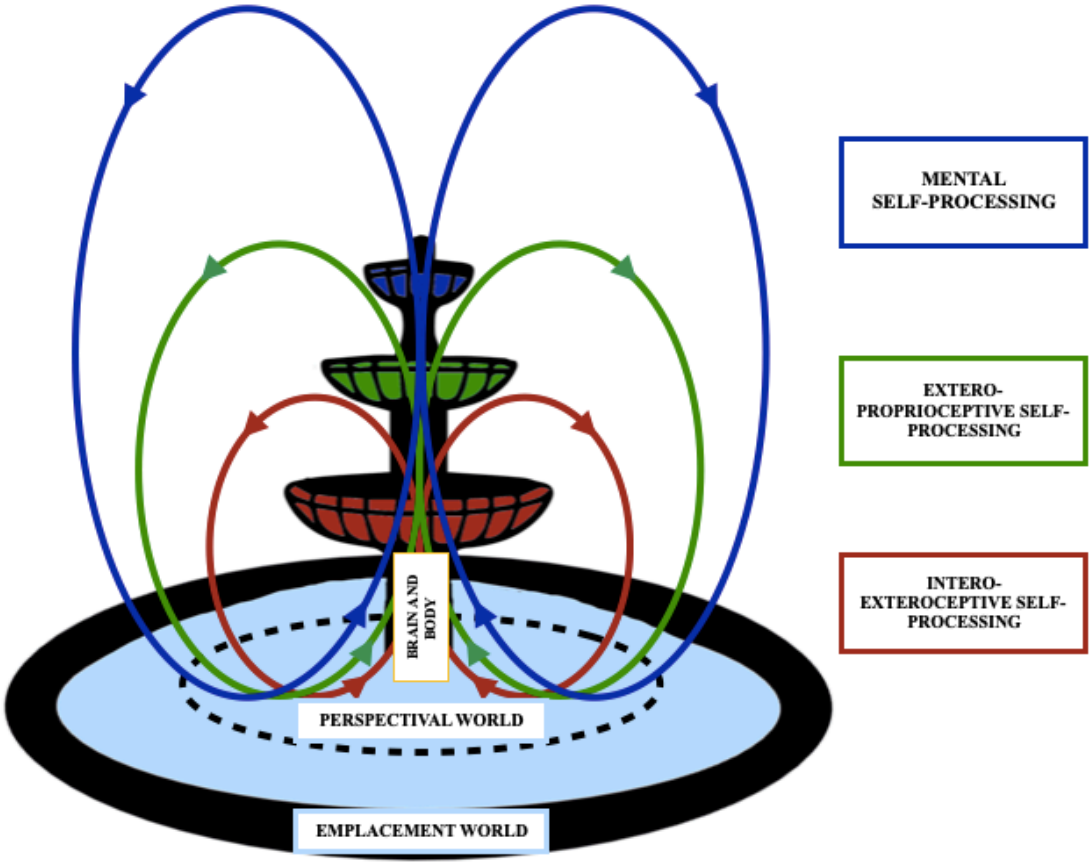

Figure 1. The three layered structure of self-processing, through which individuals experience the external and internal inputs. It works as an introjective/projective process: some environmental information is introjected through the individual's brain and body and then this information is nested into the individual's modalities of interpreting the environment (centralization); some information is then projected into the environment as meaningful forms, resulting in a proper experience. In particular, the first layer projects sensations, the second layer projects perceptions and the third layer projects cognitions. In this way, sensations, perceptions and cognitions are the products of this process of introjecting information and projecting forms. For example, pain is the result of this process of introjecting some physical information

(there is a wound on my arm) and projecting some kind of semantization upon that information, resulting in the form of "my pain" (there does not exist an objective pain, but there is always "my pain, in this precise moment", that derives from my personal way of processing the physical information of having a wound).
Self-processing is thus the relationship between the environmental information and the way the system formalizes this information. In the figure we represent the brain/ body/environment system as a fountain: the water on the floor of the fountain represents the environmental information that is introjected and the water that flows from the layers of the fountain represents the formalizations that are projected upon the introjected environmental information. The whole structure is the mechanism of self-processing. It is important to stress that self-processing is a dynamic process and that the introjected/projected water is never the same water, since we continuously self-process environmental information.

In particular, the first layer, namely the *intero-exteroceptive self-processing* (Qin et al., 2020), processes the interaction between the individual (i.e., a part itself of the environment) and the environment at a physiological level, that is, for example, through gastrointestinal and cardiorespiratory *sensations*. From now on, we will refer to this process as *sensing* the interactions that take place in the world (both internal and external to the subject). This kind of self-processing should not be thought of as only *interoceptive*, but also as *exteroceptive* (hence *intero-exteroceptive self-processing*), since the living body is always situated in the relational network which is the emplacement world. In such a way, there is always a mutual relationship between internal and external.

The second layer is nested in the first one in a climax of differentiation, and is called *extero-proprioceptive self-processing* (Qin et al., 2020). It processes the interaction between the individual (i.e., a part itself of the environment) and the environment at a proprioceptive level, that is, for example, through bodily *perceptions*. From now on, we will refer to this process as *perceiving* the interactions that take place in the world (both internal and external to the subject). Through this layer the interaction in which POV is involved is processed in a more coherent and centered way. This is what allows POV to experience itself as a proprioceptively integrated being, at the same time embedded in its environment and differentiated from it.

The third layer, the *mental self-processing* (Qin et al., 2020) is nested in the extero-proprioceptive layer and finalizes the experience of differentiation of POV from the environment. The mental self-processing processes the interaction between the individual (i.e., a part itself of the environment) and the environment at a mental/ cognitive level, that is, for example, through rational *cognitions*. From now on, we will refer to this process as *cognizing* the interactions that take place in the world (both internal and external to the subject). Through this layer, POV mediates the interaction in which it is involved at an abstract and cognitive level. The mental self-processing enables POV to cognize the environmental information in the form of conceptualizations of the world.

Moving from the first to the third layer, it is possible to trace a gradual increase in the subjective experienced differentiation of POV from the environment (see **Figure 1**). This is linked to a more and more centered, condensed and synthesized self-processing that leads to a more and more coherent and meaningful subjective experience (from *sensing*, through *perceiving*, to *cognizing*). The resulting subjective experience is more and more centralized around a sense that is no more only self-related but that is also *self-referential* (Northoff et al., 2006).

To make an example of the self-processing functioning, let us consider the case of you coming back home after a long journey. You see your mother on the doorstep. Your heartbeat increases along with your breathing rate. You are happy. You recall all the times that you missed her when you were far away, you think about other moments of reunification with her, you foreshadow your next goodbye. Let us now analyze this encounter.

At an interoceptive/physiological level, you *sense* the interaction of you-seeing-your-mother-on-the-doorstep through changes in your physiology. Here we can see the mechanism of intero-exteroceptive self-processing in action, mediating the interaction of you-seeing-your-mother-on-the-doorstep in a physiological/ interoceptive way (i.e., your heartbeat increases, you get teary eyes etc.).

At a proprioceptive/affective level, you *perceive* the interaction of you-seeing-your-mother-on-the-doorstep through changes in your proprioceptively integrated body

and in your emotions. Here we can see the mechanism of extero-proprioceptive self-processing in action, mediating the interaction of you-seeing-your-mother-on-the-doorstep in a proprioceptive/emotional way, so that you feel yourself as an individual (emplaced in but also differentiated from the world) who is happy in that very moment.

Eventually, at a mental level, you *cognize* the interaction of you-seeing-your-mother-on-the-doorstep through changes in your thoughts. Here we can see the mechanism of mental self-processing in action, mediating the interaction of you-seeing-your-mother-on-the-doorstep in a cognitive/rational way, so that you can abstract from what you are experiencing in that precise moment and you can start thinking (warning: this abstraction is always based on an actual interaction).

5. The construction of self-processing through development

Let us now consider what has been said from a developmental perspective, since, as we already stressed, we think it is crucial to understand the concepts linked to the capability of processing the world and thus other individuals. At the beginning of life, every newborn passes through stages in which they receive physiological, emotional and attentional heteroregulation (Feldman, 2007b). Thanks to this heteroregulation, the newborn introjects these different modes of regulation resulting in an acquired autoregulation capacity.

We can observe the process from heteroregulation to autoregulation unfolding in three different stages: biological/physiological regulation; emotional regulation and attentional regulation. At the basis of the whole process we can trace the mechanism of *synchronization*. As we will deepen in the third Chapter of this work, synchronization is a mechanism that applies to all the world's phenomena (Strogatz, 1997) and that is the substrate for the three stages that we introduced, in a way that better synchrony at the first stage corresponds to better synchrony at the following stage and so on (Feldman, 2007b). As highlighted by Feldman (Feldman, 2007b), the construct of synchrony has been applied to a range of phenomena, from the micro-level of cells, neurons, and genes (Blenkinsop & Lang, 2006; Klemm & Bornholdt,

2005) to the macro level of population growth and weather change (Di Paolo, 2001) and the mental realm of the unconscious (Jung, 1961).

We assume that these processes of synchronization and desynchronization that occur in the interaction between the caregiver and the infant are internalized in the infant in a way that they become introjected patterns that are then projected in his/her following interactions[33]. Therefore, the infant processes the world (in both its external and internal components) always through these acquired (but ever-changing) patterns. These processing modes result in the different layers of self-processing that we described above, through which the developing individual integrates the interactions in which he/she is immersed in a more and more coherent framework.

6. Predictions

The patterns of synchronization and desynchronization described above can be thought as priors present in every interaction. This happens in a recursive way, meaning that the patterns of synchronization and desynchronization experienced in a certain interaction are always carried out in the following interactions. Moreover, every interaction continuously shapes the patterns of synchronization and desynchronization of every interacting agent. At the same time, every interacting agent shapes the interaction through his/her introjected patterns of synchronization and desynchronization (warning: we are always immersed in a relational, interactive and transindividual network (Simondon, 2020)).

We hypothesize that this recursive process is what we previously called self-processing. The three-layered structure that we depicted works as an introjective/ projective process, in order to maintain homeostasis (Pezzulo et al., 2015; U. Sandler, 2017). This process is experienced at the level of the lived body as *predictions*, both conscious and unconscious. Predictions have been extensively

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[33] This seems to us similar to the idea of "repetition" conceptualized by Freud in *Remembering, Repeating and Working-Through* (Freud, S. (1914). Remembering, Repeating and Working-Through (Further Recommendations on the Technique of Psycho-Analysis II). In *The Standard Edition of the Complete Psychological Works of Sigmund Freud* (Vol. 12, pp. 145-156).).

addressed as “mental representations” (for a discussion on this approach see (Fuchs, 2011, 2018; Northoff et al., 2020b)). We claim that they can be conceived this way only with respect to the part of the predictive process that is experienced at a conscious level. For example, let us consider the formation of the concept (concepts and predictions are considered here as synonyms) of “dog”. The concept of “dog” is formed through the whole set of interactions between the individual and what he/she addresses as a dog, in a way that the particular patterns of synchronization and desynchronization experienced (both at a conscious and at an unconscious level) by the individual in those interactions are introjected in the individual’s system and influence his/her future interactions. When these experiences are conscious, the individual fantasizes about them, forming those abstract thoughts that we ordinarily call representations (the individual figures them as “proper scenes”). We hypothesize that this happens also at an unconscious level.

In the three-layered structure, self-processing (i.e., this continuous process of introjecting/projecting) seems to take place at every level, both consciously and unconsciously. Indeed various authors have underlined the fact that this process happens not only at a mental/cognitive level, but also in an interoceptive, exteroceptive and emotional level (Barrett & Simmons, 2015; Park & Blanke, 2019; Seth, 2013). Moreover, we hypothesize that self-processing, at every layer, is composed of both a conscious component and an unconscious one. Tentatively, we could say that at the intero-exteroceptive level the unconscious component is prevalent relatively to the conscious one.

It is also important to remind that we process only a section of what happens in a certain interaction because, by virtue of the morphophysiological characteristics of our sense organs and our particular intrinsic neural timescales (Golesorkhi et al., 2021), we can only experience a limited part of the frequency spectrum (Golesorkhi et al., 2021; Nagel, 1974).

7. Synchronic and diachronic components of the interaction

Taking as a starting point Kirchhoff and Kiverstein's 2020 paper (Kirchhoff & Kiverstein, 2020), we claim that every interaction implicates a *synchronic* and a *diachronic* component. We argue that the deep connection of the brain to the body and the rest of the world constitutes the synchronic component of the interaction. We hypothesize that without this synchronic component, interactions would not take place and thus consciousness and experience would not be possible. We say so because we think that the ecological relationship between the world and its parts (i.e., every possible POV) is what allows for consciousness and experience (Northoff, 2019). Moreover, the synchronic component also constitutes the mechanism of introjection/projection of patterns of synchronization and desynchronization that we addressed as self-processing, since this mechanism always occurs in a "here-and-now" space and time.

However, the patterns of synchronization and desynchronization that are at stake in every interaction between interacting agents are also diachronic. The diachronic component is due to the fact that the interacting agents are always dynamic, as they unfold over time (Kirchhoff & Kiverstein, 2020). This unfolding over time occurs through cycles of interaction in which the process of introjecting/projecting patterns of synchronization and desynchronization is always involved.

We want to argue that, in every interaction, synchronic and diachronic components are always intertwined in a way that every introjection and every projection always "carry out" patterns of synchronization and desynchronization. These patterns of synchronization and desynchronization are introjected and projected through moments of synchronization (and this is what makes the patterns synchronic)[34]. At the same time, they are introjected and projected by temporally and spatially characterized agents, that unfold dynamically over time (and this is what makes the patterns diachronic) (**Figure 2**).

[34] We will deepen the phenomenon of synchronization in the next chapter.

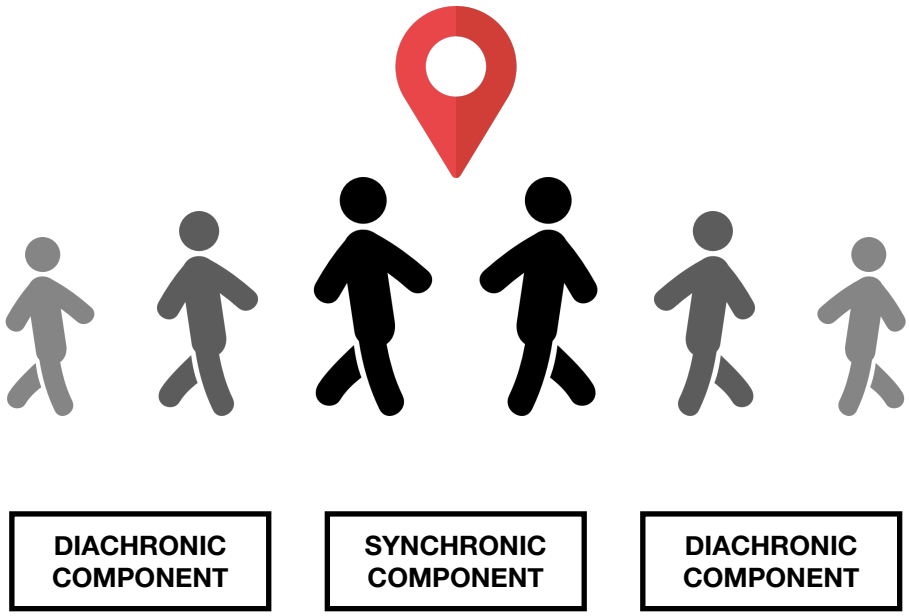

Figure 2. Every interaction is composed of a synchronic element, which is given by the fact that the interacting agents find themselves in the same temporo-spatial coordinates, and a diachronic element, given by the fact that they carry a "story" that unfolds over time.

Referring to the conceptualization of Northoff and Smith (Georg Northoff, 2022b) we could say that the synchronic component of the interaction regards the ecological background layer of POV, while the diachronic component regards the mental surface layer of POV, meaning the self-processing itself, since it is what has the capability of keeping something from every synchronic interaction. This happens thanks to the phenomenon of *memory*, which has been widely conceptualized and analyzed both in the philosophical field (Agostino D'Ippona, 1952; Aristotele, 350 b.C.; Bergson, 1896; Husserl, 1928; Platone, 370 b.C), in the psychological one (Atkinson, 1968; Bartlett, 1954; Ebbinghaus, 1885) and in the neuroscientific one (Kandel, 2007; Milner et al., 1998; Morris, 1981). It is important to point out that the two components can never be thought as distinct, as they together constitute POV, in its ecological and ontological situatedness and in its temporal and spatial unfolding.

8. Self-processing and the empathic process: the self/other-processing

Being every POV always embedded in the world and being the world an intersubjective space, POV itself often needs to process other POVs, meaning other individuals endowed with an inner self. This way of processing other living individuals has been called *empathy* and we have already presented various theoretical approaches that have been used to study it. The aim of our work is to read the empathic capability as a specific application of the general capability of processing the world. In particular, we stress that the empathic process is not something that is completely different from the self-processing. On the contrary, following the aesthetic theory, we, as humans, always tend to process the world as composed of animate beings, meaning that we always tend to see "life" in what we interact with, even if we are in front of inanimate objects that, when met as *symbols* (Florenskij, 2007), evoke an invisible vital sense on the basis of their visible structure. This kind of *apperception* (Lipps, 1903/06) is what allows us to see the world as full of life and, on this basis, to empathize with it[35].

In some cases, though, the interactions we have with other entities actually require that we recognize an inner vital sense in them. These are the cases in which we interact with other living individuals. The more these individuals are similar to us, that is to our *type* (Stein, 1989), the more our processing their inner vital sense is realistic and reliable. So we are "better empathizer" with other human individuals than with every other individuals or entities in the world. This means that our empathic perception and understanding of an individual that belongs to another species is simply less accurate, since we "apperceive" and we transcend a lot beyond our perceptions[36], in a way that our predictions are built on an unbalanced mechanism of projecting more than what is introjected.

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[35] We highlight that, as we already noticed, Lipps contextualizes empathy in the field of knowledge, as that specific knowledge oriented towards others, meaning towards entities in which we can recognize/project a vital sense, such as the artistic objects.

[36] We will deepen this point in the last chapter of this work, the one that is dedicated to the *Public perception of animal testing*.

Following this line and the theory of a "relational self", we stress that the empathic process and the self-processing are two sides of the same process through which the POV, with its mental surface layer, experiences the world in which it is situated with its background ecological layer. In this way, we could talk about *self/other-processing* to address human experience in the world.

9. Empathy and sympathy

After having presented the self-component of what we called self/other-processing, let us now come to the other-component, through an analysis of *empathy*. In order to deepen our definition of empathy on the basis of what we stressed about the synchronic and the diachronic components of every interaction, we think it would be relevant now to focus on a terminological disambiguation. The disambiguation we intend to track is the one between empathy and *sympathy*. Before addressing the topic of empathy itself, indeed, the philosophical tradition of the 18th century, with authors such as David Hume and Adam Smith, was focused on the intersubjective experience of feeling sympathy. In particular they define sympathy as the ability to share and, in addition, also understand the feelings of others (Hume, 1739-40; Smith, 1759)[37]. Despite the use of a different term (sympathy), it seems that this conceptualization made by Hume and Smith is similar to the one that the contemporaneous analysis has elaborated to address the phenomenon of empathy. Also for empathy, indeed, it is recognized the duplicity of being a complex and layered experience, as we will see more in depth in the next paragraph. However, in order to have a wider view of the considered phenomena, we want now to deepen the terminological distinction.

Both "empathy" and "sympathy" are composed of the Greek word πάθος, which can mean "suffering" as well as "experiencing" or "feeling". The difference between the two concepts is in their prefix: the one of sympathy (συν) means "with"; the one of

[37] Even if they both consider sympathy as a fundamental aspect of human nature, only Smith opens the concept to the ethical dimension, by stressing that the sympathetic experience of having access to others' experiences is the foundation of our ability to make moral judgements.

empathy (ἐν) means "into". So, following this terminological distinction, by "sympathy" we intend to indicate the experience of "fellow-feeling" or "feeling together" with someone else, that is the experience of immediately *sharing* his/her emotion[38]. "Empathy", instead, will be read by us as the process of acceding also to a cognitive component, that lets us experience others' experiences (although in a non-original way, as highlighted by Stein (Stein, 1989)) with both an automatic and direct physiological activation and a cognitive elaboration of that basic feeling, through which we can recognize that the experience we are in front of is someone else's experience. In this sense, empathy can be defined as the ability of "putting" oneself "into" someone else's shoes, that is experience.

This means that, for example, when observing someone crying we are able to understand several things through empathy: that probably he/she is crying because he/she is sad, what it means to be sad, that being sad is not pleasant, that probably some bad event made that person sad, that probably we could do something for him/her and so forth. Summing up, through empathy we are able to contextualize what we see and to put it into a narrative framework, so that someone who is crying is seen as a person with an identity and a history and his/her history led him/her to be sad in this precise moment. We feel sad for him/her and with him/her, but we are able to distinguish our vicarious, our secondary sadness from the original one. In this way, we put ourselves into the world and we know the world right through this process.

Thanks to this clarification, we intend to define empathy as the diachronic process of contextualizing other's experience into a wider framework and as knowing and understanding others' experience through our own experience, while sympathy can be thought of as the synchronic sharing of an experience with someone else in a precise moment[39] (**Figure 3**).

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[38] That sometimes can happen even without understanding it and without being aware of what is going on.

[39] We will deepen, in the next Chapter, the synchronic mechanisms that are in action when empathizing with someone.

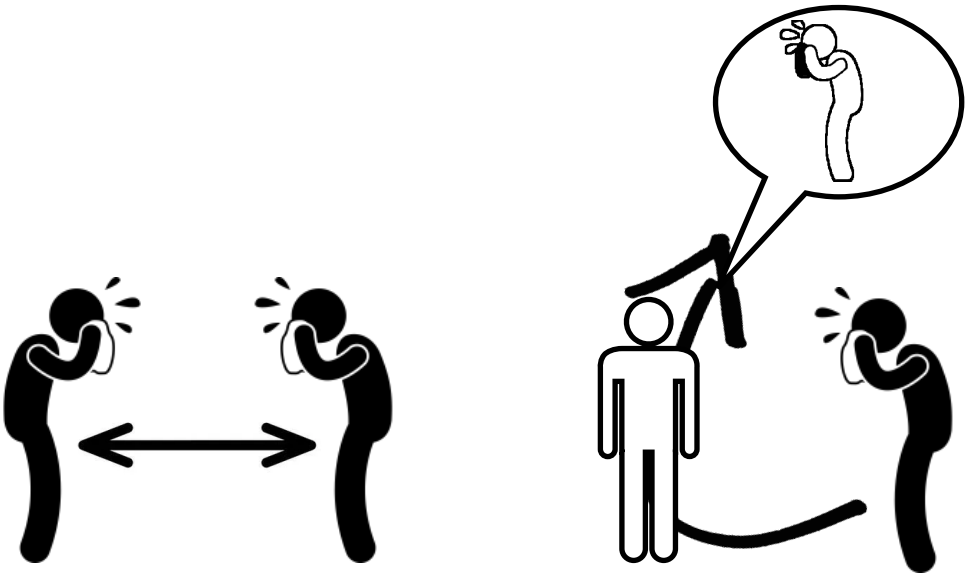

Figure 3. The left figure shows the simultaneous and synchronic event of sharing a feeling with someone (sympathy). The right figure shows the diachronic event of one empathizer experiencing an empathized. As we will observe, this process of experiencing others is composed of an "introjection/projection" mechanism, through which we experience an inner physiological activation in response to someone else's activity and we elaborate this activation both in an emotive and a cognitive way. After this inner elaboration, we then hand the experience to the empathized, recognized as another self.

We stress that empathy and sympathy, intended in this way, must be thought as intertwined, since it is both true that the "fellow-feeling" experience can lead to, through a bottom-up mechanism, the empathic act and that the "feeling-into" can facilitate the sympathetic encounter.

10. Introjection and projection in the empathic process

After having observed that we can bring empathy back to the capability of processing the world (in which also living individuals are present) (i.e. self/other-processing), we want now to describe the phenomenon from a more empirical perspective. When empathizing with someone, we process the experience of the empathized through what we defined a perceptual-hermeneutical process. Our empathic understanding of

the other person is shaped by the experience we have on the basis of his/her presence and, in addition, also by our previous experiences (i.e. empathy is also the result of learning processes (Preston, 2007)). We thus propose that empathic knowledge, as well as knowledge in general, is mediated through a subjective elaboration of environmental cues[40].

We stressed that empathy is the capability of knowing others' experiences. Empathy indeed has been often associated with the capability of having a Theory of Mind, that is the ability to attribute mental states to other individuals (David Premack, 1978). But what does it mean to "know"? First, we want to remind that we do not refer to purely cognitive knowledge. In fact, as we already stressed, empathy itself is not only a cognitive capability, but it is a process that involves different kinds of experiences, including the cognitive one. Second, we want to disambiguate that the knowledge we have about others' experiences will never be a complete and total knowledge of the original experience lived by the empathized individual, as also Husserl and Stein stressed (Husserl, 1937; Stein, 1989).

We intend here to read the empathic process, leading to the kind of knowledge we have just described, on the basis of two elements, elaborated respectively by Lipps and Stein. In particular, we intend to focus on the element of *imitation/projection* that Lipps takes into account (Lipps, 1897b) and, on the other hand, on the element of the *non-originality* of the empathic experience, proposed by Stein (Stein, 1989).

We think that the mechanism at the basis of the empathic process is composed of what we could call an *introjection/projection* dynamic, that is similar to the one described by Lipps[41]. Through this mechanism, we can experience the others' experiences in a self-related way, meaning in a non-original way. Thanks to the

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[40] The focus on the fact that the subjective elaboration is made upon environmental cues is fundamental to avoid an absolute subjectivistic perspective. According to Lipps, the activity that I can observe in things is given to them by me, but not in an arbitrary way, rather, in a necessary way Lipps, T. (1906/2002). Einfühlung und ästherischer Genuss. *Die Zukunft, 54*, 100-114. .

[41] We substituted the term "introjection" to the one "imitation", since we think it describes better the unconsciousness of the mechanism and, in addition, also the fact that the cues coming from the empathized individual are integrated into the psycho-physiological structure of the empathizing individual.

discovery of the mirror neurons (di Pellegrino et al., 1992), we have elements to say that when observing someone, some parts of our brain activate in response to that observation. Taken together, these parts compose the so called Mirror Neuron System (MNS) (involving areas like the Primary Motor Cortex, the Inferior Frontal Gyrus, the Inferior Parietal Lobule, the Superior Temporal Sulcus and the Occipital Lobe) (Rajmohan & Mohandas, 2007), which is often thought as being implicated in some functions linked to social cognition, language and empathy itself.

So after this discovery, researchers have started to associate the phenomenon of empathy to an automatic and motor activation that would lead to an emotive and cognitive elaboration. Taken together, in the form of a continuous cyclic process, these motor, emotive and cognitive components lead to experience another individual's emotive state.

But how does this introjection/projection mechanism work? When we are in front of another individual, our system, starting from our body, is provoked by the presence of the other. Following Merleau-Ponty (Merleau-Ponty, 1960), we can say that our body is "touched" by the other. By saying that we are "touched" by the other's presence, we intend that our system reacts to this presence (and thus to the expressions, the movements and the behaviors of the other individual that immediately evoke his/her experience) with some physiological, neural, behavioral and psychological activations, meaning with an *experience*. This experience is the result of the introjection of some temporo-spatial patterns coming from the outer world, which are then integrated, "nested", into our own inner temporo-spatial patterns.

To describe it better, the other individual's expressions, movements and behaviors (temporo-spatial patterns) provoke a reaction in our system (that Lipps called *imitation*, in which the mirror neurons are probably involved). Our system integrates, "nests", this activation into its own temporo-spatial patterns, meaning into what it has already learned and experienced during the life. So to "introject" the cues coming from the other individual means to react to them with an automatic and unconscious

activation and then to integrate (nest) this synchronic activation into a diachronic and meaningful context.

The second mechanism that compose the empathic process is the *projection*. Before describing it, we intend to notice that we cannot think of them as to separate mechanisms, since they act together, as a dynamic whole, and there is not a specific chronological order for their occurrence. In fact, they continuously influence each other, describing a sort of circle that slightly reminds to the *hermeneutic circle*[42].

After these clarifications, we can now describe the mechanism of *projection*. It is first and foremost what allows our system to recognize that the non-original experience we had on the basis of the introjected patterns is *original* for the person we are empathizing with. Through projection, we give this experience back to its owner and, in doing this, the self-other distinction experience becomes explicit. Being such a distinction explicit, the only way we can access other's experience is through a hermeneutical effort that is based both on the introjected patterns and on our own personal already existing patterns. The result is a knowledge of the other that is never total but that, exactly for this reason, leads to the possibility of an interaction and an encounter between two distinct individuals. In Pavel Florenskij's words (Florenskij, 2004), we can say that knowledge always derives from acts of "love", since it requires the effort of "getting out" of one's self to reach an always unreachable other. In this sense, to "get out", to "project", to "give back the experience to the owner" are all synonymous that describe the effort of understanding another self on the basis of an experience that involves the whole psycho-physical organism and not just one layer (such as the cognitive one).

So we can see that the empathic knowledge is not an arbitrary attribution of states and experiences, instead it is an infinite process that can never lead to a precise overlap between the experience of the empathizer and the one of the empathized, but that it is based upon a dynamic introjective/projective process (**Figure 4**).

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[42] The hermeneutic circle is a principle that describes the process of interpretation as cyclical and guided by pre-understandings. The complete comprehension of a text or phenomenon is reached by understanding the details in relation to the whole and the whole in relation to the details. The interpretation of a text or phenomenon is always influenced by the interpreter's pre-existing understandings, knowledge, and perspective.

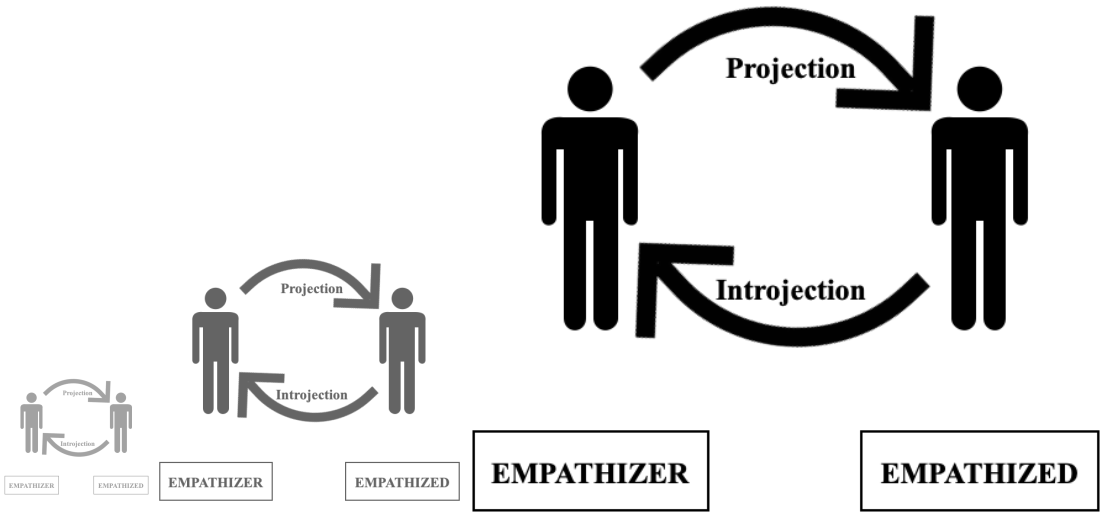


Figure 4. The dynamic process of empathy is composed of an introjection stage, through which some inputs coming from the empathized are introjected by the empathizer; and a projection stage, through which the empathizer attributes some mental and emotional states to the empathized, in a recursive way. The projection is always based upon the introjection and also upon previous introjections based upon past experiences (regarding, for example, what it is like to feel a certain emotion both from a physiological and from a mental perspective, what that emotion means for a certain culture and so forth).

11. The multi-layered structure of the empathic process

Given these theoretical clarifications, let us now delve into the neuroscientific contributions to the study of empathy. From this perspective, empathy has been seen as composed of different but not separable experiences belonging to the same process (Preston & de Waal, 2002). In particular, we can identify three sub-phenomena that constitute the proper multi-layered phenomenon of empathy. We intend to consider them as three layers of the same empathic process. According to De Waal's "perception-action model", they seem to be nested within each other (de Waal & Preston, 2017).

We will refer to the first and most basic one as *sensorimotor resonance*, and it can be described as the automatic mimicry and synchronization of expressive body language (e.g., facial expressions) during the observation of another person. It is prior to the experience of emotional 'matching' and it provides a gateway through which we can

understand the thoughts and feelings of others (Decety, 2012, 2008; Dimberg, 1990; Iacoboni, 2009; Meltzoff & Decety, 2003). The areas attributed to sensorimotor resonance include: superior temporal cortex, inferior parietal lobule, inferior frontal cortex, pre-motor and primary motor cortex forming the mirror neuron system and the somatosensory cortex (Blair, 2005; Carr et al., 2003; Fogassi et al., 2001; Gazzola et al., 2007; Vemuri & Surampudi, 2015).

The second layer is *emotional empathy*. It is the ability to share the emotional state of another individual (Decety & Jackson, 2004; Preston & de Waal, 2002). It is thought to be supported by areas like inferior frontal gyrus (IFG) and inferior prefrontal gyrus, inferior parietal lobe (IPL), anterior cingulate cortex (ACC), anterior insula (AI), amygdala, ventrolateral frontal cortex, superior temporal cortex while cognitive empathy mainly covers the temporo-parietal (A.E. Foster, 2019; Dvash, 2014; Simone G. Shamay-Tsoory et al., 2009; Vemuri & Surampudi, 2015; Yu & Chou, 2018).

The third layer is *cognitive empathy*, the ability to comprehend the feelings, emotions, thoughts, beliefs, and intentions of others. This includes understanding the emotional and mental world of another individual, and it involves the ability to "put oneself into another's shoes" (Baron-Cohen, 2013; Frith & Frith, 2005). It is thought to be controlled by areas like the medial prefrontal cortex, the temporoparietal junction (TPJ), the medial temporal lobe, paracingulate cortex and dorsal prefrontal cortex (Dongen, 2020; Dvash, 2014; Karpouzian-Rogers et al., 2021; Naghavi, 2022; Shamay-Tsoory, 2015; S. G. Shamay-Tsoory et al., 2009; Trieu, 2019; Vemuri & Surampudi, 2015; Winters et al., 2021; Yu & Chou, 2018). Moreover, neuroanatomical studies have shown a correlation between this phenomenon and the default mode network (DMN) (Oliveira Silva et al., 2018).

These three nested layers are inter-dependent, both from a learning-developmental perspective (i.e., bottom-up) and from a regulatory one (i.e., top-down) (Panksepp & Panksepp, 2013; Preston & de Waal, 2002) (**Figure 5**). We want to stress that in order to talk about empathy, all these three layers must be present and well integrated between each other.

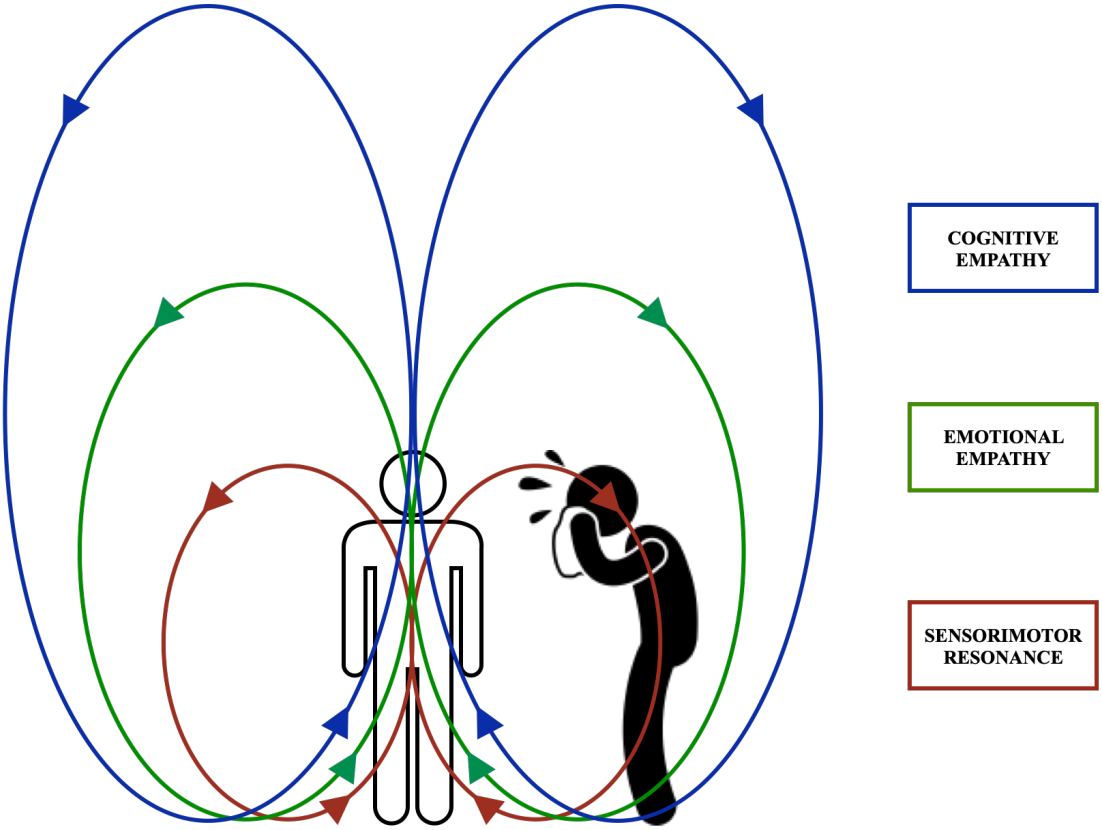


Figure 5. The three layered structure of empathy, through which individuals can process the environmental information coming from other objects or individuals. Empathy works as an introjective/projective process: some environmental information coming from the empathized is introjected in the empathizer's brain and body and some formalizations about the experience of the empathized are then projected in him/her. In particular, the sensorimotor layer projects physiological sensations of resonance (through automatic mechanisms of mimicry); the emotional layer projects emotive perceptions and the cognitive layer projects cognitive interpretations of the mental and emotional state of the observed object or individual. In this way, when in front of a crying person, we introject some cues of that scene (according to what is salient for our personal experience) and we project a semantization of those cues, meaning that we elaborate those cues and we experience them in the form of physiological sensations, emotive perceptions, cognitive interpretations. The result of this process is our empathizing with the observed object or individual, our nesting his/her/its experience into our personal one. It is important to notice that this process of empathic introjection/projection is based upon environmental information and therefore it is not an arbitrary attribution of our experience into someone or something else.

12. From self-other bonding to self-other distinction: the construction of time and space

But where do these distinct but not separable layers come from? In the first chapter of our work we stressed that empathy requires both a *self-other bonding* experience (that occurs during the first moments of life) and a *self-other distinction* experience that starts to occur after the earliest moments (Rochat, 2003). The self-other bonding experience, as Scheler points out in his reading of the phenomenon of *unipathy*, is fundamental to associate the synchronic feeling of connection with other individuals to a pleasant experience. Scheler's perspective can be confirmed also from a neuroscientific perspective, thanks to which we can observe that in every social species it is very important, for a proper development of the individuals, the contact and the bonding with significant ones (Čater, 2022; Feldman, 2017; Lima et al., 2010). This also applies for the phenomenon of empathy itself, which seems to be impaired not only in subjects who have undergone early trauma (Levy et al., 2019), but also in ones who have been prematurely separated from their mother (Khalifeh et al., 2019).

On the other hand, the self-other distinction experience is fundamental to maintain an equilibrate psychophysical distance between one's self and the other self in order to experience the other and not be fuse with him/her (Steinbeis, 2016).

So if the psychophysical development of an in individual happens in a healthy way, whenever he/she is in front of other individuals, his/her psychophysical structure has access to both bonding and distinction patterns, that have been acquired through development. We stress that the bonding patterns constitute what we called the synchronic component of the interaction, while the distinction patterns constitute what we called the diachronic component of the interaction. They both are fundamental for a healthy empathic interaction.

In the next Chapter we will deepen the synchronic component of the empathic interaction, through an analysis of the concept of synchrony, that we can recognize as the most basic and constitutive layer that we can observe and measure during every inter-individual interaction (Feldman, 2017) including the empathetic one (Levy &

Feldman, 2019; A. Ulmer Yaniv et al., 2021) and the altruistic one (Valdesolo & Desteno, 2011). In addition, a good degree of synchrony between parents and child during the very first moments seems to be also what allows for a proper development of the empathetic process itself (Feldman, 2007a).

In addition to this, we stress that the diachronic coponent derives from the temporo-spatial expansion that leads from the self-other bonding to the self-other distinction. We intend now to deepen this concept of temporo-spatial expansion. During the self-other bonding period, every layer of both the self-processing (intero-exteroceptive processing, extero-proprioceptive processing and mental processing) and the empathic process (sensorimotor resonance, emotional empathy and cognitive empathy) are condensed in a unique undifferentiated nucleus that precedes and prepares every capability of processing the stimuli. Through development, the brain-body system starts to build its own inner temporo-spatial structure distinguished to but also connected to the temporo-spatial structure of the environment[43] that makes the developing individual develop a self-experience distinguished from the environment. This temporo-spatial construction determines what we defined the temporo-spatial expansion of the self-other experience (from bonding to distinction) (**Figure 6**).

[43] We described this temporo-spatial construction in the first Chapter of our work.

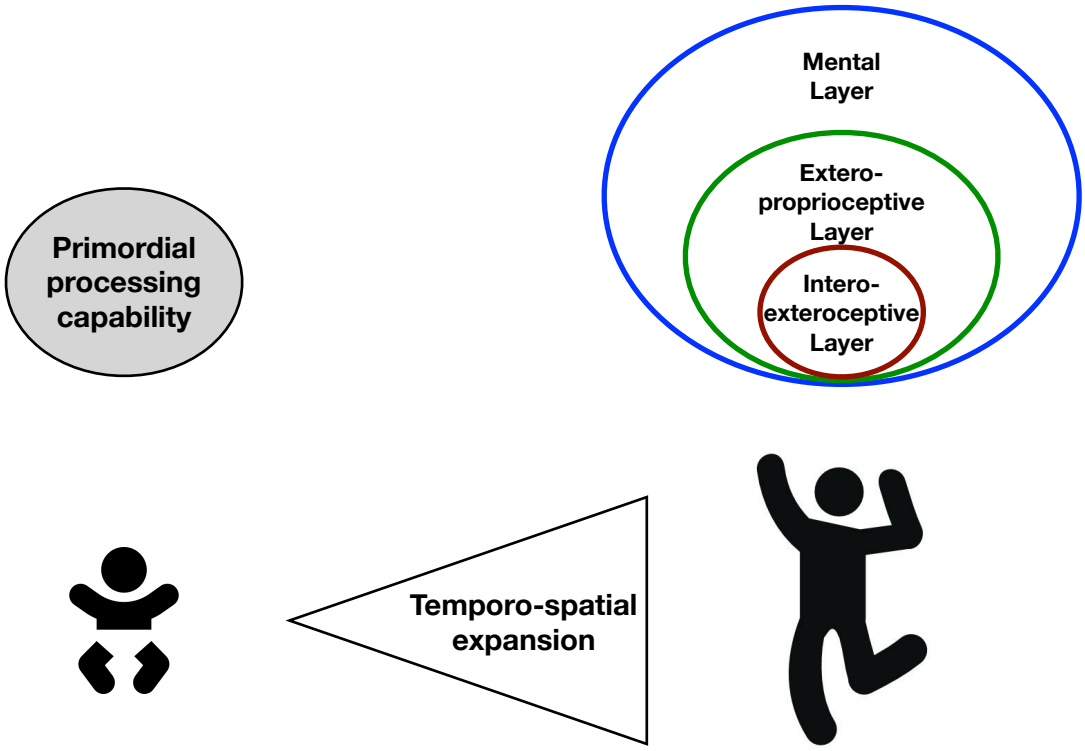


Figure 6. The temporo-spatial expansion follows the individual's development and leads to the construction of the self/other processing structure, through which the individual can experience (i.e. sense, perceive and cognize) the world, including other individuals. From an undifferentiated nucleus, through development and through learning processes, the multilayered structure is built.

So both the synchronic experience and the diachronic construction are fundamental not only for experiencing other individuals, but also for experiencing one's own self. Thanks to this clarifications, we can see how much the phenomena of self-processing and empathic process are intertwined to each other.

In order to offer a neuroscientific analysis for the three layered structure of empathic process, we performed an activation likelihood estimate (ALE) meta-analysis of previous functional imaging studies investigating empathy that consider the sub-phenomena of sensorimotor resonance, emotional empathy and cognitive empathy in their experimental paradigm. Then, we compared the results of our meta-analysis with the ones relative to the three layers of the self-processing, found by Qin and colleagues (Qin et al., 2020), to look for overlapping regions.

13. Methods

Articles included in this meta-analysis were collected from a literature search on Pubmed, which was concluded by March, 2022. Search terms include keywords on general or specific aspects of empathy, such as "emotional empathy", "emotional contagion", "cognitive empathy", etc. All search terms were combined with "fMRI" to include only functional neuroimaging studies.

After the initial search, a total of 1151 articles were found. A screening procedure was then performed using the inclusion and exclusion criteria below. After the screening process, a total of 32 studies were included in the final analyses. See **Figure 7** for the detailed paper selection procedure and **Table 1** for a summary of the tasks included in the papers.

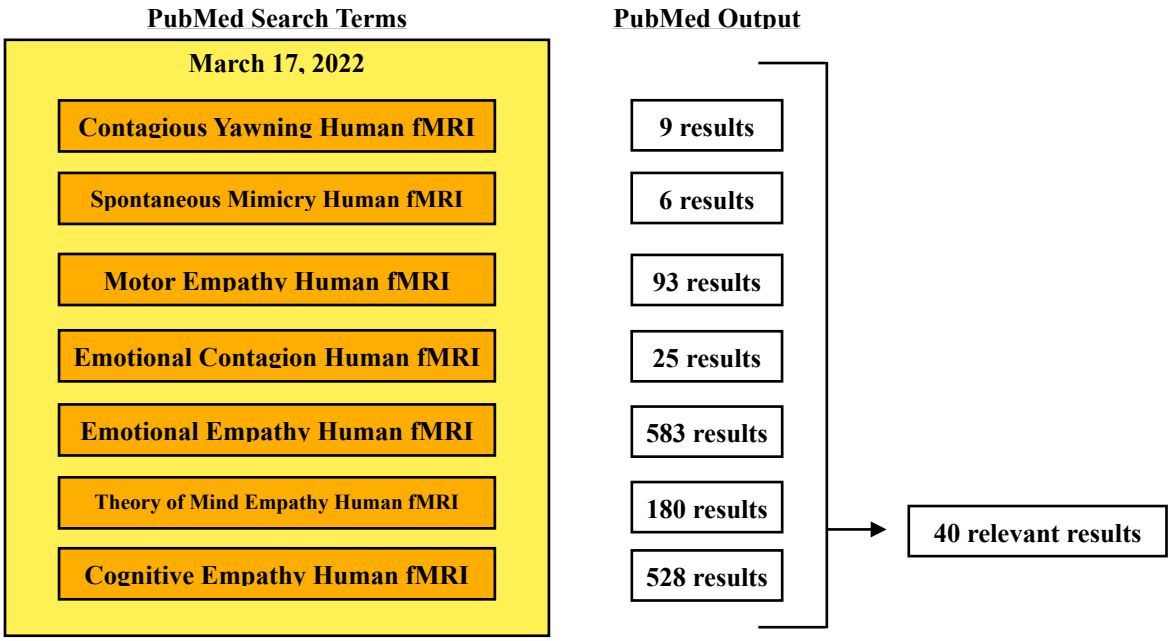


Figure 7. PRISMA flow chart of screening process for reviewed studies

Sensorimotor Resonance studies:

(Gazzola et al., 2006; Haker, 2013; Holle et al., 2012; Leslie et al., 2004; Nahab et al., 2009; Platek, 2010; Prehn-Kristensen et al., 2009; Raz et al., 2014; Schmitgen et al., 2016; Schurmann et al., 2005; Zaki J, 2012)

Emotional Empathy studies:

(Aziz-Zadeh et al., 2010; Bodden ME, 2013; Borja Jimenez et al., 2020; Bruneau et al., 2015; Bruneau et al., 2012; Chakrabarti et al., 2006; de Gelder et al., 2004; Harrison et al., 2006; Jacoby N, 2016; Kanske et al., 2015; Lawrence et al., 2006; Mackes et al., 2018; Nummenmaa et al., 2008; Oliver LD, 2018; Parkinson & Wheatley, 2014; Schmidt et al., 2021; Schnell et al., 2011; Schulte-Ruther et al., 2007; Seitz et al., 2008; Shany et al., 2021)

Cognitive Empathy studies:

(Bodden ME, 2013; Bruneau et al., 2015; Henry et al., 2021; Hervé et al., 2013; Hynes et al., 2006; Jacoby N, 2015; Kanske et al., 2015; Kim JW, 2005; Krämer et al., 2010; Lamm et al., 2007; Nummenmaa et al., 2008; Oliver LD, 2018; Raz et al., 2014; Reniers RL, 2014; Schmidt et al., 2021; Schmitgen et al., 2016; Schnell et al., 2011; Shany et al., 2021; Takahashi et al., 2015; Völlm et al., 2006; Zaki J, 2012)

Empathy Layer	Experimental Task	Number of papers
Sensorimotor Resonance	Yawn contagion	4
Sensorimotor Resonance	Scratch contagion	1
Sensorimotor Resonance	Embodied simulation	1
Sensorimotor Resonance	Anxiety smell	1
Sensorimotor Resonance	Face viewing	2
Sensorimotor Resonance	Hand and Mouth action	1
Sensorimotor Resonance	Eye gaze	1
Emotional Empathy	Prosody perception	1
Emotional Empathy	Emotions processing	12
Emotional Empathy	Emotional pain	3
Emotional Empathy	Social perception	1
Emotional Empathy	1st person affective processing	2
Emotional Empathy	Affective Theory of Mind	1

Empathy Layer	Experimental Task	Number of papers
Cognitive Empathy	Mentalizing about others' emotions	5
Cognitive Empathy	Imaging others' emotions	1
Cognitive Empathy	Emotion rating	1
Cognitive Empathy	Cognitive elaboration	3
Cognitive Empathy	Theory of Mind	7
Cognitive Empathy	3st person affective processing	2
Cognitive Empathy	False belief task	2

Table 2. Tasks included in the ALE meta-analysis, divided in the three sub-phenomena of interest.

13.1. Inclusion Criteria

We only included studies about empathy that could give us information about the neural activities linked to the different layers of empathy we previously described (i.e., sensorimotor resonance, emotional empathy and cognitive empathy). To this purpose, we included studies that had, in their experimental paradigms, specific tasks for studying, separately, one or more of the three layers. In particular, for the first layer, we included tasks dedicated to sensorimotor phenomena such as the contagious yawning, face viewing, contagious scratching, processing the odor of anxiety; for the second layer, we included tasks dedicated to emotional phenomena such as prosody perception, emotional pain processing, different emotions processing, affective perception of others; for the third layer, we included tasks dedicated to phenomena such as mentalizing about emotive expressions and emotional pain, imagining others' experiences, cognitive empathy, Theory of Mind. We only included studies that investigated the empathic phenomenon in the adult population. We focused on the spatial domain (fMRI – including activation and connectivity).

13.2. Exclusion criteria

We did not include studies which analyzed the phenomenon of empathy through particular case studies, such as seizures, lesions, or different diseases, i.e., neurodegenerative diseases, stroke, alzheimer, fibromyalgia, epilepsy, dementia, tourette syndrome, sclerosi multipla, aneurysmal subarachnoid hemorrhage, huntington disease, mild cognitive impairment etcetera. We excluded studies on empathy in substance use disorders (i.e., LSD, cocaine, alcohol, MDMA…) or the influence of other substances on the phenomenon of empathy (i.e., nitric oxide, methylphenidate, magnesium acetyl taurate, paracetamol…). We did not consider how empathy is affected by violent contexts. We did not include studies that analyzed how empathy is influenced by gender transition or studies that investigate gender-related differences on the phenomenon of empathy. We did not examine studies that considered how empathy is affected by racial biases and ingroup/ outgroup biases. We excluded studies on meditation, compassion, altruism, helping behaviors, and charity. We did not examine studies that analyzed empathy through tasks that involved moral judgment, disgust, competitive contexts and social power, conflicts or gambling tests, reward, job interviews and humorous contexts. We did not include studies in which empathy was analyzed from the perspective of the empathized. We excluded studies whose participants were medical staff, psychotherapists, physicians or musicians. We did not include how empathy is affected by sleep related phenomena. We excluded studies that analyzed empathy focusing on the differences between pleasant and unpleasant touch and pleasant and unpleasant emotion. We did not consider studies which investigated dispositional empathy, empathizing vs systemizing personalities, trait empathy and how it affects the resting state. We did not consider studies that focused on how empathy is influenced by parents-infant relationships. We excluded studies that investigated empathy in particular psychiatric conditions such as post traumatic stress disorder, somatoform disorder, somatoform pain disorder, borderline disorder, narcissism, depression, psychopathy, autism, anxiety. We did not consider studies that investigated the influence of oxytocin on empathic behaviors. We excluded studies

that investigated empathy for pain or other studies performed considering the phenomenon of empathy as a whole and not in one of its sub-phenomena. We did not include EEG, MEG and PET studies.

13.3. ALE method

We used the software GingerALE 3.0.2 to perform our ALE meta-analysis. The ALE approach, which stands for activation likelihood estimation, is an automated quantitative approach for voxel-wise neuroimaging meta-analyses (A.R. Laird, 2005; P.E. Turkeltaub, 2002). It calculates the probabilities for foci (i.e. coordinates for maximum activations) reported in the studies to be "true" convergence across different laboratories, reflecting meaningful mental operations rather than random clustering in the brain (P.E. Turkeltaub, 2002; S.B.S. Eickhoff, 2009). After our analysis, we performed a conjunction analysis between the layers of empathy and each layer of self-processing.

14. Results

In **Table 2**, we show the supra-threshold clusters for the whole empathic process and for the three layers of empathy. We performed the analysis setting the threshold at $p < 0.01$, with a minimum cluster size of 200 mm^3.

Three layered structure of empathy								
#	**Hemi**	**Gyrus**	**Cell Type**	**Volume (mm^3)**	**Peak Z Value**	**X**	**Y**	**Z**
1	L	45.2% Inferior Frontal Gyrus, 24.2% Superior Temporal Gyrus, 14.3% Middle Temporal Gyrus, 9.9% Insula, 3.1% Middle Frontal Gyrus, 2.8% Precentral Gyrus	24.2% BA38, 22.7% BA 47, 17.6% BA 45, 14.3% BA 21, 7.7% BA 13, 4.8% BA 44, 3.3% BA 9, 1.8% BA 46	9768	7.01	-46	26	-8

Three layered structure of empathy								
#	**Hemi**	**Gyrus**	**Cell Type**	**Volume (mm^3)**	**Peak Z Value**	**X**	**Y**	**Z**
2	73.5 % L, 26.5 % R	60.4% Medial Frontal Gyrus, 39.3% Superior Frontal Gyrus	65.2% BA 9, 27.1% BA 8, 7.4% BA 6	7112	7.17	-8	56	32
3	L	52.5% Superior Temporal Gyrus, 38.8% Middle Temporal Gyrus, 6.6% Supramarginal Gyrus, 2.1% Inferior Parietal Lobule	53.7% BA 39, 25.2% BA 22, 8.7% BA 40, 8.3% BA 19, 4.1% BA 21	6672	5.38	-54	-58	20
4	R	57.6% Superior Temporal Gyrus, 33.3% Middle Temporal Gyrus, 5.6% Supramarginal Gyrus, 2.8% Insula	36.1% BA 22, 34% BA 39, 10.4% BA 13, 8.3% BA 19, 6.3% BA 40, 2.8% BA 21, 2.1% BA 41	6584	6.41	52	-54	22
5	R	57.7% Superior Temporal Gyrus, 28.5% Middle Temporal Gyrus, 9.2% Insula, 4.2% Sub-Gyral	45.6% BA 38, 34.7% BA 21, 12.1% BA 22, 7.1% BA 13	6088	5-25	50	-16	-12
6	83.6 % L, 16.4 % R	53.5% Precuneus, 24.2% Cingulate Gyrus, 15.6% Posterior Cingulate, 6.6% Cuneus	57.4% BA 31, 35.2% BA 7, 5.1% BA 23, 2.3% BA 30	4464	5.91	-2	-52	32
7	67.1 % L, 32.9 % R	48.7% Medial Frontal Gyrus, 43.4% Superior Frontal Gyrus, 7.9% Cingulate Gyrus	75.9% BA 6, 17.5% BA 32, 4.4% BA 8, 2.2% BA 24	3928	4.98	-4	16	46
8	R	95.5% Inferior Frontal Gyrus, 4.5% Precentral Gyrus	61.4% BA 45, 11.4% BA 47, 10.2% BA 13, 5.7% BA 46, 4.5% BA 44	2736	5-91	56	30	2

Three layered structure of empathy								
#	**Hemi**	**Gyrus**	**Cell Type**	**Volume (mm^3)**	**Peak Z Value**	**X**	**Y**	**Z**
9	85.6 % L, 14.4 % R	54.8% Medial Frontal Gyrus, 45.2% Anterior Cingulate	45.2% BA 32, 29.8% BA 11, 25% BA 10	2528	4.65	0	42	-20
10	R	54.5% Cuneus, 36.4% Lingual Gyrus, 9.1% Middle Occipital Gyrus	77.3% BA 17, 22.7% BA 18	2048	4.53	12	-96	16
11	78% L, 22% R	87.8% Cingulate Gyrus, 12.2% Paracentral Lobule	57.3% BA 24, 32.9% BA 31, 9.8% BA 23	1680	4.51	0	-16	40
12	L	45.6% Pyramis, 35.4% Inferior Semi-Lunar Lobule, 18% Uvula		1648	5.08	-28	-80	-36
13	R	59.1% Middle Frontal Gyrus, 40.9% Inferior Frontal Gyrus	72.7% BA 9, 13.6% BA 44, 9.1% BA 45, 4.5% BA 46	1472	4.53	48	20	24
14	R	55% Pyramis, 38.5% Inferior Semi-Lunar Lobule, 4.7% Uvula, 1.2% Cerebellar Tonsil		1352	4.7	28	-80	-36
15	L	98.3% Parahippocampal Gyrus, 1.7% Superior Temporal Gyrus	67.2% Amygdala, 22.4% Hippocampus, 8.6% BA 34, 1.7% BA 38	1312	3.65	-30	-4	-18
16	L	93.1% Middle Frontal Gyrus, 6.9% Precentral Gyrus	BA 6	1280	4.43	-42	6	52
17	L	78.9% Middle Temporal Gyrus, 21.1% Superior Temporal Gyrus	47.4% BA 21, 7.9% BA 22	1056	3.37	-52	-36	0

Three layered structure of empathy								
#	**Hemi**	**Gyrus**	**Cell Type**	**Volume (mm^3)**	**Peak Z Value**	**X**	**Y**	**Z**
18	L	65.5% Inferior Occipital Gyrus, 25.9% Middle Occipital Gyrus, 8.6% Fusiform Gyrus	91.4% BA 18, 8.6% BA19	928	3.88	-32	-90	-8
19	R	50% Inferior Occipital Gyrus, 50% Middle Occipital Gyrus	BA 19	832	3.83	44	-74	0
20	R	Inferior Frontal Gyrus	BA 47	704	3.89	34	30	-18
21	L	68.6% Parahippocampal Gyrus, 14.3% Lentiform Nucleus	37.1% BA 34, 28.6% Amygdala, 20% BA 28, 14.3% Medial Globus Pallidus	648	3.32	-20	-12	-14
22	R	78.3% Claustrum, 21.7% Insula	BA 13	632	3.79	32	24	-2
23	L	Thalamus	33.3% Ventral Anterior Nucleus, 12.5% Anterior Nucleus	592	3.48	-4	-2	0
24	L	Inferior Parietal Lobule	BA 40	424	3.36	-54	-32	28
25	R	55.6% Inferior Frontal Gyrus, 44.4% Middle Frontal Gyrus	55.6% BA 45, 44.4% BA 46	344	3.33	52	30	16
26	L	Superior Frontal Gyrus	BA 6	328	3.56	-4	6	70

Three layered structure of empathy								
#	**Hemi**	**Gyrus**	**Cell Type**	**Volume (mm^3)**	**Peak Z Value**	**X**	**Y**	**Z**
27	R	75% Parahippocampal Gyrus, 25% Lentiform Nucleus	50% BA 28, 25% Amygdala, 25% Medial Globus Pallidus	296	3.28	18	-10	-14
28	R	67.9% Lentiform Nucleus, 32.1% Claustrum	Putamen	296	3.27	32	8	8
29	L	70% Claustrum, 30% Insula	BA 13	288	2.93	-40	-8	0
30	L	55% Transverse Temporal Gyrus, 45% Superior Temporal Gyrus	60% BA 41, 40% BA 42	280	3.28	-62	-20	8
31	R	Parahippocampal Gyrus	62.5% BA 35, 37.5% BA 28	264	2.77	26	-24	-8
32	R	Caudate	52.2% Caudate Head, 47.8% Caudate Body	264	3.03	10	6	2
33	L	57.7% Precentral Gyrus, 38.5% Inferior Frontal Gyrus, 3.8% Middle Frontal Gyrus	57.7% BA 6, 42.3% BA 9	264	3.19	-54	6	32
34	R	89.3% Pyramis, 10.7% Declive		224	3.36	10	-82	-26
35	90% L Cerebellum, 10% L	90% Declive, 10% Lingual Gyrus	BA 18	208	2.82	-20	-76	-12

Sensorimotor Resonance								
#	**Hemi**	**Gyrus**	**Cell Type**	**Volume (mm^3)**	**Peak Z Value**	**X**	**Y**	**Z**
1	R	45.9% Inferior Frontal Gyrus, 39.8% Precentral Gyrus, 14.3% Middle Frontal Gyrus	41.8% BA 6, 32.7% BA 9, 13.3% BA 44, 8.2% BA 45, 3.1% BA 4, 1% BA 8	2504	3.64	54	14	16
2	R	Fusiform Gyrus	BA 37	1752	4.07	48	-60	-4
3	L	44.7% Declive, 31.1% Tuber, 9.9% Culmen, 7.5% Uvula, 6.8% Fusiform Gyrus	5.6% BA 37, 1.2% BA 19	1416	3.78	-38	-66	-26
4	69.7% R, 30.3% L	75% Medial Frontal Gyrus, 25% Superior Frontal Gyrus	BA 6	1392	3.6	8	-2	62
5	L	61.6% Precentral Gyrus, 31.4% Inferior Frontal Gyrus, 7% Middle Frontal Gyrus	61.6% BA 6, 38.4% BA 9	1336	4.38	-54	8	32
6	R	75.4% Insula, 10.5% Extra-Nuclear, 10.5% Inferior Frontal Gyrus, 3.5% Precentral Gyrus	70.2% BA 13, 17.5% BA 47, 3.5% BA 44	1216	3.59	42	12	-12
7	L	70.3% Inferior Occipital Gyrus, 29.7% Middle Occipital Gyrus	75.7% BA 19, 24.3% BA 18	1072	4.23	-42	-80	-4
8	L	92% Inferior Parietal Lobule, 8% Superior Parietal Lobule	92% BA 40, 8% BA 7	1072	4.46	-34	-42	50
9	L	Middle Frontal Gyrus	BA 6	1040	3.82	-24	-2	46
10	R	Middle Occipital Gyrus	80% BA 19, 20% BA 37	1008	4.41	44	-74	4
11	L	90.9% Insula, 9.1% Claustrum	BA 13	896	3.98	-42	-6	4

Sensorimotor Resonance								
#	**Hemi**	**Gyrus**	**Cell Type**	**Volume (mm^3)**	**Peak Z Value**	**X**	**Y**	**Z**
12	R	64.3% Superior Temporal Gyrus, 21.4% Middle Temporal Gyrus, 14.3% Insula	42.9% BA 42, 21.4% BA 22, 21.4% BA 41, 14.3% BA 13	696	3.14	58	-40	4
13	67.7% L, 32.3% R	51.6% Anterior Cingulate, 48.4% Cingulate Gyrus	45.2% BA 24, 41.9% BA 32, 12.9% BA 33	680	3.19	0	30	26
14	95.3% R, 4.7% L	Precuneus	BA 7	648	3.74	6	-50	56
15	L	Culmen		568	3.51	-8	-34	-20
16	L	Thalamus	Subthalamic Nucleus	528	3.42	-4	-10	-4
17	L	57.1% Lingual Gyrus, 39.3% Fusiform Gyrus, 3.6% Inferior Occipital Gyrus	71.4% BA 18, 28.6% BA 17	520	3.5	-20	-100	-10
18	L	Inferior Parietal Lobule	BA 40	440	3.17	-56	-28	26
19	R	65% Inferior Occipital Gyrus, 20% Middle Occipital Gyrus, 15% Fusiform Gyrus	80% BA 18, 10% BA 19, 10% BA 17	408	3.17	32	-94	-8
20	L	92.6% Insula, 7.4% Precentral Gyrus	77.8% BA 13, 7.4% BA 44	368	3.2	-44	18	-2
21	R	100% Middle Temporal Gyrus	BA 21	296	3.1	56	-4	-24
22	R	80% Insula, 20% Inferior Frontal Gyrus	BA 13	216	3.29	40	26	6

Emotional empathy								
#	**Hemi**	**Gyrus**	**Cell Type**	**Volume (mm^3)**	**Peak Z Value**	**X**	**Y**	**Z**
1	70.2 % L, 29.8 % R	59.6% Medial Frontal Gyrus, 39.4% Superior Frontal Gyrus, 1.1% Middle Frontal Gyrus	70.7% BA 9, 25% BA 8, 4.3% BA 6	4280	4.96	-8	56	30
2	L	72.2% Inferior Frontal Gyrus, 12% Superior Temporal Gyrus, 7.6% Insula, 6.3% Precentral Gyrus, 1.9% Extra-Nuclear	46.2% BA 47, 25.3% BA 45, 12% BA 38, 8.2% BA 44, 5.7% BA 13	3760	4.44	-46	26	-10
3	R	76.9% Inferior Frontal Gyrus, 20.5% Insula, 2.6% Precentral Gyrusentiform Nucleus, 4.5% Caudate	51.3% BA 45, 30.8% BA 13, 9% BA 47, 2.6% BA 44, 1.3% BA 46	2184	4.67	52	30	-2
4	94.7 % L, 5.3% R	46.8% Cingulate Gyrus, 40.4% Precuneus, 7.4% Posterior Cingulate, 5.3% Cuneus	71.3% BA 31, 25.5% BA 7, 3.2% BA 23	1480	3.82	-2	-54	32
5	L	75.3% Lentiform Nucleus, 24.7% Caudate	74% Putamen, 24.7% Caudate Body, 1.4% Lateral Globus Pallidus	1456	3.54	-22	10	6
6	R	41.7% Inferior Frontal Gyrus, 20% Extra-Nuclear, 16.7% Claustrum, 15% Insula, 6.7% Sub-Gyral	51.7% BA 47, 31.7% BA 13	1384	3.48	32	28	-16
7	R	Parahippocampal Gyrus	65.2% BA 28, 30.4% BA 35, 4.3% Lateral Geniculum Body	1136	3.54	26	-24	-8

Emotional empathy								
#	**Hemi**	**Gyrus**	**Cell Type**	**Volume (mm^3)**	**Peak Z Value**	**X**	**Y**	**Z**
8	L	63.3% Medial Frontal Gyrus, 36.7% Anterior Cingulate	63.3% BA 11, 36.7% BA 32	1008	4.32	0	40	-20
9	L	41.9% Medial Frontal Gyrus, 31.4% Superior Frontal Gyrus, 26.7% Cingulate Gyrus	50% BA 32, 37.2% BA 6, 7% BA8, 5.8% BA 24	1008	4.11	-4	16	46
10	R	66.7% Superior Temporal Gyrus, 22.2% Supramarginal Gyrus, 11.1% Middle Temporal Gyrus	66.7% BA 39, 22.2% BA 40, 11.1% BA 22	912	3.63	60	-54	22
11	L	55.8% Transverse Temporal Gyrus, 44.2% Superior Temporal Gyrus	53.5% BA 41, 46.5% BA 42	880	4.18	-62	-20	8
12	R	90% Lingual Gyrus, 10% Cuneus	50% BA 18, 50% BA 17	752	3.64	20	-94	0
13	67.4 % R, 32.6 % L	95.3% Medial Frontal Gyrus, 4.7% Superior Frontal Gyrus	BA 6	696	3.1	6	6	60
14	R	60% Lingual Gyrus, 20% Fusiform Gyrus, 20% Inferior Occipital Gyrus	60% BA 18, 40% BA 19	672	3.63	42	-72	-2
15	R	50.6% Inferior Semi-Lunar Lobule, 47% Pyramis, 2.4% Uvula		664	3.62	26	-82	-38
16	L	Parahippocampal Gyrus	Amygdala	560	3.25	-30	-4	-16
17	R	Superior Temporal Gyrus	BA 38	536	3.75	44	18	-36
18	L	Cingulate Gyrus	78.3% BA 24, 17.4% BA 31, 4.3% BA 23	488	3.27	0	-16	40

Emotional empathy								
#	**Hemi**	**Gyrus**	**Cell Type**	**Volume (mm^3)**	**Peak Z Value**	**X**	**Y**	**Z**
19	R	Cuneus	BA 17	432	3.61	12	-96	16
20	R	Lentiform Nucleus	Putamen	408	2.73	28	4	6
21	R	Fusiform Gyrus	BA 37	384	2.87	40	-48	-16
22	L	Middle Frontal Gyrus	BA 6	376	3.31	-42	4	52
23	R	66.7% Superior Temporal Gyrus, 27.8% Insula, 5.6% Sub-Gyral	66.7% BA 22, 27.8% BA 13, 5.6% BA 21	336	3.16	50	-16	-12
24	L	Superior Temporal Gyrus	BA 38	328	3.09	-46	12	-38
25	L	Inferior Parietal Lobule	BA 40	312	2.92	-54	-32	26
26	L	87.5% Middle Frontal Gyrus, 12.5% Superior Frontal Gyrus	BA 9	304	3.2	-30	42	22
27	L	81.3% Superior Temporal Gyrus, 18.8% Middle Temporal Gyrus	56.3% BA 22, 43.8% BA 39	288	3.23	-54	-60	18
28	L	90% Claustrum, 10% Insula	BA 13	280	3.01	-40	-8	-4
29	R	Caudate	Caudate Body	280	3.18	14	8	20
30	R	Lentiform Nucleus	66.7% Hypothalamus, 33.3% Medial Globus Pallidus	272	2.59	18	-10	-14
31	R	71.4% Middle Occipital Gyrus, 28.6% Fusiform Gyrus	71.4% BA 18, 28.6% BA 19	272	3.1	34	-84	-6

Emotional empathy								
#	**Hemi**	**Gyrus**	**Cell Type**	**Volume (mm^3)**	**Peak Z Value**	**X**	**Y**	**Z**
32	L	Superior Frontal Gyrus	BA 6	272	3.28	-6	6	70
33	L	Thalamus		240	2.59	-8	-32	-12
34	L	69.2% Uvula, 30.8% Pyramis		208	3.01	-14	-78	-32

Cognitive Empathy								
#	**Hemi**	**Gyrus**	**Cell Type**	**Volume (mm^3)**	**Peak Z Value**	**X**	**Y**	**Z**
1	L	51.1% Superior Temporal Gyrus, 42.5% Middle Temporal Gyrus, 4.1% Supramarginal Gyrus, 2.3% Inferior Parietal Lobule	56.4% BA 39, 25.2% BA 22, 9% BA 19, 6.4% BA 40, 2.6% BA 21	6656	5.94	-44	-58	24
2	R	55.8% Superior Temporal Gyrus, 28.8% Middle Temporal Gyrus, 9.4% Insula, 4.3% Sub-Gyral, 1.7% Inferior Frontal Gyrus	47.2% BA 38, 32.2% BA 21, 11.6% BA 22, 7.3% BA 13, 1.7% BA 47	6288	5.23	48	14	-26
3	74.9 % L, 25.1 % R	57.7% Medial Frontal Gyrus, 42.3% Superior Frontal Gyrus	57.1% BA 9, 33.9% BA 8, 9.1% BA 6	5840	6.3	-8	54	34
4	75.2 % L, 24.8 % R	52.9% Precuneus, 21.2% Posterior Cingulate, 20.6% Cingulate Gyrus, 5.2% Cuneus	52% Ba 31, 35.3% BA 7, 7.2% BA 23, 5.6% BA 30	5288	5.02	-2	-60	38
5	R	53% Superior Temporal Gyrus, 31.7% Middle Temporal Gyrus, 12.2% Insula, 2.4% Supramarginal Gyrus	36% BA 39, 28.7% BA 22, 22% BA 13, 9.1% BA 19, 3% BA 40, 1.2% BA 41	4680	6.62	52	-54	22

Cognitive Empathy								
#	**Hemi**	**Gyrus**	**Cell Type**	**Volume (mm^3)**	**Peak Z Value**	**X**	**Y**	**Z**
6	L	56.9% Middle Temporal Gyrus, 42% Superior Temporal Gyrus, 1.1% Inferior Frontal Gyrus	55.9% BA 21, 43.1% BA 38, 1.1% BA 47	3824	5.72	-52	4	-30
7	L	91.6% Inferior Frontal Gyrus, 8.4% Insula	49.5% BA 47, 40% BA 45, 8.4% BA 13	3144	6.43	-46	28	-6
8	L	45.1% Inferior Semi-Lunar Lobule, 42.1% Pyramis, 9.9% Uvula, 2.6% Cerebellar Tonsil		2184	5.62	-26	-80	-36
9	72.8 % L, 27.2 % R	55.6% Anterior Cingulate, 44.4% Medial Frontal Gyrus	54.3% BA 32, 43.2% BA 10, 1.2% BA11	2104	4.24	0	48	-16
10	R	Inferior Frontal Gyrus	78.6% BA 45, 8.9% BA 47, 8.9% BA 46	1896	5	56	30	2
11	R	75% Superior Temporal Gyrus, 25% Middle Temporal Gyrus	50% BA 22, 25% BA 21, 25% BA 41	1888	5.13	48	-36	2
12	L	64.6% Middle Temporal Gyrus, 35.4% Superior Temporal Gyrus	40% BA 21, 33.8% BA 22	1376	4.14	-56	-34	0
13	L	63.3% Superior Frontal Gyrus, 34.2% Medial Frontal Gyrus, 2.5% Cingulate Gyrus	78.5% BA 6, 19% BA 32, 2.5% BA 8	1320	3.59	-2	18	58
14	L	95.2% Middle Frontal Gyrus, 4.8% Precentral Gyrus	BA 6	1168	3.54	-34	6	58

Cognitive Empathy								
#	**Hemi**	**Gyrus**	**Cell Type**	**Volume (mm^3)**	**Peak Z Value**	**X**	**Y**	**Z**
15	57.1 % R, 42.9 % L	40.5% Cingulate Gyrus, 35.7% Paracentral Lobule, 23.8% Medial Frontal Gyrus	38.1% BA 24, 33.3% BA 6, 28.6% BA 31	1136	3.43	0	-14	40
16	R	64.1% Pyramis, 29.8% Inferior Semi-Lunar Lobule, 4.6% Uvula		1048	4.04	30	-80	-36
17	L	Parahippocampal Gyrus	72.9% Amygdala, 22.9% Hippocampus, 4.2% BA 34	792	3.2	-28	-2	-22
18	L	74.1% Middle Frontal Gyrus, 25.9% Inferior Frontal Gyrus	85.2% BA 9, 14.8% BA 46	736	3.47	-46	22	26
19	R	81% Middle Frontal Gyrus, 19% Sub-Gyral	BA 6	568	3.18	36	4	52
20	R	85.7% Middle Frontal Gyrus, 14.3% Precentral Gyrus	BA 9	504	3.76	48	20	24
21	R	50% Cuneus, 50% Lingual Gyrus	BA 17	496	3.9	24	-94	4
22	L	94.2% Declive, 5.8% Lingual Gyrus	BA 18	488	3.49	-20	-76	-12
23	R	Caudate	76.3% Caudate Body, 23.7% Caudate Head	408	3.26	12	8	4
24	L	78.6% Parahippocampal Gyrus, 14.3% Lentiform Nucleus	35.7% BA 28, 28.6% BA 34, 21.4% Amygdala, 14.3% Medial Globus Pallidus	400	2.97	-18	-12	-16
25	R	95.9% Pyramis, 2% Pyramis of Vermis, 2% Uvula		392	3.6	10	-82	-26

Cognitive Empathy								
#	**Hemi**	**Gyrus**	**Cell Type**	**Volume (mm^3)**	**Peak Z Value**	**X**	**Y**	**Z**
26	L	52.9% Caudate, 47.1% Thalamus	52.9% Caudate Head, 11.8% Anterior Nucleus, 5.9% Ventral Anterior Nucleus	344	2.91	-4	0	0
27	R	Lingual Gyrus	BA 18	336	2.86	12	-90	0
28	R	85.7% Parahippocampal Gyrus, 14.3% Lentiform Nucleus	57.1% BA 34, 14.3% BA 28, 14.3% Amygdala, 14.3% Putamen	312	3.39	22	2	-18
29	L	77.3% Inferior Occipital Gyrus, 22.7% Middle Occipital Gyrus	BA 18	312	2.85	-34	-90	-6
30	R	50% Declive, 50% Lingual Gyrus	BA 18	304	3.1	24	-76	-10

Table 2. Supra-threshold clusters for the three layers of empathy.
Abbreviations: Hemi—hemisphere; L—left; R—right; BA—Brodmann Area.

14.1. Self and Empathy comparison results

After our analysis, we proceeded by performing another ALE meta-analysis to compare our results with the result obtained by Qin and colleagues (Qin et al., 2020), in order to look for overlapping regions between our empathy map and Qin's one on the three layers of self-processing. We present now the results of this comparison.

In **Table 3**, we show the supra-threshold clusters for the comparison between the three layers of empathy and the ones of self-processing. We performed the analysis setting the threshold at $p < 0.01$.

Three layers of empathy conj. Three layers of self-processing								
#	**Hemi**	**Gyrus**	**Cell Type**	**Volume (mm^3)**	**Peak Z Value**	**X**	**Y**	**Z**
1	L	Cingulate Gyrus	BA 24	184	0.0009	0	-17	40

Three layers of empathy conj. Three layers of self-processing								
#	**Hemi**	**Gyrus**	**Cell Type**	**Volume (mm^3)**	**Peak Z Value**	**X**	**Y**	**Z**
2	L	Cingulate Gyrus	BA 31	88	0.0009	-3	-54	30
3	L	Insula	BA 13	72	0.0009	-41	-4	3

Three layers of self-processing conj. Sensorimotor Resonance								
#	**Hemi**	**Gyrus**	**Cell Type**	**Volume (mm^3)**	**Peak Z Value**	**X**	**Y**	**Z**
1	L	Insula	BA 13	200	0.0009	-41	-4	3
2	L	Insula	BA 13	56	0.0008	-40	18.7	-2.7

Three layers of self-processing conj. Emotional Empathy								
#	**Hemi**	**Gyrus**	**Cell Type**	**Volume (mm^3)**	**Peak Z Value**	**X**	**Y**	**Z**
1	L	Cingulate Gyrus	BA 24	288	0.0009	0	-17	40
2	L	70% Cingulate Gyrus, 30% Posterior Cingulate	BA 31	144	0.0009	-3	-54	30
3	R	Inferior Occipital Gyrus	BA 18	8	0.0008	38	-84	-4

Three layers of self-processing conj. Cognitive Empathy								
#	**Hemi**	**Gyrus**	**Cell Type**	**Volume (mm^3)**	**Peak Z Value**	**X**	**Y**	**Z**
1	L	Cingulate Gyrus	BA 24	184	0.0009	0	-16	40
2	R	Superior Temporal Gyrus	BA 39	48	0.0008	53	-57	23
3	L	Parahippocampal Gyrus	Amygdala	8	0.0008	-24	-4	-22

Interoceptive Processing conj. Sensorimotor Resonance								
#	**Hemi**	**Gyrus**	**Cell Type**	**Volume (mm^3)**	**Peak Z Value**	**X**	**Y**	**Z**
1	L	92.9% Insula, 7.1% Claustrum	BA 13	480	0.0009	-41	-4	3

Interoceptive Processing conj. Sensorimotor Resonance								
#	Hemi	Gyrus	Cell Type	Volume (mm^3)	Peak Z Value	X	Y	Z
2	L	Insula	BA 13	8	0.0007	-40	20	0

Exteroceptive Processing conj. Sensorimotor Resonance								
#	Hemi	Gyrus	Cell Type	Volume (mm^3)	Peak Z Value	X	Y	Z
1	L	Insula	BA 13	136	0.0008	-40	18	-3

Mental-self-Processing conj. Sensorimotor Resonance								
#	Hemi	Gyrus	Cell Type	Volume (mm^3)	Peak Z Value	X	Y	Z
1	L	Insula	BA 13	120	0.0008	-40	20	-2

Interoceptive Processing conj. Emotional Empathy								
#	Hemi	Gyrus	Cell Type	Volume (mm^3)	Peak Z Value	X	Y	Z
1	L	92.9% Insula, 7.1% Claustrum	BA 13	480	0.0009	-41	-4	3
2	L	Insula	BA 13	8	0.0007	-40	20	0

Exteroceptive Processing conj. Emotional Empathy								
#	Hemi	Gyrus	Cell Type	Volume (mm^3)	Peak Z Value	X	Y	Z
1	L	Inferior Occipital Gyrus	BA 18	128	0.0009	36	-82	-4

Mental-self-Processing conj. Emotional Empathy								
#	Hemi	Gyrus	Cell Type	Volume (mm^3)	Peak Z Value	X	Y	Z
1	L	Cingulate Gyrus	BA 24	456	0.0009	0	-17	40

Mental-self-Processing conj. Emotional Empathy								
#	**Hemi**	**Gyrus**	**Cell Type**	**Volume (mm^3)**	**Peak Z Value**	**X**	**Y**	**Z**
2	L	82.1% Cingulate Gyrus, 10.7% Posterior Cingulate, 7.1% Precuneus	BA 31	344	0.0009	-3	-54	30

Interoceptive Processing conj. Cognitive Empathy								
#	**Hemi**	**Gyrus**	**Cell Type**	**Volume (mm^3)**	**Peak Z Value**	**X**	**Y**	**Z**
1	L	Parahippocampal Gyrus	Amygdala	104	0.0008	-24	-3	-21
2	L	Parahippocampal Gyrus	75% Amygdala, 12.5% BA 34, 12.5% BA 28	64	0.0008	-18	-8	-18

Exteroceptive Processing conj. Cognitive Empathy								
#	**Hemi**	**Gyrus**	**Cell Type**	**Volume (mm^3)**	**Peak Z Value**	**X**	**Y**	**Z**
-	-	-	-	-	-	-	-	-

Mental-self-Processing conj. Cognitive Empathy								
#	**Hemi**	**Gyrus**	**Cell Type**	**Volume (mm^3)**	**Peak Z Value**	**X**	**Y**	**Z**
1	L	Cingulate Gyrus	BA 24	384	0.0009	0	-16	40
2	R	85.7% Superior Temporal Gyrus, 14.3% Middle Temporal Gyrus	71.4% BA 39, 28.6% BA 22	192	0.0008	53	-57	23
3	L	Thalamus	Anterior Nucleus	56	0.0008	-6	0	4
4	L	Middle Temporal Gyrus	BA 39	24	0.0007	-45	-62	25
5	L	Superior Temporal Gyrus	BA 39	8	0.0007	-46	-60	26

Table 3. Conjunction analysis between our results and the ones by Qin et al. (2020). Respectively, we compared: the whole self-processing structure with the whole empathic structure; the whole self-processing structure with each one of the three

layers of empathy (i.e. sensorimotor resonance, emotional empathy and cognitive empathy); sensorimotor resonance with interoceptive processing, exteroceptive processing and mental-self-processing; emotional empathy with interoceptive processing, exteroceptive processing and mental-self-processing; cognitive empathy with interoceptive processing, exteroceptive processing and mental-self-processing.

15. Conjunction analysis

The three layers of empathy shares with the three layers of self-processing two cluster activations in the left cingulate gyrus (BA 24 and BA 31) and one in the left insula (BA 13).

The sensorimotor resonance layer shares with the three layers of self-processing two cluster activations in the left insula (BA 13). It shares with the interoceptive processing layer two cluster activations in the left insula (BA 13). It shares with the exteroceptive processing layer a cluster activation in the left insula (BA 13). It shares with the mental-self-processing layer in the left insula (BA 13).

The emotional empathy layer shares with the three layers of self-processing a cluster activation in the left cingulate gyrus (BA 24), another one in the left cingulate gyrus and posterior cingulate (BA 31) and one in the right inferior occipital gyrus (BA 18). It shares with the interoceptive processing layer two cluster activations in the left insula and claustrum (BA 13) and in the left amygdala. It shares with the exteroceptive processing layer a cluster activation in the right inferior occipital gyrus (BA 18). It shares with the mental-self-processing layer two cluster activations in the left cingulate gyrus (BA 24) and in the left cingulate gyrus, posterior cingulate and precuneus (BA 31).

The cognitive empathy layer shares with the three layers of self-processing cluster activations in the left cingulate gyrus (BA 24), in the superior temporal gyrus (BA 39) and in the left amygdala. It share with the interoceptive processing layer two cluster activations in the left amygdala. It does not share any cluster activation with the exteroceptive processing layer. It shares with the mental-self-processing layer five cluster activations in the left cingulate gyrus (BA 24), in the right superior temporal gyrus and middle temporal gyrus (BA 39, BA 22), in the left thalamus, in

the left middle temporal gyrus (BA 39) and in the left superior temporal gyrus (BA 39).

16. Discussion

Our results suggest that self-processing is in action in the different phenomena of empathy described in literature, i.e. sensorimotor resonance, emotional empathy and cognitive empathy. In particular, the sensorimotor resonance phenomenon shows an involvement of the left insula. Both right and left insula are thought to be associated to the phenomenon of self (Qin et al., 2020). However, the right insula has been recognized to play a fundamental role in self-referential tasks (Babo-Rebelo, 2016; D'Argembeau et al., 2005; Modinos et al., 2009; Scalabrini et al., 2019). These findings have supported the hypothesis according to which the right insula would be more suitable than the left insula for mediating and processing self-specificity, thus being the "glue" that keeps together the whole process of the self. In this way, it could be related to personal identity that we consider the highest centralization of stimuli and thus experience (Scalabrini et al., 2021). Conversely, being the left insula particularly involved in the interoceptive processing, we could interpret its involvement also in the sensorimotor resonance as a mean for integrating sensory and motor information coming from the empathized individual. In this way, we could hypothesize that, as well as the right insula has a role in mediating self-specificity, the left insula has a role in mediating the representation of the empathized individual's sensations through the empathizer's system.

The emotional empathy phenomenon shows the involvement of all the three layers of self-processing. In particular, it involves the interoceptive processing through the left insula and the amygdala, the exteroceptive processing through the inferior occipital gyrus and the mental-self-processing through the left cingulate gyrus and the precuneus. Notably, the involvement of amygdala suggests a link between the subjective experience of one's own emotions and the subjective experience of others' emotions (i.e. the non-original experience of other's experience). The involvement of the inferior occipital gyrus suggests that the emotional empathy phenomenon is

linked to an exteroceptive perception and recognition of faces and bodies (Haxby, 2000; Rossion, 2003) and also to the the process of self-recognition (Devue et al., 2007; Platek et al., 2006; Uddin et al., 2005). In addition, being precuneus associated to self-awareness and reflective functions (Cavanna & Trimble, 2006; Lou et al., 2004; Northoff & Bermpohl, 2004), its involvement in the emotional empathy phenomenon suggests that the emotional stimulus given by the contact with the other's experience is mediated by self-referential processing.

The cognitive empathy phenomenon shows the involvement of the interoceptive processing through the left amygdala and of the mental-self-processing through the left cingulate gyrus, the right superior temporal gyrus, middle temporal gyrus and the left thalamus. The involvement of the amygdala and the thalamus demonstrates that also in the cognitive empathy the interoceptive processing plays a role through bottom-up mechanisms, since the three layers of self-processing are nested within each other (from interoceptive processing, to mental-self-processing through exteroceptive processing) (Qin et al., 2020). These mechanisms are balanced by top-down mechanisms that activate higher cognitive areas such as the ventromedial prefrontal cortex, which is associated to the mental-self-processing (Qin et al., 2020). Unfortunately, this area did not come out in our analysis, although there are evidences, from literature, that it is highly involved in cognitive empathy tasks (Beadle, 2018; Shamay-Tsoory et al., 2003; Shamay-Tsoory, 2009).

In conclusion, our analysis demonstrated that the areas involved in self-processing are also involved in the phenomenon of empathy. This supports our hypothesis that empathy is a self-related process, meaning a non-original experience of another individual's experience. When saying that empathy is self-related, we intend that the empathic experience is mediated by our introjecting information and projecting the form of our personal experience of the other individual. In this way, self-processing and empathy are not two separate acts, but they "dance" together in what we experience as the complex phenomenon of self/other-processing.

References

A.E. Foster, Z. S. Y. (2019). Teaching Empathy in Healthcare. Building a New Core Competency. Springer International Publishing.

A.R. Laird, P. M. F., C.J. Price, D.C. Glahn, A.M. Uecker, J.L. Lancaster, P.E. Turkeltaub, P. Kochunov, P.T. Fox. (2005). ALE meta-analysis: controlling the false discovery rate and performing statistical contrasts. *Hum. Brain Mapp., 25*, 155-164.

Agostino D'Ippona. (1952). The Confessions. City of God. On Christian Doctrine. Encyclopaedia Britannica.

Andersen, S. M., & Chen, S. (2002). The relational self: an interpersonal social-cognitive theory. *Psychological Review, 109*, 619–645.

Arisaka, Y. (2001). The Ontological Co-Emergence of 'Self and Other' in Japanese Philosophy. *Journal of consciousness studies, 8*, 197-208.

Aristotele. (350 b.C.). De memoria et reminiscentia.

Atkinson, R. C. S., R.M. (1968). Human memory: A proposed system and its control processes. In K. W. S. Spence, J.T. (Ed.), *The psychology of learning and motivation* (Vol. 2). Academic Press.

Aziz-Zadeh, L., Sheng, T., & Gheytanchi, A. (2010, 2010/1//). Common Premotor Regions for the Perception and Production of Prosody and Correlations with Empathy and Prosodic Ability. *PLoS One, 5*(1), e8759-e8759. https://doi.org/10.1371/journal.pone.0008759

Babo-Rebelo, M. W., N.; Adam, C.; Hasboun, D.; Tallon-Baudry, C. (2016). Is the Cardiac Monitoring Function Related to the Self in Both the Default Network and Right Anterior Insula? *Philos. Trans. R. Soc. B Biol. Sci., 371*.

Baron-Cohen, S., Helen Tager-Flusberg, and Michael Lombardo, eds. (2013). Understanding other minds: Perspectives from developmental social neuroscience. Oxford university press.

Barrett, L. F., & Simmons, W. K. (2015, Jul). Interoceptive predictions in the brain. *Nat Rev Neurosci, 16*(7), 419-429. https://doi.org/10.1038/nrn3950

Bartlett, F. C. (1954). *Remembering*. Macmillan.

Beadle, J. N., Sergio Paradiso, and Daniel Tranel. (2018). Ventromedial prefrontal cortex is critical for helping others who are suffering. *Frontiers in Neurology*.

Bergson, H. (1896). Matière et mémoire. Essai sur la relation du corps à l'esprit.

Blair, R. J. (2005, Dec). Responding to the emotions of others: dissociating forms of empathy through the study of typical and psychiatric populations. *Conscious Cogn, 14*(4), 698-718. https://doi.org/10.1016/j.concog.2005.06.004

Blenkinsop, T. A., & Lang, E. J. (2006, Feb 8). Block of inferior olive gap junctional coupling decreases Purkinje cell complex spike synchrony and rhythmicity. *J Neurosci, 26*(6), 1739-1748. https://doi.org/10.1523/JNEUROSCI.3677-05.2006

Bodden ME, K. D., Knake S, Menzler K, Heverhagen JT, Sommer J, Kalbe E, Krach S, Dodel R. (2013). Comparing the neural correlates of affective and cognitive theory of mind using fMRI: Involvement of the basal ganglia in affective theory of mind. *Adv Cogn Psychol, 15*(1), 32-43.

Borja Jimenez, K. C., Abdelgabar, A. R., De Angelis, L., McKay, L. S., Keysers, C., & Gazzola, V. (2020, 2020/8//). Changes in brain activity following the voluntary control of empathy. *Neuroimage, 216*, 116529-116529. https://doi.org/10.1016/j.neuroimage.2020.116529

Bruneau, E. G., Jacoby, N., & Saxe, R. (2015, 2015/7//). Empathic control through coordinated interaction of amygdala, theory of mind and extended pain matrix brain regions. *Neuroimage, 114*, 105-119. https://doi.org/10.1016/j.neuroimage.2015.04.034

Bruneau, E. G., Pluta, A., & Saxe, R. (2012, 2012/1//). Distinct roles of the 'Shared Pain' and 'Theory of Mind' networks in processing others' emotional suffering. *Neuropsychologia, 50*(2), 219-231. https://doi.org/10.1016/j.neuropsychologia.2011.11.008

Campos, M. V., Gutierrez, A. M. L. (Eds.). (2015). *Temporal points of view.* Springer. https://doi.org/https://doi.org/10.1007/978-3-319-19815-6

Carr, L., Iacoboni, M., Dubeau, M. C., Mazziotta, J. C., & Lenzi, G. L. (2003, Apr 29). Neural mechanisms of empathy in humans: a relay from neural systems for imitation to limbic areas. *Proc Natl Acad Sci U S A, 100*(9), 5497-5502. https://doi.org/10.1073/pnas.0935845100

Čater, M., Majdič, G. (2022). How early maternal deprivation changes the brain and behavior? *The European journal of neuroscience, 55*, 2058–2075. https://doi.org/https://doi.org/10.1111/ejn.15238

Cavanna, A. E., & Trimble, M. R. (2006, Mar). The precuneus: a review of its functional anatomy and behavioural correlates. *Brain, 129*(Pt 3), 564-583. https://doi.org/10.1093/brain/awl004

Chakrabarti, B., Bullmore, E., & Baron-Cohen, S. (2006, 2006/9//). Empathizing with basic emotions: Common and discrete neural substrates. *Social Neuroscience, 1*(3-4), 364-384. https://doi.org/10.1080/17470910601041317

D'Argembeau, A., Collette, F., Van der Linden, M., Laureys, S., Del Fiore, G., Degueldre, C., Luxen, A., & Salmon, E. (2005, Apr 1). Self-referential reflective activity and its relationship with rest: a PET study. *Neuroimage, 25*(2), 616-624. https://doi.org/10.1016/j.neuroimage.2004.11.048

Damasio, A. (1994). Descartes' Error: Emotion, Reason, and the Human Brain. Putnam Publishing.

Damasio, A. (1999). The Feeling of What Happens: Body and Emotion in the Making of Consciousness. Harcourt Brace.

David Premack, G. W. (1978). Does the chimpanzee have a theory of mind? *Behavioral and Brain Sciences, Volume 1*(Issue 4: A Special Issue on Cognition and Consiousness in Nonhuman Species), pp. 515 - 526.

de Gelder, B., Snyder, J., Greve, D., Gerard, G., & Hadjikhani, N. (2004, 2004/11//). Fear fosters flight: A mechanism for fear contagion when perceiving emotion expressed by a whole body. *Proceedings of the National Academy of Sciences, 101*(47), 16701-16706. https://doi.org/10.1073/pnas.0407042101

de Waal, F. B. M., & Preston, S. D. (2017, 2017/8//). Mammalian empathy: behavioural manifestations and neural basis. *Nature Reviews Neuroscience, 18*(8), 498-509. https://doi.org/10.1038/nrn.2017.72

Decety, J., and Margarita Svetlova. (2012). Putting together phylogenetic and ontogenetic perspectives on empathy. *Developmental Cognitive Neuroscience, 2*, 1-24.

Decety, J., and Meghan Meyer. (2008). From emotion resonance to empathic understanding: a social developmental neuroscience account. *Development and Psychopathology, 20*, 1053-1080.

Decety, J., & Jackson, P. L. (2004, Jun). The functional architecture of human empathy. *Behav Cogn Neurosci Rev, 3*(2), 71-100. https://doi.org/10.1177/1534582304267187

Descartes, R. (1637). Discours de la méthode pour bien conduire sa raison et chercher la vérité dans les sciences, plus la dioptrique, les météores et la géométrie.

Devue, C., Collette, F., Balteau, E., Degueldre, C., Luxen, A., Maquet, P., & Bredart, S. (2007, Apr 27). Here I am: the cortical correlates of visual self-recognition. *Brain Res, 1143*, 169-182. https://doi.org/10.1016/j.brainres.2007.01.055

Di Paolo, E. A. (2001, Mar). Rhythmic and non-rhythmic attractors in asynchronous random Boolean networks. *Biosystems, 59*(3), 185-195. https://doi.org/10.1016/s0303-2647(01)00102-2

di Pellegrino, G., Fadiga, L., Fogassi, L., Gallese, V., & Rizzolatti, G. (1992). Understanding motor events: a neurophysiological study. *Exp Brain Res, 91*(1), 176-180. https://doi.org/10.1007/BF00230027

Dimberg, U. (1990, Sep). Facial electromyography and emotional reactions. *Psychophysiology, 27*(5), 481-494. https://doi.org/10.1111/j.1469-8986.1990.tb01962.x

Dongen, J. D. M. v. (2020). The Empathic Brain of Psychopaths: From Social Science to Neuroscience in Empathy. *Front. Psychol.*

Dvash, J. S.-T., Simone G. (2014). Theory of Mind and Empathy as Multidimensional Constructs. *Topics in Language Disorders, 34*(4).

Ebbinghaus, H. (1885). *Über das Gedächtnis*.

Feldman, R. (2007a). Mother-infant synchrony and the development of moral orientation in childhood and adolescence: Direct and indirect mechanisms of developmental continuity. *American Journal of Orthopsychiatry, 77*(4), 582-597. https://doi.org/10.1037/0002-9432.77.4.582

Feldman, R. (2007b, 2007/3//). Parent-infant synchrony and the construction of shared timing; physiological precursors, developmental outcomes, and risk conditions. *Journal of Child Psychology and Psychiatry, 48*(3-4), 329-354. https://doi.org/10.1111/j.1469-7610.2006.01701.x

Feldman, R. (2017, Feb). The Neurobiology of Human Attachments. *Trends Cogn Sci, 21*(2), 80-99. https://doi.org/10.1016/j.tics.2016.11.007

Florenskij, P. (2004). The Pillar and Ground of the Truth: An Essay in Orthodox Theodicy in Twelve Letters. Princeton University Press.

Florenskij, P. (2007). Il simbolo e la forma: scritti di filosofia della scienza. Bollati Boringhieri.

Fogassi, L., Gallese, V., Buccino, G., Craighero, L., Fadiga, L., & Rizzolatti, G. (2001, Mar). Cortical mechanism for the visual guidance of hand grasping movements in the monkey: A reversible inactivation study. *Brain, 124*(Pt 3), 571-586. https://doi.org/10.1093/brain/124.3.571

Freud, S. (1914). Remembering, Repeating and Working-Through (Further Recommendations on the Technique of Psycho-Analysis II). In *The Standard Edition of the Complete Psychological Works of Sigmund Freud* (Vol. 12, pp. 145-156).

Frith, C., & Frith, U. (2005, Sep 6). Theory of mind. *Curr Biol, 15*(17), R644-646. https://doi.org/10.1016/j.cub.2005.08.041

Fuchs, T. (2011). The brain – A mediating organ. *ournal of Consciousness Studies, XVIII*, 196-221.

Fuchs, T. (2018). Ecology of the brain. The phenomenology and biology of the embodied mind. Oxford University Press.

Gazzola, V., Aziz-Zadeh, L., & Keysers, C. (2006, 2006/9//). Empathy and the Somatotopic Auditory Mirror System in Humans. *Current Biology, 16*(18), 1824-1829. https://doi.org/10.1016/j.cub.2006.07.072

Gazzola, V., Rizzolatti, G., Wicker, B., & Keysers, C. (2007, May 1). The anthropomorphic brain: the mirror neuron system responds to human and robotic actions. *Neuroimage, 35*(4), 1674-1684. https://doi.org/10.1016/j.neuroimage.2007.02.003

Georg Northoff, D. S. (2022a). The subjectivity of self and its ontology: From the world–brain relation to the point of view in the world. *Theory & Psychology*.

Georg Northoff, D. S. (2022b). The subjectivity of self and its ontology: From the world–brain relation to the point of view in the world. *Theory Psychology*.

Gergen, K. J. (2011). The Relational Self. In *Relational Being: Beyond Self and Community*. Oxford Academic.

Golesorkhi, M., Gomez-Pilar, J., Zilio, F., Berberian, N., Wolff, A., Yagoub, M. C. E., & Northoff, G. (2021, Aug 16). The brain and its time: intrinsic neural timescales are key for input processing. *Commun Biol, 4*(1), 970. https://doi.org/10.1038/s42003-021-02483-6

Haker, H., Kawohl, W., Herwig, U., & Rössler, W. (2013). Mirror neuron activity during contagious yawning—an fMRI study. *Brain Imaging and Behavior, 7*, 28-34.

Harrison, N. A., Singer, T., Rotshtein, P., Dolan, R. J., & Critchley, H. D. (2006, 2006/6//). Pupillary contagion: central mechanisms engaged in sadness processing. *Social Cognitive and Affective Neuroscience, 1*(1), 5-17. https://doi.org/10.1093/scan/nsl006

Haxby, J. V., Hoffman, E. A., & Gobbini, M. I. (2000). The distributed human neural system for face perception. *Trends in Cognitive Sciences, 4*.

Heidegger, M. (1927). *Sein und Zeit*.

Henry, A., Raucher-Chéné, D., Obert, A., Gobin, P., Vucurovic, K., Barrière, S., Sacré, S., Portefaix, C., Gierski, F., Caillies, S., & Kaladjian, A. (2021, 2021/11//). Investigation of the neural correlates of mentalizing through the Dynamic Inference Task, a new naturalistic task of social cognition. *Neuroimage, 243*, 118499-118499. https://doi.org/10.1016/j.neuroimage.2021.118499

Herring, J. (2019). The Concept of the Relational Self. In *Law and the Relational Self*. Cambridge University Press.

Hervé, P.-Y., Razafimandimby, A., Jobard, G., & Tzourio-Mazoyer, N. (2013, 2013/1//). A Shared Neural Substrate for Mentalizing and the Affective Component of Sentence Comprehension. *PLoS One, 8*(1), e54400-e54400. https://doi.org/10.1371/journal.pone.0054400

Holle, H., Warne, K., Seth, A. K., Critchley, H. D., & Ward, J. (2012, 2012/11//). Neural basis of contagious itch and why some people are more prone to it. *Proceedings of the National Academy of Sciences, 109*(48), 19816-19821. https://doi.org/10.1073/pnas.1216160109

Hume, D. (1739-40). A Treatise of Human Nature. John Noon.

Husserl, E. (1928). Vorlesungen zur Phänomenologie des inneren Zeitbewusstseins.

Husserl, E. (1937). Zur Phänomenologie der Intersubjektivität: Texte aus dem Nachlass (Vol. II). Martinus Nijhoff.

Hynes, C. A., Baird, A. A., & Grafton, S. T. (2006, 2006/1//). Differential role of the orbital frontal lobe in emotional versus cognitive perspective-taking. *Neuropsychologia, 44*(3), 374-383. https://doi.org/10.1016/j.neuropsychologia.2005.06.011

Iacoboni, M. (2009, 2009/1//). Imitation, Empathy, and Mirror Neurons. *Annual Review of Psychology, 60*(1), 653-670. https://doi.org/10.1146/annurev.psych.60.110707.163604

Jacoby N, B. E., Koster-Hale J, Saxe R. (2015). Localizing Pain Matrix and Theory of Mind networks with both verbal and non-verbal stimuli. *Neuroimage*.

Jacoby N, B. E., Koster-Hale J, Saxe R. (2016). Localizing Pain Matrix and Theory of Mind networks with both verbal and non-verbal stimuli. *Neuroimage*.

Jung, C. G. (1961). Memories, dreams, reflections. Collins and Routledge.

Kandel, E. R. (2007). In Search of Memory: The Emergence of a New Science of Mind. W. W. Norton & Company.

Kanske, P., Böckler, A., & Singer, T. (2015). Models, Mechanisms and Moderators Dissociating Empathy and Theory of Mind. In (pp. 193-206). https://doi.org/10.1007/7854_2015_412

Karpouzian-Rogers, T., Cobia, D., Petersen, J., Wang, L., Mittal, V. A., Csernansky, J. G., & Smith, M. J. (2021). Cognitive Empathy and Longitudinal Changes in Temporo-Parietal Junction Thickness in Schizophrenia. *Front Psychiatry, 12*, 667656. https://doi.org/10.3389/fpsyt.2021.667656

Khalifeh, S., Khodagholi, F., Moghtadaei, M., Behvarmanesh, A., Kheradmand, A., & Ghazvini, H. (2019). Effects of Maternal Deprivation on Anxiety, Depression, and Empathy in Male and Female Offspring of Wistar Rats in the Face of Novel Objects. *Galen Med J, 8*, e1093. https://doi.org/10.31661/gmj.v0i0.1093

Kim JW, K. J., Jeong BS, Ki SW, Im DM, Lee SJ, Lee HS. (2005). Neural mechanism for judging the appropriateness of facial affect. *Brain Res Cogn Brain Res*, 659-667.

Kirchhoff, M. D., & Kiverstein, J. (2020). Attuning to the World: The Diachronic Constitution of the Extended Conscious Mind. *Front Psychol, 11*, 1966. https://doi.org/10.3389/fpsyg.2020.01966

Klemm, K., & Bornholdt, S. (2005, Dec 20). Topology of biological networks and reliability of information processing. *Proc Natl Acad Sci U S A, 102*(51), 18414-18419. https://doi.org/10.1073/pnas.0509132102

Krämer, U. M., Mohammadi, B., Doñamayor, N., Samii, A., & Münte, T. F. (2010, 2010/1//). Emotional and cognitive aspects of empathy and their relation to social

cognition—an fMRI-study. *Brain Research, 1311*, 110-120. https://doi.org/10.1016/j.brainres.2009.11.043

Lamm, C., Batson, C. D., & Decety, J. (2007, 2007/1//). The Neural Substrate of Human Empathy: Effects of Perspective-taking and Cognitive Appraisal. *Journal of Cognitive Neuroscience, 19*(1), 42-58. https://doi.org/10.1162/jocn.2007.19.1.42

Lawrence, E. J., Shaw, P., Giampietro, V. P., Surguladze, S., Brammer, M. J., & David, A. S. (2006, 2006/2//). The role of 'shared representations' in social perception and empathy: An fMRI study. *Neuroimage, 29*(4), 1173-1184. https://doi.org/10.1016/j.neuroimage.2005.09.001

Leslie, K. R., Johnson-Frey, S. H., & Grafton, S. T. (2004, 2004/2//). Functional imaging of face and hand imitation: towards a motor theory of empathy. *Neuroimage, 21*(2), 601-607. https://doi.org/10.1016/j.neuroimage.2003.09.038

Levy, J., & Feldman, R. (2019, 2019/1//). Synchronous Interactions Foster Empathy. *Journal of Experimental Neuroscience, 13*, 117906951986579-117906951986579. https://doi.org/10.1177/1179069519865799

Levy, J., Goldstein, A., & Feldman, R. (2019, Apr 23). The neural development of empathy is sensitive to caregiving and early trauma. *Nat Commun, 10*(1), 1905. https://doi.org/10.1038/s41467-019-09927-y

Lima, A. R., Mello, M. F., & Mari Jde, J. (2010, Jul). The role of early parental bonding in the development of psychiatric symptoms in adulthood. *Curr Opin Psychiatry, 23*(4), 383-387. https://doi.org/10.1097/yco.0b013e32833a51ce

Lipps, T. (1897). Raumästhetik und geometrisch-optische Täuschungen [Aesthetics of space and geometrical optical illusions]. Leipzig: J. A. Barth.

Lipps, T. (1903/06). Ästhetik. Psychologie des Schönen und der Kunst. Voss.

Lipps, T. (1906/2002). Einfühlung und ästherischer Genuss. *Die Zukunft, 54*, 100-114.

Lou, H. C., Luber, B., Crupain, M., Keenan, J. P., Nowak, M., Kjaer, T. W., Sackeim, H. A., & Lisanby, S. H. (2004, Apr 27). Parietal cortex and representation of the mental Self. *Proc Natl Acad Sci U S A, 101*(17), 6827-6832. https://doi.org/10.1073/pnas.0400049101

Mackes, N. K., Golm, D., O'Daly, O. G., Sarkar, S., Sonuga-Barke, E. J. S., Fairchild, G., & Mehta, M. A. (2018, 2018/9//). Tracking emotions in the brain –

Revisiting the Empathic Accuracy Task. *Neuroimage, 178*, 677-686. https://doi.org/10.1016/j.neuroimage.2018.05.080

Meltzoff, A. N., & Decety, J. (2003). What imitation tells us about social cognition: a rapprochement between developmental psychology and cognitive neuroscience. *Philos Trans R Soc Lond B Biol Sci., 358(1431)*, 491–500.

Merleau-Ponty, M. (1960). Le philosophe et son ombre. In *Signes*. Gallimard.

Milner, B., Squire, L. R., & Kandel, E. R. (1998, Mar). Cognitive neuroscience and the study of memory. *Neuron, 20*(3), 445-468. https://doi.org/10.1016/s0896-6273(00)80987-3

Modinos, G., Ormel, J., & Aleman, A. (2009). Activation of anterior insula during self-reflection. *PLoS One, 4*(2), e4618. https://doi.org/10.1371/journal.pone.0004618

Morris, R. (1981). Spatial localization does not require the presence of local cues. *Learn Motiv., 12*.

Nagel, T. (1974). What Is It Like to Be a Bat? *The Philosophical Review, 83(4)*, 435–450.

Naghavi, J. B. F. (2022). The Neuroendocrinology of Empathy. *Neuroscience*.

Nahab, F. B., Hattori, N., Saad, Z. S., & Hallett, M. (2009, May). Contagious yawning and the frontal lobe: an fMRI study. *Hum Brain Mapp, 30*(5), 1744-1751. https://doi.org/10.1002/hbm.20638

Northoff, G. (2019). Lessons From Astronomy and Biology for the Mind-Copernican Revolution in Neuroscience. *Front Hum Neurosci, 13*, 319. https://doi.org/10.3389/fnhum.2019.00319

Northoff, G., & Bermpohl, F. (2004, Mar). Cortical midline structures and the self. *Trends Cogn Sci, 8*(3), 102-107. https://doi.org/10.1016/j.tics.2004.01.004

Northoff, G., Heinzel, A., de Greck, M., Bermpohl, F., Dobrowolny, H., & Panksepp, J. (2006, May 15). Self-referential processing in our brain--a meta-analysis of imaging studies on the self. *Neuroimage, 31*(1), 440-457. https://doi.org/10.1016/j.neuroimage.2005.12.002

Northoff, G., Wainio-Theberge, S., & Evers, K. (2020, Jul). Spatiotemporal neuroscience - what is it and why we need it. *Phys Life Rev, 33*, 78-87. https://doi.org/10.1016/j.plrev.2020.06.005

Nummenmaa, L., Hirvonen, J., Parkkola, R., & Hietanen, J. K. (2008, 2008/11//). Is emotional contagion special? An fMRI study on neural systems for affective and cognitive empathy. *Neuroimage, 43*(3), 571-580. https://doi.org/10.1016/j.neuroimage.2008.08.014

Oliveira Silva, P., Maia, L., Coutinho, J., Frank, B., Soares, J. M., Sampaio, A., & Gonçalves, Ó. (2018, 2018/2//). Empathy by default: Correlates in the brain at rest. *Psicothema, 30*(1), 97-103. https://doi.org/10.7334/psicothema2016.366

Oliver LD, V. J., Neufeld RWJ, Dziobek I, Mitchell DGV. (2018). Greater involvement of action simulation mechanisms in emotional vs cognitive empathy. *Soc Cogn Affect Neurosci., 1*(4).

P.E. Turkeltaub, G. F. E., K.M. Jones, T.A. Zeffiro. (2002). Meta-analysis of the functional neuroanatomy of single-word reading: method and validation. *Neuroimage, 16*, 765-780.

Panksepp, J. (1998). Affective Neuroscience. The Foundations of Human and Animal Emotions. Oxford University Press.

Panksepp, J., & Panksepp, J. B. (2013, 2013/8//). Toward a cross-species understanding of empathy. *Trends in Neurosciences, 36*(8), 489-496. https://doi.org/10.1016/j.tins.2013.04.009

Park, H. D., & Blanke, O. (2019, May). Coupling Inner and Outer Body for Self-Consciousness. *Trends Cogn Sci, 23*(5), 377-388. https://doi.org/10.1016/j.tics.2019.02.002

Parkinson, C., & Wheatley, T. (2014, 2014/3//). Relating Anatomical and Social Connectivity: White Matter Microstructure Predicts Emotional Empathy. *Cerebral Cortex, 24*(3), 614-625. https://doi.org/10.1093/cercor/bhs347

Pezzulo, G., Rigoli, F., & Friston, K. (2015, Nov). Active Inference, homeostatic regulation and adaptive behavioural control. *Prog Neurobiol, 134*, 17-35. https://doi.org/10.1016/j.pneurobio.2015.09.001

Platek, S. M. (2010). Yawn, yawn, yawn, yawn; yawn, yawn, yawn! The social, evolutionary and neuroscientific facets of contagious yawning. *Front Neurol Neurosci, 28*, 107-112. https://doi.org/10.1159/000307086

Platek, S. M., Loughead, J. W., Gur, R. C., Busch, S., Ruparel, K., Phend, N., Panyavin, I. S., & Langleben, D. D. (2006, Feb). Neural substrates for functionally discriminating self-face from personally familiar faces. *Hum Brain Mapp, 27*(2), 91-98. https://doi.org/10.1002/hbm.20168

Platone. (370 b.C). *Fedro*.

Prehn-Kristensen, A., Wiesner, C., Bergmann, T. O., Wolff, S., Jansen, O., Mehdorn, H. M., Ferstl, R., & Pause, B. M. (2009, 2009/6//). Induction of Empathy by the Smell of Anxiety. *PLoS One, 4*(6), e5987-e5987. https://doi.org/10.1371/journal.pone.0005987

Preston, S. D. (2007). A perception-action model for empathy. In T. F. P. W. (Eds.) (Ed.), *Empathy in mental illness*. Cambridge University Press.

Preston, S. D., & de Waal, F. B. (2002, Feb). Empathy: Its ultimate and proximate bases. *Behav Brain Sci, 25*(1), 1-20; discussion 20-71. https://doi.org/10.1017/s0140525x02000018

Qin, P., Wang, M., & Northoff, G. (2020, Aug). Linking bodily, environmental and mental states in the self-A three-level model based on a meta-analysis. *Neurosci Biobehav Rev, 115*, 77-95. https://doi.org/10.1016/j.neubiorev.2020.05.004

Rajmohan, V., & Mohandas, E. (2007, Jan). Mirror neuron system. *Indian J Psychiatry, 49*(1), 66-69. https://doi.org/10.4103/0019-5545.31522

Raz, G., Jacob, Y., Gonen, T., Winetraub, Y., Flash, T., Soreq, E., & Hendler, T. (2014, 2014/1//). Cry for her or cry with her: context-dependent dissociation of two modes of cinematic empathy reflected in network cohesion dynamics. *Social Cognitive and Affective Neuroscience, 9*(1), 30-38. https://doi.org/10.1093/scan/nst052

Reniers RL, V. B., Elliott R, Corcoran R. (2014). Empathy, ToM, and self-other differentiation: an fMRI study of internal states. *Soc Neurosci., 1*, 50-62.

Rochat, P. (2003). Five levels of self-awareness as they unfold early in life. *Consciousness and Cognition, 12*.

Rossion, B., Caldara, R., Seghier, M., Schuller, A. M., Lazeyras, F., & Mayer, E. (2003). A network of occipito-temporal face-sensitive areas besides the right middle fusiform gyrus is necessary for normal face processing. *Brain: a journal of neurology*.

S.B.S. Eickhoff, A. R. A. L., C. Grefkes, L.E. Wang, K. Zilles, P.T. Fox. (2009). Coordinate-based activation likelihood estimation meta-analysis of neuroimaging data: a random-effects approach based on empirical estimates of spatial uncertainty. *Hum. Brain Mapp.*, 2907-2926.

Scalabrini, A., Ebisch, S. J. H., Huang, Z., Di Plinio, S., Perrucci, M. G., Romani, G. L., Mucci, C., & Northoff, G. (2019, Dec 17). Spontaneous Brain Activity Predicts Task-Evoked Activity During Animate Versus Inanimate Touch. *Cereb Cortex, 29*(11), 4628-4645. https://doi.org/10.1093/cercor/bhy340

Scalabrini, A., Wolman, A., & Northoff, G. (2021, Oct 2). The Self and Its Right Insula-Differential Topography and Dynamic of Right vs. Left Insula. *Brain Sci, 11*(10). https://doi.org/10.3390/brainsci11101312

Schmidt, S. N. L., Hass, J., Kirsch, P., & Mier, D. (2021, 2021/5//). The human mirror neuron system—A common neural basis for social cognition? *Psychophysiology, 58*(5). https://doi.org/10.1111/psyp.13781

Schmitgen, M. M., Walter, H., Drost, S., Rückl, S., & Schnell, K. (2016, 2016/4//). Stimulus-dependent amygdala involvement in affective theory of mind generation. *Neuroimage, 129*, 450-459. https://doi.org/10.1016/j.neuroimage.2016.01.029

Schnell, K., Bluschke, S., Konradt, B., & Walter, H. (2011, 2011/1//). Functional relations of empathy and mentalizing: An fMRI study on the neural basis of cognitive empathy. *Neuroimage, 54*(2), 1743-1754. https://doi.org/10.1016/j.neuroimage.2010.08.024

Schulte-Ruther, M., Markowitsch, H. J., Fink, G. R., & Piefke, M. (2007, Aug). Mirror neuron and theory of mind mechanisms involved in face-to-face interactions: a functional magnetic resonance imaging approach to empathy. *J Cogn Neurosci, 19*(8), 1354-1372. https://doi.org/10.1162/jocn.2007.19.8.1354

Schurmann, M., Hesse, M. D., Stephan, K. E., Saarela, M., Zilles, K., Hari, R., & Fink, G. R. (2005, Feb 15). Yearning to yawn: the neural basis of contagious yawning. *Neuroimage, 24*(4), 1260-1264. https://doi.org/10.1016/j.neuroimage.2004.10.022

Seitz, R. J., Schäfer, R., Scherfeld, D., Friederichs, S., Popp, K., Wittsack, H. J., Azari, N. P., & Franz, M. (2008, 2008/3//). Valuating other people's emotional face expression: a combined functional magnetic resonance imaging and electroencephalography study. *Neuroscience, 152*(3), 713-722. https://doi.org/10.1016/j.neuroscience.2007.10.066

Seth, A. K. (2013, Nov). Interoceptive inference, emotion, and the embodied self. *Trends Cogn Sci, 17*(11), 565-573. https://doi.org/10.1016/j.tics.2013.09.007

Shamay-Tsoory, S. (2015). The neuropsychology of empathy: evidence from lesion studies. *Revue de neuropsychologie, 7*.

Shamay-Tsoory, S. G., Aharon-Peretz, J., & Perry, D. (2009, Mar). Two systems for empathy: a double dissociation between emotional and cognitive empathy in inferior frontal gyrus versus ventromedial prefrontal lesions. *Brain, 132*(Pt 3), 617-627. https://doi.org/10.1093/brain/awn279

Shamay-Tsoory, S. G., Aharon-Peretz, J., & Perry, D. (2009, 2009/3//). Two systems for empathy: a double dissociation between emotional and cognitive empathy in inferior frontal gyrus versus ventromedial prefrontal lesions. *Brain, 132*(3), 617-627. https://doi.org/10.1093/brain/awn279

Shamay-Tsoory, S. G., Tomer, R., Berger, B. D., & Aharon-Peretz, J. (2003, Apr 1). Characterization of empathy deficits following prefrontal brain damage: the role of the right ventromedial prefrontal cortex. *J Cogn Neurosci, 15*(3), 324-337. https://doi.org/10.1162/089892903321593063

Shamay-Tsoory, S. G. A.-P., J.; Perry, D. (2009). Two systems for empathy: A double dissociation between emotional and cognitive empathy in inferior frontal gyrus versus ventromedial prefrontal lesions. *Brain, 132*.

Shany, O., Greental, A., Gilam, G., Perry, D., Bleich−Cohen, M., Ovadia, M., Cohen, A., & Raz, G. (2021, 2021/12//). Somatic engagement alters subsequent neurobehavioral correlates of affective mentalizing. *Human Brain Mapping, 42*(18), 5846-5861. https://doi.org/10.1002/hbm.25640

Simondon, G. (2020). *Individuation in light of notions of form and information* (T. Adkins, Trans.; Vol. Volume 2 of Posthumanities Series). University of Minnesota Press.

Smith, A. (1759). The Theory of Moral Sentiments. Millar & Kincaid.

Stein, E. (1989). *On the Problem of Empathy* (W. Stein, Trans.). ICS Publications.

Steinbeis, N. (2016, Jan 19). The role of self-other distinction in understanding others' mental and emotional states: neurocognitive mechanisms in children and adults. *Philos Trans R Soc Lond B Biol Sci, 371*(1686), 20150074. https://doi.org/10.1098/rstb.2015.0074

Strogatz, S. H. (1997). Spontaneous synchronization in nature. *Proceedings of International Frequency Control Symposium*, 2-4. https://doi.org/10.1109/FREQ.1997.638513

Takahashi, H. K., Kitada, R., Sasaki, A. T., Kawamichi, H., Okazaki, S., Kochiyama, T., & Sadato, N. (2015, 2015/12//). Brain networks of affective mentalizing revealed

by the tear effect: The integrative role of the medial prefrontal cortex and precuneus. *Neuroscience Research, 101*, 32-43. https://doi.org/10.1016/j.neures.2015.07.005

Thompson, E. (2001). Empathy and Consciousness. *Journal of consciousness studies, 5-7*, 1-32.

Tononi, G., & Koch, C. (2015, May 19). Consciousness: here, there and everywhere? *Philos Trans R Soc Lond B Biol Sci, 370*(1668). https://doi.org/10.1098/rstb.2014.0167

Trieu, M., Foster, A., Yaseen, Z.S., Beaubian, C., & Calati, R. (2019). Neurobiology of Empathy. In *Teaching Empathy in Healthcare. Building a New Core Competency*. Springer Nature Switzerland.

U. Sandler, L. T. (2017). The S-Lagrangian and a theory of homeostasis in living systems. *Physica A, 471*, 540-553.

Uddin, L. Q., Kaplan, J. T., Molnar-Szakacs, I., Zaidel, E., & Iacoboni, M. (2005, Apr 15). Self-face recognition activates a frontoparietal "mirror" network in the right hemisphere: an event-related fMRI study. *Neuroimage, 25*(3), 926-935. https://doi.org/10.1016/j.neuroimage.2004.12.018

Ulmer Yaniv, A., Salomon, R., Waidergoren, S., Shimon-Raz, O., Djalovski, A., & Feldman, R. (2021, Apr 6). Synchronous caregiving from birth to adulthood tunes humans' social brain. *Proc Natl Acad Sci U S A, 118*(14). https://doi.org/10.1073/pnas.2012900118

Valdesolo, P., & Desteno, D. (2011, Apr). Synchrony and the social tuning of compassion. *Emotion, 11*(2), 262-266. https://doi.org/10.1037/a0021302

Vallortigara, G. (2021). Pensiei della mosca con la testa storta. Adelphi Edizioni.

Vemuri, K., & Surampudi, B. R. (2015, 2015/8//). An Exploratory Investigation of Functional Network Connectivity of Empathy and Default Mode Networks in a Free-Viewing Task. *Brain Connectivity, 5*(6), 384-400. https://doi.org/10.1089/brain.2014.0260

Völlm, B. A., Taylor, A. N. W., Richardson, P., Corcoran, R., Stirling, J., McKie, S., Deakin, J. F. W., & Elliott, R. (2006, 2006/1//). Neuronal correlates of theory of mind and empathy: A functional magnetic resonance imaging study in a nonverbal task. *Neuroimage, 29*(1), 90-98. https://doi.org/10.1016/j.neuroimage.2005.07.022

Wallace, K. (2019). A Theory of the Relational Self: The Cumulative Network Model. *HUMANA.MENTE Journal of Philosophical Studies, 12*, 189-220.

Winters, D. E., Pruitt, P. J., Fukui, S., Cyders, M. A., Pierce, B. J., Lay, K., & Damoiseaux, J. S. (2021, Jun 18). Network functional connectivity underlying dissociable cognitive and affective components of empathy in adolescence. *Neuropsychologia, 156*, 107832. https://doi.org/10.1016/j.neuropsychologia.2021.107832

Yu, C. L., & Chou, T. L. (2018). A Dual Route Model of Empathy: A Neurobiological Prospective. *Front Psychol, 9*, 2212. https://doi.org/10.3389/fpsyg.2018.02212

Zaki J, W. J., Ochsner K. (2012). Task-dependent neural bases of perceiving emotionally expressive targets. *Front Hum Neurosci*.

Chapter III

BUILDING ON NATURE.

SYNCHRONIZATION IN INTER-PERSONAL RELATIONSHIPS

1. Introduction

As we saw in the previous Chapter, empathy is an intersubjective and inter-relational phenomenon that can be described as a process composed of both synchronic and diachronic elements. In particular, we stress that the diachronic component of empathy is constituted by the fact that empathy is built over time, through the processes linked to memory and through the narrative nature of the human identity that Paul Ricoeur recognizes (Ricoeur, 1984, 1985, 1988) and that constitutes the sense of "I" we all experience (Wittmann, 2015).

On the other hand, we stress that the synchronic component of empathy is constituted by a physical spontaneous phenomenon that occurs in many different circumstances. This phenomenon is *synchronization* and it is a fundamental phenomenon of nature (Strogatz, 1997; Winfree, 1967, 1980, 1987). It is known to be present in many phenomena ranging from physical or chemical elements, to interpersonal and social events, passing through animals and biological structures. The fact that it is an ubiquitous phenomenon in nature is evident from the synchronous flowering of some plants (Mas & Yanovsky, 2009), the responsiveness of the cells (Tassinari et al., 2022), the coordinated behavior and communication of some animal species (Buck & Buck, 1968; Couzin, 2018; Laplagne & Elias Costa, 2016; Leniowski & Wegrzyn, 2018; Nagy et al., 2018), the synchronous ore-forming of some complex chemical systems (Ningqiang Liu, 2021), the synchronization of atoms (Arif Warsi Laskar, 2020)or that of clocks (Kapitaniak, 2012), or again the construct which has been studied in the context of human interactions of biobehavioral synchrony (Feldman, 2017). The growing amount of research that many disciplines are producing regarding synchronization is an evidence of the spreading of the interest regarding this phenomenon. In this Chapter, we will try to define it and we will observe it in action especially in the interpersonal field, through the analysis of synchronization mechanisms at the basis of attachment and empathy.

2. Definition of synchronization

We can observe a variety of different but similar definitions of the term. According to the APA dictionary, synchronization can be primarily described as the "simultaneous occurrence of things or events". When it occurs at an interpersonal level, synchronization can be described as the temporal coordination of movement across individuals (Dybowski et al., 2022), the motivation to act together, by predicting others' behavior (Hove, 2008; Sebanz et al., 2006), and the act of moving at the same time, which may blur self-other boundaries (Sebanz et al., 2006; Sommerville & Decety, 2006) and which seems to lead to increased affiliative behavior (Hove, 2008; Jacques, 2012; Valdesolo et al., 2010; Wiltermuth & Heath, 2009).

Other definitions (Nowak et al., 2017) consider different levels of the phenomenon: the system level and the level of elements. In the first case, synchronization refers to the coordination in time among the states or dynamics of the elements comprising the system (Schmidt, 2008), while in the second case, it can be viewed in terms of mutual influence, with consistent signals arriving at an element from other elements (Engel et al., 2001; Singer, 1999; Uhlhaas et al., 2009).

Synchronization is also described in the interpersonal relationship as the dynamic and reciprocal adaptation of the temporal structure of behaviors between interactive partners (E. Delaherche, 2012), or the reciprocal exchange of information whereby individuals adjust minds and bodies in a graded and dynamic manner (Gallotti et al., 2017).

We can notice that there is a common element that is shared by every different definition of synchronization. This element is the dynamical nature of the phenomenon, meaning the spatiotemporal component, which we intend to consider as the common currency between all the different levels in which a phenomenon can be observed (Northoff et al., 2020a). Since synchronization includes both spatial and temporal components, it is structured both topographically and dynamically.

Stressing that the dynamic component determines the specificity of synchronization is in line with the etymology of the term, which derives from Greek synkhronos,

from syn- “together” (see syn-) and khronos “time”, meaning “happening at the same time”.

3. Synchronization and alignment

It is important to disambiguate the concept of “synchrony” (with this term we refer to the concept that describes the actual mechanism of synchronization itself) from other terms that describe different although correlated phenomena.

The first disambiguation that we want to make is the one between synchrony and *alignment*. While synchronization refers to the bidirectional coupling of oscillators (Lakatos et al., 2019), being in this way symmetric, alignment refers to the asymmetric adaptation of a system to a stimulus (Northoff & Huang, 2017; Northoff & Zilio, 2022a). Through alignment, one of the two systems adapts its “rhythm” to the one of the other system. This adaptation takes more time than the bidirectional coupling of synchronization, but could also be prior to a condition in which the two systems themselves are better synchronized between each other. In this sense, we could say that empathy can be read as a form of alignment, through which a system (the brain-body system of an individual) adapts its elements to a stimulus coming from another system (the brain-body system of another individual). We can observe both that this “macro” adaptation can derive from “micro” spontaneous mechanisms of synchronization (the automatic resonance response to other individuals) and that it leads to the occurrence of other more evident mechanisms of synchronization (the complete experience of empathizing with someone or, as we saw, the experience of sympathizing with him/her). In this way, describing empathy as a form of alignment, we understand better the concept of it involving both synchronic (i.e. the mechanisms of synchronization that we will describe) and diachronic (i.e. the process of adaptation that, being given by the memory and narrative components we already described, unfolds over time) elements.

4. Phenomenology

Let us now consider the phenomenology of the phenomena we described (i.e. synchronization and alignment).

The first phenomenon, *synchronization*, can occur at different levels, such as the physical, chemical, physiological and neuronal ones. These kinds of synchronization can be experienced in different ways from a psychological frame of reference. First of all, we must notice that most of the experiences of synchronization are considered positive by the agents who share it. It can be present as a form of feeling coordinated, of being in unison, or in phase, or "on the same page/wavelength". It can be described as a form of agreement between individuals that are in harmony together. Sometimes, for example in the case of being synchronized with a musical rhythm, the experience is described as a flow, that is the feeling of being totally immersed in the activity and of having everything under control (Stupacher, 2019). Synchronization can be also experienced through the phenomenon we defined *sympathy*, that is sharing someone else's emotional state and "fellow-feeling" with him/her. When sympathizing with someone, we can feel one with that person (Scheler, 2008).

In rarer cases, the experience can be so relevant and deep that the individual feels his/her consciousness as altered, as totally expanded to the point that time and space become dissolved. This is the case of what Nabokov calls "cosmic synchronization" (Sisson, 1994).

As we anticipated, an experience in which we can feel *alignment* is empathy. As we already observed, the concept of empathy was originally proposed by the Aesthetic Theory, in the form of the concept of *Einfühlung* which literally means "in-feeling." *Einfühlung* captured the aesthetic activity of transferring one's own feeling into the forms and shapes of objects (Lanzoni, 2018).

This early definition of empathy supports our reading empathy as a form of alignment of the individual to what he/she is perceiving. It is possible to suggest that ultimately empathy may lead to what we have called *sympathy* (Gieser, 2008), as also Scheler suggests (Scheler, 2008). In this sense, it is possible to say that an

alignment with somebody can lead to more synchronous interaction later on (Gieser, 2008). Empathy can be thus described as the process of entering the perceptual world of another person:

> Entering the private perceptual world of the other and becoming thoroughly at home in it. It involves being sensitive, moment to moment, to the changing felt meanings which flow in this other person, to the fear or rage or tenderness or confusion or whatever, that he/she is experiencing. It means temporarily living in his/her life […]. It means frequently checking with him/her as to the accuracy of your sensings, and being guided by the responses you receive. […] To be with another in this way means that for the time being you lay aside the views and values you hold for yourself in order to enter another world without prejudice (Rogers, 1975).

From this definition, we can easily see how empathy involves also a diachronic development that can be recognized as an effort to "reach" a reliable form of the other (projection) after having "dragged" into the self the information coming from him/her (introjection).

5. Synchronization in nature

As we pointed out in the introduction, synchronization occurs throughout nature and can be observed at all levels from the atomic to the biological to the social level, since it occurs when elements behave like oscillators (Kelso, 2021).

Historically, the first observation of the phenomenon of synchronization was clock synchronization, discovered in 1657 by the Dutch scientist Christiaan Huygens (Huygens, 1673). Huygens was hanging two pendulum clocks on a wooden bar supported by two chairs. He observed that, albeit swinging independently of each other at the beginning, after about half an hour, the two pendulums synchronized their frequency. Specifically, they synchronized their frequencies in opposite directions, in what since has been then called out-of-phase synchronization or anti-synchronization (Huygens, 1673; Kapitaniak, 2012; Pikovsky, 2001).

Synchronization has been also observed at the atomic level of quantum theory. Laskar and colleagues (Arif Warsi Laskar, 2020) brought atoms to a temperature close to zero using magnetic fields and lasers. This process made them behavior as “natural oscillators”. They then stored a pulse of light in these atoms, to obtain their synchronization in accordance with the applied optical and magnetic fields. This lets us observe that atoms can oscillate and thereby synchronize with each other with their specific degree of synchronization. Synchronization has also been studied in geology in both seismology (de Rubeis, 2010) and geochemistry.

Lately, oscillations and synchronization of multiple oscillators have been demonstrated to be an essential requisite in living cells (Muehsam, 2014). What is even more important to note, is that aberrant oscillatory patterns are particularly associated with various diseases. Researchers are working on the possibility to use physical energies to modulate stem cell homeostasis, that is in line with a major role of the physical forces described above in the specification of living process (Tassinari et al., 2022).

We can find examples of synchrony also in the plant reign, where we can observe the synchronous flowering of some plants (Mas & Yanovsky, 2009), or the synchronization of plants to the circadian system to regulate their circadian rhythmicity of physiological and developmental processes such as the flowering time Mas & Yanovsky (2009).

Different animal species show synchronous behaviors as mechanisms of adaptation and survival as well. This is the case, for example, of the strategy of collective migration used by different animal species, such as birds or fishes, to move towards more hospitable environments, for mating or breeding reasons, or minimize competition, predation, infection or parasitism (Couzin, 2018). They are known to rely not only on both genetic and sensory information to synchronize their timing and their choices, but also on social cues and learning. One of the most popular behaviors in which we can observe synchronization is the one of fireflies flashing in unison (Buck & Buck, 1968). Sarfati and colleagues (Sarfati et al., 2021) show that when the density of the fireflies is low, their flashes appear uncorrelated. At high density,

instead, the flashes appear to be synchronous, within periodic bursts. They also observed that active fireflies interact with the swarm locally, rather than globally, resulting in a linear propagation of information. This is common also in other social species that perform collective behaviors (Attanasi A, 2014; Lecheval et al., 2018; Ling et al., 2019). Interestingly, in the context of superior mammals like macaques, we can observe that synchrony has more probabilities to occur among individuals that are located closer (Nishikawa et al., 2021). Synchronization is also an important aspect of parental care in many social species of birds. For example, Leniowski and Wegrzyn (Leniowski & Wegrzyn, 2018) demonstrated that a synchronized breeding between the two parents reduces parental activity, and consequently disturbance, at the nest and increased nest survival time.

6. Neural synchronization

Synchronization can also be observed in the brain. The brain is composed of different regions, that are connected between each other both structurally and functionally (Bullmore & Sporns, 2009). These regions range from the sensory unimodal ones like auditory, visual, and somatosensory areas (Catal et al., 2022; Wengler et al., 2020) and the associative transmodal ones like the prefrontal cortex and the default-mode network (DMN) (Margulies et al., 2016; Smallwood et al., 2021). The sensory regions are less structurally and functionally connected among each other than the associative transmodal ones, that are densely connected (Margulies et al., 2016; Smallwood et al., 2021). The continuum from unimodal to transmodal regions is also characterized by a set of specific timescales: sensory regions present faster timescales, while associative regions present longer timescales (Engel et al., 2001; Golesorkhi et al., 2021; Gollo, 2019; Gollo et al., 2015; Murray et al., 2014; Wolff et al., 2022). This means that the brain is characterized by different regions with a peculiar topographic and dynamic organization that exhibit slow associative and faster sensory areas. Each region can be thus conceived as an oscillator which is more or less synchronized with other regions.

7. Synchronization in human interactions

It is possible to observe synchronization in some phenomena of consciousness like memory (Fell & Axmacher, 2011; Varela et al., 2001), in synchronous human phenomena like applause (Neda et al., 2000), games and competitions (Duarte et al., 2013; Hugo Folgado, 2018; Reinero et al., 2021), in interpersonal speech (Amiriparian et al., 2019), in inter-brain neural synchronization (Ana Lucía Valencia, 2020) and so forth. We will thus delve into how synchronization affects two interpersonal phenomena, that are attachment and empathy. Indeed, we think that, being synchronization such a foundational and basic phenomenon, it is important to see its role both in the empathic experience and also in the one that, as we said, is at its basis, namely attachment.

7.1. Synchronization and attachment

According to Ainsworth (Ainsworth, 1963), attachment is a "secure base from which to explore". Later, Bowlby (Bowlby, 1969/1982) described attachment as a unique relationship between an infant and his/her caregiver that is the foundation for further healthy development. Bowlby considered attachment as an inherent biological response and behavioral system in place to provide satisfaction of basic human needs. Attachment bonds are marked by two key characteristics: they are selective (specific to attachment target) and enduring (long-lasting) (Feldman, 2012). Both features are mediated by synchronization on a very biological and physiological basis. For instance, synchronization between mother and infant can be traced in their coupled heart rhythms (Feldman, 2011), hormonal release (Feldman et al., 2010), and brain activation patterns (Nguyen et al., 2021). Such physiological synchrony seems to translate into neuronal, behavioral and psychological synchrony, allowing the infants to synchronize with other attachment partners throughout life: with partners, close friends, and group members (Feldman, 2017).

7.1.1. Physiological synchronization in attachment

From a physiological point of view, Schneider and colleagues (Schneider et al., 2022) tested synchronization in the phenomenon of attachment by analyzing the synchronization of skin conductance response (SCR), to assess autonomic arousal, a specific aspect of adolescents' emotion regulation in response to emotionally laden stimuli. Through this technique, they found that adolescents who experienced warmth in interaction with their parents showed a quicker and larger skin conductance response to comfort pictures.

Feldman and colleagues (Feldman, 2011) investigated the physiological synchronization between mother and infant through the measurement of mother and infant's cardiac outputs during face-to-face interactions. They found that mother and infant coordinate heart rhythms within lags of less than 1s. They also found that the concordance between maternal and infant biological rhythms increased significantly during episodes of affect and vocal synchrony compared to non-synchronous moments.

In addition, Feldman's research group also analyzed mother-infant physiological synchronization in the case of premature infants (Feldman et al., 2014). They used the Kangaroo Care (KC) intervention to provide maternal-newborn skin-to-skin contact to 73 premature infants for 14 consecutive days and compared the results with 73 case-matched control subjects who received standard incubator care. KC was found to be effective both in mothers and in infants: it increased autonomic functioning and maternal attachment behavior in the postpartum period, reduced maternal anxiety and enhanced child cognitive development and executive functions from 6 months to 10 years. By 10 years of age, children receiving KC showed attenuated stress response, organized sleep, and better cognitive control.

7.1.2. Neuronal synchronization in attachment

From a neurobiological point of view, it is possible to study synchronization in the mother-infant dyad through the observation of brain-to-brain coupling in key nodes of the social brain.

Bembich and colleagues (Bembich et al., 2022) used hyperscanning, a functional neuroimaging approach that allows studying functional synchronization between two brains (i.e. interpersonal brain synchronization (IBS)), to assess if the empathic cortical response of a mother to her baby's pain is synchronized with the neonatal cortical response to the painful stimulation. Authors found that, when observing a heel prick done on her own newborn, mothers showed a bilateral activation of the posterior parietal cortex, including the right anterior parietal cortex. They also observed a complex functional synchronization between maternal and neonatal brains. Through these findings, they concluded that brain areas involved in mother–newborn relationship appear to be already co-regulated at birth.

Kim and colleagues (Kim et al., 2022) used functional magnetic resonance imaging to examine the functional connectivity (FC) similarity between mothers and newborns during the first 3 months after the infant's birth. Through their measurements, they observed that similarity in FC between infant and mother can be identified within the first few months after birth. Across the brain networks, they found that the sensorimotor, auditory, and visual networks exhibited, on average, a greater similarity between mothers and infants. Furthermore, they observed that similarity between mothers and infants increases with the infant's age, suggesting that FC may become more similar between generations as an infant's brain develops. Then, they found that fewer years of maternal education were associated with a greater FC similarity between mothers and infants, suggesting that lower maternal education level may influence the infant's brain development and the developmental trajectories to cause premature similarity to the mothers' brain profiles.

7.1.3. Behavioral synchronization in attachment

From a behavioral point of view, synchronization in the mother-infant dyad can be investigated through the observation of nonverbal behaviors. Those behaviors include gaze, affect, vocal, and touch modalities and it has been studied in mother-infant interactions since the 1950s. This behavioral synchrony seems to entrain the

neonate's physiological periodicities of sucking, crying, and circadian rhythmicity (Feldman, 2006; Stern, 1977).

Some examples of behavioral synchrony repertoire in humans are: gaze at the infant's face, "motherese" high-pitched vocalizations, affectionate touch - a behavior akin to the "lickingand-grooming" of mammals that shapes the pup's life-long stress reactivity and the cross-generation transmission of parenting (Champagne & Meaney, 2001) - and careful adaptation to the infant's state and signals (Barratt et al., 1992; Cohen, 1979; Feldman & Eidelman, 2003; Feldman et al., 2002; Fleming et al., 1997; Miller & Holditch-Davis, 1992; Minde et al., 1985). It is possible to observe behavioral synchrony starting from the third month of life, and over the next six months, until infants reach the age of intersubjectivity at around 9 months, when social interactions become more complex and evolve into a more mature give-and-take mutuality (Feldman, 2007a; Stern, 1985).

The synchrony experience undergoes further transformation toward the end of the first year, when infants start using symbols, enlarging the previously nonverbal communication also to the verbal one (Bates, 1987; Feldman, 2007a). It is important to stress that these allostatic mechanisms are shown to be bidirectional (Feldman et al., 2010; Wass, 2019). On the one hand, parents influence the child through direct behaviors such as touch (Feldman & Eidelman, 2003; Feldman et al., 2010; Waters et al., 2019) and verbal ones, including parental teaching (Skoranski et al., 2017) and the parental modeling of positive affect (Bridgett et al., 2015). On the other hand, the child influences the parents. This has been demonstrated through the examination of the parents' changes in response to stressors (Ham & Tronick, 2009), during tabletop play (Cohn, 1988), and through measurements of the parents' autonomic and neural responses to recordings of infants' crying (Bornstein et al., 2017; Out et al., 2010).

Synchronization in attachment has also been measured using the *parent–child synchrony Coding Interactive Behavior* (CIB) construct (Feldman et al., 2013; Levy et al., 2017; Pratt et al., 2018; Pratt et al., 2019).

Ulmer Yaniv and colleagues (Adi Ulmer Yaniv et al., 2021) measured synchronization in parent-child relationship across different ages, by analyzing the

parent-child synchrony construct in different groups: infancy, preschool, adolescence, young adulthood. They observed that synchrony increased considerably from infancy to adulthood across all participants in the three groups, suggesting that adult children, with respect to infants, are engaged in a fluent and co-regulated mutual exchange with their mothers. In addition, they can reciprocally attend to the social communications of both partners.

Another interesting behavioral analysis was performed by Schneider and colleagues (Schneider et al., 2022) in the same study we considered in the physiological part. In addition to observing the skin conductance response, they measured adolescents' visual attention to pictures of distress and comfort, through the assessment of eye movements. As a result, authors found that adolescents whose parental interactions were high in warmth spent more time looking at comfort pictures.

7.1.4. Synchronization levels in attachment

Given these findings, we can observe that the phenomenon of attachment shows different levels and different kinds of interpersonal synchronization, from the physiological, to the neuronal and the behavioral ones (**Figure 1**). All together, they allow for the emergence of the attachment phenomenon itself, the bonding experience which is fundamental for the development of the individual, since it prepares the temporospatial expanded phenomenon of self/other-processing and thus of empathy.

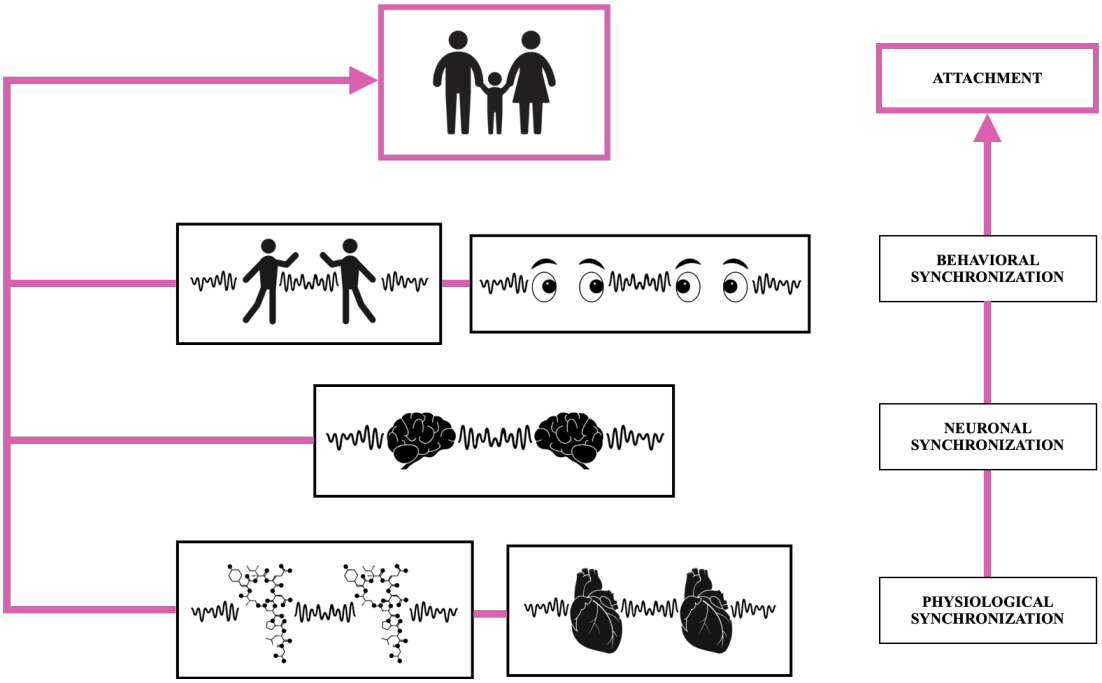


Figure 1. The mechanism of synchronization in action in the phenomenon of human attachment. At the physiological level, we can observe a synchronization of the heart rhythms (Feldman, 2011), the hormonal release (Feldman, 2017) and the skin conductance (Feldman & Eidelman, 2003; Schneider et al., 2022). At a neuronal level, we can observe synchronization in the brain-to-brain coupling (Bembich et al., 2022; Djalovski et al., 2021; Kim et al., 2022; Nguyen et al., 2021). At the behavioral level, we can observe synchronization in the neonatal sucking, crying, and circadian rhythmicity (Feldman, 2006; Stern, 1977), in the gaze at the infant's face, 'motherese' high-pitched vocalizations, affectionate touch (Champagne & Meaney, 2001), in the careful adaptation of the caregiver to the infant's state and signals (Barratt et al., 1992; Cohen, 1979; Feldman, 2017; Fleming et al., 1997; Miller & Holditch-Davis, 1992; Minde et al., 1985). Therefore, we state that all these layers in which synchronization occurs, together produce the proper complex phenomenon of human attachment.

7.2. Synchronization and empathy

As we already observed, the empathic process develops through the parents-infant bond (Feldman, 2015, 2017) and interaction that, during the first years of life, leads to the emergence of the predisposition for empathy, that we described as the capability of processing, and thus knowing, others' emotive state. We intend now to analyze the layers of synchrony that builds the phenomenon of empathy.

7.2.1. Physiological synchronization in empathy

From a physiological perspective, it is very interesting to highlight the results found by Heydrich and colleagues (Heydrich et al., 2021). In their study, they used the Own Body Transformation (OBT) task, which consisted of a schematic virtual body with the flashing of a silhouette surrounding it, either synchronously or asynchronously with the timing of participants' heartbeats. The participants were instructed to imagine taking the perspective and position of the virtual body. Evaluating the impact of this cardio-visual synchrony on reaction times and accuracy rates in the OBT authors showed that synchronous cardio-visual stimulation results in an improved performance during the OBT task in participants with high empathic ability, suggesting that better physiological synchrony is indeed associated to better empathic results.

Goldstein and colleagues (Goldstein et al., 2017) investigated the role of touch in inter-partner physiological synchronization during empathy for pain. Authors evaluated participants' electrocardiogram (ECG) and respiration rates, while they underwent a task in which a subject observed another subject receiving (or not) a painful stimulus. They found that the partner's touch increased interpersonal respiration coupling both with the painful stimulus and without it and increased heart rate coupling when in presence of the painful stimulus. Moreover, physiological coupling was diminished by pain in the absence of the partner's touch. These results suggest that social touch and empathy for pain are associated to interpersonal physiological coupling.

Dor Ziderman and colleagues (Dor-Ziderman et al., 2021) investigated how participants synchronized with the distress shown in a video of a person sharing a painful autobiographical story from her past. The main measure they used was to evaluate synchrony with the target's distress, that is the temporal correspondence between the observer's subjective and physiological response time courses and the target's distress time-course. The authors demonstrated that the subjective distress resonance was accompanied by significant synchrony with distress in participants'

autonomic (cardiovascular and electrodermal) and facial (corrugator) responses. These results support a resonance model of affective empathy, suggesting that during empathic interactions the target's and observer's systems become coupled between each other.

7.2.2. Neuronal synchronization in empathy

From a neurobiological point of view, it is possible to study synchrony in the empathic process through the observation of brain-to-brain coupling during an empathic interaction.

Xu and colleagues (Lei Xu et al., 2020) used inter-subject phase synchronization (ISPS) to analyze the dynamic synchronization of brain networks to task-features in task-fMRI data. Through this measure, they observed two distinct networks synchronized during physical pain observation: one with anterior insula and midcingulate regions strongly engaged in vicarious pain and another with parietal and inferior frontal regions associated with social cognitive processes which may modulate and support the physical pain empathic response.

In another study, Peng et al. (Peng et al., 2021) used electroencephalographic (EEG) hyper-scanning technique to assess neuronal and behavioral activity during a Pain-Sharing task in which high- or low-intensity pain stimulation was randomly delivered to one participant of a dyad on different experimental trials. Their results support the hypothesis that sharing a painful experience triggers emotional resonance between pairs of individuals through brain-to-brain synchronization of neuronal α-oscillations recorded over the sensorimotor cortex, and this emotional resonance further strengthens social bonds and motivates prosocial behavior within pairs of individuals.

Toppi and colleagues (Toppi et al., 2022) measured inter-brain alignment during positive empathy, which they describe as the ability to vicariously experience others' joy. Their approach is based on the simultaneous recording of multi-subject EEG signals during a shared positive experience. They found that during the positive experience, both subjects showed the Late Positive Potential (LPP), an ERP

component related to emotion processing, as well as an inter-subject ERPs synchronization in the related time window. They also found that the brain circuits subtending the ERP-synchronization corresponded to key-regions of personal and vicarious reward.

7.2.3. Behavioral synchronization in empathy

From a behavioral point of view, it is possible to investigate synchrony in the empathic process through the observation of verbal and nonverbal behavior.

Koehne and colleagues (Koehne et al., 2016) investigated the effect of perceived interpersonal synchrony during a simple interactive tapping task (adapted from (Cacioppo et al., 2014)) on cognitive and emotional empathy in individuals with and without autism. Analyses showed that non-autistic subjects reported more cognitive empathy towards their partner if the partner had followed them in a synchronous way compared to an asynchronous way.

In a study of Fujiwara and Daibo (Fujiwara & Daibo, 2022), authors simultaneously measured behavior matching (posture mirroring, evaluated through the correlation of coordinate points in each frame was calculated) and interactional synchrony (quantified as the convergence of timing and rhythm, which represents simultaneous movement and interaction rhythms, respectively) in an automated fashion during an interaction of strangers' dyads. They demonstrated that behavior matching was positively associated with empathic accuracy of thoughts (the degree of congruence between the interactant's inference of the partner's thoughts and feelings (i.e., inference) and the partner's self-reported thoughts and feelings (i.e., answer)).

7.2.4. Synchronization levels in empathy

As for the attachment, we can observe that the phenomenon of empathy shows different levels and different kinds of interpersonal synchronization, from the physiological, to the neuronal and the behavioral ones (**Figure 2**). These levels represent the synchronic component that every empathic interaction involves. From these mechanisms, the whole phenomenon of empathy emerges, both as a synchronic and diachronic event.

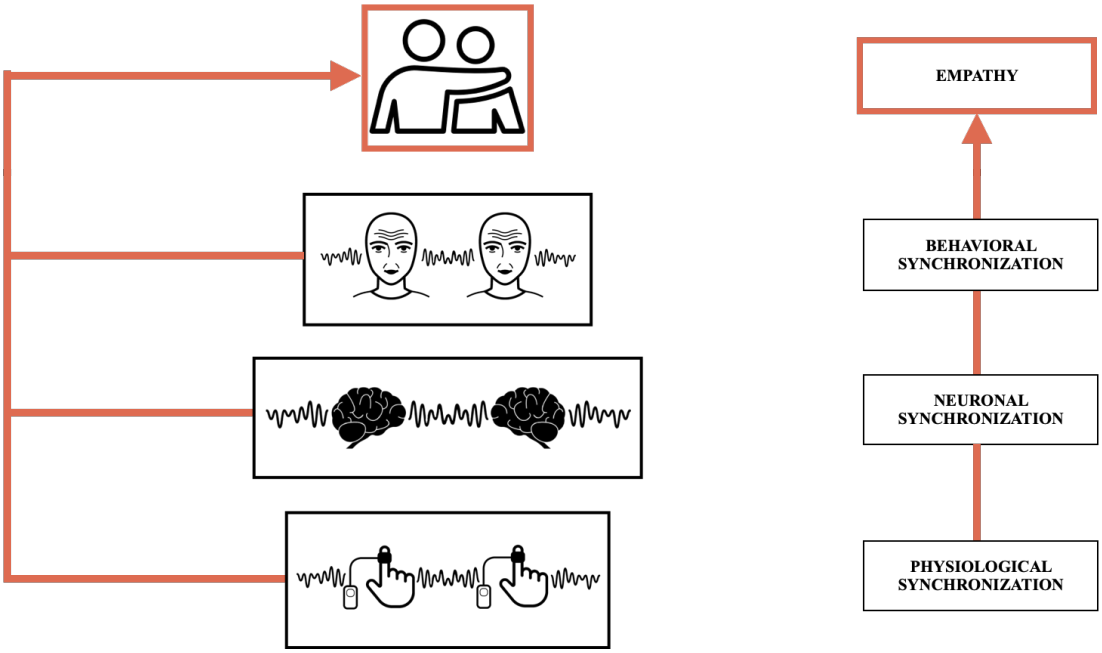


Figure 2. The mechanism of synchronization in action in the phenomenon of human empathy. At the physiological level, we can observe a synchronization of cardiovascular and electrodermal activity (Dor-Ziderman et al., 2021; Goldstein et al., 2017; Heydrich et al., 2021). At the neuronal level, we can observe synchronization in the brain-to-brain coupling (Peng et al., 2021; Toppi et al., 2022; L. Xu et al., 2020). At the psychological and behavioral level, we can observe synchronization in the behavior matching (Fujiwara & Daibo, 2022), in the perceived interpersonal synchrony during an interactive tapping task (Cacioppo et al., 2014; Koehne et al., 2016), in synchronized distress and facial (corrugator) responses (Dor−Ziderman et al., 2021). We thus state that the occurrence of synchronization at all these different levels is what leads to the whole phenomenon of empathy.

8. A critique to the synchronization model of empathy

Someone could dispute the role of synchronization in the phenomenon of empathy, by taking as examples some kinds of empathic experiences that are different from the conceptual form of empathy that we described. For example, does a doctor synchronize with its own patients? Or, can we synchronize with someone in a delusional state, under the effect of drugs that block the sympathetic system (i.e., that reduces the possibility of physiological synchronization) or in coma? In addition, can

we synchronize with a painting or with an art piece? How about an autistic child? With a robot? Many other examples could be made. In these case, it is hard to say that the relationship is based on synchronization layers that we described. Yet, we say that even in these cases we can experience some degree of empathy. For example, as Luigina Mortari stresses, a doctor, and thus also a psychiatrist, needs to possess and train empathy among his/her skills, in order to take care of patients (Mortari, 2015). Even those in different psychiatric disorders or conditions, such as psychotic patients, schizophrenic ones, autistic people and so forth. In the context of the empathic experience towards art, we can take the example of "Can't Help Myself" created by the duo Sun Yuan e Peng Yu (2016-2019). In this piece of art, a mechanical arm that helplessly tries to contain a pool of viscous red liquid seeping out across the floor. When watching this scene, the spectator spontaneously empathizes with the robotic arm even if it is not alive. The concept of empathy itself raised in the context of the aesthetic theory, as we saw. This means that we can actually experience empathy towards art, even without synchronizing with another physiology or neuronal system. According to the theory of the "Uncanny Valley", proposed by Masahiro Mori (Mori, 1970), we can also empathize with robots, especially if they present a certain degree of similarity with the human being.

These examples suggest that there are cases in which we have empathy without or with less synchronization and thus that empathy does not require, as a necessary feature, synchronization, as also demonstrates the study of Deuter, C. and colleagues, in which they found a negative correlation between empathy and different kinds of synchronization (Deuter et al., 2018).

The aim of our work is to build a theoretical model of empathy, to do so we instrumentally narrowed its definition by identifying the borders of absolute empathy principle. On the other hand, we also hypothesize the existence of different forms of empathy. In fact, when from the theoretical concept of empathy, we come to the practical field in which various empathies exist, we can see that, in addition to be multi-layered in its structure, empathy is multi-layered in its application. This means that there is a graduality in the phenomena in which it presents. The different kinds

of empathies (i.e. a form of emotional contagion without cognitive elaboration, a learned cognitive empathic capability that does not require autonomic arousal, empathic concern towards animals, Stendhal syndrome towards art and so on) show different levels of synchronization, that go from no synchronization to complete synchronization. In addition, the empathy-empathies relationship (Boella, 2018) expects also that every person experiences empathy in his/her own particular way. So in the same situation, someone could tend to synchronize more than someone else with an observed individual and yet both experience empathy.

So from the ideal perfect form of empathy that we described in our theoretical model, down to the "Uncanny valley" (**Figure 5**), the cases in which we can experience empathy are many, ranging from total empathy (unlikely to be experienced in its wholeness) to zero empathy, or even discomfort (when in front of corpses or zombies). Between these two poles, we stress that all the different cases can be considered cases in which we experience, at different degrees, different forms of empathy.

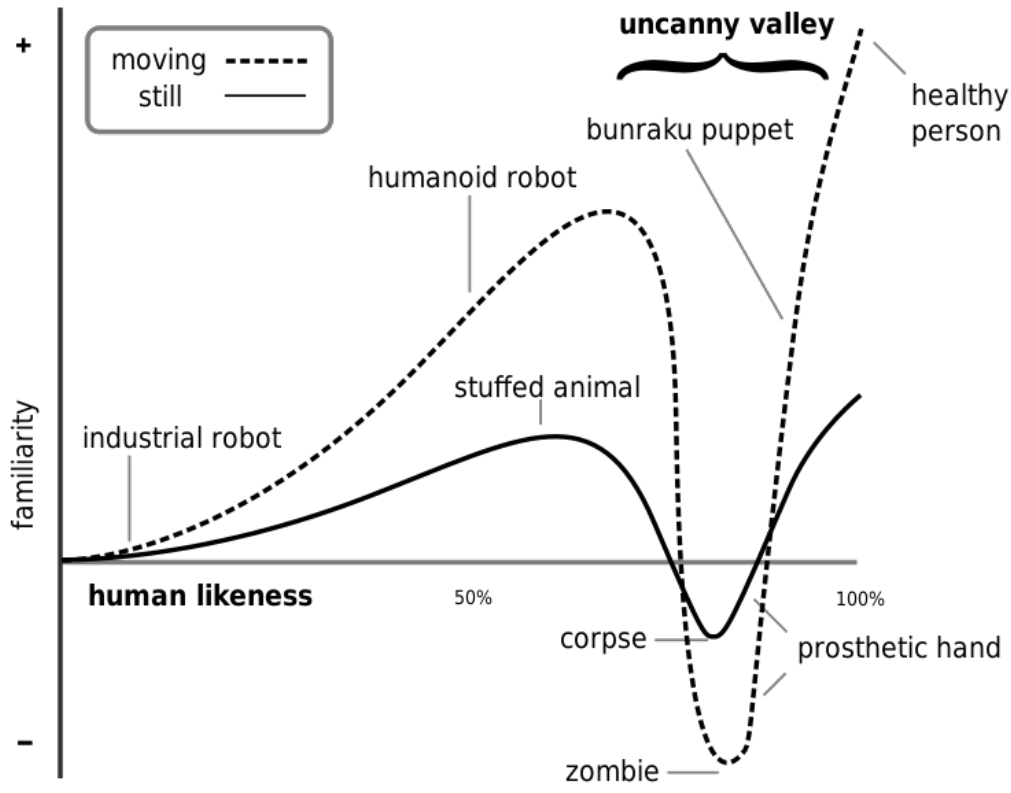


Figure 5. The uncanny valley is the region of negative emotional response. Movement and familiarity amplifies the emotional response.

9. *Discussion*

In this Chapter we analyzed the phenomenon of synchronization, a mechanism that we can trace in every different field of nature. Being synchronization such a diffused process, it is very important to think of it as irreducible to any specific discipline. In fact, it is a common element between the disciplines. It is a basic natural mechanism upon which many complex interactions are built. If we depict nature as a layered structure, in which every different level derives from the levels below, in a continuum of complexity, we can observe synchronization phenomena in each level. In this structure, the layers below build the ones above, in a local-to-global manner, and the ones above entrain the ones below, in a global-to-local manner. Synchronization is thus what we can define as the "common currency" between every different but connected aspect of nature (Northoff, 2020) (**Figure 3**).

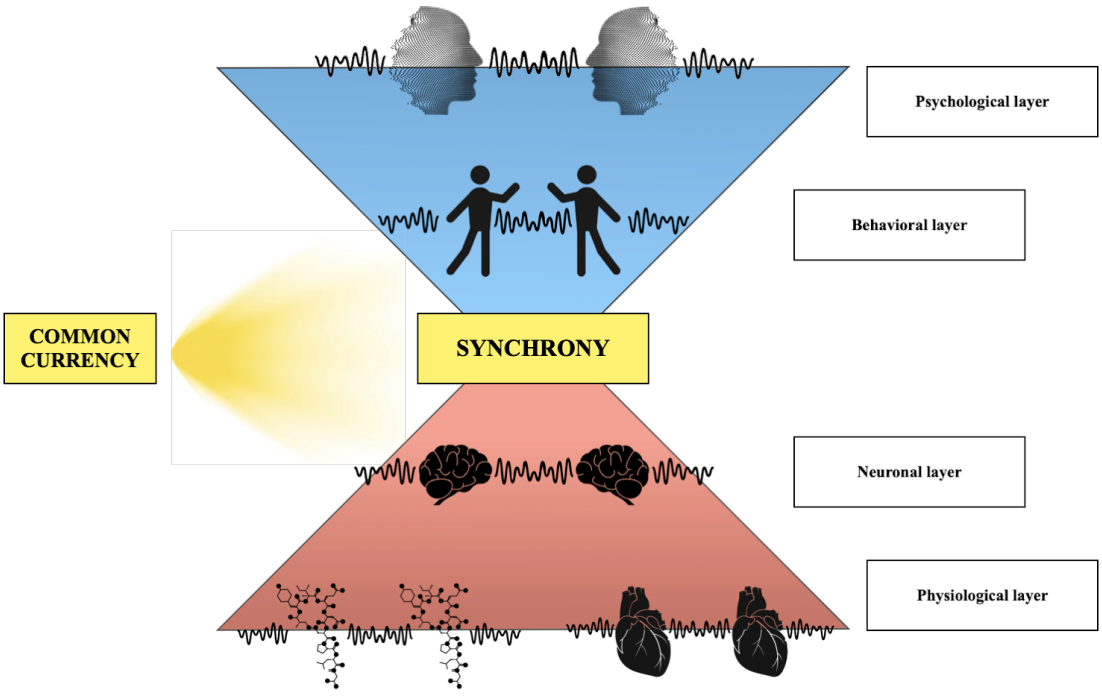


Figure 4: This figure shows that synchronization is a common element between every different layer of nature. It is the element that connects these layers, i.e., their common currency (Northoff, 2020).

After noticing that synchronization is spread in every phenomenon of nature, we focused our attention on two human phenomena, that are attachment and empathy, in which the interactions are in different cases supported by mechanisms of synchronization between the individuals (**Figure 4**).

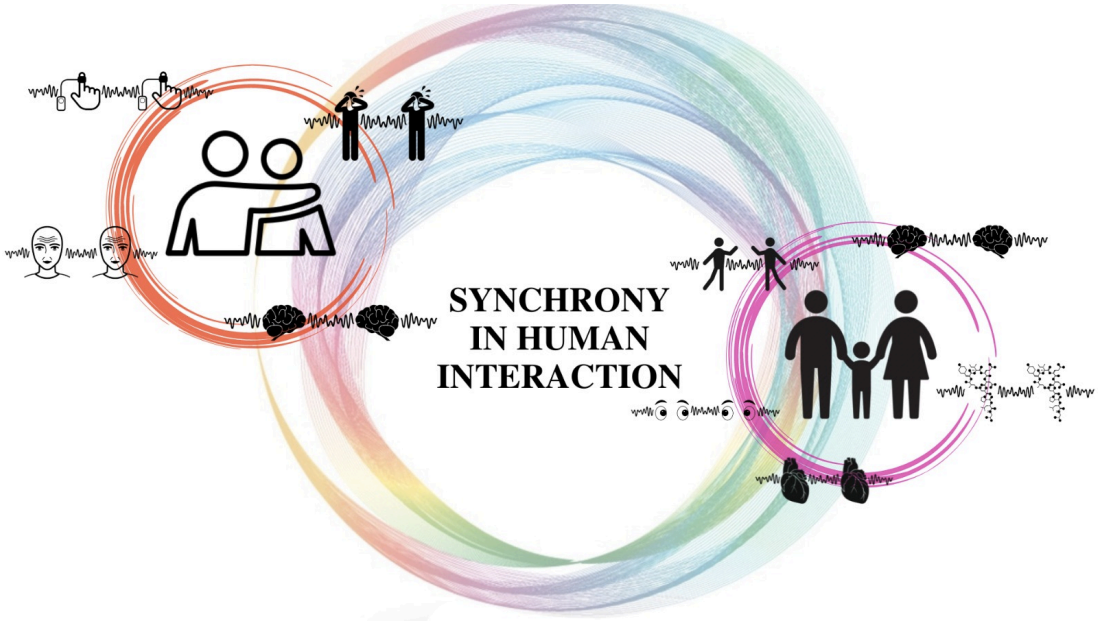


Figure 4. The different kinds of synchrony that have been studied in both attachment and empathy, showing that synchrony at the different levels (physiological, psychological, neural, motoric etcetera…) is a basic mechanism for human interactions.

Of course, attachment and empathy are two different phenomena. While attachment is characterized by what we called the self-other bonding experience, for empathy, also the self-other differentiation experience is fundamental. This means that, if synchronization is actually a necessary phenomenon for the attachment experience, since it prepares all the learned future interpersonal relationships by hetero-regulating the developing individual's rhythms, empathy, in some forms, can occur without the support of synchronization mechanisms. A mature individual, indeed, has his/her own auto-regulation capability and, may not need to rely on synchronization patterns that come from the outside. He/she can elaborate an experience also on the basis of previous experiences and models.

When emphasizing the fundamental nature of synchronization, we should not neglect the importance of desynchronization. In fact, it is from patterns of synchronization and desynchronization that both continuity and discontinuity in time and space are possible, structuring the reality in a dynamically and topographically differentiated way.

References

Ainsworth, M. (1963). The development of infant-mother interaction among the Ganda. In F. BM (Ed.), *Determinants of infant behavior* (pp. 67–112). Wiley.

Amiriparian, S., Han, J., Schmitt, M., Baird, A., Mallol-Ragolta, A., Milling, M., Gerczuk, M., & Schuller, B. (2019). Synchronization in Interpersonal Speech. *Front Robot AI, 6*, 116. https://doi.org/10.3389/frobt.2019.00116

Ana Lucía Valencia, T. F. (2020). What binds us? Inter-brain neural synchronization and its implications for theories of human consciousness. *Neuroscience of Consciousness, 2020*.

Arif Warsi Laskar, P. A., Suprodip Mondal, Parag Katiyar, Sai Vinjanampathy, Saikat Ghosh. (2020). Observation of Quantum Phase Synchronization in Spin-1 Atoms. *Physical Review Letters, 125*.

Attanasi A, C. A., Del Castello L, Giardina I, Melillo S, Parisi L, et al. (2014). Collective behaviour without collective order in wild swarms of midges. *PLOS Computational Biology, 10*.

Barratt, M. S., Roach, M. A., & Leavitt, L. A. (1992, Oct). Early channels of mother-infant communication: preterm and term infants. *J Child Psychol Psychiatry, 33*(7), 1193-1204. https://doi.org/10.1111/j.1469-7610.1992.tb00938.x

Bates, E., O'Connell, B., Shore, C. (1987). Language and communication in infancy. In J. D. O. (Ed.) (Ed.), *Handbook of infant development* (pp. 149–203). John Wiley Sons.

Bembich, S., Saksida, A., Mastromarino, S., Travan, L., Di Risio, G., Cont, G., & Demarini, S. (2022, Mar). Empathy at birth: Mother's cortex synchronizes with that of her newborn in pain. *Eur J Neurosci, 55*(6), 1519-1531. https://doi.org/10.1111/ejn.15641

Boella, L. (2018). Empatie. L’esperienza empatica nella società del conflitto. Raffaello Cortina Editore.

Bornstein, M. H., Putnick, D. L., & Esposito, G. (2017, Jun). Continuity and Stability in Development. *Child Dev Perspect, 11*(2), 113-119. https://doi.org/10.1111/cdep.12221

Bowlby, J. (1969/1982). Attachment and loss: Vol. 1. Attachment. 2. Basic Books.

Bridgett, D. J., Burt, N. M., Edwards, E. S., & Deater-Deckard, K. (2015, May). Intergenerational transmission of self-regulation: A multidisciplinary review and

integrative conceptual framework. *Psychol Bull, 141*(3), 602-654. https://doi.org/10.1037/a0038662

Buck, J., & Buck, E. (1968, Mar 22). Mechanism of rhythmic synchronous flashing of fireflies. Fireflies of Southeast Asia may use anticipatory time-measuring in synchronizing their flashing. *Science, 159*(3821), 1319-1327. https://doi.org/10.1126/science.159.3821.1319

Bullmore, E., & Sporns, O. (2009, Mar). Complex brain networks: graph theoretical analysis of structural and functional systems. *Nat Rev Neurosci, 10*(3), 186-198. https://doi.org/10.1038/nrn2575

Cacioppo, S., Zhou, H., Monteleone, G., Majka, E. A., Quinn, K. A., Ball, A. B., Norman, G. J., Semin, G. R., & Cacioppo, J. T. (2014, Sep 26). You are in sync with me: neural correlates of interpersonal synchrony with a partner. *Neuroscience, 277*, 842-858. https://doi.org/10.1016/j.neuroscience.2014.07.051

Catal, Y., Gomez-Pilar, J., & Northoff, G. (2022, Jan 30). Intrinsic Dynamics and Topography of Sensory Input Systems. *Cereb Cortex*. https://doi.org/10.1093/cercor/bhab504

Champagne, F., & Meaney, M. J. (2001). Like mother, like daughter: evidence for non-genomic transmission of parental behavior and stress responsivity. *Prog Brain Res, 133*, 287-302. https://doi.org/10.1016/s0079-6123(01)33022-4

Cohen, S. E., Beckwith, L. (1979). Preterm infant interaction with the caregiver in the first year of life and competence at age two. *Child Development, 50*, 767–776.

Cohn, J. F., Tronick, E. Z. (1988). Mother-infant face-to-face interaction: Influence is bidirectional and unrelated to periodic cycles in either partner's behavior. *Developmental Psychology, 24*.

Couzin, I. D. (2018, Oct). Synchronization: The Key to Effective Communication in Animal Collectives. *Trends Cogn Sci, 22*(10), 844-846. https://doi.org/10.1016/j.tics.2018.08.001

de Rubeis, V. D., Czechowski, Z., and Teisseyre, R. (Eds.). (2010). Synchronization and Triggering: from Fracture to Earthquake Processes. In *Geoplanet: Earth and Planetary Sciences* (Vol. 1). Springer.

Deuter, C. E., Nowacki, J., Wingenfeld, K., Kuehl, L. K., Finke, J. B., Dziobek, I., & Otte, C. (2018, Nov). The role of physiological arousal for self-reported emotional empathy. *Auton Neurosci, 214*, 9-14. https://doi.org/10.1016/j.autneu.2018.07.002

Djalovski, A., Dumas, G., Kinreich, S., & Feldman, R. (2021, Feb 1). Human attachments shape interbrain synchrony toward efficient performance of social goals. *Neuroimage, 226*, 117600. https://doi.org/10.1016/j.neuroimage.2020.117600

Dor-Ziderman, Y., Cohen, D., Levit-Binnun, N., & Golland, Y. (2021, Oct). Synchrony with distress in affective empathy and compassion. *Psychophysiology, 58*(10), e13889. https://doi.org/10.1111/psyp.13889

Dor−Ziderman, Y., Cohen, D., Levit−Binnun, N., & Golland, Y. (2021, 2021/10//). Synchrony with distress in affective empathy and compassion. *Psychophysiology, 58*(10). https://doi.org/10.1111/psyp.13889

Duarte, R., Araujo, D., Correia, V., Davids, K., Marques, P., & Richardson, M. J. (2013, Aug). Competing together: Assessing the dynamics of team-team and player-team synchrony in professional association football. *Hum Mov Sci, 32*(4), 555-566. https://doi.org/10.1016/j.humov.2013.01.011

Dybowski, K., Raczka, B., Postarnak, S., Castro, S. L., & Silva, S. (2022, Jan 24). Interpersonal Synchronization Protects Against the Antisocial Outcomes of Frustration. *Psychol Rep*, 332941211054771. https://doi.org/10.1177/00332941211054771

E. Delaherche, M. C., A. Mahdhaoui, C. Saint-Georges, S. Viaux and D. Cohen. (2012). Interpersonal Synchrony: A Survey of Evaluation Methods across Disciplines. *IEEE Transactions on Affective Computing, 3*, 349-365. https://doi.org/10.1109/T-AFFC.2012.12

Engel, A. K., Fries, P., & Singer, W. (2001, Oct). Dynamic predictions: oscillations and synchrony in top-down processing. *Nat Rev Neurosci, 2*(10), 704-716. https://doi.org/10.1038/35094565

Feldman, R. (2006, Jan). From biological rhythms to social rhythms: Physiological precursors of mother-infant synchrony. *Dev Psychol, 42*(1), 175-188. https://doi.org/10.1037/0012-1649.42.1.175

Feldman, R. (2007). Mother-infant synchrony and the development of moral orientation in childhood and adolescence: Direct and indirect mechanisms of developmental continuity. *American Journal of Orthopsychiatry, 77*(4), 582-597. https://doi.org/10.1037/0002-9432.77.4.582

Feldman, R. (2012, Mar). Oxytocin and social affiliation in humans. *Horm Behav, 61*(3), 380-391. https://doi.org/10.1016/j.yhbeh.2012.01.008

Feldman, R. (2015, Jun). The adaptive human parental brain: implications for children's social development. *Trends Neurosci, 38*(6), 387-399. https://doi.org/10.1016/j.tins.2015.04.004

Feldman, R. (2017, Feb). The Neurobiology of Human Attachments. *Trends Cogn Sci, 21*(2), 80-99. https://doi.org/10.1016/j.tics.2016.11.007

Feldman, R., & Eidelman, A. I. (2003, Apr). Skin-to-skin contact (Kangaroo Care) accelerates autonomic and neurobehavioural maturation in preterm infants. *Dev Med Child Neurol, 45*(4), 274-281. https://doi.org/10.1017/s0012162203000525

Feldman, R., Eidelman, A. I., Sirota, L., & Weller, A. (2002, Jul). Comparison of skin-to-skin (kangaroo) and traditional care: parenting outcomes and preterm infant development. *Pediatrics, 110*(1 Pt 1), 16-26. https://doi.org/10.1542/peds.110.1.16

Feldman, R., Gordon, I., Influs, M., Gutbir, T., & Ebstein, R. P. (2013, Jun). Parental oxytocin and early caregiving jointly shape children's oxytocin response and social reciprocity. *Neuropsychopharmacology, 38*(7), 1154-1162. https://doi.org/10.1038/npp.2013.22

Feldman, R., Gordon, I., Schneiderman, I., Weisman, O., & Zagoory-Sharon, O. (2010, Sep). Natural variations in maternal and paternal care are associated with systematic changes in oxytocin following parent-infant contact. *Psychoneuroendocrinology, 35*(8), 1133-1141. https://doi.org/10.1016/j.psyneuen.2010.01.013

Feldman, R., Magori-Cohen, R., Galili, G., Singer, M., Louzoun, Y. (2011). Mother and infant coordinate heart rhythms through episodes of interaction synchrony. *Infant behavior development, 34*, 569–577.

Feldman, R., Rosenthal, Z., & Eidelman, A. I. (2014, Jan 1). Maternal-preterm skin-to-skin contact enhances child physiologic organization and cognitive control across the first 10 years of life. *Biol Psychiatry, 75*(1), 56-64. https://doi.org/10.1016/j.biopsych.2013.08.012

Fell, J., & Axmacher, N. (2011, Feb). The role of phase synchronization in memory processes. *Nat Rev Neurosci, 12*(2), 105-118. https://doi.org/10.1038/nrn2979

Fleming, A. S., Steiner, M., & Corter, C. (1997, Oct). Cortisol, hedonics, and maternal responsiveness in human mothers. *Horm Behav, 32*(2), 85-98. https://doi.org/10.1006/hbeh.1997.1407

Fujiwara, K., & Daibo, I. (2022, Jan 2). Empathic accuracy and interpersonal coordination: behavior matching can enhance accuracy but interactional synchrony

may not. *J Soc Psychol, 162*(1), 71-88. https://doi.org/10.1080/00224545.2021.1983509

Gallotti, M., Fairhurst, M. T., & Frith, C. D. (2017, Feb). Alignment in social interactions. *Conscious Cogn, 48*, 253-261. https://doi.org/10.1016/j.concog.2016.12.002

Gieser, T. (2008). Embodiment, emotion and empathy: A phenomenological approach to apprenticeship learning. *Anthropological Theory, 8*, 299–318.

Goldstein, P., Weissman-Fogel, I., & Shamay-Tsoory, S. G. (2017, Jun 12). The role of touch in regulating inter-partner physiological coupling during empathy for pain. *Sci Rep, 7*(1), 3252. https://doi.org/10.1038/s41598-017-03627-7

Golesorkhi, M., Gomez-Pilar, J., Zilio, F., Berberian, N., Wolff, A., Yagoub, M. C. E., & Northoff, G. (2021, Aug 16). The brain and its time: intrinsic neural timescales are key for input processing. *Commun Biol, 4*(1), 970. https://doi.org/10.1038/s42003-021-02483-6

Gollo, L. L. (2019, Feb 5). Exploring atypical timescales in the brain. *Elife, 8*. https://doi.org/10.7554/eLife.45089

Gollo, L. L., Zalesky, A., Hutchison, R. M., van den Heuvel, M., & Breakspear, M. (2015, May 19). Dwelling quietly in the rich club: brain network determinants of slow cortical fluctuations. *Philos Trans R Soc Lond B Biol Sci, 370*(1668). https://doi.org/10.1098/rstb.2014.0165

Ham, J., & Tronick, E. (2009, 2009/11//). Relational psychophysiology: Lessons from mother–infant physiology research on dyadically expanded states of consciousness. *Psychotherapy Research, 19*(6), 619-632. https://doi.org/10.1080/10503300802609672

Heydrich, L., Walker, F., Blättler, L., Herbelin, B., Blanke, O., & Aspell, J. E. (2021, 2021/1//). Interoception and Empathy Impact Perspective Taking. *Frontiers in Psychology, 11*. https://doi.org/10.3389/fpsyg.2020.599429

Hove, M. J. (2008). Shared circuits, shared time, and interpersonal synchrony. *Behavioral and Brain Sciences, 31*.

Hugo Folgado, R. D., Pedro Marques, Bruno Gonçalves Jaime Sampaio. (2018). Exploring how movement synchronization is related to match outcome in elite professional football. *Science and Medicine in Football, 2*, 101-107. https://doi.org/10.1080/24733938.2018.1431399

Huygens, C. (1673). *Horologium Oscillatorium*. Dawsons of Pall Mall.

Jacques, L., Roger, T., Dean., Freya, Bailes. (2012). Synchronization can influence trust following virtual interaction. *Experimental Psychology, 50*, 53-63. https://doi.org/10.1027/1618-3169/A000173

Kapitaniak, M., Czolczynski, K., Perlikowski, P., Stefanski, A., Kapitaniak, T. (2012). Synchronization of clocks. *Physics Reports, 517*, 1-69.

Kelso, J. A. S. (2021, Apr 27). Unifying Large- and Small-Scale Theories of Coordination. *Entropy (Basel), 23*(5). https://doi.org/10.3390/e23050537

Kim, P., Chen, H., Dufford, A. J., Tribble, R., Gilmore, J., & Gao, W. (2022, Jul 21). Intergenerational neuroimaging study: mother-infant functional connectivity similarity and the role of infant and maternal factors. *Cereb Cortex, 32*(15), 3175-3186. https://doi.org/10.1093/cercor/bhab408

Koehne, S., Hatri, A., Cacioppo, J. T., & Dziobek, I. (2016, 2016/1//). Perceived interpersonal synchrony increases empathy: Insights from autism spectrum disorder. *Cognition, 146*, 8-15. https://doi.org/10.1016/j.cognition.2015.09.007

Lakatos, P., Gross, J., & Thut, G. (2019, Sep 23). A New Unifying Account of the Roles of Neuronal Entrainment. *Curr Biol, 29*(18), R890-R905. https://doi.org/10.1016/j.cub.2019.07.075

Lanzoni, S. (2018). *Empathy. A History*. Yale University Press.

Laplagne, D. A., & Elias Costa, M. (2016). Rats Synchronize Locomotion with Ultrasonic Vocalizations at the Subsecond Time Scale. *Front Behav Neurosci, 10*, 184. https://doi.org/10.3389/fnbeh.2016.00184

Lecheval, V., Jiang, L., Tichit, P., Sire, C., Hemelrijk, C. K., & Theraulaz, G. (2018, Apr 25). Social conformity and propagation of information in collective U-turns of fish schools. *Proc Biol Sci, 285*(1877). https://doi.org/10.1098/rspb.2018.0251

Leniowski, K., & Wegrzyn, E. (2018, May 9). Synchronisation of parental behaviours reduces the risk of nest predation in a socially monogamous passerine bird. *Sci Rep, 8*(1), 7385. https://doi.org/10.1038/s41598-018-25746-5

Levy, J., Goldstein, A., & Feldman, R. (2017, 2017/7//). Perception of social synchrony induces mother–child gamma coupling in the social brain. *Social Cognitive and Affective Neuroscience, 12*(7), 1036-1046. https://doi.org/10.1093/scan/nsx032

Ling, H., McLvor, G. E., Westley, J., van der Vaart, K., Yin, J., Vaughan, R. T., Thornton, A., & Ouellette, N. T. (2019, Oct 31). Collective turns in jackdaw flocks: kinematics and information transfer. *J R Soc Interface, 16*(159), 20190450. https://doi.org/10.1098/rsif.2019.0450

Margulies, D. S., Ghosh, S. S., Goulas, A., Falkiewicz, M., Huntenburg, J. M., Langs, G., Bezgin, G., Eickhoff, S. B., Castellanos, F. X., Petrides, M., Jefferies, E., & Smallwood, J. (2016, Nov 1). Situating the default-mode network along a principal gradient of macroscale cortical organization. *Proc Natl Acad Sci U S A, 113*(44), 12574-12579. https://doi.org/10.1073/pnas.1608282113

Mas, P., & Yanovsky, M. J. (2009, Oct). Time for circadian rhythms: plants get synchronized. *Curr Opin Plant Biol, 12*(5), 574-579. https://doi.org/10.1016/j.pbi.2009.07.010

Miller, D. B., & Holditch-Davis, D. (1992, Jun). Interactions of parents and nurses with high-risk preterm infants. *Res Nurs Health, 15*(3), 187-197. https://doi.org/10.1002/nur.4770150305

Minde, K., Perrotta, M., & Marton, P. (1985, Mar). Maternal caretaking and play with full-term and premature infants. *J Child Psychol Psychiatry, 26*(2), 231-244. https://doi.org/10.1111/j.1469-7610.1985.tb02262.x

Mori, M. (1970). Bukimi no tani - The uncanny valley. *Energy, 7*.

Mortari, L. (2015). *Filosofia della cura*. Raffaello Cortina Editore.

Muehsam, D. V., C. (2014). Life rhythm as a symphony of oscillatory patterns: electromagnetic energy and sound vibration modulates gene expression for biological signaling and healing. *GLOBAL ADVANCES IN HEALTH AND MEDICINE, 3*, 40-55.

Murray, J. D., Bernacchia, A., Freedman, D. J., Romo, R., Wallis, J. D., Cai, X., Padoa-Schioppa, C., Pasternak, T., Seo, H., Lee, D., & Wang, X. J. (2014, Dec). A hierarchy of intrinsic timescales across primate cortex. *Nat Neurosci, 17*(12), 1661-1663. https://doi.org/10.1038/nn.3862

Nagy, M., Couzin, I. D., Fiedler, W., Wikelski, M., & Flack, A. (2018, May 19). Synchronization, coordination and collective sensing during thermalling flight of freely migrating white storks. *Philos Trans R Soc Lond B Biol Sci, 373*(1746). https://doi.org/10.1098/rstb.2017.0011

Neda, Z., Ravasz, E., Vicsek, T., Brechet, Y., & Barabasi, A. L. (2000, Jun). Physics of the rhythmic applause. *Phys Rev E Stat Phys Plasmas Fluids Relat Interdiscip Topics, 61*(6 Pt B), 6987-6992. https://doi.org/10.1103/physreve.61.6987

Nguyen, T., Schleihauf, H., Kungl, M., Kayhan, E., Hoehl, S., & Vrticka, P. (2021, Jul). Interpersonal Neural Synchrony During Father-Child Problem Solving: An fNIRS Hyperscanning Study. *Child Dev, 92*(4), e565-e580. https://doi.org/10.1111/cdev.13510

Ningqiang Liu, N. P., Qingjie Gong, Yongshun Liu, Chongwen Yu, Stefano Albanese. (2021). Spatio-temporal synchronization in complex ore-forming systems: Mesoscale case study in south China. *Journal of Geochemical Exploration, 231*.

Nishikawa, M., Suzuki, M., & Sprague, D. S. (2021, Oct). Activity synchrony and travel direction synchrony in wild female Japanese macaques. *Behav Processes, 191*, 104473. https://doi.org/10.1016/j.beproc.2021.104473

Northoff, G., & Huang, Z. (2017, Sep). How do the brain's time and space mediate consciousness and its different dimensions? Temporo-spatial theory of consciousness (TTC). *Neurosci Biobehav Rev, 80*, 630-645. https://doi.org/10.1016/j.neubiorev.2017.07.013

Northoff, G., Wainio-Theberge, S., & Evers, K. (2020, Jul). Is temporo-spatial dynamics the "common currency" of brain and mind? In Quest of "Spatiotemporal Neuroscience". *Phys Life Rev, 33*, 34-54. https://doi.org/10.1016/j.plrev.2019.05.002

Northoff, G., Wainio-Theberge, S., Evers, K. (2020). Is temporo-spatial dynamics the "common currency" of brain and mind? In Quest of "Spatiotemporal Neuroscience". *Physics of life reviews, 33*, 34–54. https://doi.org/https://doi.org/10.1016/j.plrev.2019.05.002

Northoff, G., & Zilio, F. (2022, Feb 13). From Shorter to Longer Timescales: Converging Integrated Information Theory (IIT) with the Temporo-Spatial Theory of Consciousness (TTC). *Entropy (Basel), 24*(2). https://doi.org/10.3390/e24020270

Nowak, A., Vallacher, R. R., Zochowski, M., & Rychwalska, A. (2017). Functional Synchronization: The Emergence of Coordinated Activity in Human Systems. *Front Psychol, 8*, 945. https://doi.org/10.3389/fpsyg.2017.00945

Out, D., Pieper, S., Bakermans-Kranenburg, M. J., Zeskind, P. S., & van Ijzendoorn, M. H. (2010, Nov). Intended sensitive and harsh caregiving responses to infant crying: the role of cry pitch and perceived urgency in an adult twin sample. *Child Abuse Negl, 34*(11), 863-873. https://doi.org/10.1016/j.chiabu.2010.05.003

Peng, W., Lou, W., Huang, X., Ye, Q., Tong, R. K.-Y., & Cui, F. (2021, 2021/9//). Suffer together, bond together: Brain-to-brain synchronization and mutual affective empathy when sharing painful experiences. *Neuroimage, 238*, 118249-118249. https://doi.org/10.1016/j.neuroimage.2021.118249

Pikovsky, A., Rosenblum, M., Kurths, J. (2001). A universal concept in nonlinear sciences. *Self, 2*.

Pratt, M., Goldstein, A., & Feldman, R. (2018, Sep 11). Child brain exhibits a multi-rhythmic response to attachment cues. *Soc Cogn Affect Neurosci, 13*(9), 957-966. https://doi.org/10.1093/scan/nsy062

Pratt, M., Zeev-Wolf, M., Goldstein, A., & Feldman, R. (2019, Jul 13). Exposure to early and persistent maternal depression impairs the neural basis of attachment in preadolescence. *Prog Neuropsychopharmacol Biol Psychiatry, 93*, 21-30. https://doi.org/10.1016/j.pnpbp.2019.03.005

Reinero, D. A., Dikker, S., & Van Bavel, J. J. (2021, Jan 18). Inter-brain synchrony in teams predicts collective performance. *Soc Cogn Affect Neurosci, 16*(1-2), 43-57. https://doi.org/10.1093/scan/nsaa135

Ricoeur, P. (1984, 1985, 1988). *Time and Narrative* (K. M. a. D. Pellauer, Trans.). University of Chicago Press.

Rogers, C. R. (1975). Empathic: An unappreciated way of being. *The Counseling Psychologist, 5*, 2-10.

Sarfati, R., Hayes, J. C., & Peleg, O. (2021, Jul). Self-organization in natural swarms of Photinus carolinus synchronous fireflies. *Sci Adv, 7*(28). https://doi.org/10.1126/sciadv.abg9259

Scheler, M. (2008). *The nature of sympathy*. Transaction Publishers.

Schmidt, R. C., Richardson, M. J. (2008). Dynamics of Interpersonal Coordination. In V. K. J. E. A. Fuchs (Ed.), *Coordination: Neural, Behavioral and Social Dynamics* (pp. 281-308). Springer. https://doi.org/https://doi.org/10.1007/978-3-540-74479-5_14

Schneider, M., Obsuth, I., Szymanska, M., Mathieu, J., Nezelof, S., Lyons-Ruth, K., & Vulliez-Coady, L. (2022, May 2). Attachment-based parent-adolescent interaction linked to visual attention and autonomic arousal to distress and comfort stimuli. *BMC Psychol, 10*(1), 112. https://doi.org/10.1186/s40359-022-00821-9

Sebanz, N., Bekkering, H., & Knoblich, G. (2006, Feb). Joint action: bodies and minds moving together. *Trends Cogn Sci, 10*(2), 70-76. https://doi.org/10.1016/j.tics.2005.12.009

Singer, W. (1999, Sep). Neuronal synchrony: a versatile code for the definition of relations? *Neuron, 24*(1), 49-65, 111-125. https://doi.org/10.1016/s0896-6273(00)80821-1

Sisson, J. B. (1994). Nabokov's Cosmic Synchronization and "Something Else". *Nabokov Studies, 1*, 155-177. https://doi.org/doi:10.1353/nab.2011.0097

Skoranski, A. M., Lunkenheimer, E., & Lucas-Thompson, R. G. (2017, Nov). The effects of maternal respiratory sinus arrhythmia and behavioral engagement on mother-child physiological coregulation. *Dev Psychobiol, 59*(7), 888-898. https://doi.org/10.1002/dev.21543

Smallwood, J., Bernhardt, B. C., Leech, R., Bzdok, D., Jefferies, E., & Margulies, D. S. (2021, Aug). The default mode network in cognition: a topographical perspective. *Nat Rev Neurosci, 22*(8), 503-513. https://doi.org/10.1038/s41583-021-00474-4

Sommerville, J. A., & Decety, J. (2006, Apr). Weaving the fabric of social interaction: articulating developmental psychology and cognitive neuroscience in the domain of motor cognition. *Psychon Bull Rev, 13*(2), 179-200. https://doi.org/10.3758/bf03193831

Stern, D. N. (1977). The first relationship: Infant and mother. Harvard University Press.

Stern, D. N. (1985). The Interpersonal World of the Infant: A View from Psychoanalysis and Developmental Psychology. Basic Books.

Strogatz, S. H. (1997). Spontaneous synchronization in nature. *Proceedings of International Frequency Control Symposium*, 2-4. https://doi.org/10.1109/FREQ.1997.638513

Stupacher, J. (2019). The experience of flow during sensorimotor synchronization to musical rhythms. *Musicae Scientiae, 23*, 348-361.

Tassinari, R., Cavallini, C., Olivi, E., Facchin, F., Taglioli, V., Zannini, C., Marcuzzi, M., & Ventura, C. (2022, Mar 15). Cell Responsiveness to Physical Energies: Paving the Way to Decipher a Morphogenetic Code. *Int J Mol Sci, 23*(6). https://doi.org/10.3390/ijms23063157

Toppi, J., Siniatchkin, M., Vogel, P., Freitag, C. M., Astolfi, L., & Ciaramidaro, A. (2022, Oct 14). A novel approach to measure brain-to-brain spatial and temporal alignment during positive empathy. *Sci Rep, 12*(1), 17282. https://doi.org/10.1038/s41598-022-18911-4

Uhlhaas, P. J., Pipa, G., Lima, B., Melloni, L., Neuenschwander, S., Nikolic, D., & Singer, W. (2009). Neural synchrony in cortical networks: history, concept and current status. *Front Integr Neurosci, 3*, 17. https://doi.org/10.3389/neuro.07.017.2009

Ulmer Yaniv, A., Salomon, R., Waidergoren, S., Shimon-Raz, O., Djalovski, A., & Feldman, R. (2021, 2021/4//). Synchronous caregiving from birth to adulthood tunes humans' social brain. *Proceedings of the National Academy of Sciences, 118*(14). https://doi.org/10.1073/pnas.2012900118

Valdesolo, P., Ouyang, J., & DeSteno, D. (2010). The rhythm of joint action: Synchrony promotes cooperative ability. *Journal of Experimental Social Psychology, 46*, 693-695.

Varela, F., Lachaux, J. P., Rodriguez, E., & Martinerie, J. (2001, Apr). The brainweb: phase synchronization and large-scale integration. *Nat Rev Neurosci, 2*(4), 229-239. https://doi.org/10.1038/35067550

Wass, S. V., Smith, C. G., Clackson, K., Gibb, C., Eitzenberger, J., Mirza, F. U. (2019). Parents mimic and influence their infant's autonomic state through dynamic affective state matching. *Current Biology, 29*, 2415-2422.

Waters, L., Loton, D. J., Grace, D., Jacques-Hamilton, R., & Zyphur, M. J. (2019). Observing Change Over Time in Strength-Based Parenting and Subjective Wellbeing for Pre-teens and Teens. *Front Psychol, 10*, 2273. https://doi.org/10.3389/fpsyg.2019.02273

Wengler, K., Goldberg, A. T., Chahine, G., & Horga, G. (2020, Oct 27). Distinct hierarchical alterations of intrinsic neural timescales account for different manifestations of psychosis. *Elife, 9*. https://doi.org/10.7554/eLife.56151

Wiltermuth, S. S., & Heath, C. (2009, Jan). Synchrony and cooperation. *Psychol Sci, 20*(1), 1-5. https://doi.org/10.1111/j.1467-9280.2008.02253.x

Winfree, A. T. (1967, Jul). Biological rhythms and the behavior of populations of coupled oscillators. *J Theor Biol, 16*(1), 15-42. https://doi.org/10.1016/0022-5193(67)90051-3

Winfree, A. T. (1980). *The Geometry of Biological Time*. Springer Berlin, Heidelberg. https://doi.org/https://doi.org/10.1007/978-3-662-22492-2

Winfree, A. T. (1987). The Timing of Biological Clocks. Scientific American Press.

Wittmann, M. (2015, Dec 15). Modulations of the experience of self and time. *Conscious Cogn, 38*, 172-181. https://doi.org/10.1016/j.concog.2015.06.008

Wolff, A., Berberian, N., Golesorkhi, M., Gomez-Pilar, J., Zilio, F., & Northoff, G. (2022, Feb). Intrinsic neural timescales: temporal integration and segregation. *Trends Cogn Sci, 26*(2), 159-173. https://doi.org/10.1016/j.tics.2021.11.007

Xu, L., Bolt, T., Nomi, J. S., Li, J., Zheng, X., Fu, M., Kendrick, K. M., Becker, B., & Uddin, L. Q. (2020, May 11). Inter-subject phase synchronization differentiates neural networks underlying physical pain empathy. *Soc Cogn Affect Neurosci, 15*(2), 225-233. https://doi.org/10.1093/scan/nsaa025

Xu, L., Bolt, T., Nomi, J. S., Li, J., Zheng, X., Fu, M., Kendrick, K. M., Becker, B., & Uddin, L. Q. (2020, 2020/5//). Inter-subject phase synchronization differentiates neural networks underlying physical pain empathy. *Social Cognitive and Affective Neuroscience, 15*(2), 225-233. https://doi.org/10.1093/scan/nsaa025

Chapter IV

INTRA-SPECIFIC AND INTER-SPECIFIC EMPATHIC-LIKE BEHAVIORS. A RODENT MODEL

1. Introduction

Thanks to advanced methodologies such as brain imaging techniques (Computed Tomography Scan (CT), Magnetic Resonance Imaging (MRI), Functional Magnetic Resonance Imaging (fMRI), Diffusion-Weighted MRI (DWI), Positron Emission Tomography Scan (PET), Diffusion Tensor Imaging (DTI)), brain recording techniques (Electroencephalography (EEG)), research has reached a major development in the investigation of the empathic phenomenon, as well as in other related phenomena, like consciousness and self. However, much more could be done by studying the biochemical and molecular mechanisms that underly these phenomena. Of course, we cannot follow this experimental path with humans. But we can do it with laboratory animals.

Although, a prerequisite for implementing this kind of analysis on animals, would be to understand whether or not animals themselves show empathic-like behaviors and which kinds. We know from literature that behaviors that are usually assimilated to the phenomenon of empathy, are shared by many social species, including rodents (Sivaselvachandran et al., 2018). Among these behaviors, we can observe *mimicry* and *imitation* (Horowitz, 2003; Mancini et al., 2013; Zentall, 2001), *emotional contagion* (Hernandez-Lallement et al., 2022; Nakahashi & Ohtsuki, 2018; Palagi et al., 2020; Perez-Manrique & Gomila, 2022) and also *prosocial behavior* (Ben-Ami Bartal et al., 2011).

The most common rats paradigm to study these behaviors are based on the study of emotional contagion and prosocial behavior (Meyza & Knapska, 2018). In the emotional contagion paradigms, a rat is exposed to a cage mate which has been repeatedly defeated. In these tests the observer rat shows an increased sensitivity to pain or altered cognitive functions, meaning that being in contact with a stressed cage mate has a high influence on the brain (Bruchey et al., 2010; Carnevali et al., 2017; Jeon & Shin, 2011; Knapska et al., 2006; Langford, 2006; Smith et al., 2021; Smith et al., 2016). In the prosocial behavior paradigms, a rat is enclosed into a restrain and a cage mate has the possibility to release it (Ben-Ami Bartal et al., 2011; Sato et al., 2015).

All these paradigms are based on an animal being exposed to a suffering or a restrained companion. This means that the animals has no choice but to deal with that negative state. In order to have a more active paradigm, in which a rat can choose whether to be exposed to a negative emotive state or not, we propose a behavioral rodent model that uses a three chamber apparatus, through which we can observe, measure and evaluate intra-specific and inter-specific behavioral responses to different emotional stimuli.

2. Materials and Methods

2.1. Animals

Male Wistar rats, bred at the animal facility of the University of Camerino, Italy. Rats were housed three per cage in a temperature (20–22 °C) and humidity (45–50%) controlled room with a reverse 12 h light/dark cycle (lights off at 8 AM). During the entire residence in the facility, animals were offered free access to tap water and food pellets (4RF18, Mucedola, Settimo Milanese, Italy). Before the tests, rats were handled 5 min daily for one week, by the same operators who performed the experiments. Experiments were conducted during the dark phase of the light/dark cycle. All the procedures were conducted in adherence with the European Community Council Directive for Care and Use of Laboratory Animals and the National Institutes of Health Guide for the Care and Use of Laboratory Animals. Italian Ministry of Health approval 1D580.24.

2.2. Apparatus

We built a three chambers apparatus (**Figure 1**), which is divided in two levels, separated by a grid. In the lower level there are three separate chambers. One of them is empty, in another one there is the Free rat, that can freely move in the chamber and that models a neutral emotional state and in the third chamber there is the rat that models an altered emotional state (**Figure 2**). On the upper level there is the Actor rat that freely moves along the grid, above the three chambers and that can hear, see and

smell the animals below without any chance to directly interact with them (**Figure 3**).

Figure 1. The three chambers apparatus that we built and covered in black tape. The three chambers in the lower level are separated to each other, while the upper level is a unique arena located above the chambers. The two levels are divided by a grid on which an Actor animal can freely move.

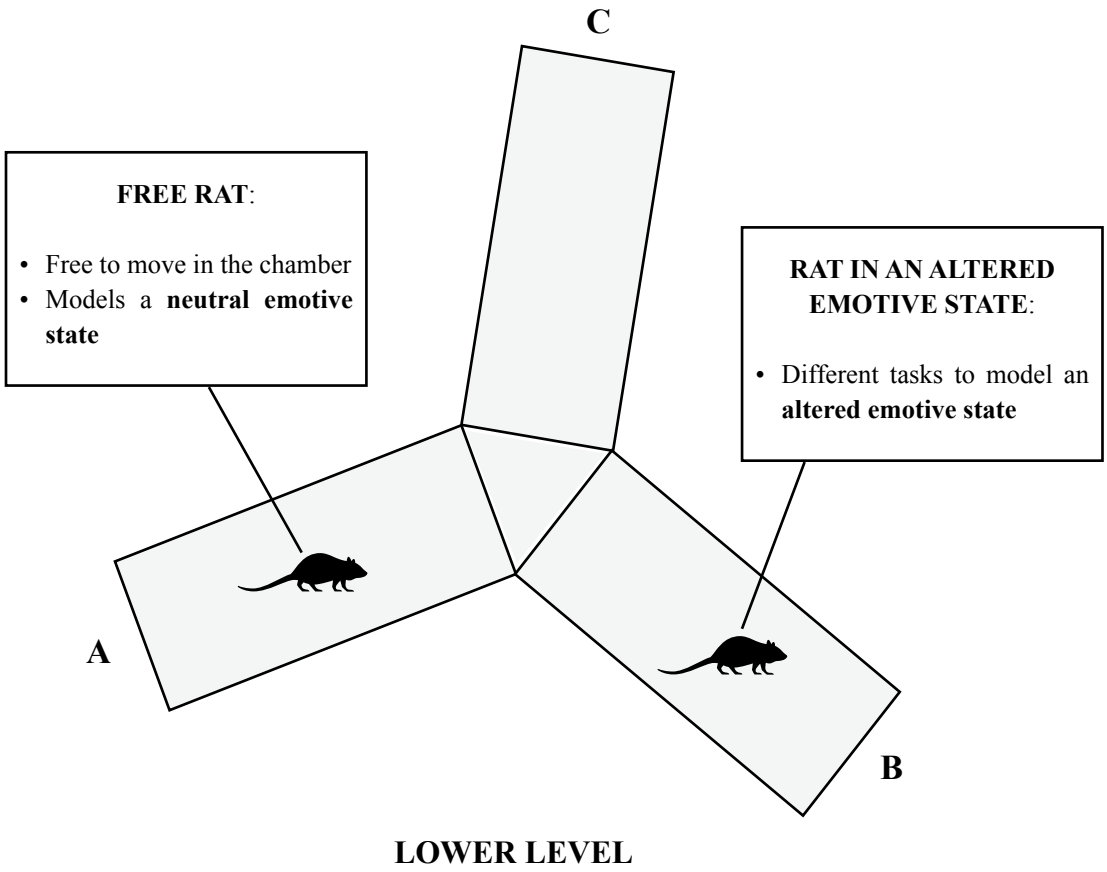


Figure 2. The lower level of the apparatus. In the Chamber A there is the Free rat; in the Chamber B there is the rat which models an altered emotive state (negatively or positively emotive state, depending on the task); Chamber C is empty.

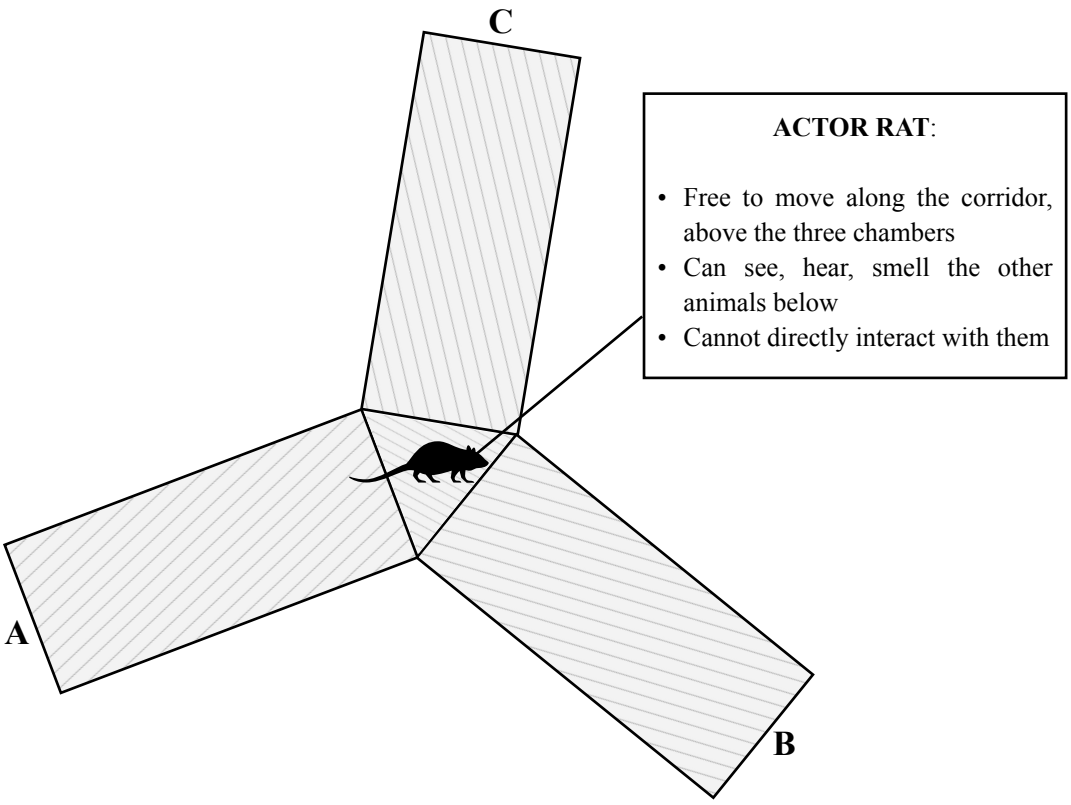


Figure 3. The upper level of the apparatus, where the Actor rat is free to move along the grid above the three Chambers below.

2.3. Test

Both Actor rats and Free rats were habituated for two days, 5 minutes each day, to the apparatus. On the third day, we performed the 6 minutes test, during which the Actor rat was free to explore the apparatus with the other two animals in the chambers below.

Experiment 1 (N=27; 9 Actor rats, 9 Shocked rats, 9 Free rat): each Actor rat was exposed to two cage-mates, one modeling a neutral emotive state (Free rat) and the other one modeling a negatively altered emotive state (Shocked rat). During the whole test, the Shocked rat was enclosed into a restraint and received three foot shocks (1 mA current, lasting 1 second), at T = 0 s; T = 2 min; T = 4 min.

Three other control experiments were carried out to validate our procedure.

Experiment 2 (N=30; 10 Actor rats, 10 Saccharin rats, 10 Free rats): each Actor rat was exposed to two cage-mates, one modeling a neutral emotive state (Free rat) and the other one modeling a positively altered emotive state (Saccharin rat). During the whole test, the Saccharin rat had free access to saccharin;

Experiment 3 (N=24; 8 Actor rats, 8 Shocked rats, 8 Free rats): each Actor rat was exposed to two non cage-mates unfamiliar rats, one modeling a neutral emotive state (Free rat) and the other one modeling a negatively altered emotive state (Shocked rat). During the whole test, the Shocked rat was enclosed into a restraint and received three foot shocks (1 mA current, lasting 1 second), at T = 0 s; T = 2 min; T = 4 min.

Experiment 4 (N=18; 6 Actor rats, 6 Shocked mice, 6 Free mice): each Actor rat was exposed to two mice, one modeling a neutral emotive state (Free mouse) and the other one modeling a negatively altered emotive state (Shocked mouse). During the whole test, the Shocked mouse was enclosed into a restraint and received three foot shocks (1 mA current, lasting 1 second), at T = 0 s; T = 2 min; T = 4 min.

In all the experiments, the Actor rats were naive to the shock experience, to the saccharin and to the mice.

2.4. Measures

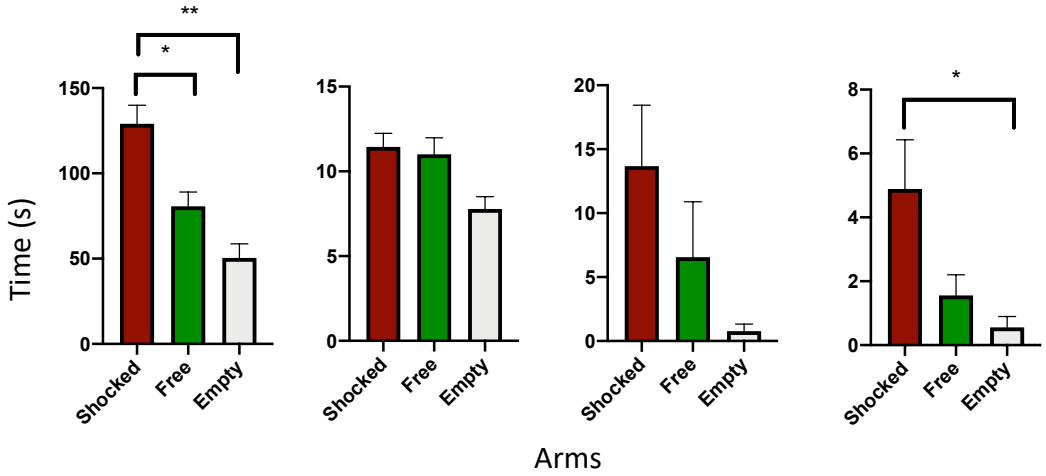
For all the four experiments, we evaluated the behavior of the Actor rat by measuring four parameters: 1) the time (in seconds) the Actor spent above each chamber; 2) the number of entries in each arm located above the three chambers; 3) the time spent digging above each chamber (a measure of tentative interaction with the what below); 4) the number of the diggings events in each chamber.

2.5. Statistical analysis

All behavioral experiments were analyzed by one-way analysis of variance (ANOVA) with arms (Shocked = arm above the Shocked rat, Free = arm above the Free rat, Empty = arm above the empty chamber) as between subjects factors. The analysis were followed by Bonferroni post-hoc test when appropriate, and statistical significance was conventionally set at $p < 0.05$.

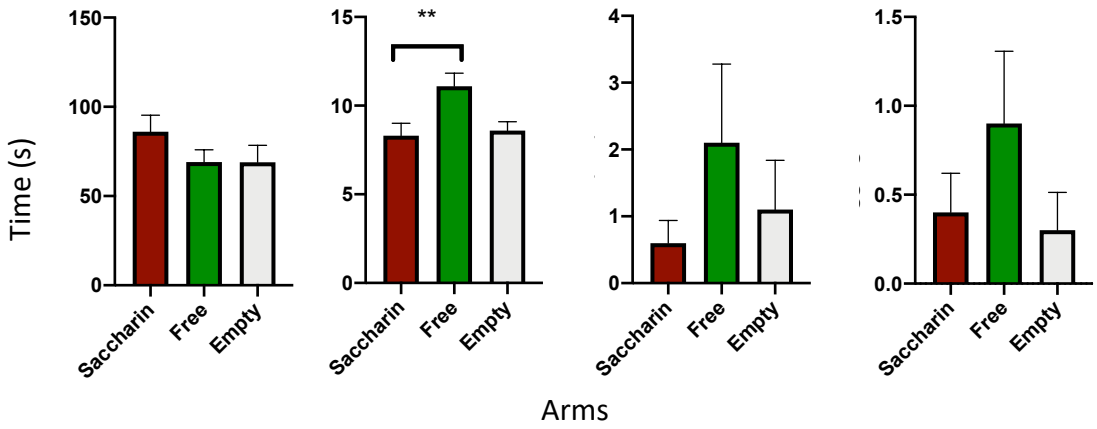
3. Results

Experiment 1: For the time spent by Actor rat above each chamber, the one-way ANOVA revealed a significant difference between the three arms (Shocked, Free and Empty) [F (1.557, 12.46) = 14.21, P=0.0010]. Subsequent post-hoc analysis showed that there is a difference between the Shocked arm and the Free arm (P=0.0440), as well as between the Shocked arm and the Empty arm (P=0.0063). For the number of entries, the one-way ANOVA revealed a significant difference between the three arms [F (1.280, 10.24) = 16.67, P=0.0014]. The post-hoc analysis confirmed differences between Shocked and Empty arms (P=0.0002). For the time the Actor spent digging above the cambers, the one-way ANOVA showed a significant difference between the arms [F (1.899, 15.19) = 4.418, P=0.0323], although the subsequent post-hoc analysis did not reveal any significant result. For the number of digging events, one-way ANOVA showed a significant difference between the arms [F (1.268, 10.14) = 8.896, P=0.0104]. The post-hoc test confirmed a significant difference between Shocked and Empty arms (P=0.0263).

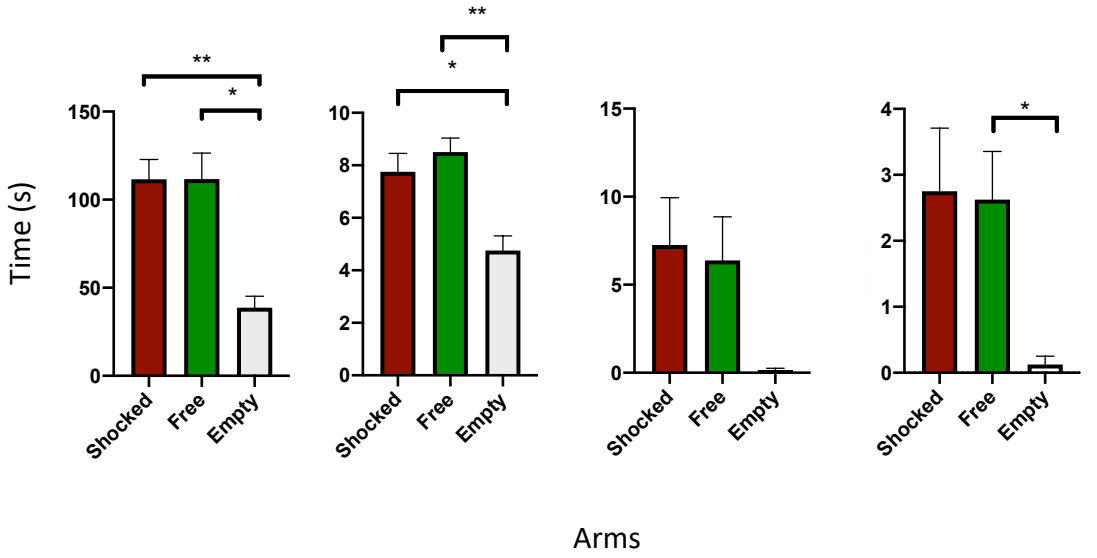


Experiment 2: For the time spent by the Actor rat above each chamber, the one-way ANOVA did not reveal any significant difference between the arms (Saccharin, Free, Empty). For the number of entries, ANOVA revealed a significant difference between

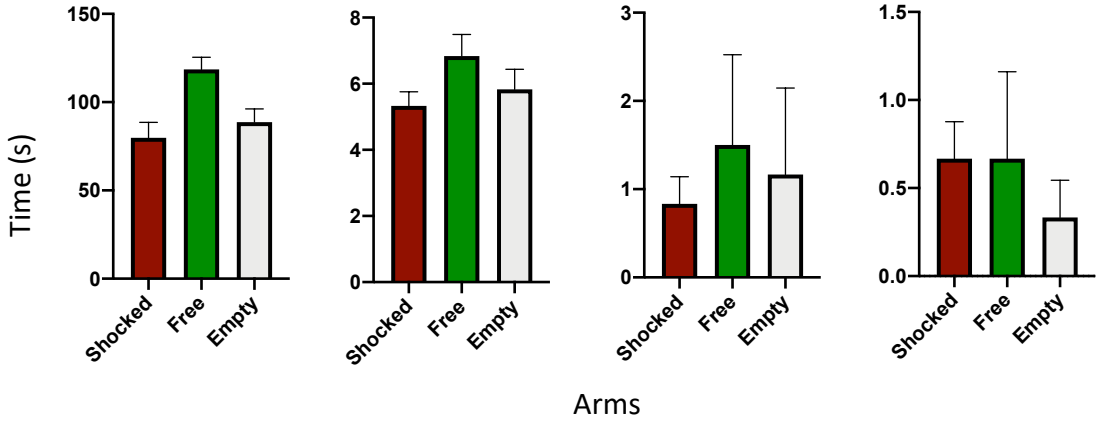
the three arms [F (1.755, 15.80) = 7.498, P=0.0064]. Post-hoc analysis confirmed a difference between Saccharin and Free arms (P=0.0048). For the time the Actor spent digging above the cambers and for the number of digging events, one-way ANOVA did not reveal any difference between arms.



Experiment 3: For the time spent by Actor rat above each chamber, one-way ANOVA revealed a significant difference between the three arms (Shocked, Free and Empty) [F (1.456, 10.19) = 11.09, P=0.0044]. Subsequent post-hoc analysis showed that there is a difference between Shocked and Empty arms (P=0.0011), as well as between the Free arm and the Empty arm (P=0.0212). For the number of entries, one-way ANOVA revealed a significant difference between the three arms [F (1.853, 12.97) = 17.18, P=0.0003]. Post-hoc analysis showed differences between Shocked arm Empty arms (P=0.0162), as well as between the Free and the Empty one (P=0.0026). For the time the Actor spent digging above the cambers, the one-way ANOVA did not reveal any difference. For the number of digging events, one-way ANOVA showed a significant difference between arms [F (1.594, 11.16) = 5.310, P=0.0293]. Post-hoc analysis, showed a significant difference between Free and Empty arms (P=0.0336).



Experiment 4: For the time spent by the Actor rat above each chamber, one-way ANOVA revealed a significant difference between the three arms [F (1.814, 9.070) = 4.802, P=0.0403], although the post-hoc analysis did not confirm the significant difference. For the number of entries, as well as for the time spent digging in each arm and for the number of digging events, ANOVA did not reveal any significant difference.



4. Discussion

Results show that Actor rats in Experiment 1 spent significantly more time in the arm above the Shocked mate than above the other two arms (i.e. the one with the Free mate and the Empty one). Also the time spent digging above the Shocked mate and

the number of digging events, although without a significant result, seem to show a trend to be higher in the first condition than in the others. We do not observe the same preference for the emotionally altered animal in the other three Experiments (i.e. the Saccharin drinking rat, the Shocked unfamiliar rat and the Shocked mouse). First of all, this reveals that for rats, a negative emotive state of a familiar animal is more relevant than a negative emotive state of an unfamiliar animal or of an animal of another species. This is in line with what literature shows about different social species (Ben-Ami Bartal et al., 2021; Decety & Svetlova, 2012; Jeon et al., 2010; Langford, 2006; Masserman et al., 1964; Preston & de Waal, 2002), including humans (Echols S, 2012; Lamm, 2010; Levine et al., 2005; Sturmer et al., 2006).

In addition, it also reveals that a positive emotive state is less relevant than a negative one. This is particularly interesting, since it could mean that from an evolutionary perspective, it is more important to be sensitive and responsive towards negative states with respect to positive ones. However, different researches focus on the role of "positive empathy" (Mobbs et al., 2009; Reis, 2010; Sylvia A. Morelli, 2015) and, for this reason, we think it could be promising to deepen this element through specific tasks.

Taken together, these results show that the preference for the suffering companion reflects an empathic-like concern and not any other element like, as noticed by some critical works, the desire for social contact (L.P. Schwartz, 2016; Silberberg et al., 2014). In fact, the Actor animal could freely chose to approach the chamber of the Free companion instead of the one of the Shocked animal, which is also restrained and thus way less active and prone to interact (although a full interaction is impossible, due to the grid between the two levels of the apparatus).

The fact that the rats had never first-personally experienced the shock before being exposed to the shocked animals is also very important, as it suggests that they are able to detect the suffering of a mate, even without any previous knowledge about that negative state. Since from literature we have evidence that previous experiences have influence on empathic-like behaviors (Atsak et al., 2011; Toyoshima et al.,

2021), it would be interesting to observe the behavior of Actor rats with previous shock experiences.

In conclusion, our results support the fact that rats' empathic-like behavior is mediated by familiarity and by the type of emotive state, that they are able to distinguish and detect. They also confirm that rats show particular kinds of empathic-like behaviors, such as emotional contagion and prosocial behaviors, as many studies demonstrated (Akyazi I, 2014; Atsak et al., 2011; Langford, 2006; Panksepp & Lahvis, 2011)(Ben-Ami Bartal et al., 2011).

We believe that the model presented here is very useful to study the empathic-like behavioral response of rats subjected to different emotional stimuli. The novel apparatus that we developed offers the possibility to build tasks in which the Actor rat can chose to approach another animal choosing between different conditions, without being influenced by the motivation for social interaction.

In future studies we plan to manipulate the Actor behavior to delineate at neurocircuitry and neurochemical levels the mechanisms controlling its emotional response.

References

Akyazi I, E. E. (2014). Transmission of stress between cagemates: a study in rats. *Physiology & Behavior, 123*, 114–118.

Atsak, P., Orre, M., Bakker, P., Cerliani, L., Roozendaal, B., Gazzola, V., Moita, M., & Keysers, C. (2011). Experience modulates vicarious freezing in rats: a model for empathy. *PLoS One, 6*(7), e21855. https://doi.org/10.1371/journal.pone.0021855

Ben-Ami Bartal, I., Breton, J. M., Sheng, H., Long, K. L., Chen, S., Halliday, A., Kenney, J. W., Wheeler, A. L., Frankland, P., Shilyansky, C., Deisseroth, K., Keltner, D., & Kaufer, D. (2021, Jul 13). Neural correlates of ingroup bias for prosociality in rats. *Elife, 10*. https://doi.org/10.7554/eLife.65582

Ben-Ami Bartal, I., Decety, J., & Mason, P. (2011, Dec 9). Empathy and pro-social behavior in rats. *Science, 334*(6061), 1427-1430. https://doi.org/10.1126/science.1210789

Bruchey, A. K., Jones, C. E., & Monfils, M. H. (2010, Dec 6). Fear conditioning by-proxy: social transmission of fear during memory retrieval. *Behav Brain Res, 214*(1), 80-84. https://doi.org/10.1016/j.bbr.2010.04.047

Carnevali, L., Montano, N., Statello, R., Coude, G., Vacondio, F., Rivara, S., Ferrari, P. F., & Sgoifo, A. (2017, Aug). Social stress contagion in rats: Behavioural, autonomic and neuroendocrine correlates. *Psychoneuroendocrinology, 82*, 155-163. https://doi.org/10.1016/j.psyneuen.2017.05.017

Decety, J., & Svetlova, M. (2012, Jan). Putting together phylogenetic and ontogenetic perspectives on empathy. *Dev Cogn Neurosci, 2*(1), 1-24. https://doi.org/10.1016/j.dcn.2011.05.003

Echols S, C. J. (2012). It's more than skin deep: empathy and helping behavior across social groups. In Decety J (Ed.), *Empathy: from bench to bedside*. MIT Press.

Hernandez-Lallement, J., Gomez-Sotres, P., & Carrillo, M. (2022, Jan). Towards a unified theory of emotional contagion in rodents-A meta-analysis. *Neurosci Biobehav Rev, 132*, 1229-1248. https://doi.org/10.1016/j.neubiorev.2020.09.010

Horowitz, A. C. (2003, Sep). Do humans ape? Or do apes human? Imitation and intention in humans (Homo sapiens) and other animals. *J Comp Psychol, 117*(3), 325-336. https://doi.org/10.1037/0735-7036.117.3.325

Jeon, D., Kim, S., Chetana, M., Jo, D., Ruley, H. E., Lin, S. Y., Rabah, D., Kinet, J. P., & Shin, H. S. (2010, Apr). Observational fear learning involves affective pain

system and Cav1.2 Ca2+ channels in ACC. *Nat Neurosci, 13*(4), 482-488. https://doi.org/10.1038/nn.2504

Jeon, D., & Shin, H. S. (2011, 2011/10//). A Mouse Model for Observational Fear Learning and the Empathetic Response. *Current Protocols in Neuroscience, 57*(1). https://doi.org/10.1002/0471142301.ns0827s57

Knapska, E., Nikolaev, E., Boguszewski, P., Walasek, G., Blaszczyk, J., Kaczmarek, L., & Werka, T. (2006, Mar 7). Between-subject transfer of emotional information evokes specific pattern of amygdala activation. *Proc Natl Acad Sci U S A, 103*(10), 3858-3862. https://doi.org/10.1073/pnas.0511302103

L.P. Schwartz, A. S., A.H. Casey, D.N. Kearns, B. Slotnick. (2016). Does a rat release a soaked conspecific due to empathy? *Anim Cogn, 1939*.

Lamm, C., Meltzoff, A. N., & Decety, J. (2010). How do we empathize with someone who is not like us? A functional magnetic resonance imaging study. *Journal of Cognitive Neuroscience, 22*, 362–376.

Langford, D. J., Crager, S. E., Shehzad, Z., Smith, S. B., Sotocinal, S. G., Levenstadt, J. S., Chanda, M. L., Levitin, D. J., & Mogil, J. S. (2006). Social modulation of pain as evidence for empathy in mice. *Science, 312*, 1967–1970.

Levine, M., Prosser, A., Evans, D., & Reicher, S. (2005, Apr). Identity and emergency intervention: how social group membership and inclusiveness of group boundaries shape helping behavior. *Pers Soc Psychol Bull, 31*(4), 443-453. https://doi.org/10.1177/0146167204271651

Mancini, G., Ferrari, P. F., & Palagi, E. (2013). Rapid facial mimicry in geladas. *Sci Rep, 3*, 1527. https://doi.org/10.1038/srep01527

Masserman, J. H., Wechkin, S., & Terris, W. (1964, Dec). "Altruistic" Behavior in Rhesus Monkeys. *Am J Psychiatry, 121*, 584-585. https://doi.org/10.1176/ajp.121.6.584

Meyza, K., & Knapska, E. (2018, 2018/12//). What can rodents teach us about empathy? *Current Opinion in Psychology, 24*, 15-20. https://doi.org/10.1016/j.copsyc.2018.03.002

Mobbs, D., Yu, R., Meyer, M., Passamonti, L., Seymour, B., Calder, A. J., Schweizer, S., Frith, C. D., & Dalgleish, T. (2009, May 15). A key role for similarity in vicarious reward. *Science, 324*(5929), 900. https://doi.org/10.1126/science.1170539

Nakahashi, W., & Ohtsuki, H. (2018, Mar 7). Evolution of emotional contagion in group-living animals. *J Theor Biol, 440*, 12-20. https://doi.org/10.1016/j.jtbi.2017.12.015

Palagi, E., Celeghin, A., Tamietto, M., Winkielman, P., & Norscia, I. (2020, Apr). The neuroethology of spontaneous mimicry and emotional contagion in human and non-human animals. *Neurosci Biobehav Rev, 111*, 149-165. https://doi.org/10.1016/j.neubiorev.2020.01.020

Panksepp, J. B., & Lahvis, G. P. (2011, 2011/10//). Rodent empathy and affective neuroscience. *Neuroscience & Biobehavioral Reviews, 35*(9), 1864-1875. https://doi.org/10.1016/j.neubiorev.2011.05.013

Perez-Manrique, A., & Gomila, A. (2022, Jan). Emotional contagion in nonhuman animals: A review. *Wiley Interdiscip Rev Cogn Sci, 13*(1), e1560. https://doi.org/10.1002/wcs.1560

Preston, S. D., & de Waal, F. B. (2002, Feb). Empathy: Its ultimate and proximate bases. *Behav Brain Sci, 25*(1), 1-20; discussion 20-71. https://doi.org/10.1017/s0140525x02000018

Reis, H. T., Smith, S. M., Carmichael, C. L., Caprariello, P. A., Tsai, F.-F., Rodrigues, A., & Maniaci, M. R. (2010). Are you happy for me? How sharing positive events with others provides personal and interpersonal benefits. *journal of Personality and Social Psychology, 99*, 311–329.

Sato, N., Tan, L., Tate, K., & Okada, M. (2015, Sep). Rats demonstrate helping behavior toward a soaked conspecific. *Anim Cogn, 18*(5), 1039-1047. https://doi.org/10.1007/s10071-015-0872-2

Silberberg, A., Allouch, C., Sandfort, S., Kearns, D., Karpel, H., & Slotnick, B. (2014, May). Desire for social contact, not empathy, may explain "rescue" behavior in rats. *Anim Cogn, 17*(3), 609-618. https://doi.org/10.1007/s10071-013-0692-1

Sivaselvachandran, S., Acland, E. L., Abdallah, S., & Martin, L. J. (2018, 2018/8//). Behavioral and mechanistic insight into rodent empathy. *Neuroscience & Biobehavioral Reviews, 91*, 130-137. https://doi.org/10.1016/j.neubiorev.2016.06.007

Smith, M. L., Asada, N., & Malenka, R. C. (2021, 2021/1//). Anterior cingulate inputs to nucleus accumbens control the social transfer of pain and analgesia. *Science, 371*(6525), 153-159. https://doi.org/10.1126/science.abe3040

Smith, M. L., Hostetler, C. M., Heinricher, M. M., & Ryabinin, A. E. (2016, Oct). Social transfer of pain in mice. *Sci Adv, 2*(10), e1600855. https://doi.org/10.1126/sciadv.1600855

Sturmer, S., Snyder, M., Kropp, A., & Siem, B. (2006, Jul). Empathy-motivated helping: the moderating role of group membership. *Pers Soc Psychol Bull, 32*(7), 943-956. https://doi.org/10.1177/0146167206287363

Sylvia A. Morelli, M. D. L. a. J. Z. (2015). The Emerging Study of Positive Empathy. *Social and Personality Psychology Compass, 9*, 57–68.

Toyoshima, M., Mitsui, K., & Yamada, K. (2021, Nov 20). Prior stress experience modulates social preference for stressed conspecifics in male rats. *Neurosci Lett, 765*, 136253. https://doi.org/10.1016/j.neulet.2021.136253

Zentall, T. R. (2001). Imitation in animals: evidence, function, and mechanisms. *Cybernetics & Systems*.

Chapter V

THE ROLE OF EMPATHY IN PUBLIC PERCEPTION: THE CASE OF LABORATORY ANIMAL TESTING

1. Introduction

As we noticed in the second Chapter of this work, the empathic understanding we can have of another individual presents a gradient of "accuracy", that depends upon the fact the it results both from a *perception* (which we described as an *introjection* mechanism) and from an *apperception* (which we described as a *projection* mechanism). This means that there are cases in which our empathizing with individuals that belong to other species can be influenced by predictions that derive from already and fixed introjected patterns, meaning from personal experience and sensitivity. This can result in some distorted representations of the other individual's emotive state that could not correspond to how that emotive state actually is. So some empathic and compassionate acts are usually guided by a preference based on a similarity between the empathizer and the empathized (Miralles et al., 2019)[44]. Some empathic distortions can be produced also by other factors, such as the perception of vulnerability and fragility in a particular individual with respect to others. This can lead sometimes to experience more empathy towards, for example, a beaten animal than towards a beaten human being (Levin, 2017). In addition, an empathic preference could also be linked to the fact of relying more on emotional information than on cognitive ones, so that, as Paul Bloom notices (Bloom, 2016), people could be more prone to save one child's life instead of many children's life, because they have listened that child's story.

All these biases that affect and modulates the empathic capability are common and derive from the fact that, as we saw also through our animal model, empathic behaviors themselves depend upon many factors. Among these factors, both the context and the personal experience have a particular influence on how we empathize with others. To be aware of such a bias-dependent nature of empathy can prevent from negative consequences of some actions, such as, for example, transmitting delicate information that could cause an exaggerated empathic reaction. An emblematic case is the laboratory animal testing. Being often victim of prejudices

[44] This is in line with Stein's hypothesize of empathizing more with an individual that belongs to the same type or to a similar one as the empathizer (Stein, 1989).

and biases connected to the limitations of the empathic capability, animal experimentation is usually associated to a “cruel” practice. In this Chapter, we will outline historical, ethical, and philosophical aspects that stem from the recognition that animal testing is essential to advance biomedical research and that it is required for the development of drugs and vaccines that meet both human and veterinary needs.

2. Public perception on laboratory animal testing

In recent years, the use of laboratory animals in biomedical research has been a matter of intense public debate. The most recent statistics suggest that about half of the Western population, who generally are sensitive to this discussion, are in favor of animal testing, but the other half oppose it. Over the years, the European Union (EU), Canada, the United States, and several other countries have introduced laws to regulate the use of laboratory animal testing. These laws are generally well balanced and have been promulgated after consulting the main stakeholders (i.e., researchers, patient associations, associations for the protection of animals, and so forth) who are sensitive to this matter.

Unfortunately, despite these efforts, the public debate has often suffered from misleading information that is disseminated by individuals or groups who oppose animal testing. Researchers have neglected to respond to such aggressive media campaigns with adequately effective communication. A prototypical example is the widespread use of the term “vivisection” that is used in an effort to stigmatize laboratory animal testing, notwithstanding the fact that science abhors vivisection, which is an illegal behavior that was banned by law and abandoned decades ago. Something similar is also happening in the case of vaccination, against which false information campaigns have been launched by groups of people who are generically identified as “Anti-Vaxers”. These groups deny the success of vaccination strategies to eradicate several serious infectious diseases, such as smallpox and poliomyelitis, although such opposition to vaccination carries an incalculable risk of severe public health damage.

The recent SARS-CoV2 pandemic and its social and political impact and dramatic consequences on public health systems are bringing new attention to the value of biomedical research. This situation provides an opportunity to replace disinformation with a constructive debate on the importance of animal testing and vaccination. In recent decades, much has been done to protect the rights of laboratory animals, but it is also clear that, based on present knowledge and available technologies, in specific research fields it is not possible to completely abandon in vivo animal testing by replacing it with alternative methods.

3. Animals and humans: an historical view

From an evolutionary perspective, we as *Homo sapiens* started our journey through time much later than several other species. Since the moment we developed our fine-tuned biological structures and uniquely complex central nervous system, we became "transcendent" beings (**Table 1**). We started to *symbolize* (**Table 1**), develop complex abstract thinking, and act accordingly. This high cognitive abilities are unlikely so well developed in other animal species, and this is what makes us different from them.

Term	Description
Transcendence	Human capability of "going beyond" what is material and concrete. For example, we can say that we "transcend" a perceptive stimulus, such as physical pain, when we elaborate it at a secondary level by analyzing it in terms of abstract concepts (e.g., "pity," "cruelty," or "injustice"). We are "transcendent" beings because we can think and act according to abstract concepts.
Symbolization	From the capability of transcendence comes the concept of symbolization, by which we assign an evocative value to what we find in our perceptive experience, both at a linguistic level (by nominating things or by speaking about what is absent) and at psychological, moral, philosophical, social levels (by explaining phenomena through some conceptual senses; e.g., the concept of God).

Term	Description
Utilitarism	An ethical theory founded by the philosophers Jeremy Bentham and John Stewart Mill between the 18th and the 19th centuries. According to utilitarianism, a right action is the one that promotes happiness or prevent pain for every affected subject.
Speciesism	The practice of considering and treating members of a species as morally superior to members of the other species.
Deontology	An ethical theory according to which the morality of an action should be evaluated on the basis of its intrinsic rightfulness or wrongfulness and not on the basis of its consequences.
Moral status	A subject has his own moral status if he is considered, under certain general rules, worthy of having rights and a moral consideration among other moral subjects.
Moral agents or active moral subjects	Differently from “moral patient” or “passive moral subject,” a moral agent is a subject that has the capability of acting accordingly to his awareness and of recognizing that every action could have consequences on other subjects. A moral patient, instead, is a subject who has to be respected, on the basis of his rights or of another subject's duties, but without having his own duties.
Awareness	The capability of being conscious of what is perceived, sensed, felt, thought and so forth.
Responsibility	The capability of foreseeing the consequences of one's behavior and of changing it according to them.

We can use memories to attribute meanings, interpret the present, and think in perspective to anticipate the future. Through evolution, we also progressively acquired high cognitive faculties that are utilized to explore ways to improve our living conditions. We learned to use objects as tools and employ other animals to reach our aims, which is oftentimes linked to survival instincts but in some other cases independent from them, such as in the case of arts or companionship.

Animal domestication and breeding have been fundamental to the development of cultural and social human structures. Through domestication and breeding, humans

could become sedentary because it was possible to have food and help without the need to hunt or be nomadic. The first animal that was domesticated was the dog, which was

> the culmination of a process that initiated with European hunter-gatherers and the canids with whom they interacted (Thalmann et al., 2013).

After the dog, other animals were also domesticated, such cows, pigs, and sheep, which were bred for food, clothes, or help with strenuous work, mostly in agriculture. Later, horses and several other animals became important to guarantee the functioning of increasingly complex societies.

In parallel, humans have learned to use animals for less immediate and urgent purposes. Domestication has become a way to select some completely captive species to be used for other purposes, such as companionship, entertainment, and scientific research. To develop new knowledge and improve peoples' lives, particularly relevant has become the use of animals in the fields of medicine, pharmacology, biology, physiology, and cognitive psychology, among others.

In the age of Hippocrates (Hippocrates, IV B.C.) the dissection of human corpses was prohibited, and animals were used to study human anatomy by analogy.

> The parallels between human and animal physiology and pathology were noted long ago, and the practice that we today call 'animal research' is rooted back to the period of the ancient Egypt and Greece (National Research Council (US) Committee to Update Science, 2004).

During the 17th century, modern science, still in its infancy, was influenced by ideas of one of the most prominent philosophers of the time, Renée Descartes. According to his thinking, animals resemble material machines that lack intellect or spiritual elements, which are possessed by humans only. As a consequence of this vision, beginning in the 17th century, the use of animals in science steadily increased. In the 19th century, Charles Darwin published his most fundamental work, *On the Origin of*

Species by Means of Natural Selection, or the Preservation of Favoured Races in the Struggle for Life (Darwin, 1859), in which he showed profound similarities between human and nonhuman animals. In the 20th century, thanks to the irreplaceable contribution of laboratory animal experiments, new branches of science, such as pharmacology and immunology, were developed.

At the time of Hippocrates, Aristotle, and Galen and generally until the 18th century, animals were used for experiments without moral or legal restrictions because it was considered the only possible and legitimate way to avoid using humans. In the later 17th and 18th centuries, a moral debate began. Darwin himself was immersed in the public controversy about the use of live animals for scientific purposes. Opinions ranging from not allowing experimentation on animals to testing them if no pain was inflicted and finally to let the animal feel pain. Darwin, being an animal lover, although conflicted, found vivisection justifiable only for true physiological investigations but not simply for "mere damnable and detestable curiosity". In 1875, Darwin was one of 53 witnesses called by the Royal commission to testify on the practice of using live animal testing. In his statement, he emphasized that progress in physiology was possible only with the aid of experiments on living animals, but that the animals must be rendered insensible to pain.

Public awareness of the need to control the use of experimental animals progressively increased, leading to the promotion of specific legislation, such as "An Act Against Plowing by the Tayle, and Pulling the Wool Off Living Sheep", which was passed by the Parliament of Ireland in 1635 and was one of the first known laws on animal protection. In the 20th century, because of the explosion of biomedical sciences, the use of animals for laboratory testing increased enormously, creating conditions for the establishment of a new area of research, laboratory animal science.

> This is a multidisciplinary branch of science aimed at contributing to the quality of experiments in which animals are used and at improving their welfare. It encompasses the biology of laboratory animals, their environmental requirements, genetic and microbiological standardization, prevention and

treatment of disease, experimental techniques, anesthesia, analgesia and euthanasia, alternatives to their use, and ethics (Baumans, 2005).

4. The use of laboratory animals today

Experiments on laboratory animals today are conducted at the global level for different scopes and in different fields of study. Laboratory animals are employed to model humans' and other animals' pathologies, develop new pharmaceutical products, produce vaccines, and perform toxicological studies. A recent report indicated that in 2015, 37 countries, for which statistics are available, reported the use of 41.8 million experimental procedures (defined according to the European Union Directive 2010/63/EU; article 3,1) performed on laboratory animals worldwide (Taylor & Alvarez, 2019). The most widespread use of experimental animals occurs in China, with an estimated number of 20,496,670 procedures, followed by Japan and the United States with an adjusted number of approximately 15,000,000 procedures each. By far, the most commonly used animals are mice and rats, followed by birds, fish, reptiles, amphibians, and cephalopods. Significantly fewer dogs and monkeys are used, mostly in China and the United States. In total, the number of dogs and monkeys used in the 36 countries that communicated the data was 112,265 and 92,431, respectively (Taylor & Alvarez, 2019). Another statistical report indicated that, between 2014 and 2016 in Europe, the total number of procedures conducted on laboratory animals has been rather stable ranging from 10,356,578 to 10,853,401 (Taylor & Rego Alvarez, 2019).

In all countries, animal experimentation is strictly controlled by specific laws and can only be conducted in compliance with them. A general principle that underlies these laws and that is also valorized by the internationally recognized and accepted guidelines of the *Guide for the Care and Use of Laboratory Animals* (Council, 2010) is the "Replace, Reduce, Refine" (3R) principle (Hendriksen, 2009; Rusche, 2003), which was first suggested by the English researchers William Russell and Rex Burch in 1959 (Russell, 1959). According to the 3Rs, experimental procedures must always respect the following three basic principles.

- According to “replace”, any time possible, the use of animals should be replaced with in vitro or in silico tests (Balls, 2002; Doke & Dhawale, 2015) or with invertebrates (Giacomotto & Segalat, 2010; Wolf & Rockman, 2008).
- According to “reduce”, the number of animals used should always be kept to the absolute minimum that is needed for a specific experiment. The information that is gathered per animal should always be maximized to reduce the number of animals used as much as possible.
- According to “refine”, researchers must study and adopt a series of methods to improve laboratory animals' welfare, such as caring about their housing conditions and minimizing pain, suffering, and distress.

The 3R principles are currently considered the most efficient and morally acceptable way to guarantee animals’ rights on the one hand and advance scientific progress on the other.

In the United States, animal testing procedures were for the first time regulated by the Animal Welfare Act (AWA) of 1966, which has been amended four times (1970, 1976, 1985, and 1991). The AWA is integrated in the Public Health Service (PHS) Policy on the Humane Care and Use of Laboratory Animals that was published in 1985 and is periodically updated. The PHS policy requires research institutions to establish and maintain appropriate measures to ensure the adequate care and use of animals that are involved in animal testing and research.

In Europe, the use of laboratory animals for research was first regulated by EU Directive 86/609EEC and more recently by Directive 2010/63/EU ("Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the Protection of Animals Used for Scientific Purposes," 2010) that applies to all live nonhuman vertebrate animals, including independently feeding larval forms, fetal forms of mammals from the last third of gestation during normal development, and live cephalopods (Art. 1 [3]). The 3R principles are one of the main inspirational elements of 2010/63/EU. After the EU Directive was promoted, EU member states had to comply with it by establishing their own national laws to regulate the care and use of laboratory animals, authorize research protocols for animal experimentation,

and supervise proper application of the norms. Proposed research projects, in addition to guaranteeing animal welfare, must use the lowest neurologically evolved species within the constraints of the experiment and the lowest number of subjects possible. 2010/63/EU is a well-balanced directive that was passed after years of discussion between various stakeholders, including researchers, patient associations, and animal protection associations.

Unfortunately, the translation of this EU Directive into national laws has generated some differences between EU member states. Italy, for example, introduced its "D.Lgs.vo 26/14" in 2014, which consists of an unprecedented restrictive interpretation of 2010/63/EU. Additionally, contrary to EU legislation, the use of laboratory animals for xenotransplantation experiments or studying substances of abuse is prohibited, thus creating a significant negative bias in the biomedical research potential of Italy compared with other EU member states. It is worth mentioning also the example of Germany that, in addition to translating the EU Directive into a national law, similarly to Switzerland has implemented the principle of animal protection in its constitution.

5. Animal right activism

Undoubtedly, animal right movements have contributed to important progresses towards the establishment of a balanced relationship between humans and other animal species. For example, they have contributed to enhance the awareness of the scientific community to the use of laboratory animals in biomedical research. They provided a significant contribution to the promulgation of laws that balancing between the different views allow an adequate protection of laboratory animals without hampering biomedical research. Moreover, they have had a critical role in promoting the recognition of equality between humans and other animal species, so that in some cases, the principle of protection of animal rights has been introduced in national constitutional laws.

On the other hand, it should be condemned when animal right activism leads to inappropriate initiatives, often by single or small groups of individuals, that acting

against the law strikes research centers and hospitals or attempt to discredit science. There are examples of scientists that due to alleged accuses by animal right activists have been illegally hindered in their research or have been removed from some of their responsibilities and then found innocent by the court. Occasionally, assaults on research centers, universities, and hospitals have been organized to free the laboratory animals. These actions have detrimental consequences not only for the institutions but also for the animals that bred in captivity and are not able to survive in natural environments.

Beyond these considerations, it is clear that the use of laboratory animals in science is a matter of intense public debate that is based on legal, moral, and ethical evaluations. To adequately address this issue, it is important to structure the discussion within a well-defined theoretical framework.

6. Theoretical views

It is not easy to find concordance between opinions in ethical debates. General scientific data that unquestionably support any one of the different positions may not be sufficient. Consequently, a particular empathy-based position is perceived as a universally valid philosophical position. As Immanuel Kant pointed out, however, the only universally relevant moral statement is one that, under the same conditions, can be recognized as valid by anyone who is endowed with reason (Kant, 2017).

The ethical debate about animal rights is one example in which a universally valid moral statement is difficult to imagine—multiple diverse positions are worthy of consideration (DeGrazia, 1999). For example, such authors as Peter Singer and Tom Regan, although starting from different points of view, have provided arguments that support the thesis that it is wrong to use animals. Other authors, such as the utilitarian Raymond G. Frey and Peter Carruthers, embrace contractualism and stand for the practice of laboratory animal testing.

In *Animal Liberation* (Singer, 1975), Singer applies the "Principle of Equal Consideration of Interests." According to this principle, humans and other animal species must have the same interests and rights. Singer criticizes what he calls

"speciesism" (**Table 1**), a morally wrong practice of treating one animal species as morally more important than others. Singer anchors this equality principle between members of different species to the experience of suffering, which is common to people and animals. According to this utilitarian perspective (**Table 1**), everyone who feels pain and suffering naturally wants to avoid them; consequently, provoking pain is cruel and disrespectful of others' rights.

Regan instead bases his defense of animal rights on a deontological argument (**Table 1**), according to which the concept of the "intrinsic value" of a subject-of-a-life, a definition that cannot only be applied to humans but also to animals. In fact, animals are living beings, and this is sufficient to assert that, like humans, animals should never be considered objects. These two different but convergent theoretical approaches support a common position according to which the use of animals for food or testing has to be avoided as a morally unacceptable practice.

Like Singers, Frey (Frey, 1980, 1988) supports the principle of utilitarianism, but he comes to an opposite conclusion. According to him, animals, in contrast to humans, are not aware of "interests," beliefs, or desires; therefore, it is wrong to attribute the same value to humans and other living species.

Another opponent of the equalitarian vision is Carruthers (Carruthers, 1992), who justifies the use of animals based on the fact that they do not have the same mental capacity as humans. According to Carruthers, animals can have beliefs and desires and engage in practical reasoning in response to them. Animals can feel pain and fear and can suffer, but they are not "rational agents" because they are not able to govern their behavior in accordance with universal moral rules that are obeyed by most members of a community. Hence, no animal has the "moral standing" that only humans have. According to Carruthers' conclusion, because animals do not have the same moral status (**Table 1**) as humans, they cannot have the same rights. In other words, he states that moral agents (**Table 1**) like humans (i.e., subjects who have moral responsibilities) must postpone responsibilities toward animals to promote their interests. Carruthers further pushes his position to the extreme by asserting that

> a duty not to slaughter your neighbor's dog might be an instance of a duty not to damage others' property (DeGrazia, 1999).

As can be seen, general discussions about whether it is right or wrong to use animals in scientific research can lead to many disagreements and unsatisfactory conclusions for anyone. The fundamental question is why we should care about human rights more than animal rights. There is likely no unique or universal answer to this question, and there are equally sustainable and even opposing ethical positions on this matter. When engaging in this debate, it would be useful to concentrate as much as possible on a few elements.

7. Active and passive moral subject and responsibility

By virtue of their complex and multi-layered psycho-physiological structure we described in the previous Chapters, humans are able to base their intersubjective life in what we can call "moral sense" (Hume, 1739-40; Smith, 1759). Through this faculty, we inhabit the world by thinking at ourselves as "active moral subjects", endowed with the capability of making choices whose consequences can affect also other subjects. Conversely, the behavior of nonhuman animals is to a large extent instinctual. They do not recognize their own moral status and their own rights. In fact, they do not need to rely on a moral sense. They simply live the world. Hence, animals should be viewed as "passive moral subjects", whose rights arise from other beings' capability to recognize them.

The moral sense makes humans sensitive to a sort of "response" towards others subjects existence. From this urge to "respond" to others by also taking care of them, it emerges the uniquely human experience that Hans Jonas calls "responsibility" (Jonas, 1984) (**Table 1**). On the basis of this principle, to take care of animals is more a matter of human "duty", than of actual animals' rights, since animals do not recognize, need, express and stand for their own rights. So, as responsible "active moral subjects", humans must respect animals, but without neglecting themselves and their own species. Indeed, human adaptation among other

species has to deal with two different capabilities that sometimes risk to be in contrast between each other: on one hand, the capability to make progress and research requires the use of other species as instruments; on the other hand, the capability to recognize others individuals and thus their rights, requires actions of care and protection towards them.

At the threshold between this two banks, the responsibility plays a fundamental role: it links the two capabilities together, creating that liminal space we call ethics, where every action should be pondered, in order not to fall completely into one of the two sides.

8. Animal testing is not cruelty

Another element to consider is the concept of cruelty because, in most cases, animal experimentation is perceived as a cruel practice by the general public. Of course, for humans, it is a moral imperative to abhor cruelty. We should not harm animals by using them for experimentation if this means to be cruel. However, is the use of laboratory animals cruel when they are used for the "right purpose"? Are we performing acts of cruelty, or are we fulfilling a necessity? Cruelty must be condemned as a wrong behavior; to do so, however, we must first clearly define it.

We think that the first element that makes an act cruel is awareness (**Table 1**). To be considered cruel, a person must be aware of the fact that he is harming someone or something else by provoking unnecessary pain or suffering. Without awareness, there is no cruelty. So, for example, a person who does not have the mental faculties to recognize others' suffering should not be judged as cruel. The second element that we consider important is the ability to "symbolize" the act, which we already described as the capacity to attribute to it a specific meaning and value.

The third condition for an act to be considered cruel is that it must be done *freely*, without a reason, scope, or need, and only with an inner intention of satisfying some personal pleasure, such as the pleasure of inflicting harm only for the sake of it. The difference between a non-cruel act and a cruel act resides in the intention behind it. If the intention is informed by a very strong *need* that requires that act and that act only,

with no other possible alternatives, then the act could be considered non-cruel even if it is harmful to others. Instead, if the intention that motivates an act that causes harm to another individual is based on a personal interest or satisfying unnecessary pleasure, then the act can be judged as cruel. One of the arguments against animal research is that it is freely enacted cruel behavior. Based on the elements delineated above, animal testing can be considered cruel only if a scientist acts in the absence of a necessity and if he uses an animal to satisfy a personal desire to harm or experience pleasure from harming. On the contrary, it cannot be considered cruel if the work of a scientist reflects the necessity of improving humans' and other species' lives.

9. Animal experimentation is a necessity and a "good cause"

Of course, we must also reflect on the concept of "necessity", which directly derives from the concept of "need". A need is opposite to the desire for an unnecessary pleasure. Ethical and bioethical norms recommend the avoidance of unnecessary pleasure if it harms others' rights, but they cannot suppress a natural need. If animal testing is the only way (or the most appropriate way) to improve the condition of people and their pets who suffer or save their lives, then this can be viewed as a legitimate need.

Another element to consider is the principle of "good cause". As animal rights' supporters contend, a cause that is good for humans may not be good for other animal species that are employed for that purpose. Conversely, what is not a good cause is not necessarily a bad cause either. Under ethically controlled circumstances, even if the cause could not be good for the animals that are used because, for example, they do not themselves benefit from being used, it is not necessarily bad in absolute terms. Testing drugs on laboratory animals is also useful for developing medications to ameliorate or save the lives of our pets and other nonhuman animals in general.

This argument should be carefully considered by those who believe that ethics cannot be speciesist, and it cannot consider only what is best for humans because, as

explained above, laboratory animals are also used to protect and improve the lives of other animal species.

10. Can biomedical research avoid using laboratory animals?

In addition to the ethical and theoretical perspectives that are discussed above, in which we sought to clarify that experimental research is a necessity and not cruel, we should also consider the practical reasons why biomedical research cannot avoid the use of animal testing.

As mentioned previously, the use of laboratory animals adheres to the principle of "good cause", and it is conducted in compliance with laws that are promoted to guarantee animals' rights. The 3R principles are the basic principles that have inspired current laws that regulate the use of laboratory animals. Consistent with the 3Rs is a commitment to engage in animal testing only when valid alternatives are unavailable. The main possible alternatives to in vivo tests are in vitro cell and tissue cultures or in silico computer-assisted experiments (Ranganatha & Kuppast, 2012). These alternative methods are indeed largely practiced in biomedical research, and their use has greatly contributed to the *reduction* of laboratory animals. Nonetheless, the complexity of various organs (e.g., the brain) and difficulty mimicking the function of a human organism in vitro or in silico make it impossible to fully replace in vivo laboratory animal testing. In fact, in most cases, the only way to study pathologies that afflict both humans and other species is by replicating them in animal models. The efficacy and toxicity of new drugs and vaccines, at some point in their development, can only be studied in living animals (Lipinski & Hopkins, 2004). Testing a drug on a single cell or using an in silico approach (or both) would certainly help identify important characteristics of molecules that make them viable or not for further development. However, verification of their efficacy and safety profile is possible only if animal testing is performed. The alternative to this is an unsustainable risk (and thus unethical) to develop treatments without proven safety and efficacy. To prevent these risks, drug regulatory agencies stipulate that any new

medication, vaccine, or cure in general must be tested in laboratory animals prior to entering the clinical stage.

The history of thalidomide offers the most famous example of what can happen if drugs are developed in the absence of adequate preclinical testing. In 1957, this drug was commercialized to treat insomnia, headaches, and nausea after having been tested only in rodents, but never during pregnancy. Unfortunately, it was extensively used by women to treat nausea and vomiting during pregnancy (Vargesson, 2015). During that period, an unprecedented number of cases of phocomelia and other birth defects occurred in all 46 countries where the drug was marketed. Years later, thalidomide was identified as the cause of this disaster and subsequently withdrawn from the market. This led to some controversies about the predictive ability of animal experimentation (Shanks et al., 2009).

The dramatic experience with thalidomide is often recalled to support positions against the use of laboratory animals in biomedical research. However, two facts need to be considered. The first is the logical fallacy and hasty generalization of the assertion that animal testing on thalidomide was not predictive and therefore any animal testing is not predictive. In fact, there are several other cases in which the use of laboratory animals has been very important for the early detection of drug toxicity. The second and most important fact, when the story of thalidomide is viewed from a different perspective, demonstrates the importance of using laboratory animals in preclinical research. The problem with this drug arose from the insufficient evaluation of its toxicity in laboratory animals, from the fact that all of the experiments were conducted in rodents (which were shown to be less sensitive to thalidomide compared with other species, including humans) and from the lack of tests during pregnancy. Hence, what caused the problem was not the poor predictive validity of animal testing but rather the inappropriate animal model that was used and insufficient preclinical investigations of the drug.

This dramatic experience led to the establishment of new guidelines and laws to regulate the preclinical testing of drugs. For example, these new guidelines stipulated that any new molecule or vaccine must be tested on at least two different animal

species before moving to the clinical stage. Thanks to advances in the optimal use of laboratory animals, the risks for humans can be minimized by detecting the toxicity of new drugs very early during development. Recent data indicate that approximately 80% of compounds that are under development fail to enter the clinical stage, and approximately 40% of them are stopped after a lack of tolerability or signs of toxicity are found in laboratory animals (Waring et al., 2015).

11. Conclusions

Although the moral debate about using animals for scientific research is far from providing universally acceptable answers, we tried to address it from different points of view, both theoretical and practical ones. To go even deeper into the matter, we think that it is also important to explore some practical examples. For instance, let us consider the recent experience with the SARS-Cov2 pandemic that began around December 2019 in Wuhan, China, and spread worldwide in less than 3 months. We rapidly learned how dangerous this virus is. In the absence of effective medications or specific vaccines, several countries implemented what they viewed as necessary measures to control further spread of the disease. Such measures included lockdowns and social isolation to protect their populations and give biomedical researchers sufficient time to develop effective treatments.

As “active moral subjects”, we can decide whether to use or not use laboratory animal testing to advance research on SARS-Cov2. A hypothetical scenario can be constructed in which we choose not to practice laboratory animal testing for biomedical research. Our knowledge of the disease would progress much slower. Based on current scientific knowledge, new drugs or vaccines could not be developed. To reduce the risk of infections, we would likely be forced to live in social isolation for very long periods of time, from months to years.

One alternative might be to simply ignore or disregard the epidemic and maintain our usual lifestyles. In such a scenario, the disease would rapidly spread, many people would become infected, and many casualties would arise, especially in less developed countries where healthcare systems are relatively poorly developed and

insufficiently organized to face this infectious disease. History has taught us that this indeed happened several times in the past during plague, smallpox, and cholera epidemics. These catastrophic events were followed by even more dramatic experiences, including long-lasting famines and wars, that impoverished entire populations and killed millions of people. One such example was the so-called "Black Death", a fatal pandemic of bubonic plague that devastated whole populations in Europe, Africa, and Asia between 1346 and 1353 and resulted in 75–200 million deaths.

Thanks to advances in science, however, today medications and vaccines can be developed in relatively short periods of time, thus mitigating the impact of SARS-Cov2 that otherwise could be catastrophic. Acting rapidly and efficiently in biomedical research means that we need to use laboratory animals. In addition, existing medications that we are using to mitigate the consequences of SARS-Cov2 infection, such as drugs or vaccines that are approved for humans or other animals, were developed after extensive testing in laboratory animals. Is it an acceptable moral decision not to use them because they were initially tested in animals?

For ethical reasons, an individual with full cognitive capacity can decide not to use drugs that were developed from animal testing. This is an acceptable position because individuals possess full cognitive capacity. More complex is when such a choice is made by people who suffer from cognitive impairments, psychological instability, or other cases of compromised judgment.

Moreover, an unacceptable position would be when an individual's conscientious objection is imposed on other people to limit their access to drugs or other medical treatments. For example, the "no-vax" position is not ethically acceptable because reducing the number of people who are vaccinated consequently heightens the risk of spreading an infectious disease in the whole population, with severe consequences especially for those who, because of specific circumstances (i.e., immunodepression), cannot be vaccinated.

Unfortunately, unfair or misleading information, characterized by high emotional loads, that depict laboratory animals as victims of human progress has a tremendous

impact on this ethical debate, and public opinion can be easily swayed by it. As Daniel Kahneman (Kahneman, 2012; Tversky & Kahneman, 1974) pointed out in his theory of heuristics and bias, particularly in complex situations, when it is difficult to provide an exhaustive answer (i.e., in ethical debates), humans engage in cognitive processes that "substitute" the original question with an alternative one that is easier to answer. For example, if the question is, "How many laboratory animals are you willing to sacrifice to advance human knowledge about a certain disease and develop a new medication?" then the alternative question is, "How much emotion do I feel when I save the life of animals that are otherwise used for laboratory testing?" The answer to this latter question does not respond to the original one but provides a rapid solution to the ethical dilemma.

If this is the cognitive process that contributes to biasing public opinion toward the protection of animal rights to the detriment of societal progress and human health, then scientists should probably reconsider the way they are the vehicles of information about their own research work. To communicate rational information and statistical data on how many human lives biomedical research can save by developing a new medication will probably not work. But if the ethical question is posed differently, such as, "How many people who suffer from untreatable disease are you willing to save by allowing laboratory animal testing?" then the heuristic questions will be, "How much emotion do I feel when I save human beings who suffer from a disease that threatens their lives?" At the margin between these two views is the fundamental role of responsibility, which links the needs of being responsible for the rights of both humans and other animals to create a liminal space we call ethics. In this space, every action must be pondered, and appropriate questions need to be asked to find the right balance when engaging in open and healthy debate. The example of SARS-Cov2 is both real and recent and tells us that our responsibility is to act consciously to find an optimal balance between protecting animal rights and the obligation to act in an attempt to advance human society and improve the quality of life of our own species. So we believe that it is an opportunity

for science to pose the right questions to raise public awareness about the importance of animal testing in biomedical research.

References

Balls, M. (2002). Future improvements: replacement in vitro methods. *ILAR J, 43 Suppl*, S69-73. https://doi.org/10.1093/ilar.43.suppl_1.s69

Baumans, V. (2005, Aug). Science-based assessment of animal welfare: laboratory animals. *Rev Sci Tech, 24*(2), 503-513. https://www.ncbi.nlm.nih.gov/pubmed/16358504

Bloom, P. (2016). Against Empathy: The Case for Rational Compassion. Ecco Books.

Carruthers, P. (1992). *The Animals Issue: Moral Theory in Practice* (C. U. Press, Ed.). Cambridge University Press.

Council, C. f. t. U. o. t. G. f. t. C. a. U. o. L. A. N. R. (2010). *Guide for the Care and Use of Laboratory Animals: Eighth Edition*. National Academies Press.

Darwin, C. (1859). On the Origin of Species by Means of Natural Selection, or the Preservation of Favoured Races in the Struggle for Life. John Murray.

DeGrazia, D. (1999). Animal ethics around the turn of the twenty-first century. *J Agric Environ Ethics, 11*, 111-129. https://doi.org/10.1023/a:1009504617295

Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the Protection of Animals Used for Scientific Purposes. (2010). *Official Journal of the European Union 276 33-79*.

Doke, S. K., & Dhawale, S. C. (2015, Jul). Alternatives to animal testing: A review. *Saudi Pharm J, 23*(3), 223-229. https://doi.org/10.1016/j.jsps.2013.11.002

Frey, R. G. (1980). Interests and Rights: The Case Against Animals. Oxford University Press.

Frey, R. G. (1988, Summer). Moral standing, the value of lives, and speciesism. *Between Species, 4*(3), 191-201. https://doi.org/10.15368/bts.1988v4n3.8

Giacomotto, J., & Segalat, L. (2010, May). High-throughput screening and small animal models, where are we? *Br J Pharmacol, 160*(2), 204-216. https://doi.org/10.1111/j.1476-5381.2010.00725.x

Hendriksen, C. F. (2009, Mar). Replacement, reduction and refinement alternatives to animal use in vaccine potency measurement. *Expert Rev Vaccines, 8*(3), 313-322. https://doi.org/10.1586/14760584.8.3.313

Hippocrates. (IV B.C.). *Corpus Hippocraticum*.

Hume, D. (1739-40). A Treatise of Human Nature. John Noon.

Jonas, H. (1984). Das Prinzip Verantwortung: Versuch einer Ethik für die technologische Zivilisation. Suhrkamp Taschenbuch.

Kahneman, D. (2012). Thinking, Fast and Slow. Penguin Books.

Kant, I. (2017). *The Metaphysics of Morals* (D. L., Ed.). Cambridge University Press.

Levin, J. A., A; Irvine, L. (2017). Are People More Disturbed by Dog or Human Suffering? Influence of Victim's Species and Age. *Society and Animals Journal, 25*(1).

Lipinski, C., & Hopkins, A. (2004, Dec 16). Navigating chemical space for biology and medicine. *Nature, 432*(7019), 855-861. https://doi.org/10.1038/nature03193

Miralles, A., Raymond, M., & Lecointre, G. (2019, Dec 20). Empathy and compassion toward other species decrease with evolutionary divergence time. *Sci Rep, 9*(1), 19555. https://doi.org/10.1038/s41598-019-56006-9

National Research Council (US) Committee to Update Science, M., and Animals. (2004). *Science, Medicine, and Animals*. National Academies Press (US). https://doi.org/10.17226/10733

Ranganatha, N., & Kuppast, I. (2012). A review on alternatives to animal testing methods in drug development. *International Journal of Pharmacy and Pharmaceutical Sciences, 4*(SUPPL 5), 28-32.

Rusche, B. (2003). The 3Rs and animal welfare - conflict or the way forward? *ALTEX, 20*(Suppl 1), 63-76. https://www.ncbi.nlm.nih.gov/pubmed/14671703

Russell, W. M. S., Burch, R.L., and Hume, C.W. (1959). *The Principles of Humane Experimental Technique*. Methuen.

Shanks, N., Greek, R., & Greek, J. (2009, Jan 15). Are animal models predictive for humans? *Philos Ethics Humanit Med, 4*, 2. https://doi.org/10.1186/1747-5341-4-2

Singer, P. (1975). Animal Liberation. A New Ethics for Our Treatment of Animals. Random House.

Smith, A. (1759). The Theory of Moral Sentiments. Millar & Kincaid.

Taylor, K., & Alvarez, L. R. (2019, Nov-Dec). An Estimate of the Number of Animals Used for Scientific Purposes Worldwide in 2015. *Altern Lab Anim, 47*(5-6), 196-213. https://doi.org/10.1177/0261192919899853

Taylor, K., & Rego Alvarez, L. (2019). A summary of EU national statistical reports of animal experiments in 2014-2016. *ALTEX, 36*(2), 314-319. https://doi.org/10.14573/altex.1812211

Thalmann, O., Shapiro, B., Cui, P., Schuenemann, V. J., Sawyer, S. K., Greenfield, D. L., Germonpre, M. B., Sablin, M. V., Lopez-Giraldez, F., Domingo-Roura, X., Napierala, H., Uerpmann, H. P., Loponte, D. M., Acosta, A. A., Giemsch, L., Schmitz, R. W., Worthington, B., Buikstra, J. E., Druzhkova, A., Graphodatsky, A. S., Ovodov, N. D., Wahlberg, N., Freedman, A. H., Schweizer, R. M., Koepfli, K. P., Leonard, J. A., Meyer, M., Krause, J., Paabo, S., Green, R. E., & Wayne, R. K. (2013, Nov 15). Complete mitochondrial genomes of ancient canids suggest a European origin of domestic dogs. *Science, 342*(6160), 871-874. https://doi.org/10.1126/science.1243650

Tversky, A., & Kahneman, D. (1974, Sep 27). Judgment under Uncertainty: Heuristics and Biases. *Science, 185*(4157), 1124-1131. https://doi.org/10.1126/science.185.4157.1124

Vargesson, N. (2015, Jun). Thalidomide-induced teratogenesis: history and mechanisms. *Birth Defects Res C Embryo Today, 105*(2), 140-156. https://doi.org/10.1002/bdrc.21096

Waring, M. J., Arrowsmith, J., Leach, A. R., Leeson, P. D., Mandrell, S., Owen, R. M., Pairaudeau, G., Pennie, W. D., Pickett, S. D., Wang, J., Wallace, O., & Weir, A. (2015, Jul). An analysis of the attrition of drug candidates from four major pharmaceutical companies. *Nat Rev Drug Discov, 14*(7), 475-486. https://doi.org/10.1038/nrd4609

Wolf, M. J., & Rockman, H. A. (2008, Oct 1). Drosophila melanogaster as a model system for genetics of postnatal cardiac function. *Drug Discov Today Dis Models, 5*(3), 117-123. https://doi.org/10.1016/j.ddmod.2009.02.002

Conclusions

The most difficult part of writing my thesis was to keep totally different approaches together and to look for a synthesis that would not banalize any of them. Many times I felt like I failed in reaching this aim. Still, I am proud of what I have done. Not only because I managed to produce a multidisciplinary work but also, and most of all, because I have never given up.

Ironically, I think that the strengths of my work coincide with its limitations. Indeed, on one hand, the contextualization of the empirical results in a theoretical framework strengthens the philosophical meditation and grounds it to a scientific understanding and, at the same time enriches the neuroscientific findings through a deep investigation of the phenomenon's ontological background. On the other hand, though, the risk of such a wide and holistic approach is to leave out some specificities of both the perspectives.

For this reason, I think that, as further theoretical steps, it would be very promising to work on a twofold direction:

- through deepening the philosophical investigation of the phenomenon of self/ other-processing, by undertaking a phenomenological analysis of how intersubjectivity shapes the subjectivity and viceversa;
- through performing more analysis on fMRI, but also EEG, results to probe for the neurobiological mechanisms that underly the phenomenon of self-other-consciousness.

In addition the proposed rodent model offers an efficient instrument to explore the empathic phenomenon, by observing how different behavioral and biological manipulations affect it.

In short, the best is yet to come!

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Lastly, I thank my family, my friends and my soulmate, with all my heart. They are the reason why, despite the million fragments that compose me, I feel one.

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[45] Catania, K. *Adattamenti meravigliosi. Sette irresistibili misteri dell'evoluzione*, Bollati Boringhieri, 2021.

Appendix

Scientific Contributions

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INVITED REVIEW

Addiction Biology SSA WILEY

Public perception of laboratory animal testing: Historical, philosophical, and ethical view

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Abstract

The use of laboratory animals in biomedical research is a matter of intense public debate. Recent statistics indicates that about half of the western population, sensitive to this discussion, would be in favor of animal testing while the other half would oppose it. Here, outlining scientific, historical, ethical, and philosophical aspects, we provide an integrated view explaining the reasons why biomedical research can hardly abandon laboratory animal testing. In this paper, we retrace the historical moments that mark the relationship between humans and other animal species. Then starting from Darwin's position on animal experimentation, we outline the steps that over time allowed the introduction of laws and rules that regulate animals' use in biomedical research. In our analysis, we present the perspectives of various authors, with the aim of delineating a theoretical framework within which to insert the ethical debate on laboratory animals research. Through the analysis of fundamental philosophical concepts and some practical examples, we propose a view according to which laboratory animals experimentation become ethically acceptable as far as it is guided by the goal of improving humans and other animal species (i.e., pets) life. Among the elements analyzed, there is the concept of *responsibility* that only active moral subjects (humans) have towards themselves and towards passive moral subjects (other animal species). We delineate the principle of *cruelty* that is useful to understand why research in laboratory animals should not be assimilated to a cruel act. Moreover, we touch upon the concepts of necessity and "good cause" to underline that, if biomedical research would have the possibility to avoid using animals, it would surely do that. To provide an example of the negative consequences occurring from not allowing laboratory animal research, we analyze the recent experience of Covid-19 epidemic. Finally, recalling the principle of "heuristics and biases" by Kahneman, we discuss why scientists should reconsider the way they are conveying information about their research to the general public.

KEYWORDS

3R principles, animal experimentation, animal rights, Covid-19, moral responsibility

1 | INTRODUCTION

In recent years, the use of laboratory animals in biomedical research has been a matter of intense public debate. The most recent statistics suggest that about half of the Western population, who generally are sensitive to this discussion, are in favor of animal testing, but the other half oppose it. Over the years, the European Union (EU), Canada, the United States, and several other countries have

introduced laws to regulate the use of laboratory animal testing. These laws are generally well balanced and have been promulgated after consulting the main stakeholders (i.e., researchers, patient associations, associations for the protection of animals, and so forth) who are sensitive to this matter. Unfortunately, despite these efforts, the public debate has often suffered from misleading information that is disseminated by individuals or groups who oppose animal testing. Researchers have neglected to respond to such aggressive media campaigns with adequately effective communication. A prototypical example is the widespread use of the term "vivisection" that is used in an effort to stigmatize laboratory animal testing, notwithstanding the fact that science abhors vivisection, which is an illegal behavior that was banned by law and abandoned decades ago. Something similar is also happening in the case of vaccination, against which false information campaigns have been launched by groups of people who are generically identified as "Anti-Vaxers." These groups deny the success of vaccination strategies to eradicate several serious infectious diseases, such as smallpox and poliomyelitis, although such opposition to vaccination carries an incalculable risk of severe public health damage.

The recent SARS-CoV2 pandemic and its social and political impact and dramatic consequences on public health systems are bringing new attention to the value of biomedical research. This situation provides an opportunity to replace disinformation with a constructive debate on the importance of animal testing and vaccination. In recent decades, much has been done to protect the rights of laboratory animals, but it is also clear that, based on present knowledge and available technologies, in specific research fields it is not possible to completely abandon in vivo animal testing by replacing it with alternative methods. The present work outlines historical, ethical, and philosophical aspects that stem from the recognition that animal testing is essential to advance biomedical research; it is required for the development of drugs and vaccines that meet both human and veterinary needs.

2 | ANIMALS AND HUMANS: AN HISTORICAL VIEW

From an evolutionary perspective, we as *Homo sapiens* started our journey through time much later than several other species. Since the moment we developed our fine-tuned biological structures and uniquely complex central nervous system, we became "transcendent" beings (Table 1). We started to *symbolize* (Table 1), develop complex abstract thinking, and act accordingly. This high cognitive abilities are unlikely so well developed in other animal species, and this is what makes us different from them.

We can use memories to attribute meanings, interpret the present, and think in perspective to anticipate the future. Through evolution, we also progressively acquired high cognitive faculties that are utilized to explore ways to improve our living conditions. We learned to use objects as tools and employ other animals to reach our aims, which is oftentimes linked to survival instincts but in some other cases independent from them, such as in the case of arts or companionship.

TABLE 1 Definition of the philosophical concepts as used

Term	Description
Transcendence	Human capability of "going beyond" what is material and concrete. For example, we can say that we "transcend" a perceptive stimulus, such as physical pain, when we elaborate it at a secondary level by analyzing it in terms of abstract concepts (e.g., "pity," "cruelty," or "injustice"). We are "transcendent" beings because we can think and act according to abstract concepts.
Symbolization	From the capability of transcendence comes the concept of symbolization, by which we assign an evocative value to what we find in our perceptive experience, both at a linguistic level (by nominating things or by speaking about what is absent) and at psychological, moral, philosophical, social levels (by explaining phenomena through some conceptual senses; e.g., the concept of God).
Utilitarianism	An ethical theory founded by the philosophers Jeremy Bentham and John Stewart Mill between the 18th and the 19th centuries. According to utilitarianism, a right action is the one that promotes happiness or prevent pain for every affected subject.
Speciesism	The practice of considering and treating members of a species as morally superior to members of the other species.
Deontology	An ethical theory according to which the morality of an action should be evaluated on the basis of its intrinsic rightfulness or wrongfulness and not on the basis of its consequences.
Moral status	A subject has his own moral status if he is considered, under certain general rules, worthy of having rights and a moral consideration among other moral subjects.
Moral agent or active moral subject	Differently from "moral patient" or "passive moral subject," a moral agent is a subject that has the capability of acting accordingly to his awareness and of recognizing that every action could have consequences on other subjects. A moral patient, instead, is a subject who has to be respected, on the basis of his rights or of another subject's duties, but without having his own duties.
Awareness	The capability of being conscious of what is perceived, sensed, felt, thought and so forth.
Responsibility	The capability of foreseeing the consequences of one's behavior and of changing it according to them.

Animal domestication and breeding have been fundamental to the development of cultural and social human structures. Through domestication and breeding, humans could become sedentary because it was possible to have food and help without the need to hunt or be nomadic. The first animal that was domesticated was the dog, which was "the culmination of a process that initiated with

European hunter-gatherers and the canids with whom they interacted."[1] After the dog, other animals were also domesticated, such cows, pigs, and sheep, which were bred for food, clothes, or help with strenuous work, mostly in agriculture. Later, horses and several other animals became important to guarantee the functioning of increasingly complex societies.

In parallel, humans have learned to use animals for less immediate and urgent purposes. Domestication has become a way to select some completely captive species to be used for other purposes, such as companionship, entertainment, and scientific research. To develop new knowledge and improve peoples' lives, particularly relevant has become the use of animals in the fields of medicine, pharmacology, biology, physiology, and cognitive psychology, among others.

In the age of Hippocrates,[2] the dissection of human corpses was prohibited, and animals were used to study human anatomy by analogy. "The parallels between human and animal physiology and pathology were noted long ago, and the practice that we today call 'animal research' is rooted back to the period of the ancient Egypt and Greece."[3] During the 17th century, modern science, still in its infancy, was influenced by ideas of one of the most prominent philosophers of the time, Renée Descartes. According to his thinking, animals resemble material machines that lack intellect or spiritual elements, which are possessed by humans only. As a consequence of this vision, beginning in the 17th century, the use of animals in science steadily increased. In the 19th century, Charles Darwin published his most fundamental work, *On the Origin of Species by Means of Natural Selection, or the Preservation of Favoured Races in the Struggle for Life*,[4] in which he showed profound similarities between human and nonhuman animals. In the 20th century, thanks to the irreplaceable contribution of laboratory animal experiments, new branches of science, such as pharmacology and immunology, were developed.

At the time of Hippocrates, Aristotle, and Galen and generally until the 18th century, animals were used for experiments without moral or legal restrictions because it was considered the only possible and legitimate way to avoid using humans. In the later 17th and 18th centuries, a moral debate began. Darwin himself was immersed in the public controversy about the use of live animals for scientific purposes. Opinions ranging from not allowing experimentation on animals to testing them if no pain was inflicted and finally to let the animal feel pain. Darwin, being an animal lover, although conflicted, found vivisection justifiable only for true physiological investigations but not simply for "mere damnable and detestable curiosity." In 1875, Darwin was one of 53 witnesses called by the Royal commission to testify on the practice of using live animal testing. In his statement, he emphasized that progress in physiology was possible only with the aid of experiments on living animals, but that the animals must be rendered insensible to pain.

Public awareness of the need to control the use of experimental animals progressively increased, leading to the promotion of specific legislation, such as "An Act Against Plowing by the Tayle, and Pulling the Wool Off Living Sheep," which was passed by the Parliament of Ireland in 1635 and was one of the first known laws on animal protection. In the 20th century, because of the explosion of biomedical sciences, the use of animals for laboratory testing increased enormously, creating conditions for the establishment of a new area of research, laboratory animal science. "This is a multidisciplinary branch of science aimed at contributing to the quality of experiments in which animals are used and at improving their welfare. It encompasses the biology of laboratory animals, their environmental requirements, genetic and microbiological standardization, prevention and treatment of disease, experimental techniques, anesthesia, analgesia and euthanasia, alternatives to their use, and ethics."[5]

3 | THE USE OF LABORATORY ANIMALS TODAY

Experiments on laboratory animals today are conducted at the global level for different scopes and in different fields of study. Laboratory animals are employed to model humans' and other animals' pathologies, develop new pharmaceutical products, produce vaccines, and perform toxicological studies. A recent report indicated that in 2015, 37 countries, for which statistics are available, reported the use of 41.8 million experimental procedures (defined according to the European Union Directive 2010/63/EU; article 3,1) performed on laboratory animals worldwide.[6] The most widespread use of experimental animals occurs in China, with an estimated number of 20,496,670 procedures, followed by Japan and the United States with an adjusted number of approximately 15,000,000 procedures each. By far, the most commonly used animals are mice and rats, followed by birds, fish, reptiles, amphibians, and cephalopods. Significantly fewer dogs and monkeys are used, mostly in China and the United States. In total, the number of dogs and monkeys used in the 36 countries that communicated the data was 112,265 and 92,431, respectively.[6] Another statistical report indicated that, between 2014 and 2016 in Europe, the total number of procedures conducted on laboratory animals has been rather stable ranging from 10,356,578 to 10,853,401.[7]

In all countries, animal experimentation is strictly controlled by specific laws and can only be conducted in compliance with them. A general principle that underlies these laws and that is also valorized by the internationally recognized and accepted guidelines of the *Guide for the Care and Use of Laboratory Animals*[8] is the "Replace, Reduce, Refine" (3R) principle,[9,10] which was first suggested by the English researchers William Russell and Rex Burch in 1959.[11] According to the 3Rs, experimental procedures must always respect the following three basic principles.

- According to "replace," any time possible, the use of animals should be replaced with in vitro or in silico tests[12,13] or with invertebrates[14–16]
- According to "reduce," the number of animals used should always be kept to the absolute minimum that is needed for a specific experiment. The information that is gathered per animal should always be maximized to reduce the number of animals used as much as possible.

- According to "refine," researchers must study and adopt a series of methods to improve laboratory animals' welfare, such as caring about their housing conditions and minimizing pain, suffering, and distress.

The 3R principles are currently considered the most efficient and morally acceptable way to guarantee animals' rights on the one hand and advance scientific progress on the other.

In the United States, animal testing procedures were for the first time regulated by the Animal Welfare Act (AWA) of 1966, which has been amended four times (1970, 1976, 1985, and 1991). The AWA is integrated in the Public Health Service (PHS) Policy on the Humane Care and Use of Laboratory Animals that was published in 1985 and is periodically updated. The PHS policy requires research institutions to establish and maintain appropriate measures to ensure the adequate care and use of animals that are involved in animal testing and research.

In Europe, the use of laboratory animals for research was first regulated by EU Directive 86/609EEC and more recently by Directive 2010/63/EU[17] that applies to all live nonhuman vertebrate animals, including independently feeding larval forms, fetal forms of mammals from the last third of gestation during normal development, and live cephalopods (Art. 1 [3]). The 3R principles are one of the main inspirational elements of 2010/63/EU. After the EU Directive was promoted, EU member states had to comply with it by establishing their own national laws to regulate the care and use of laboratory animals, authorize research protocols for animal experimentation, and supervise proper application of the norms. Proposed research projects, in addition to guaranteeing animal welfare, must use the lowest neurologically evolved species within the constraints of the experiment and the lowest number of subjects possible. 2010/63/EU is a well-balanced directive that was passed after years of discussion between various stakeholders, including researchers, patient associations, and animal protection associations.

Unfortunately, the translation of this EU Directive into national laws has generated some differences between EU member states. Italy, for example, introduced its "D.Lgs.vo 26/14" in 2014, which consists of an unprecedented restrictive interpretation of 2010/63/EU. Additionally, contrary to EU legislation, the use of laboratory animals for xenotransplantation experiments or studying substances of abuse is prohibited, thus creating a significant negative bias in the biomedical research potential of Italy compared with other EU member states. It is worth mentioning also the example of Germany that, in addition to translating the EU Directive into a national law, similarly to Switzerland has implemented the principle of animal protection in its constitution.

4 | ANIMAL RIGHT ACTIVISM

Undoubtedly, animal right movements have contributed to important progresses towards the establishment of a balanced relationship between humans and other animal species. For example, they have contributed to enhance the awareness of the scientific community to the use of laboratory animals in biomedical research. They provided a significant contribution to the promulgation of laws that balancing between the different views allow an adequate protection of laboratory animals without hampering biomedical research. Moreover, they have had a critical role in promoting the recognition of equality between humans and other animal species, so that in some cases, the principle of protection of animal rights has been introduced in national constitutional laws.

On the other hand, it should be condemned when animal right activism leads to inappropriate initiatives, often by single or small groups of individuals, that acting against the law strikes research centers and hospitals or attempt to discredit science. There are examples of scientists that due to alleged accuses by animal right activists have been illegally hindered in their research or have been removed from some of their responsibilities and then found innocent by the court. Occasionally, assaults on research centers, universities, and hospitals have been organized to free the laboratory animals. These actions have detrimental consequences not only for the institutions but also for the animals that bred in captivity and are not able to survive in natural environments.

Beyond these considerations, it is clear that the use of laboratory animals in science is a matter of intense public debate that is based on legal, moral, and ethical evaluations. To adequately address this issue, it is important to structure the discussion within a well-defined theoretical framework.

5 | THEORETICAL VIEWS

It is not easy to find concordance between opinions in ethical debates. General scientific data that unquestionably support any one of the different positions may not be sufficient. Consequently, a particular empathy-based position is perceived as a universally valid philosophical position. As Immanuel Kant pointed out, however, the only universally relevant moral statement is one that, under the same conditions, can be recognized as valid by anyone who is endowed with reason.[18]

The ethical debate about animal rights is one example in which a universally valid moral statement is difficult to imagine—multiple diverse positions are worthy of consideration.[19] For example, such authors as Peter Singer and Tom Regan, although starting from different points of view, have provided arguments that support the thesis that it is wrong to use animals. Other authors, such as the utilitarian Raymond G. Frey and Peter Carruthers, embrace contractualism and stand for the practice of laboratory animal testing.

In *Animal Liberation*,[20] Singer applies the "Principle of Equal Consideration of Interests." According to this principle, humans and other animal species must have the same interests and rights. Singer criticizes what he calls "speciesism" (Table 1), a morally wrong practice of treating one animal species as morally more important than others. Singer anchors this equality principle between members of different species to the experience of suffering, which is common to people and animals. According to this utilitarian perspective (Table 1),

everyone who feels pain and suffering naturally wants to avoid them; consequently, provoking pain is cruel and disrespectful of others' rights.

Regan instead bases his defense of animal rights on a deontological argument (Table 1), according to which the concept of the "intrinsic value" of a subject-of-a-life, a definition that cannot only be applied to humans but also to animals. In fact, animals are living beings, and this is sufficient to assert that, like humans, animals should never be considered objects. These two different but convergent theoretical approaches support a common position according to which the use of animals for food or testing has to be avoided as a morally unacceptable practice.

Like Singers, Frey[21,22] supports the principle of utilitarianism, but he comes to an opposite conclusion. According to him, animals, in contrast to humans, are not aware of "interests," beliefs, or desires; therefore, it is wrong to attribute the same value to humans and other living species.

Another opponent of the equalitarian vision is Carruthers,[23] who justifies the use of animals based on the fact that they do not have the same mental capacity as humans. According to Carruthers, animals can have beliefs and desires and engage in practical reasoning in response to them. Animals can feel pain and fear and can suffer, but they are not "rational agents" because they are not able to govern their behavior in accordance with universal moral rules that are obeyed by most members of a community. Hence, no animal has the "moral standing" that only humans have. According to Carruthers' conclusion, because animals do not have the same moral status (Table 1) as humans, they cannot have the same rights. In other words, he states that moral agents (Table 1) like humans (i.e., subjects who have moral responsibilities) must postpone responsibilities toward animals to promote their interests. Carruthers further pushes his position to the extreme by asserting that "a duty not to slaughter your neighbor's dog might be an instance of a duty not to damage others' property."[19]

As can be seen, general discussions about whether it is right or wrong to use animals in scientific research can lead to many disagreements and unsatisfactory conclusions for anyone. The fundamental question is why we should care about human rights more than animal rights. There is likely no unique or universal answer to this question, and there are equally sustainable and even opposing ethical positions on this matter. When engaging in this debate, it would be useful to concentrate as much as possible on a few elements.

6 | ACTIVE AND PASSIVE MORAL SUBJECT AND RESPONSIBILITY

The first element to consider is that the moral sense is a human characteristic that makes individuals of our species "active moral subjects." Conversely, the behavior of nonhuman animals is to a large extent instinctual. Hence, animals should be viewed as "passive moral subjects." They are unable to recognize their own moral status and their own rights. Thus, being human an "active moral subject," he also has the prerogative to recognize rights to other living subjects. The human being is thus the only "responsible" agent (Table 1). He has the responsibility to respect animals' rights but without neglecting his own and those of his species. Moreover, from a slightly different point of view, according to Hans Jonas,[24] human responsibility requires that the respect of nature and other species is a human duty more than other species' rights.

7 | ANIMAL TESTING IS NOT CRUELTY

Another element to consider is the concept of cruelty because, in most cases, animal experimentation is perceived as a cruel practice by the general public. Of course, for humans, it is a moral imperative to abhor cruelty. We should not harm animals by using them for experimentation if this means to be cruel. However, is the use of laboratory animals cruel when they are used for the "right purpose"? Are we performing acts of cruelty, or are we fulfilling a necessity? Cruelty must be condemned as a wrong behavior; to do so, however, we must first clearly define it.

We think that the first element that makes an act cruel is awareness (Table 1). To be considered cruel, a person must be aware of the fact that he is harming someone or something else by provoking unnecessary pain or suffering. Without awareness, there is no cruelty. So, for example, a person who does not have the mental faculties to recognize others' suffering should not be judged as cruel. The second element that we consider important is the ability to "symbolize" the act, which we already described as the capacity to attribute to it a specific meaning and value.

The third condition for an act to be considered cruel is that it must be done *freely*, without a reason, scope, or need, and only with an inner intention of satisfying some personal pleasure, such as the pleasure of inflicting harm only for the sake of it. The difference between a non-cruel act and a cruel act resides in the intention behind it. If the intention is informed by a very strong *need* that requires that act and that act only, with no other possible alternatives, then the act could be considered non-cruel even if it is harmful to others. Instead, if the intention that motivates an act that causes harm to another individual is based on a personal interest or satisfying unnecessary pleasure, then the act can be judged as cruel. One of the arguments against animal research is that it is freely enacted cruel behavior. Based on the elements delineated above, animal testing can be considered cruel only if a scientist acts in the absence of a necessity and if he uses an animal to satisfy a personal desire to harm or experience pleasure from harming. On the contrary, it cannot be considered cruel if the work of a scientist reflects the necessity of improving humans' and other species' lives.

8 | ANIMAL EXPERIMENTATION IS A NECESSITY AND A "GOOD CAUSE"

Of course, we must also reflect on the concept of "necessity," which directly derives from the concept of "need." A need is opposite to the

desire for an unnecessary pleasure. Ethical and bioethical norms recommend the avoidance of unnecessary pleasure if it harms others' rights, but they cannot suppress a natural need. If animal testing is the only way (or the most appropriate way) to improve the condition of people and their pets who suffer or save their lives, then this can be viewed as a legitimate need.

Another element to consider is the principle of "good cause." As animal rights' supporters contend, a cause that is good for humans may not be good for other animal species that are employed for that purpose. Conversely, what is not a good cause is not necessarily a bad cause either. Under ethically controlled circumstances, even if the cause could not be good for the animals that are used because, for example, they do not themselves benefit from being used, it is not necessarily bad in absolute terms. Testing drugs on laboratory animals is also useful for developing medications to ameliorate or save the lives of our pets and other nonhuman animals in general.

This argument should be carefully considered by those who believe that ethics cannot be speciesist, and it cannot consider only what is best for humans because, as explained above, laboratory animals are also used to protect and improve the lives of other animal species.

9 | CAN BIOMEDICAL RESEARCH AVOID USING LABORATORY ANIMALS?

In addition to the ethical and theoretical perspectives that are discussed above, in which we sought to clarify that experimental research is a necessity and not cruel, we should also consider the practical reasons why biomedical research cannot avoid the use of animal testing.

As mentioned previously, the use of laboratory animals adheres to the principle of "good cause," and it is conducted in compliance with laws that are promoted to guarantee animals' rights. The 3R principles are the basic principles that have inspired current laws that regulate the use of laboratory animals. Consistent with the 3Rs is a commitment to engage in animal testing only when valid alternatives are unavailable. The main possible alternatives to in vivo tests are in vitro cell and tissue cultures or in silico computer-assisted experiments.[25] These alternative methods are indeed largely practiced in biomedical research, and their use has greatly contributed to the *reduction* of laboratory animals. Nonetheless, the complexity of various organs (e.g., the brain) and difficulty mimicking the function of a human organism in vitro or in silico make it impossible to fully replace in vivo laboratory animal testing. In fact, in most cases, the only way to study pathologies that afflict both humans and other species is by replicating them in animal models. The efficacy and toxicity of new drugs and vaccines, at some point in their development, can only be studied in living animals.[26] Testing a drug on a single cell or using an in silico approach (or both) would certainly help identify important characteristics of molecules that make them viable or not for further development. However, verification of their efficacy and safety profile is possible only if animal testing is performed. The alternative to this is an unsustainable risk (and thus unethical) to develop treatments without proven safety and efficacy. To prevent these risks, drug regulatory agencies stipulate that any new medication, vaccine, or cure in general must be tested in laboratory animals prior to entering the clinical stage.

The history of thalidomide offers the most famous example of what can happen if drugs are developed in the absence of adequate preclinical testing. In 1957, this drug was commercialized to treat insomnia, headaches, and nausea after having been tested only in rodents, but never during pregnancy. Unfortunately, it was extensively used by women to treat nausea and vomiting during pregnancy.[27] During that period, an unprecedented number of cases of phocomelia and other birth defects occurred in all 46 countries where the drug was marketed. Years later, thalidomide was identified as the cause of this disaster and subsequently withdrawn from the market. This led to some controversies about the predictive ability of animal experimentation.[28]

The dramatic experience with thalidomide is often recalled to support positions against the use of laboratory animals in biomedical research. However, two facts need to be considered. The first is the logical fallacy and hasty generalization of the assertion that animal testing on thalidomide was not predictive and therefore any animal testing is not predictive. In fact, there are several other cases in which the use of laboratory animals has been very important for the early detection of drug toxicity. The second and most important fact, when the story of thalidomide is viewed from a different perspective, demonstrates the importance of using laboratory animals in preclinical research. The problem with this drug arose from the insufficient evaluation of its toxicity in laboratory animals, from the fact that all of the experiments were conducted in rodents (which were shown to be less sensitive to thalidomide compared with other species, including humans) and from the lack of tests during pregnancy. Hence, what caused the problem was not the poor predictive validity of animal testing but rather the inappropriate animal model that was used and insufficient preclinical investigations of the drug.

This dramatic experience led to the establishment of new guidelines and laws to regulate the preclinical testing of drugs. For example, these new guidelines stipulated that any new molecule or vaccine must be tested on at least two different animal species before moving to the clinical stage. Thanks to advances in the optimal use of laboratory animals, the risks for humans can be minimized by detecting the toxicity of new drugs very early during development. Recent data indicate that approximately 80% of compounds that are under development fail to enter the clinical stage, and approximately 40% of them are stopped after a lack of tolerability or signs of toxicity are found in laboratory animals.[29]

10 | CONCLUSIONS

Although the moral debate about using animals for scientific research is far from providing universally acceptable answers, we tried to

address it from different points of view, both theoretical and practical ones. To go even deeper into the matter, we think that it is also important to explore some practical examples. For instance, let us consider the recent experience with the SARS-Cov2 pandemic that began around December 2019 in Wuhan, China, and spread worldwide in less than 3 months. We rapidly learned how dangerous this virus is. In the absence of effective medications or specific vaccines, several countries implemented what they viewed as necessary measures to control further spread of the disease. Such measures included lockdowns and social isolation to protect their populations and give biomedical researchers sufficient time to develop effective treatments.

As "active moral subjects," we can decide whether to use or not use laboratory animal testing to advance research on SARS-Cov2. A hypothetical scenario can be constructed in which we choose not to practice laboratory animal testing for biomedical research. Our knowledge of the disease would progress much slower. Based on current scientific knowledge, new drugs or vaccines could not be developed. To reduce the risk of infections, we would likely be forced to live in social isolation for very long periods of time, from months to years.

One alternative might be to simply ignore or disregard the epidemic and maintain our usual lifestyles. In such a scenario, the disease would rapidly spread, many people would become infected, and many casualties would arise, especially in less developed countries where healthcare systems are relatively poorly developed and insufficiently organized to face this infectious disease. History has taught us that this indeed happened several times in the past during plague, smallpox, and cholera epidemics. These catastrophic events were followed by even more dramatic experiences, including long-lasting famines and wars, that impoverished entire populations and killed millions of people. One such example was the so-called "Black Death," a fatal pandemic of bubonic plague that devastated whole populations in Europe, Africa, and Asia between 1346 and 1353 and resulted in 75–200 million deaths.

Thanks to advances in science, however, today medications and vaccines can be developed in relatively short periods of time, thus mitigating the impact of SARS-Cov2 that otherwise could be catastrophic. Acting rapidly and efficiently in biomedical research means that we need to use laboratory animals. In addition, existing medications that we are using to mitigate the consequences of SARS-Cov2 infection, such as drugs or vaccines that are approved for humans or other animals, were developed after extensive testing in laboratory animals. Is it an acceptable moral decision not to use them because they were initially tested in animals?

For ethical reasons, an individual with full cognitive capacity can decide not to use drugs that were developed from animal testing. This is an acceptable position because individuals possess full cognitive capacity. More complex is when such a choice is made by people who suffer from cognitive impairments, psychological instability, or other cases of compromised judgment.

Moreover, an unacceptable position would be when an individual's conscientious objection is imposed on other people to limit their access to drugs or other medical treatments. For example, the "no-vax" position is not ethically acceptable because reducing the number of people who are vaccinated consequently heightens the risk of spreading an infectious disease in the whole population, with severe consequences especially for those who, because of specific circumstances (i.e., immunodepression), cannot be vaccinated.

Unfortunately, unfair or misleading information, characterized by high emotional loads, that depict laboratory animals as victims of human progress has a tremendous impact on this ethical debate, and public opinion can be easily swayed by it. As Daniel Kahneman[30,31] pointed out in his theory of heuristics and bias, particularly in complex situations, when it is difficult to provide an exhaustive answer (i.e., in ethical debates), humans engage in cognitive processes that "substitute" the original question with an alternative one that is easier to answer. For example, if the question is, "How many laboratory animals are you willing to sacrifice to advance human knowledge about a certain disease and develop a new medication?" then the alternative question is, "How much emotion do I feel when I save the life of animals that are otherwise used for laboratory testing?" The answer to this latter question does not respond to the original one but provides a rapid solution to the ethical dilemma.

If this is the cognitive process that contributes to biasing public opinion toward the protection of animal rights to the detriment of societal progress and human health, then scientists should probably reconsider the way they are the vehicles of information about their own research work. To communicate rational information and statistical data on how many human lives biomedical research can save by developing a new medication will probably not work. But if the ethical question is posed differently, such as, "How many people who suffer from untreatable disease are you willing to save by allowing laboratory animal testing?" then the heuristic questions will be, "How much emotion do I feel when I save human beings who suffer from a disease that threatens their lives?" At the margin between these two views is the fundamental role of responsibility, which links the needs of being responsible for the rights of both humans and other animals to create a liminal space we call ethics. In this space, every action must be pondered, and appropriate questions need to be asked to find the right balance when engaging in open and healthy debate. The example of SARS-Cov2 is both real and recent and tells us that our responsibility is to act consciously to find an optimal balance between protecting animal rights and the obligation to act in an attempt to advance human society and improve the quality of life of our own species. So we believe that it is an opportunity for science to pose the right questions to raise public awareness about the importance of animal testing in biomedical research.

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REFERENCES

1. Thalmann O, Shapiro B, Cui P, et al. Complete mitochondrial genomes of ancient canids suggest a European origin of domestic dogs. *Science*. 2013;342(6160):871-874.
2. Hippocrates. Corpus Hippocraticum. IV B.C.
3. National Research Council (US) Committee to Update Science M, and Animals. *Science, Medicine, and Animals*. Washington (DC): National Academies Press (US); 2004.
4. Darwin C. *On the Origin of Species by Means of Natural Selection, or the Preservation of Favoured Races in the Struggle for Life*. London: John Murray; 1859.
5. Baumans V. Science-based assessment of animal welfare: laboratory animals. *Rev Sci Tech*. 2005;24(2):503-513.
6. Taylor K, Alvarez LR. An estimate of the number of animals used for scientific purposes worldwide in 2015. *Altern Lab Anim*. 2019;47(5–6):196-213.
7. Taylor K, Rego Alvarez L. A summary of EU national statistical reports of animal experiments in 2014-2016. *ALTEX*. 2019;36(2):314-319.
8. Council CftUotGftCaUoLANR. *Guide for the Care and Use of Laboratory Animals*. Eighth ed. Washington, DC: National Academies Press; 2010.
9. Rusche B. The 3Rs and animal welfare—conflict or the way forward? *ALTEX*. 2003;20(Suppl 1):63-76.
10. Hendriksen CF. Replacement, reduction and refinement alternatives to animal use in vaccine potency measurement. *Expert Rev Vaccines*. 2009;8(3):313-322.
11. Russell WMS, Burch RL, Hume CW. *The Principles of Humane Experimental Technique*. London: Methuen; 1959.
12. Doke SK, Dhawale SC. Alternatives to animal testing: a review. *Saudi Pharm J*. 2015;23(3):223-229.
13. Balls M. Future improvements: replacement in vitro methods. *ILAR j*. 2002;43(Suppl):S69-S73.
14. Giacomotto J, Segalat L. High-throughput screening and small animal models, where are we? *Br J Pharmacol*. 2010;160(2):204-216.
15. Wolf MJ, Rockman HA. *Drosophila melanogaster* as a model system for genetics of postnatal cardiac function. *Drug Discov Today Dis Model*. 2008;5(3):117-123.
16. Nass R, Merchant KM, Ryan T. *Caenohabditis elegans* in Parkinson's disease drug discovery: addressing an unmet medical need. *Mol Interv*. 2008;8(6):284-293.
17. Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the Protection of Animals Used for Scientific Purposes. *Off J Eur Union*. 2010;276:33-79.
18. Kant I. *The Metaphysics of Morals*. Cambridge: Cambridge University Press; 2017.
19. DeGrazia D. Animal ethics around the turn of the twenty-first century. *J Agric Environ Ethics*. 1999;11:111-129.
20. Singer P. *Animal Liberation. A New Ethics for Our Treatment of Animals*. New York: Random House; 1975.
21. Frey RG. *Interests and Rights: The Case Against Animals*. New York: Oxford University Press; 1980.
22. Frey RG. Moral standing, the value of lives, and speciesism. *Between Species*. 1988;4(3):191-201.
23. Carruthers P. *The Animals Issue: Moral Theory in Practice*. Cambridge: Cambridge University Press; 1992.
24. Jonas H. Das Prinzip Verantwortung: Versuch einer Ethik für die technologische Zivilisation. Suhrkamp Taschenbuch; 1984.
25. Ranganatha N, Kuppast I. A review on alternatives to animal testing methods in drug development. *Int J Pharm Pharm Sci*. 2012;4(SUPPL 5):28-32.
26. Lipinski C, Hopkins A. Navigating chemical space for biology and medicine. *Nature*. 2004;432(7019):855-861.
27. Vargesson N. Thalidomide-induced teratogenesis: history and mechanisms. *Birth Defects Res C Embryo Today*. 2015;105(2):140-156.
28. Shanks N, Greek R, Greek J. Are animal models predictive for humans? *Philos Ethics Humanit Med*. 2009;4(2):1-20.
29. Waring MJ, Arrowsmith J, Leach AR, et al. An analysis of the attrition of drug candidates from four major pharmaceutical companies. *Nat Rev Drug Discov*. 2015;14(7):475-486.
30. Tversky A, Kahneman D. Judgment under uncertainty: heuristics and biases. *Science*. 1974;185(4157):1124-1131.
31. Kahneman D. *Thinking, Fast and Slow*. Melbourne: Penguin Books; 2012.

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Roberto Ciccocioppo* - Francesca Petetta**

SGUARDI MULTIFOCALI SUL DESIDERIO

Multifocal Gazes on Desire

Considering both the empirical and the speculative perspectives, desire represent a special form of motivation, typically recognizable in humans, that makes subjects experience a relationship with their inner space and, at the same time, with the space outside. Desire can occur in two different forms: when in presence of a sense of emptiness, it involves an approach towards something; when in presence of a sense of fear or anguish, it involves an avoidance of something. Linking these two dimensions, the inner and the outer ones, desire is the bridge between sensations and actions.

Keywords: Desire, Motivation, Approach, Avoidance

L'osservazione degli enti e degli eventi che ci circondano sembrano suggerirci un fatto molto semplice e profondamente affascinante: vita è per lo più movimento. Lo stare nel mondo e l'adattarsi in esso accade attraverso continui processi dinamici. Ma cos'è che provoca il movimento, da cosa scaturisce? Sappiamo che a un livello fisico la realtà è composta da una trama sottilissima e invisibile di «oggetti» che si muovono ed entrano in relazione tra loro. Il livello fisico è il sostrato fondamentale grazie al quale si struttura la vita. Ma c'è senza dubbio di più. C'è il livello biologico. A un livello biologico la realtà è composta da organismi, ovvero sistemi capaci di differenziarsi e al tempo stesso relazionarsi con altri sistemi che li circondano. Ogni singolo organismo è il rappresentante di una data specie e si muove nel mondo proprio in vista della conservazione della propria specie. A tale scopo è funzionale che gli organismi sentano una *motivazione* per muoversi.

Nell'ambito strettamente neuroscientifico, il termine *motivazione* si riferisce a tutto ciò che rende gli organismi pronti ad agire in vista di un *approccio* verso qualcosa oppure, al contrario, di un *evitamento* da qualcosa. Tutti gli organismi, da quelli più semplici a quelli più complessi, sono accomunati da tale dinamica innanzitutto biologica.

Oltre ad essa, tuttavia, sono riscontrabili, per lo meno in organismi dotati di facoltà cognitive avanzate derivanti da strutture e funzioni cerebrali e neurali sviluppate, processi che sembrano in qualche modo trascendere i meccanismi strettamente biologici. Nel caso degli esseri umani, ad esempio, la motivazione nasce non solo dalla percezione immediata di una mancanza da colmare o di qualcosa da evitare. Gli esseri umani, in virtù dello straordinariamente complesso sistema nervoso di cui sono dotati, elaborano le proprie percezioni in maniera cosciente, offrendo loro una mediazione razionale e collocandole all'interno di un contesto narrativo e significativo.

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Notiamo dunque che, se in organismi dalle strutture e dalle funzioni più elementari la motivazione si manifesta nella forma di una pulsione biologica da cui scaturiscono azioni e movimenti a stretto raggio e a breve risoluzione (p. es. la motivazione a colmare un appetito si esplicita sotto forma di ricerca che si conclude all'arrivo del soddisfacimento), nel caso degli esseri umani essa è anche animata da processi decisamente più complessi e muove gli individui sotto forma di quella tensione che possiamo definire *desiderio*.

Già i pensatori antichi hanno riflettuto sulle forme e sulle implicazioni di tale tensione. Aristotele la definisce *orexis*. Una tensione interiore che muove teleologicamente l'intenzione all'azione, per cercare il raggiungimento di un fine[1]. Per quanto inserito in un contesto profondamente diverso da quello empirico che analizzeremo, il significato aristotelico del termine è molto utile per introdurre il concetto non solo di *desiderio* ma anche, in qualche modo, di *motivazione*. Esso infatti ci immette subito nel contesto di un processo attraverso cui l'organismo sviluppa un movente per adoperarsi al fine di ottenere una condizione che si prospetta buona, migliore di quella che avrebbe rimanendo fermo.

Anche nel mondo moderno i filosofi si sono interrogati su quale sia la dinamica di tale spinta interiore che muove e dirige la vita. Tale spinta viene ad esempio letta da Spinoza al modo di uno «sforzo», di un *conatus* «col quale ciascuna cosa si sforza di perseverare nel suo essere» e che «non è altro che l'essenza attuale della cosa stessa»[2]. Collocandosi sulla soglia tra la riflessione filosofica e quella psicoanalitica, anche Sigmund Freud legge il desiderio come quel «moto psichico» che fa tendere gli individui verso un oggetto che ricordano – spesso inconsciamente – come soddisfacente[3].

Nonostante le diverse sfumature di significato e di contesti in cui il concetto di *desiderio* è inserito, in ogni riflessione sempre si fa riferimento a una tensione da parte di un ente desiderante verso oggetti desiderati, siano essi oggetti fisici, concreti e «consumabili» oppure processi psicologici mnestici-immaginativi che incidono sui moti e sui fenomeni mentali. Più recentemente l'indagine riguardante la dinamica desiderativo-motivazionale ha trovato accoglienza in un ambito disciplinare prettamente empirico, grazie allo sviluppo delle neuroscienze. Intorno agli anni 60 del '900 il neuropsichiatra statunitense Paul MacLean ha elaborato una teoria denominata «il cervello trino», secondo la quale l'encefalo sarebbe composto di tre strutture: il cervello *rettiliano*, che corrisponde al cervelletto e al tronco encefalico, è la parte più antica e primitiva ed è specializzata nei meccanismi istintivi e automatici di sopravvivenza, come la risposta «attacca o fuggi»; il cervello *mammifero*, che corrisponde al sistema limbico, è la parte che regola le emozioni, i ricordi, le abitudini e permette i processi decisionali; il cervello *umano*, che corrisponde alla neocorteccia, è la parte più sviluppata ed evoluta, e rende l'organismo capace di esprimersi attraverso il linguaggio, il pensiero astratto, l'immaginazione, i ragionamenti coscienti.

Nel contesto di una ricerca che via via si fa sempre più focalizzata a studiare i meccanismi neurobiologici alla base dei fenomeni percettivi e comportamentali

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[1] Cfr. Aristotele, *L'anima*, III, 9, 432 b, tr. it. di G. Movia, Bompiani, Milano 2001, p. 233.

[2] B. Spinoza, *Etica*, III, P. VII, tr. it. di G. Durante, note di G. Gentile, rivedute e ampliate da G. Radetti, Bompiani, Milano 2015, p. 255.

[3] Cfr. S. Freud, *L'interpretazione dei sogni* (1899), tr. it. di E. Fachinelli - H. Trettl Fachinelli in *Opere di Sigmund Freud*, 12 voll., a cura di C. Musatti, Bollati Boringhieri, Torino 1966-, III, p. 516.

macroscopici, è stato possibile analizzare la motivazione attraverso i suoi sostrati[4]. Si è osservato dunque il funzionamento del *sistema della gratificazione*[5]. Esso è responsabile della sensazione di piacere prodotta dai comportamenti che rivestono un ruolo fondamentale nel favorire la sopravvivenza della specie. Alla gratificazione si accosta anche l'*aversione* nei confronti invece di tutti gli stimoli che potrebbero mettere a repentaglio la vita dell'organismo. Di fronte a stimoli gratificanti o aversivi, molti animali non umani, quali ad esempio alcune specie di primati o di roditori, condividono la stessa tipologia di reazioni affettive – positive per ciò che produce piacere e negative per ciò che dà disgusto – che si osservano nella specie umana[6].

L'analisi neuroscientifica ha rilevato un'associazione tra la presenza di esperienze gratificanti, il rilascio del neurotrasmettitore dopamina e l'attivazione di alcune specifiche aree cerebrali, quali il *putamen*, il *nucleus accumbens* (NAcc) e il *nucleo caudato*[7]. Quando dunque un organismo approccia oggetti o eventi vantaggiosi per la propria sopravvivenza, il sistema dopaminergico della gratificazione che nasce nell'area ventrale tegmentale e termina nel NAcc si attiva e produce sensazioni piacevoli. Alcuni esperimenti condotti su pazienti depressi hanno inoltre osservato che se le aree di tale sistema vengono stimolate direttamente con degli elettrodi, si ottiene la riduzione di anedonia e dei sintomi legati allo stato depressivo e l'incremento del numero delle attività piacevoli[8].

Se, da una parte, il cervello si attiva per favorire l'approccio a ciò che rappresenta un beneficio per l'organismo, dall'altra esso si attiva anche per indurlo a fuggire da ciò che lo mette in pericolo, ad esempio con la risposta di paura. Le evidenze più solide a supporto di tale ipotesi vengono dagli studi del neuroscienziato statunitense Joseph LeDoux. Tale ipotesi, definita della «doppia via», riconosce un ruolo fondamentale all'amigdala, area cerebrale che interviene nell'elaborazione degli stimoli che evocano sensazione di paura. Essa è strettamente collegata, attraverso delle fibre nervose che percorrono la base dell'encefalo, al talamo che le fornisce un'informazione immediata a partire dagli stimoli esterni che giungono attraverso gli organi di senso. Tale informazione non è precisa, ma è molto rapida, dato che non passa attraverso una mediazione cognitiva. Questa avviene invece attraverso una seconda via, più lenta rispetto all'altra, che giunge alle aree corticali anteriori e che è in grado

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[4] W. Hofmann - L.F. Nordgren (eds.), *The Psychology of Desire*, The Guilford Press, New York 2016.

[5] J. Olds - P. Milner, *Positive Reinforcement Produced by Electrical Stimulation of Septal Area and Other Regions of Rat Brain*, «Journal of Comparative and Physiological Psychology», 47 (1954), 6, pp. 419-427; R.A. Wise, *Addictive Drugs and Brain Stimulation Reward*, «Annual Review of Neuroscience», 19 (1996), pp. 319-340; H. Hu, *Reward and Aversion*, «Annual Review of Neuroscience», 39 (2016), pp. 297-324.

[6] K.C. Berridge, *Pleasures of the Brain*, «Brain and Cognition», 52 (2003), 1, pp. 106-128.

[7] K.S. Wang - D. V. Smith - M.R. Delgado, *Using fMRI to Study Reward Processing in Humans: Past, Present, and Future*, «Journal of Neurophysiology», 115 (2016), 3, pp. 1664-1678.

[8] R.S. Shah - S.Y. Chang - H.K. Min - Z.H. Cho - C.D. Blaha - K.H. Lee, *Deep Brain Stimulation: Technology at the Cutting Edge*, «Journal of Clinical Neurology», 6 (2010), 4, pp. 167-182; T.E. Schlaepfer - M.X. Cohen - C. Frick - M. Kosel - D. Brodesser - N. Axmacher - A.Y. Joe - M. Kreft - D. Lenartz - V. Sturm, *Deep Brain Stimulation to Reward Circuitry Alleviates Anhedonia in Refractory Major Depression*, «Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology», 33 (2008), 2, pp. 368–377; B.H. Bewernick - R. Hurlemann - A. Matusch - S. Kayser - C. Grubert - B. Hadrysiewicz - N. Axmacher - M. Lemke - D. Cooper-Mahkorn - M.X. Cohen - H. Brockmann - D. Lenartz - V. Sturm - T.E. Schlaepfer, *Nucleus Accumbens Deep Brain Stimulation Decreases Ratings of Depression and Anxiety in Treatment-Resistant Depression*, «Biological Psychiatry», 67 (2010), 2, pp. 110-116.

di valutare più accuratamente lo stimolo che ha di fronte, il quale così può essere accolto dall'individuo con la possibilità che gli venga attribuito un significato di paura. Per esemplificare tali processi LeDoux descrive il caso di una persona che mentre cammina in un bosco si trova di fronte a un oggetto allungato e scuro. La primissima reazione sarebbe quella di sobbalzare, nel momento in cui si attiva il circuito sub-corticale, dando per scontato che a terra ci sia un serpente. A una seconda osservazione, tuttavia, la persona potrebbe rendersi conto, grazie all'elaborazione cognitiva del circuito corticale, che in realtà si tratta di un bastone di legno. La reazione provocata dall'attivazione del primo circuito, quindi, sarebbe di paura istintiva e priva di consapevolezza. Quella invece che segue il lavoro del secondo circuito sarebbe più ragionata e cosciente[9].

Dagli studi di LeDoux emerge dunque l'importanza dell'amigdala nel contesto delle reazioni emotive che l'organismo produce di fronte a stimoli esterni. Essa infatti ha un ruolo sia nel riconoscimento e nella codifica degli stimoli, sia anche nel ricordo di esperienze emotive segnanti. Nel momento in cui viene danneggiata, si è osservato, si hanno compromissioni nell'attivazione di altre aree adibite alla ricezione degli stimoli esterni. Se ad esempio viene presentata una serie di immagini che evocano paura a un soggetto la cui amigdala abbia subito un danno, in tale soggetto l'attivazione della corteccia visiva è compromessa. Se si presentano invece degli stimoli subliminali a soggetti che non abbiano subito danni cerebrali, si nota che di fronte a stimoli che evocano paura l'attivazione dell'amigdala è maggiore rispetto a quella che si verifica in presenza di stimoli positivi.

Se dunque l'amigdala svolge un ruolo fondamentale nell'elaborare una risposta agli stimoli che l'organismo ha di fronte, essa non è l'unica area che si attiva. In uno studio del 2008 ci si è chiesti se c'è un'area che è sempre attiva quando si osserva un'immagine che provoca desiderio, a prescindere dal tipo di immagine. Le analisi hanno rivelato attività nei circuiti della corteccia orbito-frontale, in quella medio-cingolata e in quella cingolata anteriore[10].

In uno studio del 2007, inoltre, si è osservato un fenomeno molto interessante su soggetti fumatori che subivano danni nell'area dell'insula, un'area che, integrando i segnali periferici e le funzioni cognitive superiori, è preposta alla codifica delle informazioni relative alle sensazioni corporee. Tali soggetti erano più propensi a smettere di fumare a causa di una diminuzione del desiderio nei confronti delle sigarette[11].

Altri lavori dimostrano come l'insula sia essenziale anche per l'amore e il desiderio sessuale. In particolare è stato notato che l'attivazione dell'insula anteriore è correlata all'esperienza dell'amore sentimentale, mentre l'attivazione di quella posteriore è correlata all'esperienza del desiderio sessuale. In uno studio del 2014 si è analizzato un paziente maschio che presentava una rara e circoscritta lesione all'insula anteriore. È stato messo alla prova con un compito decisionale durante il quale egli doveva valutare una serie di immagini femminili attraenti e indicare se fossero oggetto del suo desiderio amoroso oppure sessuale. Il paziente non ebbe problemi a valutare il proprio desiderio sessuale, ma mostrò deficit nell'ambito del coinvolgimento sentimentale. Questo esperimento rappresenta la prima evidenza clinica del

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[9] J.E. LeDoux, *Emotion, Memory and the Brain*, «Scientific American», 270 (1994), 6, pp. 50-57.

[10] H. Kawabata - S. Zeki, *The Neural Correlates of Desire*, «PLoS One», 3 (2008), 8, e3027.

[11] N.H. Naqvi - D. Rudrauf - H. Damasio - A. Bechara, *Damage to the Insula Disrupts Addiction to Cigarette Smoking*, «Science», 315 (2007), 5811, pp. 531-534.

fatto che l'insula anteriore potrebbe svolgere un ruolo fondamentale nell'esperienza del desiderio amoroso ma non in quella del desiderio sessuale[12].

Attraverso tali esempi possiamo osservare che a livello neurobiologico è possibile descrivere la motivazione come un fenomeno che mette in gioco una serie di circuiti neurali preposti a diverse funzioni legate principalmente alla sfera emotiva e alle risposte corporee ai differenti stimoli. Tali risposte sono talvolta immediate e istintive, se l'organismo ha bisogno di elaborare una decisione istantanea rispetto a un determinato stimolo e, in questo caso, esse sono generate principalmente da circuiti sub-corticali. In altre occasioni invece, le risposte sono frutto di una rielaborazione razionale e cosciente, laddove l'evento o l'oggetto stimolante lascino il tempo per strutturare una decisione più lunga. In ogni caso sembra lecito affermare che le dinamiche e i meccanismi dell'esperienza desiderativa siano fattori costitutivi della modalità con cui gli organismi si adattano all'ambiente in cui si trovano, elaborando decisioni, scegliendo fini, cambiando direzioni in base alla diversità degli stimoli che si presentano e rispondendo ai propri bisogni con azioni mirate, siano esse esclusivamente istintive oppure propriamente consapevoli.

In breve, questa analisi, pur non nutrendo l'ambizione della novità, intende integrare attraverso una visione neuroscientifica il concetto di *desiderio* intendendolo come quella particolare forma di motivazione che, da un lato, coinvolge attività legate all'immediatezza dei meccanismi biologici e, dall'altro, forse soprattutto, riguarda processi più profondi quali ad esempio quelli psichici, quelli cognitivi, quelli relazionali, quelli decisionali complessi.

Volendo ora tentare di cogliere l'eccedenza irriducibile del fenomeno desiderativo e volendo, allo stesso tempo, tener presente la descrizione e l'analisi empirica dei suoi sostrati neurobiologici, intendiamo definire il desiderio – riferendoci principalmente a quello umano – come una relazione sfaccettata e dal volto duplice, una relazione spesso generatrice, che produce movimenti più o meno intenzionali e sempre teleologicamente orientati.

Da un lato, desiderio è la relazione che il soggetto instaura con le proprie paure, con l'elaborazione di queste sotto forma di angoscia e, allo stesso tempo, con la prefigurazione di una condizione capace di sanarle o scacciarle. Questo primo volto del desiderio genera movimenti di evitamento.

Dall'altro, desiderio è la relazione profonda che il soggetto instaura con il vuoto delle mancanze che sente e, allo stesso tempo, con l'infinito atteso e prefigurato in cui proietta il loro soddisfacimento. Il desiderio in questo senso si configura come una chiamata interiore ad aderire a sé e al proprio vuoto, al mondo e all'infinito prospettarsi di possibilità di riempimento. Dall'incontro e dalla relazione col proprio vuoto scaturisce dunque l'approccio, cioè l'apertura e l'uscita da sé che preparano la strada all'incontro e alla relazione con l'alterità, ed è proprio questa la potenza e l'importanza del desiderio. Non solo, in quanto forma di motivazione, muove il soggetto verso i propri fini ma, più profondamente, creando modi originali per tentare di afferrare l'infinito, tesse trame intersoggettive significative e sensate, al di sopra di ogni interazione fisica e biologica. Il desiderio, insomma, fa del vivere un abitare.

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[12] S. Cacioppo, - B. Couto - M. Bolmont - L. Sedeno - C. Frum - J.W. Lewis - F. Manes - A. Ibanez - J.T. Cacioppo, *Selective Decision-Making Deficit in Love Following Damage to the Anterior Insula*, «Current Trends in Neurology», 7 (2013), pp. 15-19.