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Stimulating the brain to study social interactions and empathy

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ABSTRACT

Empathy is a multi-dimensional concept allowing humans to understand the emotions of others and respond adaptively from a social perspective. This mental process, essential to social interactions, has attracted the attention of many scholars from different fields of study but the blooming interest for empathy in cognitive neurosciences has rekindled this interest. This paper reviews the growing literature stemming from studies using brain stimulation techniques that have investigated directly or indirectly the different components of empathy, including resonance, self-other discrimination, and mentalizing. Some studies have also ventured toward the modulation of this complex process and toward the investigation of different components in populations that show reduced empathic skills. We argue that brain stimulation techniques have the potential to make a unique contribution to the field of empathy research with their exclusive capacity, compared to other brain imaging techniques, to modulate the neural systems involved in the distinct components of this process. Provided the development of innovative ecological paradigms that will put people in actual social interactions as well as comprehensive and adaptive models that can integrate research from different domains, the ultimate goal of this research domain is to devise protocols that can modulate empathy in people with developmental, neurological and psychiatric disorders.

Introduction

The study of human cognition from a social and neuroscience perspective has exploded in the last decade. The accessibility and versatility of brain mapping techniques has contributed to this frenzy and has also fueled the curiosity not only of neuroscientists, but also of psychiatrists, philosophers, lawyers, economists, policy makers, and the general public. The idea of imaging the human mind is very fascinating indeed but the rapidly evolving brain stimulation techniques (e.g. single-pulse transcranial magnetic stimulation (TMS); repetitive transcranial magnetic stimulation (rTMS); theta burst stimulation; transcranial direct current stimulation (tDCS)), have contributed to mapping but mostly to transiently modifying brain function and thus behavior. Indeed, one of the greatest advantages of brain stimulation methods over functional brain imaging techniques is that instead of observing associations between brain response patterns and certain behaviors, one can actively modulate the pattern of brain activity and measure the consequent response, therefore changing the pattern of response in lieu of simply characterizing it. From a social and cognitive neuroscience perspective, this is the future of research and part of this future is happening now.

Empathy is arguably one of the key functions driving human socialization. Empathy can be defined as the set of mental abilities allowing people to detect and understand the affective state of others, which then leads to the communication of this understanding following a prosocial intent. This is achieved while taking into account the context of the others' experience and maintaining a clear separation with one's own experience (e.g. [1,2]). The study of empathy extends that of emotions in that it always requires a minimum of two agents, typically one expressing an affective state and one responding to it. The study of empathy thus implies the analysis of someone's responses (neurophysiological and behavioral) to another person and also, and perhaps most importantly, the responses *toward* (prosocial) another person [3]. During social interactions empathy can be used to gain information on another individual's state, which can help predict their future actions but it can also help us chose our own actions with regards to this social situation.

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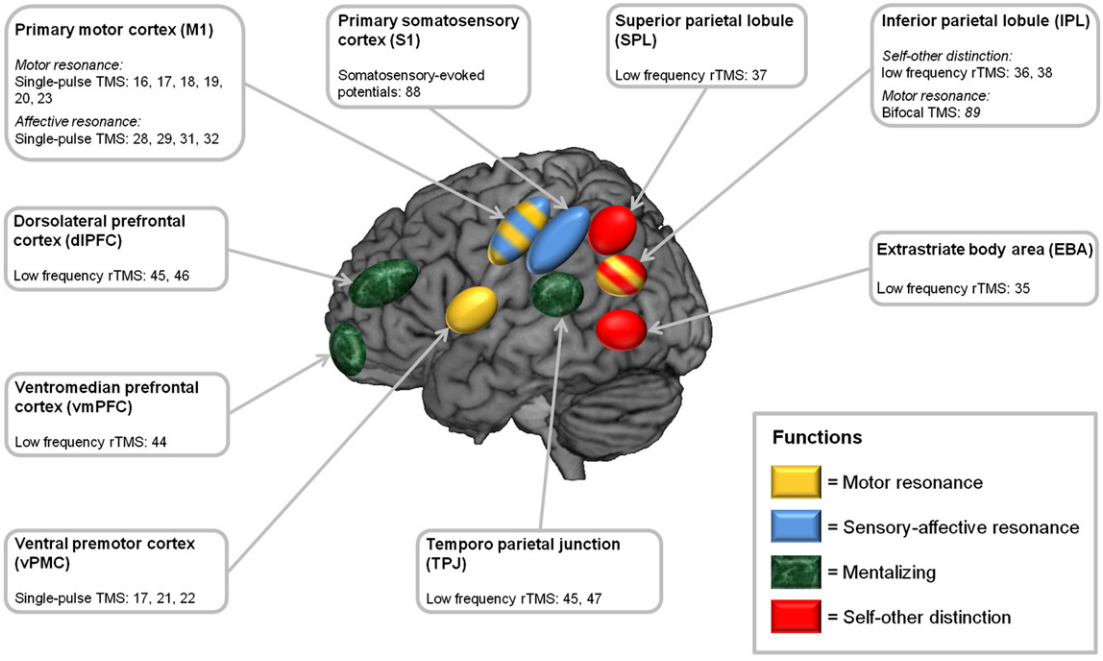

Figure 1. Overview of stimulation sites (with no regards to hemisphere) and empathy components targeted by brain stimulation studies. For the sake of clarity, representative references are provided instead of the exhaustive list of publications. Note that references [88,89] are not listed in the text but are still presented here to provide examples for these regions/functions.

There are different models of empathy in the literature but few take into account both its behavioral manifestation and the underlying cerebral architecture. Studies about the later have largely focused on separate components of empathy. Here, we propose a framework extending previous work [2,4] to review systematically the contribution of brain stimulation techniques to the understanding of the different components of this complex process (Fig. 1 and Table 1). As will be discussed throughout, it is important to keep in mind that each of these components is probably not sufficient in itself to account for empathy [2].

The perception of another person's affective state can lead to changes in the observer's brain activity generally associated with this state. Such bottom–up simulation process has been dubbed "**resonance**" to reflect its automatic nature and is postulated by many to be one of the key components of empathy, and perhaps the initiating process in the affective route toward an empathic response [5,6]. The top–down route toward empathy relies on deliberate processes that allow us to take the perspective of others, attribute mental states and intentions to others (Theory of Mind; ToM), and understand others' affective states [7]. These processes can be regrouped under the term **mentalizing**. This potent human ability allows the mental representation of other people's intents, desires and affect, even in the absence of direct sensory input [8]. This exposure to potential bombardments of other people's affective states either automatically (resonance) or deliberately (mentalizing) threatens the ability to distinguish the source (self vs. other) of an affective representation. The role of the **self-other discrimination** component is to track the attribution process [9], while **regulation** mechanisms prevent the overflow of other people' affective states onto the self experience.

As there are not yet any studies with brain simulation examining empathy as a unified process, this review presents a number of studies that have investigated one of the different components of empathy. A subsequent section will examine the few studies that have used brain stimulation with clinical or subclinical populations that are thought to have deficits in empathy. Finally, this paper will discuss future directions that could lead to more integrative approaches to the study of empathy, and which could pave the way to the noble goal of finding means to improve people's empathy through the use of brain stimulating techniques.

Social perception and the resonance system

Humans express a myriad of subtle social cues in order to communicate with each other (e.g. posture, facial expressions). This information has to be processed accurately by an observer in order to be understood correctly. In fact, the human mind seems to use mental simulations of the perceived social information in order to infer its meaning [8]. These simulations involve the reenactment of the perceived information in order to bring to memory various pieces of knowledge such as psychological states that might have been associated with this information. For example, seeing an infant being teased by other kids may elicit the memories of our own early social conflicts. The neural correlates of this subjective experience might be a simulation or resonance mechanism in the cerebral regions where these experiences were first processed. For example, seeing a child running away from another kid may trigger activity in regions of our brain that are active when we are afraid and/or when we are running. In fact, different components of social information might trigger different types of resonance, and the resonance system could thus encompass sensorimotor as well as affective information.

Stimulating the motor resonance system

One of the possible cellular processes underlying the mechanism of **motor** resonance is thought to rely on the "mirroring" property of neurons discovered in the early 1990s, by Rizzolatti's group. This seminal work demonstrated the presence of neurons in the ventral premotor cortex of primates that discharge both when performing an action and when observing this same action [10], hence the name "*mirror neurons*". These neurons were hypothesized to be a core component of motor understanding, linking perception and action. This initial discovery in primates and the

Table 1
Stimulation parameters for studies that used rTMS or tDCS to probe empathy and its components.

Study	Technique	Stimulated region	Frequency	Duration	Number of sessions	Intensity
Urgesi et al., 2007	rTMS	L and R EBA L and R vPMC	10 Hz	200 ms; 100 ms ISI (only 2 pulses)	Online rTMS during trials	120%MT
MacDonald & Paus, 2003	rTMS	L SPL L temporal cortex (ctrl)	0.6 Hz	Around 15 min	1	90% MT
Uddin et al., 2006	rTMS	R IPL L IPL (ctrl)	1 Hz	20 min	1	100% MT
Kalbe et al., 2010	rTMS	R BA9 Vertex (ctrl)	1 Hz	15 min	1	100% MT
Costa et al., 2008	rTMS	L and R dlPFC L and R TPj	1 Hz	15 min	1	90% MT
Young et al., 2010 Experiment 1	rTMS	R TPj 5 cm post. to R TPj (ctrl)	1 Hz	25 min	1	70% MSO
Young et al., 2010 Experiment 2	rTMS	R TPj 5 cm post. to R TPj (ctrl)	10 Hz	500 ms	Online rTMS during trials	60%
Balconi & Bortolotti, 2011	rTMS	FCz (BA 6) Pz (ctrl)	1 Hz	5 s	Online rTMS during trials	120% MT
Berlim et al., 2011	rTMS	L dlPFC	10 Hz	75 × 4 s trains; 26 s ITI	28 (daily for 4 wks)	120% MT
David et al., 2009	rTMS	L EBA L temporal cortex (ctrl)	1 Hz	15 min	1	90% MT (80% for 3/12 subjects)
Avenanti et al., 2007	rTMS	L vmPMC L SI L M1	1 Hz	15 min	1	100% MT
Lev-Ran et al., 2011	rTMS	vmPFC	1 Hz	100 s	1	100% MT
Krause et al., 2011	Deep rTMS	mPFC	1 Hz	15 min	1	100% MT
Boggio et al., 2009	tDCS (anodal)	M1 dlPFC V1		5 min	1	2 mA
Probic & Hamilton, 2006	rTMS	L IFG L V1/V2 (ctrl)	5 Hz	500 ms	Online rTMS during trials	110% MT

L = left; R = right; ctrl = control site; EBA = extrastriate body area; vPMC = ventral premotor cortex; TPJ = temporo-parietal junction; dlPFC = dorsolateral prefrontal cortex; SPL = superior parietal lobule; IFG = inferior frontal gyrus; IPL = inferior parietal lobule; BA = Brodmann area; S1 = primary sensory cortex; SII = secondary sensory cortex; V1 = primary visual cortex; vMPC = ventromedial premotor cortex; vmPFC = ventromedial prefrontal cortex; M1 = primary motor cortex; mPFC = medial prefrontal cortex/ ITI = inter-train interval; ISI = inter-stimulus interval; MT = motor threshold; MSO = maximum stimulator output.

subsequent discovery of similar neurons within the parietal cortex rapidly led to studies aimed at investigating this phenomenon in humans (e.g. [11,12]). Most experiments in functional neuroimaging have concluded that a network of cortical regions typically including the inferior frontal gyrus and the inferior parietal lobule also exhibited such a mirroring property (see for reviews: [13,14]; for more details see the meta-analysis of Grosbras et al. [15]). Quickly, the term "*mirror neurons system*" was coined to describe the apparent human counterpart of the mirror neurons observed in non-human primates. It is noteworthy that while a number of authors in the general field of social neuroscience associate their findings with the mirror neurons literature, little evidence indicates that mirror neurons are directly implicated in the resonance mechanism in humans. Nevertheless, this network appears to map parameters of observed actions in regions of the observer's brain that are also activated during action execution and may represent the neural correlate of resonance.

This intriguing network has raised many interesting questions and some of them have been successfully addressed using non-invasive brain stimulation, notably to map the core and the connectivity of the motor resonance system. For instance, applying TMS over the primary motor cortex (M1) during action observation has been shown to highlight subtle changes in corticospinal excitability associated with motor resonance (see [16] for a review). Further findings suggested that the ventral premotor cortex (vPMC) might be responsible for this activity via its functional connectivity with M1 during action observation (e.g. [17]). Importantly, these findings have not yet been replicated using other neuroimaging techniques such as fMRI (see the meta-analysis of Grosbras et al. [15]) which suggests that TMS might be especially suited to study motor resonance in M1. Moreover, work by Catmur et al. have indicated that motor resonance might be fashioned by sensorimotor learning associating an executed action with an observed one [17,18]. The results of TMS studies also showed that the frontal structures of the motor resonance system can process information regarding the prediction of actions based on the kinematic of movements (e.g. [19,20]). Furthermore, extracting specific information about the action of others seems to rely on these frontal regions. For example, Pobric and Hamilton [21], showed that disrupting the functioning of the inferior frontal gyrus using rTMS in participants who had to evaluate the weight of a box lifted by another person resulted in impaired weight judgment. Taken together, these findings have strengthened the hypothesis that motor resonance might be a crucial process that generates information used by higher-order cognitive processes in order to understand the actions of others.

Since motor resonance has been postulated to be a key element in action understanding, one might expect a link between the activity of the resonance system and higher-order cognitive processes such as explicit perceptual classification of actions. Cattaneo et al. [22] provided the first direct evidence that motor resonance in the inferior frontal cortex influences action perception by showing that habituation in a motor task can generate an after-effect in the judgment of observed ambiguous movements. For instance, if a participant is asked to perform a pulling action for a certain amount of time, consecutive ambiguous presentations (that could either be pulling or pushing actions) are more likely to be defined as pulling actions. As habituation effects are usually thought to be specific to a population of neurons encoding for a certain feature, it is reasonable to assume that the neurons that adapted in the motor training session are also recruited during action perception. Furthermore, Cattaneo et al. [22] reported that single-pulse TMS over the vPMC (but not over M1) briefly abolished the after-effect, thus strongly suggesting that the neurons responsible for the habituation in the motor task are located in the vPMC. This demonstration represents the first direct evidence for a causal

role of the resonance network in action understanding and suggests that habituation might be an interesting avenue for the study of motor resonance.

Of particular importance for empathy, priming an individual with social information relative to self-construal (the way people perceive the self relative to others) has also been shown to modulate activity in the corticospinal track. Obhi et al. [23] showed that presenting words referring to an interdependent self-construal type (e.g. "together") during the observation of actions induced a facilitation of the corticospinal output beyond the facilitation induced by action observation alone or by words referring to independent self-construal type ("alone"). This suggests that interdependent self-construal priming induces hyperactivation of the corticospinal track. While the processes inducing such a modulation are still unclear, these results highlight the fact that priming higher-order social processes might influence the activity of the resonance network in order to facilitate or possibly inhibit the input of social information.

Stimulating brain reactions to pain observation

Before motor resonance became a major research avenue, many had proposed that simulation of a perceived psychological state might be one of the core aspects of social interaction (e.g. [24]) and empathy. Indeed, empathy is often defined in the general population as the capacity to share the feelings of others: *to feel what he/she feels*. Pain has often been the prime candidate to study sensory/affective resonance, as it offers at least two main advantages over other affective states. First, pain communication is crucial for the survival of the self and the group, and might therefore have been deeply rooted in human biology throughout evolution. Second, pain is now understood as a complex experience comprising affective and sensory components that appear to be treated in independent regions of the brain (e.g. [25]).

Functional MRI was the first technique used to confirm the overlap between the regions responsible for experiencing pain through nociception and perceiving pain in others [26,27], thus demonstrating the sharing of the affective dimension of pain. Studies using TMS rapidly followed with the seminal study by Avenanti et al. [28] that highlighted the sensorimotor aspect of pain resonance. They indeed showed that observing a needle penetrating a specific hand muscle decreases motor-evoked potentials in the same muscle as the one being pricked in the visual presentation. This interesting finding indicated that pain resonance might also be represented in a somatotopic fashion in sensorimotor regions, a pattern that has yet to be shown with fMRI. Further results have suggested that pain resonance might include complex modulations of corticospinal activity possibly in order to mediate adaptive responses such as freezing or escaping [29]. This hypothesis implies that pain resonance may be closely linked to behavioral priming in order to facilitate reaction to a threat communicated by others [30].

As with motor resonance, it has been suggested that higher-order cognitive processes might also present top–down influences on pain resonance [3]. For instance, Avenanti et al. [31] demonstrated using single-pulse TMS that racial bias might modulate this process. They observed that the decreased MEP amplitude reported during the observation of painful stimulation was only discernible when the hand presented belonged to a member of the ingroup (similar in skin color) rather than an outgroup member (dissimilar in skin color). Interestingly, the authors reported decreased MEP amplitudes when the participants observed a hand model of a new and unknown social group (violet hand). This last observation suggests that decreased MEP size associated with perception of stimuli depicting pain can be elicited when observing an outgroup individual in pain but may be modulated by racial bias (or lack of similarity bias) regarding the outgroup members. This hypothesis is supported by the fact that greater sensorimotor responses to ingroup relative to outgroup models were found in participants with greater racial biases. Taken together, these findings indicate that while individuals can exhibit pain resonance for both ingroup and outgroup members in pain, this response can be modulated by individual characteristics of the observers.

A relationship has also been observed between pain resonance and self-reported empathy in at least one brain stimulation study (e.g. [32]; note that this relationship was not systematically found in fMRI studies on pain observation). The authors investigated the association between self-reported measures of empathy and the reduction of corticospinal outputs during pain observation. The results suggested that participants reporting higher sensory qualities in the visual presentations and higher cognitive empathy exhibited greater MEP inhibition (associated with greater pain resonance). Also, participants presenting higher personal distress in the experiment and in general empathic situations showed less MEP inhibition. These results indicate that different subcomponents of empathy may be associated in conflicting ways with the sensorimotor aspect of pain resonance.

These different brain stimulation studies, using action observation or pain perception paradigms, offer strong evidence that the sensori-affective component (or "feeling") of empathy may originate from a resonance process. However, if the sensorimotor and/or affective resonance response activate similar neural systems than the ones responsible for our own motor actions and/or emotional reactions, other systems need to be at play during empathy to insure its adaptive use during social interactions. Indeed, our ability to easily distinguish ourselves from others, in most circumstances, enables us to correctly interpret the source of our internal state.

Self-other distinction: data from brain stimulation studies

The extrastriate body area (EBA), posterior superior temporal sulcus (pSTS), temporo-parietal junction (TPJ), ventral premotor cortex, posterior and inferior parietal cortex have all been proposed to be associated with self-other distinction [33]. In order to confirm their specific roles, several rTMS studies have been conducted in which the function of one or more of these regions was altered and the consequences on self-other discrimination or agency attribution were measured behaviorally. Up to now, studies using brain stimulation techniques have mainly focused on the EBA and the parietal cortex. Results from a rTMS study showing that the EBA was involved in agency attribution [34] led researchers to investigate its possible role in self-other discrimination. For instance, David et al. [35] showed that low frequency rTMS on the EBA decreased the subjects' performance on self-other discrimination task. Similar results were found by disrupting the functioning of the inferior parietal lobule [36] or the superior parietal lobule [37]. Importantly, these studies were conducted with tasks in which subjects were asked to determine if visually presented movements were the result of their own movements or movements made by another individual. Although this particular type of task is informative about self-other distinction, it uses upper limb movements as stimuli and focuses the subject's attention on the motor aspects of these stimuli (e.g. temporal or spatial asynchrony). In our daily life, facial characteristics and expressions, not upper limb movements, are the main source of information on who this person is and how he/she feels. Accordingly, instead of using movement related stimuli, Uddin et al. [38] asked participants to determine if a face was their own or the one of a person they knew well. Importantly, the face of each subject was morphed with the face of

the other person in order to produce varying degrees of self/other faces (e.g. 90% self/10% other; 40% self/60% other). After a single session of 1 Hz rTMS on the right IPL, the authors noticed that subjects' performance was impaired. More specifically, they made more "self" responses even if the face they saw contained mostly characteristics of the "other". In a way, this result brings us a step closer to the actual self-other discrimination taking place during the visual perception of the emotional state of another individual. As both the EBA and the parietal cortex seem to be involved during self-other discrimination, it would be interesting to see if they work in concert or independently during social interactions. To answer this question, in addition to fMRI connectivity approaches, TMS could be used in dual-site paired-pulse paradigms (see [39] for a review and [40] for an example) during self-other discrimination tasks. The capacity of humans to voluntarily take the perspective of another person whether it is at the cognitive (imagine what a person would think in this situation) or the affective level (imagine what this person would feel) most certainly necessitates further computation and probably involves other brain structures in addition to those subserving the "automatic" process of self-other distinction. These processes are often included in the general function of mentalizing.

Stimulating mentalization

As mentioned before, mentalizing or theory of mind refers to our ability to infer the mental states of others. Mentalizing enables individuals to empathize and cooperate with others, accurately interpret other people's behavior, and even deceive others when necessary [41]. A recent meta-analysis of fMRI studies has highlighted the consistent activation of the TPJ and the mPFC during mentalizing tasks [42]. Again, brain stimulation techniques have mainly been used to confirm with virtual lesion paradigms the role of certain brain regions thought to be implicated in mentalizing based on previous fMRI results. For example, using a task requiring the inference of others' affective states [43], Lev-Ran et al. [44] have shown that the ventromedial prefrontal cortex (vmPFC) was involved in the learning of affective mentalizing (inferring the affective mental states of others). Indeed, the subjects' performance on the task did not improve with practice after low frequency rTMS over vmPFC, contrary to sham stimulations. This was interpreted as evidence that the vmPFC is involved in learning to use mentalization rather than in its general functioning. Other studies indicated an anatomic dissociation between the affective and the cognitive (knowledge of other beliefs or intentions) dimensions of mentalizing [45,46]. Costa et al. [45] looked at the role of the dlPFC and the TPJ during a faux-pas (affective) and a false belief (cognitive) task. They reported that the performance on the affective task was reduced after low frequency rTMS to the right and left dlPFC and the right TPJ (but not left TPJ) whereas performance on the cognitive task decreased after rTMS to the right dlPFC and the right TPJ (but not left dlPFC nor left TPJ). However, this last result has to be interpreted cautiously as others have found that low frequency rTMS to the right dlPFC did not impair performances during a cognitive mentalizing task [46]. Nonetheless, these results suggest that affective and cognitive mentalizing rely, at least partly, on different neural structures.

Right TPJ (rTPJ) involvement in mental state attribution was also shown in a clever study requiring subjects to perform moral judgments about social situations in which the intent/belief of the character (neutral, negative) and the outcome of the situations (neutral, negative) were manipulated [47]. Low frequency rTMS to the rTPJ made subjects judge attempted harm (e.g. the person intended but failed to do harm) as less morally forbidden and more morally permissible. The authors interpreted this result as evidence that subjects based their moral judgments less on the information related to the mental state of the person than on the outcome, again suggesting that the rTPJ plays a role in cognitive mentalizing [47].

Taken together these results indicate that affective mentalizing seems to rely on a widespread system including bilateral prefrontal regions whereas the system subserving cognitive mentalizing seems to be more restricted to the right hemisphere. It is clear that identifying the exact networks involved in different aspects of mentalizing will require further research that would benefit from more exhaustive mentalizing and social cognition tests (e.g. Achim et al. [48]). Additionally, it would be important to keep in mind that structures lying deeper in the brain such as the insula or cingulate cortex are also likely important for mentalizing [49,50]. A more direct examination of the involvement of these structures, however, relies on the development of deep TMS techniques (for examples, [51–53]). Already, such tools have been used to probe the role of the mPFC in mentalizing showing that this structure may be involved in affective mentalizing [54].

When empathy goes wrong: insights from brain stimulation

Another strategy to study empathy and its components with brain stimulation is to investigate populations that are known to lack empathy, often related to a deficit in one of its component described above. Deficits in empathy have been documented in several clinical conditions like schizophrenia [55], autism [56], and psychopathy [57], mostly through clinical observations, questionnaires or behavioral testing. Some neuroscientists are now using well-established TMS paradigms in order to assess possible differences in empathic neural responses between people with neurological, developmental or psychiatric disorders and healthy individuals (e.g. [58,59]). These particular studies have for the most part looked at the modulation of cortical excitability induced by the observation of others' movements or pain.

In 2005, Theoret et al. [58] studied adults with autism spectrum disorder (ASD) and showed for the first time using TMS that the motor resonance response could be altered in a population with a lack of social and emotional reciprocity. Note that this altered resonance response was only present when participants observed movements made from an egocentric perspective (as if they were watching themselves move) and not when they observed movements made from an allocentric perspective (as if someone facing them was making the movement). A recent study confirmed the presence of impairments in motor resonance in ASD subjects [60]. Interestingly, these differences do not seem to be restricted to people with a clinical diagnostic of ASD as motor resonance responses have been shown to be absent (i.e. no difference in corticospinal excitability between the action observation and baseline conditions) in healthy individuals with high traits for autism (measured with the autistic quotient: AQ [61]). This was not the case with individuals with low levels of autism trait [62].

Studies using observation of pain paradigms have the advantage of introducing a sensori-affective component in the response of the observer and as such, are perhaps one step closer to an empathy-eliciting situation than action observation. Studying individuals with ASD (Asperger syndrome), Minio-Paluello et al. [63] found that the MEPs of these individuals were not reduced during the observation of pain in others. Also, the modulation in MEPs' size was not correlated with subjects' pain intensity rating (contrary to what was found in healthy individuals). The reduction of the cortical excitability during observation of pain in others is often considered as a marker of sensorimotor resonance, a component of the empathic response. Thus, such findings have been interpreted as an indication that individuals with Asperger syndrome may have deficits in embodying the emotional states of others, which in turn

could lead to difficulties in understanding others and consequently to altered social interactions [64].

Looking at the effect of psychopathic traits in non-psychiatric individuals, Fecteau et al. [65] found that the corticospinal excitability of their subjects' was normally reduced during the observation of pain in others. This was not surprising, as their subjects presented no psychiatric condition per se. However, the amount of reduction of MEP size was positively correlated with their score on the cold-heartedness subscale of the Psychopathic Personality Inventory (PPI) (the higher the score, the greater the reduction) suggesting a link between psychopathic traits and sensory resonance. Interestingly, these different response patterns between ASD and psychopathy are in line with clinical observations associated with each of these conditions. Psychopathy is thought to be characterized by relatively normal processing of most socio-emotional cues [57], but present impairment in the use of this information. On the contrary, other conditions such as ASD are characterized by impairments in the perception of affective cues [66].

A relatively recent and influential view proposes that changes in the ratio of cortical excitability to inhibition (E/I balance) could induce the social and cognitive deficits observed in clinical conditions such as autism and schizophrenia [67–69]. The relation between social impairments and the E/I balance was demonstrated using optogenetics tools (see [70] for a review on this technique) in mice [71]. This result remains difficult to interpret at the human level. Nonetheless, if the E/I imbalance is involved in the empathy impairments of humans, brain stimulation techniques that can modulate excitatory or inhibitory activity such as rTMS/tDCS or the rhythmic activity of the brain such as transcranial alternative current stimulation (tACS) (see [72]) may have great intervention potential.

Modulating empathy and beyond: brain stimulation as an intervention

In clinical settings, empathy represents an interesting new target in the treatment of many disorders and some therapeutic avenues have already been explored to increase empathy. For instance, interventions at the molecular level have indicated that intranasal administration of oxytocin can induce transient modulation of empathy [73] and related social behaviors (see [74] for a review). Another approach has been to investigate the use of several brain stimulation techniques such as theta burst, low/high frequency rTMS, tDCS and tACS to modulate empathy-related brain activity. As reported before, brain stimulation can artificially alter (in these cases impair) various empathic processes such as motor resonance response [75], emotional/affective reactions to others' emotional state (e.g. pain) [76], self-other discrimination [38], and mentalizing [45]. If it has been shown that the different components of empathy can be modulated through brain stimulation, these results do not show that brain stimulation can have an effect on empathy per se. Still, this very question has recently been addressed in an interesting study by Balconi and Bortolotti [77]. During an emotional facial expression detection task, participants were explicitly asked to empathize with the person depicted in the stimuli ("Try to enter into another's feelings by observing the facial stimulus represented"). Inhibiting the frontal sensory motor cortex (about BA6), with low frequency rTMS resulted in impaired performance on the detection task and most importantly here, subjects were less able to empathize with the person as indicated by lower scores on a Likert-type scale on which subjects had to rate their degree of empathy. Even if the behavioral measure of empathy was limited, this result provides evidence that brain stimulation techniques can affect our empathic capabilities and could thus possibly alter social interactions. Still, all the data previously presented focused on the adverse effects brain stimulation can have on empathic processes. It is obvious that to treat clinical conditions with empathic deficits, brain stimulation should be used to increase empathy or restore the "normal" brain activity related to empathy. As impairments are usually observed after low frequency rTMS, high frequency rTMS protocols, resulting in increased excitation, could possibly be used as treatments. For example, a recent case study [78] has reported that nine sessions of high frequency deep rTMS to the bilateral medial prefrontal cortex in a woman with ASD resulted in improved self-reported social functioning evaluated with the IRI [79], AQ [61] and Ritvo Autism-Asperger Diagnostic Scale [80]. In addition, a subjective "increased capacity in empathy and perspective taking" was reported by the woman and confirmed by her family. High frequency rTMS over the dlPFC was also shown to improve mentalizing performance in a group of subjects with major depressive disorder [81], a condition often associated with impairments in social functioning [82]. Although the improvement in mentalizing performance was related to the antidepressant effect of the treatment (rTMS protocols over the dlPFC are now widely used to treat depression [83]), this result suggests that rTMS has the potential to be used as a clinical tool with conditions showing empathic impairments, whether this effect is direct or mediated by improvement in mood. Still, there is a lot of work ahead to define the systems to be targeted and the optimal settings to use in order for brain stimulation interventions to be considered as treatment tools for empathy. Furthermore, some ethical issues obviously arise with the use of brain stimulation techniques as a psychoactive intervention. For example, several pathologies that might benefit from these interventions are neurodevelopmental disorders which make young children potential beneficiaries of such interventions. However, data on the safety of brain stimulation (especially rTMS) in children remain sparse [84]. Whether it is with children or adults, researchers and clinicians should always weigh the beneficial outcome with the potential risks and carefully inform participants of the nature of the experiment/treatment, and follow published guidelines [84] for the stimulation parameters to be used.

Future perspectives and conclusion

Brain stimulation complements the correlational data from other imaging techniques by providing causal relations between specific cerebral systems and different components of empathy. Technical and ideological evolutions in this field will most likely propel our understanding of the different subsystems of empathy and bring researchers a step closer to the modulation of these neural processes in clinical settings. First, technological improvements around stimulation devices (and combinations of devices) and stimulation paradigms in terms of timing, localization and dose will allow more precise and deeper stimulations but also a better understanding of the underlying neurophysiological and neurochemical organizations of these systems. Second, and more significantly perhaps, the main advances in the study of empathy will most likely stem from a broader consensus on neurocognitive models of empathy from which innovative paradigms and behavioral measures could evolve. The study of similar constructs in other contexts, for instance emotion regulation with regards to aggressive behaviors [85] or fear, could also contribute to this field. Similarly, the systematic addition of socially relevant stimuli, such as facial expressions, to simple and well-controlled motor paradigms (e.g. [86]) will likewise help to build the knowledge on social interactions.

Ultimately, innovative paradigms, which take a more ecological perspective on social interaction tasks [48], for instance by simultaneously stimulating more than one participant that hold different roles during an interaction (e.g. [87]) are likely to yield novel insight

into the domain. Pushing the investigation one step further, by introducing means to modulate empathy, is also a very likely future, but much like the use of stimulation techniques to modulate mood or pain, lasting results on a complex function like empathy are likely to rely on multiple approaches, by combining for instance neurostimulation with pharmaceutical agents and/or psychological interventions.

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