Gender Differences in Sensorimotor Empathy for Pain: A Single-Pulse TMS Study

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Abstract

The present study aimed to examine the gender differences in empathy for pain at a sensorimotor level. Previous studies using single-pulse TMS have shown a reduction in amplitude of motor-evoked potentials (MEPs) while subjects observing needles penetrating hand of a human model which was specific to the muscle subjects observed being pricked. Twenty-five subjects (thirteen females and twelve males) participated in the study. Their TMS-induced MEPs were recorded from their right first dorsal interosseous (FDI) muscle of index finger during watching various clips depicting needles penetrating the same FDI muscle of right hand of a model. There were twelve types of clips, including pictures of hands of a woman, a man, a child and an apple, which was either pin pricked by a needle, touched by a Q-tip or at rest. Each clip was shown to the subjects eighteen times in a completely random sequence. Electromyography signals were recorded through an amplifier of an ANT ERP recording system and analyzed by ASA-Lab software. Results had been shown that women had larger MEP inhibited amplitude than men in all the stimuli. However, there were no significant differences between MEP amplitudes of different types of models' hands. The gender differences of MEPs between subjects indicate greater sensorimotor empathy in women, which is in correspondence with greater subjective responses of women to the painful clips (state empathy), which were obtained through a Visual Analogue Scale. Therefore, upon these results, we can conclude that women's stronger empathic response to observing pain in others go beyond just a subjective level and extend to a very autonomic and sensorimotor level. Women are hardwired to embody the pain of others more intensely, and this could prepare them to take action towards others' pain more rapidly.

Accepted September 21, 2017

Introduction

Empathy helps us to understand the feelings and inner mental states of others and therefore it leads us to share our experiences, needs, beliefs and purposes of each other [1-3]. Usual neuroscientific models of empathy assume that a specific motion, perception or emotion of a person activate similar representations in people who are watching that specific motion, perception or emotion [1,2].

Single-cell recording studies in chimpanzees have shown that premotor neurons are activated in both doing an action and observing the same action performed by other individual. These neurons have been called "mirror neurons" [2-5]. In a similar manner, neuroimaging studies on humans have shown that watching other people performing that action lead to activation those neural networks which are activated also when the individual himself/herself performs that action [6-9]. Another study has shown the similar effect when participants watch other people being touched and when the participants themselves have been touched [10]. Also the same effect has been observed in some studies examining the expression of an emotion and watching that expression in others [11,12]. So empathy might be based on the "mirror-matching" simulation of others' emotions and states.

Experiencing different personal painful events, from the infliction of a needle in body to the perception of an aching phantom limb [13] or distress due to the social exclusion [14] are all represented in a complicated neural network labeled as the "pain matrix". The affective components (like unpleasantness and distress) and the sensual components (like location and intensity) of the pain experience are coded in different nodes of the pain matrix [15,16]. Though pain is a private mental experience [17] the ability to understand and feel the pain of others is essential for social bonds [18]. Therefore pain makes an interesting model for assessing the theories of empathy based on the conception of shared representations.

There are some observations that propose an empathic matching of others' pain. For example, Hutchison, et al. [19] have shown that a neuron in the cingulate cortex of humans, increases its activation during both inflicting a pain on the participant and also when the participant watches other participants experiencing the same pain. Also Bradshaw and Mattingley [20] reported a case study of a patient who felt a sincere and genuine pain by watching the infliction of painful stimuli on his wife. Some functional magnetic resonance imaging (fMRI) studies have shown that only affective components of the pain matrix are necessary for empathic matching of pain in others [21-23] which suggest that only emotional representations of the pain experience would be shared between self and others.

Neurophysiological and neuroimaging studies have been showing that the action systems are so closely entangled with the pain systems that they could be considered as parts of the pain matrix which they duty is to execute appropriate reactions in response to real or potential noxious stimuli [24-27]. For example, Transcranial Magnetic Stimulation (TMS) studies have shown that real painful stimuli inflicting on the hand of subjects cause a significant inhibition in the corticospinal excitability which affect the hand's muscles [24,28-30]. Though such a close relations between pain and action systems, there is no information on the motor mapping of others' pain.

Only a few studies which most of them used fMRI, examined the neural underpinnings of empathy for pain in humans [21-23]. Despite some differences in experimental protocols, all of these studies have shown that only the affective nodes of the pain matrix is involved in empathy for pain.

On the other hand, TMS studies have pointed out the sensory-motor aspect of empathy for pain by showing a stable reduction in the excitability of hand's muscles through watching the infliction of a needle on a model's hand. The inhibition due to the observation of pain is conspicuous in several regards: First it is specific to the observation of the infliction of the needle on the "hand" and is absent during watching the infliction of needle on other parts of the body or a nonliving object. Second, it is specific to the observation of "pain" and is not present while the subject watch a non-painful stimulus touched the model. Third, the inhibition is specific to the Motor Evoked Potentials (MEPs) in electromyography (EMG) signals recorded from that specific muscle in which the model experience the infliction of needle and is absent in MEPs recorded from adjacent muscles. Fourth, this effect is clearly related to the subjective ratings of the sensory aspects not the affective aspects of the pain experience attributed to the model by subjects. Finally, the inhibition is related to the sensory empathy scores not the emotional empathy and the trait empathy.

It has been suggested that this effect might be the results of a pain resonance system which extract the basic sensory aspects of the painful experience of the model (like the location or intensity of a painful stimulus) and map them onto the motor system of the observer according to the topographical laws. This hypothesis has been endorsed by this observation that those subjects with higher inhibition also rate the model's pain more intense [31].

Transcranial Magnetic Stimulation (TMS) is a valid tools in the studies of the mirror neurons and the observation/execution matching system in humans [32]. For example, Avenanti, et al. [31] have examined this question that whether the pain systems and the action systems are related together at a social level by using TMS. They had used the single-pulse TMS in healthy subjects to assess their corticospinal modulation during watching painful and nonpainful events. Through each experimental trial, magnetic pulses were delivered on the left motor cortex and the MEPs had been recorded simultaneously from two muscles of the right hand: First Dorsal Interosseous (FDI) and Abductor Digiti Minimi (ADM). One of the consistent results obtained through these type of researches is that when subjects observe the infliction of a needle into one of these muscles, the amplitude of the MEP recorded from the same muscle in their hands would be reduced. This reduction of the MEP's amplitude is a sign of the activation of the mirror neurons [31-33].

The results from the TMS studies on the empathy for pain are apparently in contradiction with the neuroimaging studies on the subject. The first group have insisted on the role of the sensory-motor part of the pain matrix while the second group has demonstrated that this is the affective-emotional part of the pain matrix that is activated during empathy and the sensory-motor part doesn't show any activation [34]. The affective-emotional part of the pain matrix includes the Anterior Cingulate Cortex (ACC) and the Anterior Insula (AI). There are some propositions to resolve this apparent contradiction and integrate the results of these two lines of researches which will be described in the following.

One of these apparently contradictory cases is the fMRI study by Singer, et al. [23]. In this research, empathy for pain was elicited by arbitrary visual cues indicating an impending delivery of painful stimuli on a beloved one empathy for pain caused an increase in Blood Oxygen Level Dependent (BOLD) signal in the Anterior Insula and the Anterior Cingulate Cortex which both of them are components of the affective-emotional part of the pain matrix. One of the important findings of this study was the existence of a positive correlation between the neural activity and the emotional empathy scores.

Neural activities in the affective part of the pain matrix have been also reported in fMRI studies in which subjects observe pictures or movies clips of delivery of painful stimuli onto the hand or other parts of body [21,22]. TMS studies don't state that there is no activity in the affective nodes of the pain matrix; what they actually demonstrate is this notion that empathy for pain might rely on fine-grained somatic representations in addition to known affective-emotional representations.

In fact, these studies propose a link between visual representations of others' painful experiences and somatic-motor representations of experiencing the same experience by self. The results also propose that the functional mechanisms behind the link between somatic-motor visual representations is based on the inner simulation of specific features of the painful stimulus.

Keysers, et al. [10] provided evidence for a somatic resonance system by doing an fMRI study in which the BOLD signals in the Secondary Somatic Cortex (S II) have been observed during both being touched and watching other person being touched. Other structures might also be involved in the processing of watching or imagining others' pain such as thalamus, brain stem, parietal cortex and cerebellum.

Another study shows that affective and sensory-motor nodes of the pain matrix are also involved in the anticipation or expectation of a painful event [15,16]. Since the subjects were informed that no actual painful stimuli would be delivered during the experiment, this assumption seems plausible that the anticipatory feature of the sensory-motor mapping is automatic. Also another hypothesis was proposed which states that the selective embodiment of others' pain in which the sensitive dimension is larger than the emotional one, might be vital in the social learning of the reaction to others' pain. So it helps the corticospinal system of the observer to execute the flight-or-freeze reactions before experiencing the actual pain.

So we could think of two kinds of empathy which are linked together in a developmental and evolutionary scope: A simple type of empathy based on the somatic resonance which is involved in the mapping of the external stimuli onto one's own body; and a more complicated form of empathy based on the affective resonance which is involved in the emotional sharing, evaluation of the social bonds and interpersonal relations.

All in all the results of these studies show that the motor system is an important node in a complicated neural network which is involved in both the experience of pain and the empathy for pain. It is possible that a direct adjustment of some specific aspects of others' pain are made in the sensory-motor structures of the pain matrix while the emotional components of others' painful experiences are coded in the affective part of the matrix. Therefore, empathy for pain might take different forms in different nodes of the complicated pain matrix which together represent all the senses, feelings and emotions related to the pain experience.

Some philosophers have insisted that our somatic senses are inherently private. However, experiments in neurocognitive sciences are proposing that at least in humans, the social aspects of pain have been rooted in the very basic and sensory-motor levels of the neuro-processing of pain.

Another important issue in the study of empathy is the gender differences in the empathy for pain [35,36]. In a variety of empathy tasks, women have done far much better than men. In a series of studies using Electroencephalography (EEG), some differences between female and male subjects have been reported. For example, women have shown a larger Mu wave suppression than men during watching both the painful and non-painful experiences. Mu wave suppression has been shown to be a sign of empathy [35]. In addition, the Mu suppression in women is positively correlated with the scores of the "personal distress" subscale of the Interpersonal Reactivity Index (IRI) which is one of the most popular scale for measuring the trait empathy [36].

These results show that females do better than males in empathy for pain which is probably related to a higher activation in their motor cortex. Also in a more recent study, Cheng, et al. [37] reported some structural differences between male and female subjects in the brain areas related to the mirror neurons.

So far, there are some studies on the gender differences in the empathy for pain in the observers of the pain experience. To our knowledge, there is no experiment aimed to study differences in the empathy for pain in regard to the gender differences in the target of pain (model). This is our purpose in the current study. We want to examine the empathic reactions of female and male subjects to observing the infliction of pain in female and male models (targets).

In the early development of the study we decided to add a child model to our experiment. We hypothesized that the empathic reactions to the female model in pain would be greater than the empathic reactions to the male model and the reaction to the child model would be greater than the female model. Also in all three cases we expected a greater empathic response in female participants than male participants. The empathic reactions have been measured in both the subjective level (through questionnaires) and the physiological level (through TMS-induced MEP waves).

Methods

Participants

The participants were recruited voluntarily via inviting ads through four major universities in the capital city of Tehran, Iran: Sharif University of Technology, University of Tehran, University of Allame, and Shahid Beheshti University. Thirty-nine volunteers responded to our invitation. Between them, thirty-six participants showed up for the experiment. Due to difficulty to obtain a clear MEP signal, 11 of the subjects had been excluded from the ultimate experimental setup. So totally 25 participants (13 females and 12 males) were present at the ultimate set-up and the results obtained from these 25 participants have been reported in current study. Their age was in the range of 22-32 years old (Average = 25.44; SD = 2.48)

The Visual Stimuli

During the experiment, our participants watched different kinds of stimuli. These stimuli include 12 kinds of 2-second movie clips. In each clip, there were presented either a painful or a non-painful event (for control). Each of these 12 kinds of clips had been presented 12 times. The length of each clip was two seconds and there was an 8-second period between each two consecutive 2-second presentation in which participants just observed a black screen. The 12 clips included:

1. A needle moves slowly and inflicts the right hand of a man between his point finger and thumb in the FDI muscle (Man-Needle)
2. A Q-tip (ear bud) moves slowly and touch the same point in the man's hand as the needle inflicted in clip #1 (Man-Q-tip)
3. A motionless picture of the man's hand without any other object for 2 seconds
4. A needle moves slowly and inflicts the right hand of a woman between his point finger and thumb in the FDI muscle (Woman-Needle)
5. A Q-tip (ear bud) moves slowly and touch the same point in the woman's hand as the needle inflicted in clip #4 (Woman-Q-tip)
6. A motionless picture of the woman's hand without any other object for 2 seconds
7. A needle moves slowly and inflicts the right hand of a child between his point finger and thumb in the FDI muscle (Child-Needle)
8. A Q-tip (ear bud) moves slowly and touch the same point in the child's hand as the needle inflicted in clip #7 (Child-Q-tip)
9. A motionless picture of the child's hand without any other object for 2 seconds
10. A needle moves slowly and inflict an apple (Apple-Needle)
11. A Q-tip moves slowly and touches the same point in apple as needle inflicted in clip #10 (Apple-Q-tip)
12. A motionless picture of an apple without any other objects

The movie clips had been made based on two previous studies [31,38] with this difference that in addition to clips related to a man and an apple, we added clips related to a woman and a child. The clips had been presented in a 17" monitor at a distance of 80 cm from the subject.

Previous neurophysiological studies had shown that watching body limbs in motion lead to increase in corticospinal excitability [7,32,39]. Also watching a hand while manipulating tools, evoke activation in the primary motor cortex [40]. To avoid such effects in the current study, we paid attention that no movement would be made in the hands or apple by the needle or Q-tip. Also, we made sure that in no clips the holder of needle or Q-tip would not be visible.

The magnetic (TMS) pulse was delivered on the left motor cortex of the participants at the end of each presentation (a total of 144 pulses for 12*12 = 144 presentations) and the EMG signal had been recorded simultaneously from the participant's' right hand (the FDI muscle in the index finger). Presentation software (by Neurobehavioral System; NBS) had been used for timing and randomization of the stimuli delivery and for the synchronization between TMS, EMG and the task computer.

Interpersonal Reaction Index (IRI)

The trait empathy is an index of the general orientation of participants towards empathy-evoking situations. To assess the trait empathy which measures the inter-individual differences, the 28-item Interpersonal Reactivity Index (IRI) had been used.

This self-report measure was created by Davis [41]. He made IRI with this vision that empathy could be best understood if be viewed as a multidimensional construct, not a one-dimensional trait. IRI assess empathy as an attitudinal trait. This measure contains four subscales and each of them contains seven items (so IRI contains 28 items totally).

The "Perspective-taking" subscale measures the person's efforts to take others' perspectives and see the things through their eyes. The items of the "Fantasy" subscale measures the tendency to identify with fictional personalities in movies, novels, plays and other fictions. The "Empathic Concern" subscale measures the warm feelings, compassion, caring and concern for others. The "Personal Distress" subscale measures the anxiety and distress resulted from observing others experiencing a negative experience. Between them, two subscales are of greater concern for us in current study including empathic concern and personal distress.

Other studies have shown the multi-aspect nature of IRI. The internal consistency of the four subscales had been shown to be the Cronbach's alpha 0.71 to 0.77 [42]. Laurent, et al. [43] reported a Cronbach's alpha of 0.69 to 0.80. The IRI has been considered one of the best measures of empathy [44], it has been used widespread to assess the individual differences in empathy and also in neurophysiological studies [45].

Since our subjects were all native Farsi speakers, we used a translated version of IRI in Farsi [46]. This Farsi version of IRI has an internal consistency of 0.57 to 0.70 [46]. The responders rated each item in a 5-point Likert scale (from 0 to 4).

Visual Analogue Scale (VAS)

At the end of the TMS sessions, the painful stimuli (those movie clips presenting the infliction of a needle into hand) had been showed again to participants and they were asked to rate the amount of arousal and aversion (Personal distress) induced by each clip by rating it, in a scale from 0 to 10, on five subscales of the VAS (Attention, Intensity, Simulation, Aversion and Compassion).

Our Farsi version of VAS was based on the VAS used by Avenanti, et al. [31] for the same purpose. Those authors used their Italian version of VAS in four items to measure the situational empathy in four aspects (either sensory or emotional, and either self-oriented or other-oriented) as follows [31]:

i. Simulation (their inner mental simulation of the model's pain): sensory/self-oriented

ii. Intensity (the intensity of pain they attribute to the model's pain): sensory/other-oriented

iii. Aversion (the aversion they felt by watching model's pain): emotional/ self-oriented

iv. Compassion (the compassion they felt for the model): emotional/other-oriented

In the current study, in addition to the above four items, we included another item as "Attention": how much each clip attracts their attention. The reason for this was to distinguish the arousal resulted from watching pain from a general arousal resulted from watching those kinds of movie clips (non-painful ones). The ultimate items presented in our VAS were:

On a scale of 0 to 10:

I. How much the clip you watched attracted your attention?

II. How much was the pain of the person in the picture?

III. How much you imagined that pain in your mind?

IV. How much that pain was aversive to that person?

V. How much did you get upset by watching that person in pain?

Transcranial Magnetic Stimulation (TMS)

The main instrument of the experiment was the TMS (Transcranial Magnetic Stimulation) and EMG (Electromyography). By TMS, the left motor cortex of the participants had been stimulated and by EMG the electrical activity of the FDI (First Dorsal Interosseous) muscle had been recorded. At the time of the magnetic stimulation, the MEP (Motor Evoked Potentials) waves appeared in the EMG signals. Our ultimate goal was to obtain the amplitude of these MEPs which had been used in previous studies to get an indicator of the sensory-motor empathy.

The TMS instrument used in this study was a MagPro R30 manufactured by the MagVenture Company located in Denmark. This instrument works just in the biphasic mode. The coil used in current study was a butterfly (or 8-figured) one. This kind of coil, in comparison to circular coils, provide a more delicate localization (focused stimulation). The coil's type we used was MC-B70.

Electromyography (EMG)

To record the motor signals of the FDI muscle, we used one of the channels of a 64-channel EEG (Electroencephalography) instrument in our lab manufactured by ANT (Advanced Neuro Technology) in Netherlands. This instrument is mainly used for recording Event-Related Potentials (ERPs) in the brain, but also can be used to record electromyography signals. A couple of gold surface electrodes had been used to record EMG signal in current study. The ground electrode had been provided from the "GND" channel of the EEG cap.

The signal analysis of the EMG signals was done by ASA (Advanced Source Analysis) software. This software is also a product of the ANT Company and had been purchased with EEG amplifier together. By this software, we could record signals, save them and analyze them later.

Procedure

First, we made sure that the subject never has a history of psychiatric or neurological problems and hadn't use any psychotic drugs in the last month. Before entering the experiment room, the subject was asked to wash his/her hands thoroughly. Then those regions where the electrodes should be attached (the belly and the joint of the FDI muscle) had been cleaned thoroughly with alcohol. A couple of gold surface electrodes had been used in this study to record EMG signals. One of the electrodes had been attached to the belly of the FDI muscle at the right hand's index finger and the other was attached to the tendon or joint of the same muscle. The electrodes had been attached well to the subject's hand by an appropriate gluey band. A ground electrode had been attached on the back of the left wrist. The role of the ground electrode is to provide a reference for the recording signal.

EMG signals had been bandpass filtered out in 20 Hz - 1024 Hz intervals. The sample rating was 2048 Hz in this study. The EMG signals had been saved in a computer for later analysis.

An eight-figure coil (connected to a TMS MagPro R30) was placed over the left motor cortex of the subject. The coil was placed tangentially with skull so its handle makes a 45 degree angle with the middle line. By doing so. The induced electrical currency in neural tissues would be approximately perpendicular to the central sulcus which is optimum for trans-synaptic activities in the corticospinal routes [31].

The coil had been slowly moved over the left motor area in order to find the optimum location in which the MEP amplitude is maximum. This specific location is the point in which we observe the maximum twitch in the subject's finger by inducing magnetic pulse. The intensity of magnetic pulses had been fixed at 130 percent of the resting threshold. Resting threshold is defined as the minimum magnetic stimulation which produces MEPs with a minimum amplitude of 50 microvolts in 50 percent of instances. We made sure that the subject's muscle was relaxed by visual monitoring of her/ his EMG signals.

The trials had been programmed by the Presentation software to control the sequence and duration of video clips and to trigger TMS pulses and EMG recording. In each trial, one magnetic pulse had been delivered. The delivery time was set to be 500 milliseconds before the end of the clip to avoid any priming effect which might affect the magnitude of the MEP. A black screen was presented for 8 seconds between each two sequent trials. So, given that, each clip longed for 2 seconds, choosing 8 second intervals lead to 10-second intervals between each two sequent pulse delivery.

Choosing these 10-second intervals was based on a study which shows that the delivery of TMS pulses for one hour with the frequency of 0.1 Hz (i.e. one pulse every 10 seconds) would make no change in neural excitability [47]. The block in which a motionless picture of hand was presented had been chosen as the baseline for data analysis.

Totally, each clip had been presented 18 times for each subject. So, given that we had 12 different types of video clips, each subject watched 216 2-second video clips with 8-second intervals in 2160 seconds or 36 minutes. To avoid subjects from getting too tired, we split that 36-minute duration into three 12-minute parts with 10-minute intervals to rest. Subjects had been asked to watch very carefully and pay attention to the events they would see on the screen.

After the end of TMS trials, six video clips had been presented again for each subject and after the end of each, they were asked to answer the VAS questions. Those six clips were: Man-Needle, Woman-Needle, Child-Needle, Man-Q-tip, Woman-Q-tip, and Child-Q-tip. After answering VAS questions for these six clips, subjects were asked to answer the IRI questionnaire regarding their overall characteristics in everyday life.

Data analysis

EMG signals had been processed offline. Those trials with an EMG activity before the delivery of TMS pulse had been removed from further analysis (about 5% all trials). The average of MEP amplitudes for each of 12 different types of stimuli (peak-to-peak amplitude) had been computed by the ASA software for each subject in microvolt scale. Then these measures had been imported into the SPSS 15 software for statistical analysis. To compare the MEP amplitudes we used repeated measures ANOVA (Analysis of Variance). There were two factors for 12 stimuli. The first factor which we call it the "target", has four levels: man's hand, woman's hand, child's hand, and apple. The second factor which we call it the "intruder" has three levels: needle, Q-tip, and nothing (for motionless pictures).

We used one-way ANOVA to compare the VAS and IRI scores between male and female subjects. Paired-samples t-test was used to compare VAS scores for different painful stimuli (video clips Man-Needle, Woman-Needle, and Child-Needle) with each other. To find out whether there is a relation between the sensory-motor and situational empathy, we computed the correlation between MEP amplitudes and VAS scores using Pearson Correlation test. Also, we used this test to find out the relationship between the trait empathy (IRI scores) and the sensory-motor empathy (MEP amplitudes) and also between the trait empathy and situational empathy (VAS scores).

Results

Before applying repeated measures ANOVA on obtained MEP amplitudes, the Mauchly's test of Sphericity had been done for the two factors of Target (hand of man, hand of woman, hand of child, and apple) and Intruder (needle, Q-tip, and nothing) with which we categorized our 12 stimuli. The results showed that the sphericity hypothesis holds for each of these two factors but it doesn't hold for their interaction. However, since the interaction of them is not of concern in our research, it doesn't bother us. Another test which should be applied before further analyze is the Leven's Test of Equality of Error Variances. The results of this study showed that the assumption of homogeneity of variances holds for all 12 variables (MEP amplitudes for 12 different stimuli). So according to Leven's test, our results are valid.

Our ANOVA results showed a significant difference in the sensory-motor empathy (the inhibition of the MEP amplitude) between female and male participants during watching painful experiences in others ($F = 5.877^*$; $p = 0.024^*$). Females, in comparison to males, showed far much smaller MEP amplitudes in response to all 12 stimuli. With a detailed comparison of MEP amplitudes in two sexes for each of 12 stimuli, we have found the same pattern at the similar significance level for each stimulus **(Table 1)**.

Given that a reduction in the MEP amplitude is a sign of inhibition in the according section in the motor cortex and as we discussed earlier that it has been considered as an indicator of empathy in sensory-motor level, we could say that in our study we reached to this conclusion that women in comparison to men show a higher sensory-motor empathy in all situations **(Figure 1)**.

The results of ANOVA for comparing VAS scores between sexes are demonstrated in **tables 2,3 and 4**. Male and female subjects didn't show a significant difference in the "Attention" subscale of VAS, but in all other four subscales (Intensity, Simulation, Aversion and Compassion) females rated a higher score. This result shows that the stimuli captured the attention of subjects equally for men and women, but evoked a higher situational empathy in women than men. Women in comparison to men, though paying the same attention as men to the painful stimuli, rated them more painful for the person experiencing it; imagined the pain in their minds (simulate) more than men; felt more aversion toward the stimuli; and showed more compassion with the model. **Figures 2,3 and 4** show the charts in which the VAS subscales for the three painful stimuli are compared between male and female subjects.

In **Table 5**, results of the paired-samples T test for the total score of VAS for three types of painful stimuli are shown. As you can see, the VAS scores for the child-needle clip are significantly higher than the man-needle and woman-needle clips. Between the man-needle and the woman-needle clips,

Table 1. *Ranges, Means and Standard Deviations of MEP amplitudes (microVolts) and ANOVA results.*

Gender	Stimulus Type	Min	Max	Mean	SD	Gender	Stimulus Type	Min	Max	Mean	SD
Female	Man-Needle	848	5612	2348	1153	**Male**	Man-Needle	1584	7502	4110	1539
	Man-Q-tip	645	5730	2312	1272		Man-Q-tip	1598	8121	3542	2132
	Man-Nothing	1090	6071	2413	1228		Man-Nothing	1322	9016	3880	2098
	Woman-Needle	1048	5886	2417	1164		Woman-Needle	1734	8476	3798	2052
	Woman-Needle	903	5846	2034	1291		Woman-Needle	1387	7460	3385	1542
	Woman-Nothing	743	6310	2347	1408		Woman-Nothing	1918	6822	3599	1621
	Child-Needle	662	6095	2262	1293		Child-Needle	1582	9164	3946	2343
	Child-Q-tip	802	5831	2182	1223		Child-Q-tip	1619	7079	3656	1579
	Child-Nothing	795	5760	2290	1237		Child-Nothing	1406	8494	3828	1960
	Apple-Needle	810	5740	2286	1200		Apple-Needle	1461	7414	3674	1786
	Apple-Q-tip	1075	6053	2143	1283		Apple-Q-tip	1556	8290	3728	1988
	Apple-Nothing	1061	6245	2263	1340		Apple-Nothing	1490	7503	3833	1668

Source	df	MS	F ratio	Sig.
Intercept	1	2717191223	98.198**	0
Gender	1	162609567	5.877*	0.02

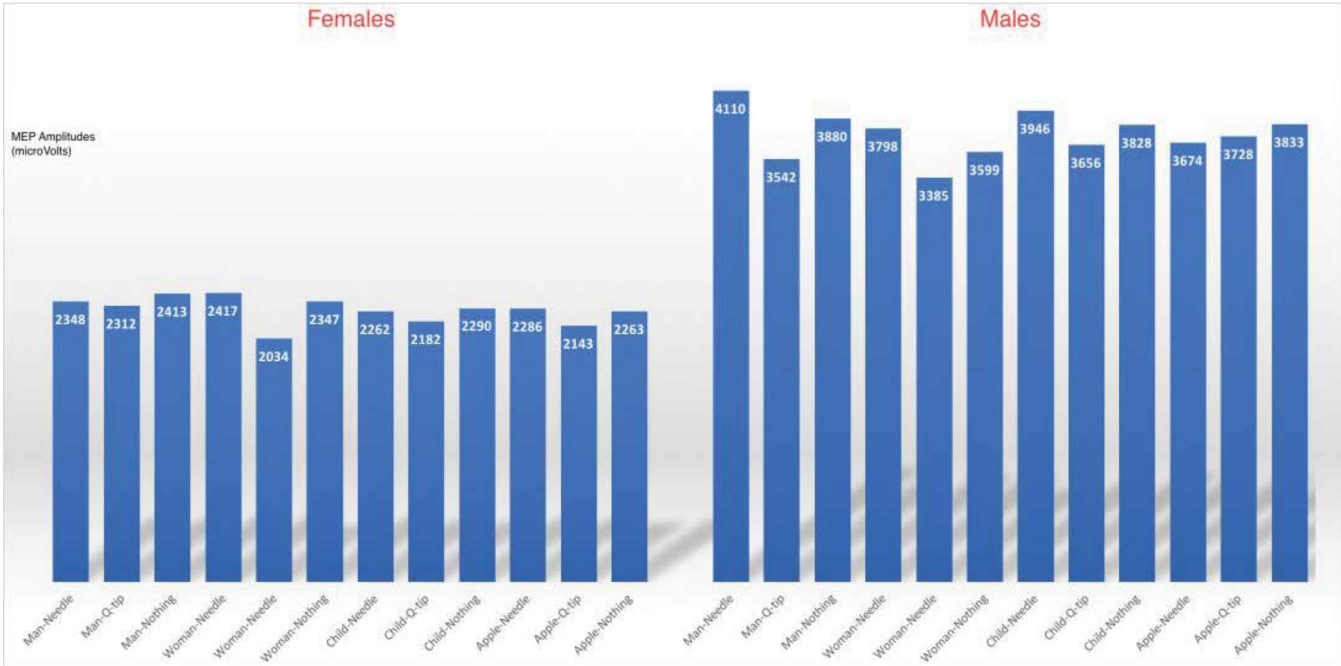

Figure 1. *Network architecture based on the nearest-neighbor method for N samples.*

Table 2. *ANOVA for comparing VAS scores between two sexes in the Man-Needle stimulus.*

VAS Subscale		SS	df	MS	Fratio	Sig.
	Within-group	1.05	1	1.05		
Attention	Between-group	101.59	23	4.417	0.238	0.063
	Total	102.64	24			
	Within-group	30.696	1	30.696		
Intensity	Between-group	118.74	23	5.163	5.946*	0.023
	Total	149.44	24			
	Within-group	56.4	1	56.4		
Simulation	Between-group	109.84	23	4.776	11.810**	0.002
	Total	166.24	24			
	Within-group	30.696	1	30.696		
Aversion	Between-group	126.74	23	5.511	5.570*	0.027
	Total	157.44	24			
	Within-group	42.683	1	42.683		
Compassion	Between-group	115.08	23	5.003	8.531**	0.008
	Total	157.76	24			

Table 3. *ANOVA for comparing VAS scores between two sexes in the Woman-Needle stimulus.*

VAS Subscale		SS	df	MS	Fratio	Sig.
	Within-group	8.308	1	8.308		
Attention	Between-group	113.69	23	4.417	1.681	0.208
	Total	122	24			
	Within-group	31.41	1	31.41		
Intensity	Between-group	100.59	23	5.163	7.182*	0.013
	Total	132	24			
	Within-group	56.4	1	56.4		
Simulation	Between-group	123.84	23	4.776	10.475**	0.004
	Total	180.24	24			
	Within-group	45.663	1	45.663		
Aversion	Between-group	90.897	23	5.511	11.554**	0.002
	Total	136.56	24			
	Within-group	51.563	1	51.563		
Compassion	Between-group	89.897	23	5.003	13.167**	0.001
	Total	141.36	24			

Table 4. *ANOVA for comparing VAS scores between two sexes in the Child-Needle stimulus.*

VAS Subscale		SS	df	MS	Fratio	Sig.
	Within-group	0.037	1	0.037		
Attention	Between-group	156.923	23	6.823	0.005	0.063
	Total	156.96	24			
	Within-group	41.85	1	41.85		
Intensity	Between-group	71.59	23	3.113	13.445**	0.001
	Total	113.44	24			
	Within-group	39.401	1	39.4		
Simulation	Between-group	96.359	23	4.19	9.405**	0.005
	Total	135.76	24			
	Within-group	31.41	1	31.41		
Aversion	Between-group	58.59	23	2.547	12.330**	0.002
	Total	90	24			
	Within-group	43.103	1	43.1		
Compassion	Between-group	54.897	23	2.387	18.058**	0
	Total	98	24			

Table 5. *Paired-Samples t-test for VAS total score in the three painful stimuli.*

Pairs	Mean	SD	t	Sig.
Man-Needle/Woman-Needle	3.12	4.7374	3.293**	0.003
Woman-Needle/Child-Needle	7.08	5.5447	6.385**	0
Man-Needle/Child-Needle	10.2	6.0069	8.490**	0

VAS scores are significantly higher in the woman-needle clip. Therefore, our subjects (both men and women) showed a greater situational empathy toward a child than an adult and in adults they showed a greater situational empathy toward females than males. These results also obtained for all five subscales of VAS individually. However, since the pattern of results was the same for all subscales and the total score, we just provide the results for VAS total score here.

To see whether our participants had a different response at a sensorimotor level towards different stimuli, we ran a Multivariate test with two factors. The first factor, labeled as "Target" includes four level: hand of man, hand of woman, hand of child and apple; and the second factor, labeled as "Intruder", includes needle, Q-tip and nothing (the hand at rest). In **Table 6**, the results of the Multivariate test are showed. As you can see, for the first factor F=1.870 which isn't significant (P = 0.166). But for the second factor F = 7.189** which is significant at the level of P< 0.01 (P = 0.004).

Table 6. *Multivariate Tests for "Target" and "Intruder" Factors.*

Factor	Type of Test	Value	F	Sig.
Target	Pillai's Trace	0.211	1.87	0.166
	Wilk's Lambda	0.789	1.87	0.166
	Hotelling's Trace	0.267	1.87	0.166
	Roy's Largest Root	0.267	1.87	0.166
Intruder	Pillai's Trace	0.395	7.189**	0.004
	Wilk's Lambda	0.605	7.189**	0.004
	Hotelling's Trace	0.654	7.189**	0.004
	Roy's Largest Root	0.654	7.189**	0.004

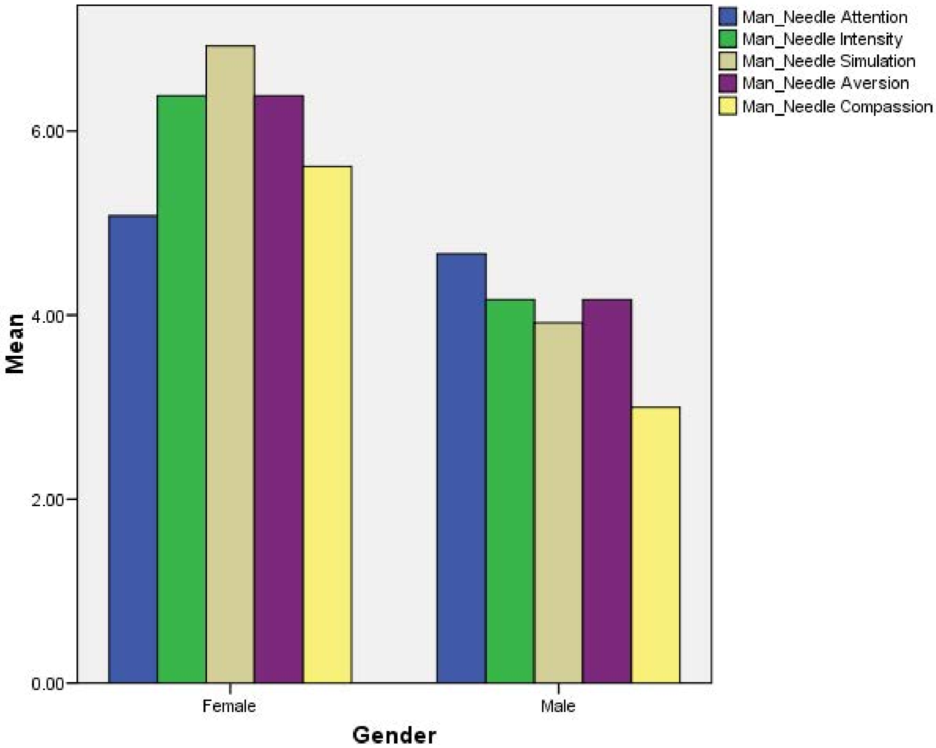

Figure 2. *Comparing VAS scores between two sexes in the Man-Needle stimulus.*

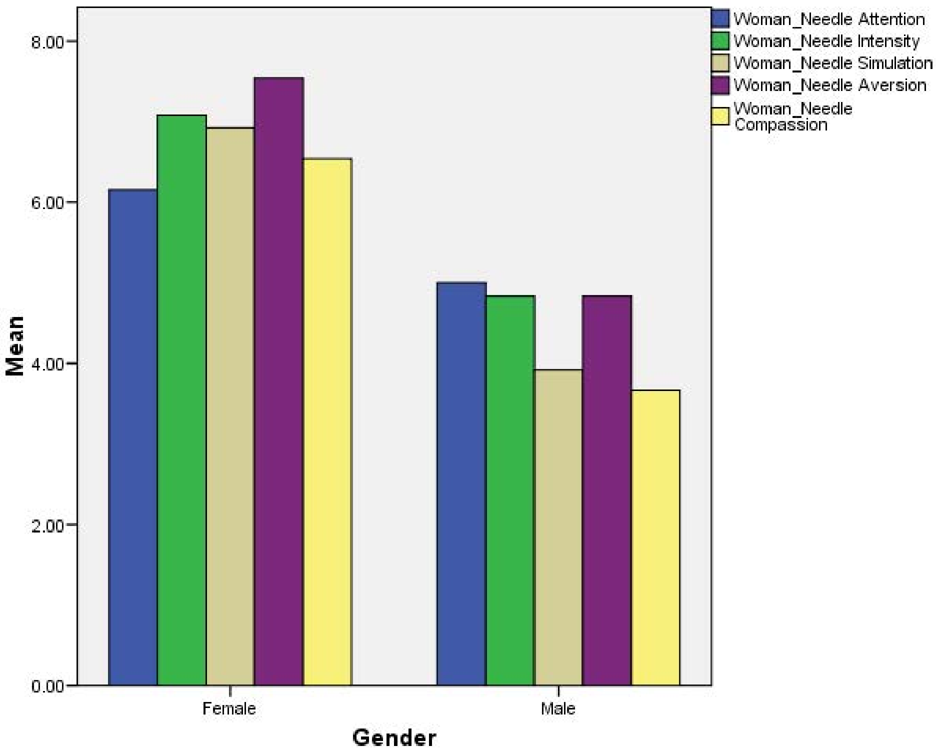

Figure 3. *Comparing VAS scores between two sexes in the Woman-Needle stimulus.*

So MEP amplitudes are significantly different from each other in regard to three conditions of intruder (needle, Q-tip and nothing). However, MEP amplitudes are not significantly different from each other in regard to four conditions of Target (hand of man, hand of woman, hand of child and apple). This result means that we haven't met our expectation to find differences in the sensory-motor responsiveness to different targets for pain (man, woman, child). In other words, our subjects showed approximately similar empathy to different clips at the sensory-motor level while they declared a higher empathy for the child than adults and for the woman than man in a subjective level (situational empathy measured by VAS).

The Pearson correlation analysis revealed no significant correlation between any of the IRI subscales and MEP

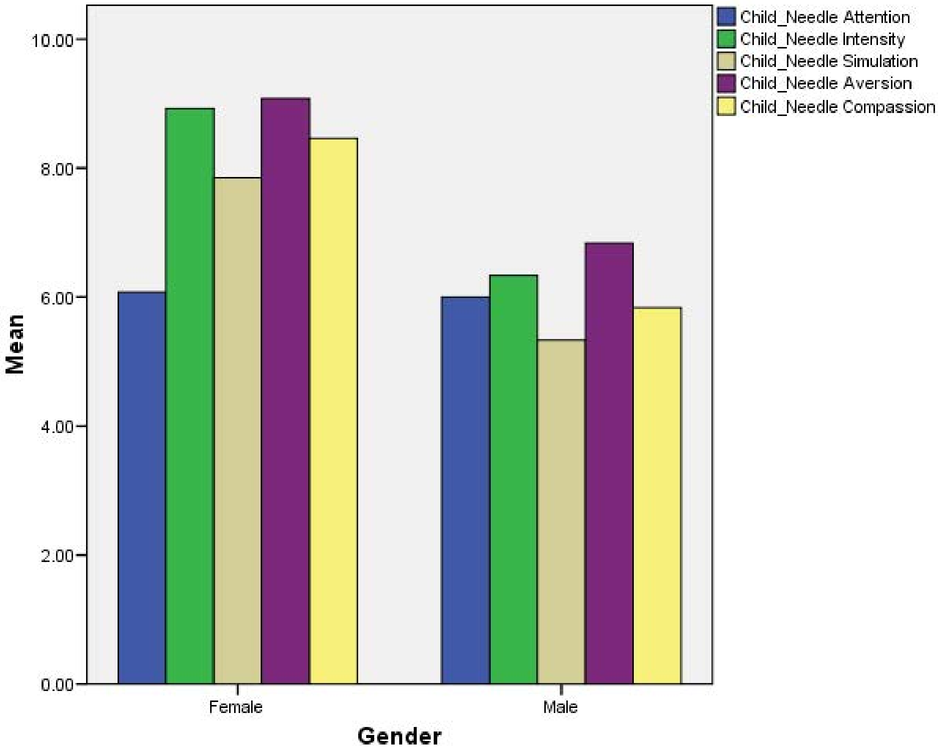

Figure 4. *Comparing VAS scores between two sexes in the Child-Needle stimulus.*

amplitudes. In other words, we found that the automatic sensory-motor empathy and the trait empathy (individual characteristics) act independently. This is exactly what we have expected from literature. For example, Avenanti, et al. [31] didn't find any correlation between the IRI scores and MEP amplitudes in their own study. Same goes with the Pearson correlation analysis between MEP amplitudes and VAS scores for the three painful stimuli. we have found no significant correlation between any VAS scores and MEP amplitudes.

Discussion

This study aimed to examine the role of gender in empathy. In order to do so, we tried to examine different aspects of empathy using different instruments. The major part of the study was dedicated to examining empathy at a sensory-motor level which was obtained by electro-magnetic stimulation over the motor cortex and recording motor signals in according muscle and measuring its MEP amplitudes. The second indicator of empathy was the situational empathy which is the subjective reports of participants on their experience of empathy toward the person in pain in a specific situation. The situational empathy had been assessed by VAS. The third indicator was the IRI questionnaire which assess the individual differences in trait in people. The main purpose of current research was to examine gender differences in these three indicators of empathy.

Our results showed that there are obvious differences in sensory-motor, situational and trait empathy between two sexes. The gender difference in sensory-motor empathy (physiological response, MEP) was the most significant between all three kinds of empathy (with the average difference of 70%). In situational empathy, there were also a significant difference (in the four subscales, intensity, simulation, aversion and compassion there was gender differences about 20-30%). Women and men didn't differ in the attention subscale which shows that the attention factor couldn't explain the higher situational empathy in women. In other words, women showed still higher situational empathy than men, even if they paid as much attention as men.

Between trait variables, women gained higher scores in the emotional empathy (empathy concern and personal distress). This result is in accordance with the results of research showing women have higher emotional empathy than men. Riggio, et al. [48] reported that while women get a higher score in emotional empathy scales, there are no difference between men and women in perspective taking and cognitive scales of empathy. Montag, et al. [49] found gender difference just in the personal distress subscale of IRI. D'Ambrosio, et al. [44] reported a higher emotional empathy in adolescent girls but found no difference between two sexes in other scales of empathy. Feizabadi, et al. [48] also found gender differences just for empathy scales of empathy (empathic concern personal distress). These results point out an important notation to us: when we examine gender differences in a multidimensional construct like empathy we should pay attention to different aspects of our construct like emotional and cognitive aspects since it's possible that gender difference only exists in one aspect diminish when we look at the average of the construct.

Our results showed that women demonstrated stronger reaction in situational empathy. This stronger conscious reaction had been (more) endorsed by this founding that women also showed stranger reactions in lowest level of brain responsiveness i.e. sensory-motor level which lies beneath the threshold of consciousness. This founding shows that although women might have a similar response to men in some dimensions of self-report empathy, they probably always show a greater empathy than men in situations including others' pain.

Also, our results showed that both sexes had more intense reaction to a woman's pain than a man's, but this effect existed only for the situational empathy, and not for the sensory-motor empathy. In the case of sensory-motor empathy, there were no difference between MEP amplitudes in regard to different targets in pain (man, women, child). Our stereotypes usually attribute traits and characteristics related to empathy and talking are of others, to women [50]. Surveys also have shown that women report higher empathy than men. However, there are unanswered questions in this regard. A meta-analysis done on 72 researches in the united states between years of 1979 to 2009 which examined the responses to IRI showed that most of those researches (69 out of 72) didn't report the results separately for men and women. So, although some studies claimed that women reported higher scores in trait empathy, it's not obvious that whether this result is stable and in exactly which aspects of empathy, women get a higher score.

As the results of repeated-measures ANOVA shows, the MEP amplitudes for the stimuli of needle, Q-tip and nothing, have significant differences between each other. However, MEP amplitudes for hand of man, hand of woman, and hand of child, don't have significant difference with each other. In other words, our subjects showed similar responses to situations of hurt to men, hurt to woman, and hurt to child in the sensory-motor level. In other words, our subjects showed same automatic empathy in the sensory-motor level to different stimuli while in the subjective level (situational empathy assessed by VAS) they empathized with the child more than the woman, and with the woman more than the man.

There are some hypotheses to explain the observed difference between two levels of empathy. The first explanation could be due to the stimuli we used in this research. It is possible that our clips couldn't appropriately differentiate between different hands (man, woman, and child). The difference between the three hands was obvious but not much salient. Especially recognizing the difference between hand of woman and hand of child was a little hard for some of the participants at first.

Another reason could be due to the essence of TMS studies. A recurring point in the TMS literature which we also encountered deeply in our research, is the high variability of MEP waves. These waves are very sensitive to the environmental factors, temperature, noise-making instruments, physical and psychological states of participants, small changes in coil's location and many other factors. That's why the same stimuli should be presented to subject's multiple times and then their results averaged.

In the current study, we presented each stimulus for 18 times. It is possible that differences in the MEP amplitude in some cases were smaller than the variance of noises and so had been lost during filtering. It might be possible that with the use of more complex signal analysis methods, these kinds of barriers would be overcome somehow. If we could make sure of the quality of our stimuli and the accuracy of our instruments then we could hypothesize more confidently about the reasons behind the found incongruences between the sensory-motor and subjective indicators of empathy.

Our results have shown that although some of the subscales of the trait empathy correlated with the situational empathy and could have predicted significant amount of it, but those correlations were not strong. This issue that whether trait empathy (i.e. the general tendency to empathize with others in everyday life) could moderate the occurrence and intensity of empathic behaviors, is a matter of debate. Part of this controversy is related to the low validity of self-report scales in predicting actual empathic behavior [51]. As we noted before, IRI had been utilized in neuroimaging studies repeatedly. In most of these researches, there were no relation between the IRI subscales and Blood Oxygen Level Dependent (BOLD) activity in brain [45]. These studies and ours propose that to assess empathy, self-report scales are not always reliable tools.

It has been suggested that empathy had an important role in motivating prosocial behaviors, managing priorities and behavioral responses, and providing motivational and affective bases for moral development. Pain had evolutionary protective functions. The long history of evolution in mammals made mother to be very sensitive to the pain and distress signs in her children. In most of primates this sensitivity had become not restricted to the mother-child relationship but all the members of the species who had a normal development would show aversion by observing others' distress [45]. As we have seen in the current study, between three painful situations (man-needle, woman-needle, and child-needle) and two groups of subjects (females and males) the strongest response belonged to the reaction of female subjects to the pain in child. However, they were no kin relationship induced in the current study. We expect that if the hand of child belonged to the subject's own child or her other relatives, her reaction would be even larger.

References

1. Decety J, Jackson P. The Functional Architecture of Human Empathy. Behavioral and Cognitive Neuroscience Reviews. 2004; 3: 71-100.

2. Gallese V. The roots of empathy: the shared manifold hypothesis and the neural basis of intersubjectivity. Psychopathology. 2003; 36: 171-180.

3. Preston SD, de-Waal FBM. Empathy: Its ultimate and proximate bases. Behavioral and Brain Sciences. 2002; 25: 1-72.

4. Gallese V, Fadiga L, Fogassi L. Action recognition in the premotor cortex. Brain. 1996; 119: 593-609.

5. Rizzolatti G, Fogassi L, Gallese V. Neurophysiological mechanisms underlying the understanding and the imitation of action. Nature Review Neuroscience. 2001; 2: 661-670.

6. Buccino G, Binkofski F, Fink GR, et al. Action observation activates premotor and parietal areas in a somatotopic manner: An fMRI study. European Journal of Neuroscience. 2001; 13: 400-404.

7. Fadiga L, Fogassi L, Pavesi G, et al. Motor facilitation during action observation: A magnetic stimulation study. Journal of Neurophysiology. 1995; 73: 2608-2611.

8. Iacoboni M, Woods RP, Brass M, et al. Cortical mechanisms of human imitation. Science. 1996; 286: 2526-2528.

9. Leslie KR, Johnson-Frey SH, Grafton ST. Functional imaging of face and hand imitation: Towards a motor theory of empathy. Neuroimage. 2004; 21: 601-607.

10. Keysers C, Bruno W, Gazzola V, et al. A touching sight: S II/PV activation during the observation and experience of touch. Neuron. 2004; 42: 335-346.

11. Carr L, Iacoboni M, Dubeau MC, et al. Neural mechanisms of empathy in humans: A relay from neural systems for imitation to limbic areas. Proceedings of National Academy of Science USA. 2003; 100: 5497-5502.

12. Wicker B, Keysers C, Plailly J, et al. Both of us disgusted in my insula: The common neural basis of seeing and feeling disgust. Neuron. 2003; 40: 655-664.

13. Flor H. Phantom-limb pain: Characteristics, causes, and treatment. Lancet Neurology. 2002; 1: 182-189.

14. Eisenberger NL, Lieberman MD, Williams KD. Does rejection hurt? An fMRI study of social exclusion. Science. 2003; 302: 290-292.

15. Ingvar M. Pain and functional imaging. Philosophical Transactions of the Royal Society of London Biological Sciences. 1999; 354: 1347-1358.

16. Rainville P. Brain mechanisms of pain affect and pain modulation. Current Opinion in Neurobiology. 2002; 12: 195-204.

17. Wittgenstein L. Philosophical Investigations. Blackwell, Oxford. 1963.

18. Williams AC. Facial expression of pain: An evolutionary account. Behavioral and Brain Science. 2002; 25: 439-488.

19. Hutchison W, Davis K, Lozano A, et al. Pain related neurons in the human cingulate cortex. Nature Neuroscience. 1999; 2: 403-405.

20. Bradshaw JL, Mattingley JB. Allodynia: a sensory analogue of motor mirror neurons in a hyperaesthetic patient reporting instantaneous discomfort to another's perceived sudden minor injury? Journal of Neurology Neurosurgery and Psychiatry. 2001; 70: 135-136.

21. Jackson PL, Meltzoff AN, Decety J. How do we perceive the pain of others? A window into the neural processes involved in empathy. NeuroImage. 2005; 24: 771-779.

22. Morrison I, Lloyd D, di-Pellegrino G, et al. Vicarious responses to pain in anterior cingulate cortex: Is empathy a multisensory. Cognitive, Affective, and Behavioral Neuroscience. 2004; 4: 270-278.

23. Singer T, Seymour B, O'Doherty J, et al. Empathy for pain involves the affective but not sensory components of pain. Science. 2004; 303: 1157-1161.

24. Farina S, Tinazzi M, Le-Pera D, et al. Pain-related modulation of the human motor cortex. Neurology Research. 2003; 25: 130-142.

25. Juottonen K. Altered central sensorimotor processing in patient with complex regional pain syndrome. Pain. 2002; 98: 315-323.

26. Wager Y, Shibata M, Sanada Y, et al. Motor cortex stimulation for phantom limb pain. Lancet. 1999; 353: 212.

27. Wager TD, Rilling JK, Smith EE, et al. Placebo-induced changes in fMRI in the anticipation and experience of pain. Science. 2004; 303: 1162-1167.

28. Farina S, Valeriani M, Rosso T, et al. Transient inhibition of the human motor cortex by Capscicin-induced pain. A study with TMS. Neuroscience letters. 2001; 314: 97-101.

29. Svensson P, Miles TS, McKay D, et al. Suppression of motor evoked potentials in a hand muscle following prolonged painful stimulation. European Journal of Pain. 2003; 7: 55-62.

30. Urban PP, Solinski M, Best C, et al. Different short-term modulation of cortical motor output to distal and proximal upper-limb muscles during painful sensory nerve stimulation. Muscle & nerve. 2004; 29: 663-669.

31. Avenanti A, Bueti D, Galati G, et al. Transcranial magnetic stimulation highlights the sensorimotor side of empathy for pain. Nature Neuroscience. 2005; 8: 955-960.

32. Maeda F, Kleiner-Fisman G, Pascual-Leone A. Motor facilitation while observing hand actions: Specificity of the effect and role of observer's orientation. Journal of Neurophysiology. 2002; 87: 1329-1335.

33. Sadeghiyeh H, Aghababaei N, Hatami J, et al. Comparing Situational and Dispositional Empathy, Considering The Role of Gender. Social Psychology Research, Summer. 2011; 1: 1-16.

34. Jackson PL, Meltzoff A N, Decety J. Perceiving others in painful situations activates the affective pain neural network. Proceedings of the Cognitive Neuroscience Society, San Francisco. 2004.

35. Han S, Fan Y, Mao L. Gender difference in empathy for pain: an electrophysiological investigation. Brain Research. 2008; 1196: 85-93.
36. Yang C, Decety J, Lee S. Gender differences in the mu rhythm during empathy for pain: An electroencephalographic study. Brain Research. 2009; 251: 176-184.
37. Cheng Y. Sex differences in the neuroanatomy of human Mirror-Neuron System: A voxel-based morphometric investigation. Neuroscience. 2009; 158: 713-720.
38. Fecteau S, Pascual-Leone A, Theoret H. Psychopathy and the mirror neuron system: Preliminary findings from a non-psychiatric sample. Psychiatry Research. 2008; 160: 137-144.
39. Gangitano M, Mottaghy FM, Pascual-Leone A. Modulation of premotor mirror neuron activity during observation of unpredictable grasping movements. European Journal of Neuroscience. 2004; 20: 2193-2202.
40. Jarvelainen J, Schurmann M, Hari R. Activation of the human primary motor cortex during observation of tool use. Neuroimage. 2004; 23: 187-192.
41. Davis MH. A Multidimensional Approach to Individual Differences in Empathy. Catalog of Selected Documents in Psychology. 1980; 10-85.
42. De-Paúl J, Pérez-Albéniz A, Guibert M, et al. Dispositional Empathy in Neglectful Mothers and Mothers at High Risk for Child Physical Abuse. Journal of Interpersonal Violence. 2008; 23: 670-684.
43. Laurent SM, Hodges SD. Gender roles and empathic accuracy: The role of communion in reading minds. Sex Roles. 2009; 60: 387-398.
44. D'Ambrosio F, Olivier M, Didon D, et al. The basic empathy scale: A French validation of a measure of empathy in youth. Personality and Individual Differences. 2009; 46: 160-165.
45. Decety J. Dissecting the Neural Mechanisms Mediating Empathy. Emotion Review. 2011; 3: 92-108.
46. Feizabadi Z, Farzad V, Aray SM. Exploratory and confirmatory factor analysis of Interpersonal Reactivity Index. Psychological and Educational Sciences Journal. 2008; 38: 157-178.
47. Chen R, et al. Depression of motor cortex excitability by low-frequency transcranial magnetic stimulation. Neurology. 1997; 48: 1398-1403.
48. Riggio RE, Tucker J, Coffaro D. Social Skills and Empathy. Personality and Individual Differences. 1989; 10: 93-99.
49. Montag C, Heinz A, Kunz D, et al. Self-reported empathic abilities in schizophrenia. Schizophrenia Research. 2007; 92: 85-89.
50. Rudman LA, Glick P. The social psychology of gender: how power and intimacy shape gender. New York, the Guilford Press. 2008.
51. Davis MH, Kraus LA. Personality and empathic accuracy. In: Ickes, W.(Ed.), Empathic Accuracy. New York, The Guilford Press. 1997; 144-168.

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