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Review article

## Meta-analysis of functional neuroimaging and dispositional variables for clinical empathy

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## ABSTRACT

Clinical empathy refers to the ability of healthcare providers (HP) to recognize and understand what patients feel. While neuroimaging investigations have identified a neural network of empathy, activation consistency of brain regions and their specific functions in clinical empathy remains unclear. Herein, we conducted meta-analyses of dispositional assessments using random-effects models and functional neuroimaging using Seed-based d Mapping with Permutation of Subject Images to ascertain the shared neural processes consistently identified as relevant to clinical empathy. The dispositional meta-analysis ( $n = 15$ ) revealed that HP exhibited higher scores on empathic concern and perspective taking. The HP neuroimaging meta-analysis ( $n = 11$ ) identified consistent activation of the anterior mid-cingulate cortex, anterior insula, and ventrolateral prefrontal cortex (vlPFC) while HP vs. controls comparison ( $n = 9$ ) did not yield robust alterations. The vlPFC mediated positive and negative functional connectivity of the insula. We revisited the framework of emotion regulation in clinical empathy. The empathetic agent flexibly shifts between affective regulatory strategies to meet contextual demands, with vlPFC figuring as the key region where this neural mechanism takes place.

## 1. Introduction

Most scientific literature (if not all) considers empathy a unique human ability, a capacity by which an individual is able to perceive another individual's inner, affective state and relate to it at an emotional level (Zaki and Ochsner, 2012). Furthermore, empathy is regarded as crucial for working towards prosocial behavior, and as a means for interpersonal cooperation and the advancement of the human species as a whole (Zaki and Ochsner, 2012).

A myriad of neuroscientific literature has recognized top-down inhibition mechanisms as paramount for eliciting empathic responses (Lamm et al., 2010). However, through the present meta-analysis on research dealing with clinical empathy in healthcare settings, we wanted to further posit that upregulation of processes is also of utmost importance in order to give rise to empathy. Clinical empathy is critical

for quality healthcare (Decety et al., 2014; Halpern, 2003), as it has been associated with clinical competence, performance, and more importantly, clinical outcomes (Hojat et al., 2011; Mercer et al., 2012; Ogle et al., 2013; Rakei et al., 2009; West et al., 2006; Yuguero et al., 2017), as well as with the well-being of the healthcare providers themselves (Dyrbye et al., 2010; Figley, 2012; Halpern, 2012; Neumann et al., 2011; Shanafelt et al., 2005). As such, the medical field demands clinical competence and empathy towards patients from these healthcare providers, even when they have no choice but to deal with emotionally taxing situations in their daily routine (Halpern, 2012; Kerasidou and Horn, 2016). For instance, having to break bad news to patients is often stressful and associated with handling difficulties, and with inducing feelings of failure, sorrow, and/or guilt (Brown et al., 2009; Fallowfield and Jenkins, 2004; Shaw et al., 2015, 2013). Facing demanding patients might also elicit anger and frustration, and experiencing a patient's

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suffering or death may prompt physicians to experience sadness or distress (Halpern, 2007). Accommodating these demands requires healthcare providers to be able to flexibly shift between different empathic response strategies during contexts that change at a high rate, and when under considerable and significant time-pressure.

From a neuroscientific point of view, clinical empathy has frequently been conceptualized as encompassing cognitive and affective components. The cognitive aspect is closely associated with the ability to acknowledge and understand another's experience (e.g., perspective taking and mental status understanding), to communicate with patients, and to take actions in helpful manners (which may entail self-regulation and executive control) (Mercer and Reynolds, 2002). All of these are subserved by the medial and dorsolateral prefrontal cortex (PFC) and right temporoparietal junction (rTPJ) (Cheng et al., 2010; Decety and Svetlova, 2012; Fan et al., 2011; Lamm et al., 2011). The affective component is associated with affective sharing between the practitioner and patients (Hojat et al., 2009). Consequently, cognitive empathy in particular was observed to have positive and beneficial effects in clinical relationships, while affective empathy was coupled with negative notions such as detachment in clinical settings, with all relevant evidence showing negative functional couplings between cognitive control (PFC and rTPJ) and empathic arousal (insula and amygdala), thus, holding that cognitive control downregulates affective sharing in order to implement detached concern (Cheng et al., 2017, 2007; Decety et al., 2010). This downregulation might dampen their negative arousal, which, in turn, would free up cognitive resources that are necessary to be of assistance, and perhaps, even when expressing empathic concern (Decety et al., 2014). Eleven out of 15 fMRI studies of clinical empathy available mentioned that there were reduced empathic neural responses in clinical practitioners ascribed to preventing healthcare providers from experiencing personal distress and anxiety (Cheng et al., 2017, 2007; Coll et al., 2017; Corradi-Dell'Acqua et al., 2019, 2021; Dirupo et al., 2021; Jackson et al., 2017; Kim et al., 2020, 2021; Said Yekta-Michael et al., 2019; Tei et al., 2014). Nevertheless, the literature on empathy exclusively driven by self-reported measures suggests that affective engagement positively influences the physician-patient relationship (Decety and Fotopoulou, 2014; Del Canale et al., 2012; Derksen et al., 2013; Di Blasi et al., 2001; Halpern, 2014; Mercer et al., 2002; Mercer and Reynolds, 2002; Neumann et al., 2012; Raket et al., 2011, 2009). Such differences among studies may be attributed to publication bias and variable paradigms, given the fact that these separate representations would underlie up- and downregulation despite common fMRI activations observed at the gross anatomical level (Woo et al., 2014). The top-down regulation of empathy, through executive functions which are implemented in the PFC, modulates perceptual inputs and automatic emotional processing and adds flexibility, allowing an individual to react (or not) to the affective states of others. This meta-cognitive feedback is continually updated by bottom-up information, and in return provides top-down input through up- and/or downregulation (Decety and Moriguchi, 2007). While downregulation contributes to cognitive inhibition of affective processing in order to prevent healthcare providers from experiencing personal distress, upregulation helps healthcare providers generate empathetic responses to recognize and understand patients' suffering.

To fill in this gap, we integrated self-assessed dispositional and functional magnetic resonance imaging (fMRI) studies of clinical empathy via a meta-analytical approach. By taking into account the literature on empathic flexibility and decision-making that ventrolateral prefrontal cortex (vlPFC) plays a key role (Koch et al., 2018), we posited that simultaneously evaluating alternate options through a mechanism of up- and downregulation is necessary in order to quickly shift between emotional regulatory strategies and successfully achieve empathic flexibility. This study has a theory-based and hypothesis-oriented algorithm as follows: (1) a meta-analysis within healthcare providers to examine whether they exhibit consistent activation in the neural network for empathy, with a null hypothesis that they did not have any

consistent activation in the empathy network; (2) a meta-analysis of comparisons between healthcare providers and controls to test whether healthcare providers really showed reduced activation in the empathy network, with a null hypothesis that healthcare providers as compared to controls had reduced activation in the empathy network; and (3) a seed-based functional connectivity analysis in the vlPFC in response to empathy-eliciting stimuli in our previous fMRI data (Cheng et al., 2017).

## 2. Methods

### 2.1. Literature search and inclusion

#### 2.1.1. Dispositional assessments

A literature search was conducted to identify publications using the Interpersonal Reactivity Index (IRI) as empathy assessments for healthcare providers (Davis, 1980, 1983). Being an extensively used multidimensional instrument designed to assess dispositional empathy, the IRI contains four seven-item subscales, each of which examines a separate facet of empathy. The perspective taking (IRI-PT) subscale measures the self-reported tendency to automatically adopt the psychological viewpoint of others. The empathic concern (IRI-EC) subscale evaluates the tendency to experience compassion and feelings of sympathy for unfortunate others. In regards to clinical empathy, the IRI-EC is referred to as evaluating affective empathy, while the IRI-PT is commonly considered to measure cognitive empathy. The 28 items are answered on a five-point Likert scale ranging from "does not describe me well" to "describes me very well".

Using keywords 'health professionals', 'healthcare providers', 'healthcare workers', 'physicians', 'nurses' and 'clinicians' to thoroughly check cited articles, relevant articles were assessed for eligibility. Since we focused on group comparisons between healthcare providers and controls, the inclusion criteria for the meta-analyses of dispositional empathy were as follows:

- (1) The study had to include at least two groups of participants, one of whom was healthcare providers or medical students with clinical experience; and.
- (2) Participants had to have a dispositional outcome, as measured by at least two IRI subscales: IRI-EC and IRI-PT.

#### 2.1.2. fMRI studies

Likewise, we conducted a comprehensive search for fMRI studies that measured pain empathy in healthcare providers. Keywords for the search on PubMed were 'empathy', coupled with either 'fMRI' or 'neural', and one of the following: 'health professionals', 'healthcare providers', 'healthcare workers', 'physicians', 'nurses', 'clinicians' and 'clinical practice'. In addition, 'clinical empathy' and 'physician empathy' were searched. We also added potential articles through selected reference lists and author publications. To be included in our meta-analysis, studies had to meet the following inclusion criteria:

- (1) The study had to have an fMRI experiment with measures to elicit participants' empathy; and.
- (2) Participants had to be healthcare providers or medical students with clinical experiences, regardless of the presence of a control group.

All stimuli had to be contrasted with a baseline or neutral stimuli, i.e., pain > no-pain. The studies' fMRI outcomes needed to report peak coordinates, its peak value, and voxel-wise threshold in the whole-brain data; if not, we contacted the authors to obtain such data. Additionally, one newly published study assessing brain connectivity and empathic abilities in psychotherapists was added to the dispositional and fMRI meta-analysis (Olalde-Mathieu et al., 2022). Our identifying process was in accordance with the PRISMA guidelines (Fig. 1).

### 2.2. Meta-analyses of dispositional assessments

The meta-analyses of dispositional measures operated on effect sizes. After the means, standard deviations, and group subjects were collected,

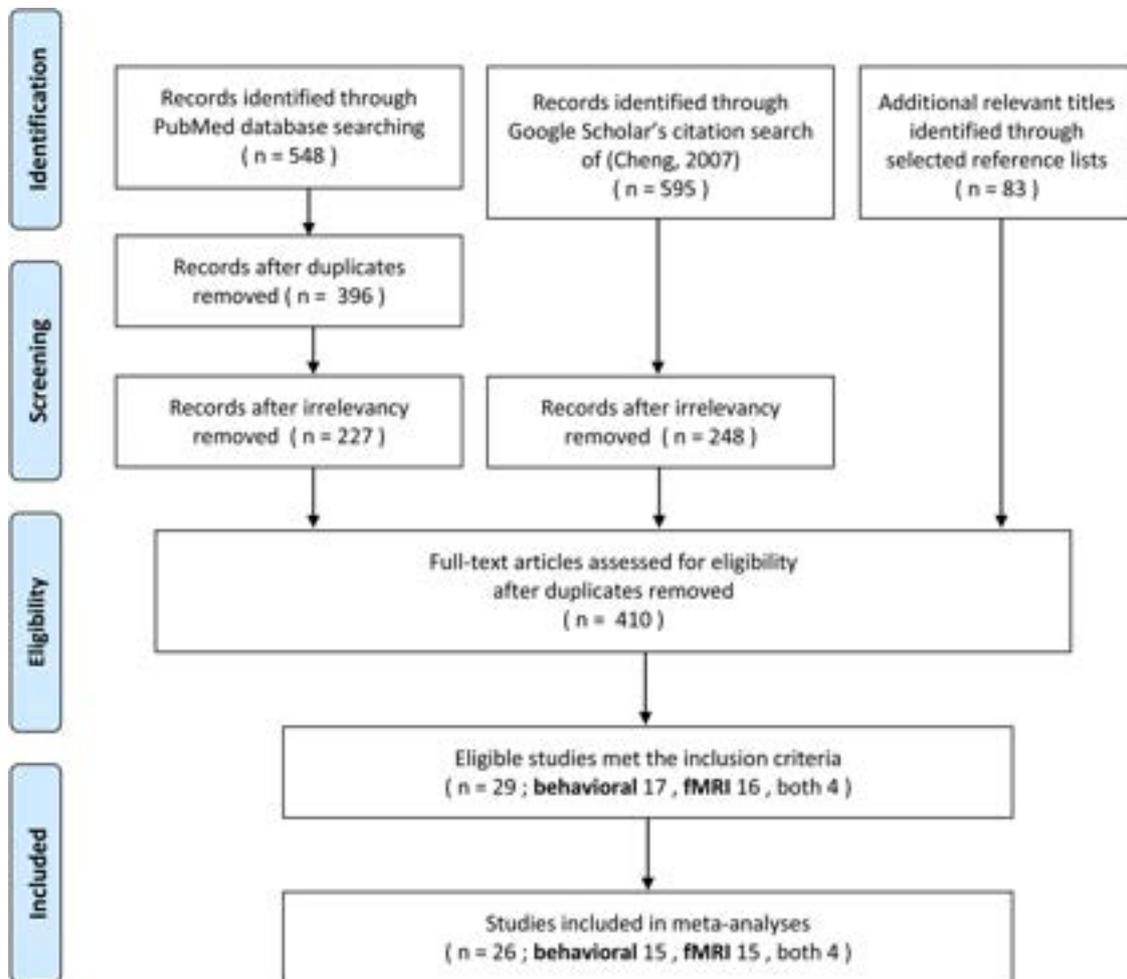


Fig. 1. Flow diagram of studies included and excluded at each stage of identification and verification following PRISMA guidelines (Moher et al., 2009).

the standardized mean difference (SMD) based on Hedges'  $g$  was computed for each individual study. This was calculated using the mean differences between healthcare providers and controls, and dividing them by the pooled standard deviation. Considering both within- and between-study variances, studies were weighted to produce a combined SMD by using random-effects models. All dispositional data were analyzed and visualized through the Cochrane Review Manager (RM, v5.4).

## 2.3. fMRI meta-analyses

### 2.3.1. Software processing

We used Seed-based d Mapping with Permutation of Subject Images method (SDM-PSI, v6.22) to perform the coordinate-based fMRI meta-analysis. Data contrasting 'pain > neutral' were extracted from the studies. For those studies in which there was a control group, data of 'pain > neutral' in the controls, 'healthcare providers > controls', and 'controls > healthcare providers' were additionally collected. Peak coordinates were converted to the MNI coordinate system via the Yale BioImage Suite web application, and peak values were collected in the form of  $t$ -statistics; otherwise they were exchanged by the statistics converter in the SDM Project web. The software pre-processes individual studies by estimating the most likely effect size in each voxel to impute a statistical map of the contrast of each study. Multiple imputations of the study map were used to avoid biases arising from single imputations. Maps from different imputations were permuted and then combined into a mean integral image using a standard random-effects model and Rubin's rule. SDM-PSI also utilizes an anisotropic approach, which

assigns values to neighboring voxels based on their spatial covariances instead of pure distances (Albajes-Eizagirre et al., 2019; Radua et al., 2012).

### 2.3.2. Analyses

Results of mean analyses were thresholded at a family-wise error (FWE) rate of  $p < 0.05$  with a cluster extent of at least 40 voxels.  $I^2$  statistics indicating the heterogeneity between studies were assessed by extracting estimates of each peak coordinate. Egger's test was used to examine small-study effects. The final outcome was visualized with MRICron software.

Since coordinate-based meta-analyses were tested for spatial convergence rather than true activations, regions that survived the threshold had to be conceptually interpreted as follows: 'the greater activation is more frequently reported in this region than the remaining areas of the brain' (Müller et al., 2018). Here, the PSI algorithm enabled us to formally test whether the effects of a voxel differed from 0 (Albajes-Eizagirre et al., 2019). Therefore, for narrative purposes, we describe the region that was statistically outstanding as an 'activation'.

## 3. Results

### 3.1. Included studies

Our literature search identified 29 studies that met the inclusion criteria of either dispositional or fMRI research. However, two dispositional studies were excluded due to incomplete statistical data; one fMRI article was an extended investigation of a previous study, and thus was

also discarded. Eventually, 26 studies published between 2007 and 2022 qualified for the meta-analyses (15 using dispositional measures, 15 using fMRI data, and four including both).

Regarding the meta-analysis of dispositional measures, the 15 studies included 1373 subjects. Physicians (295), nurses (109), and medical students (156) accounted for the majority of the 663 healthcare providers, with psychotherapists (83), physiotherapists (12), and supporting care staff (8) among the other professionals.

In the fMRI meta-analysis, the 15 included studies (eleven of which recruited controls) comprised a total of 602 subjects. Nearly three-fifths of the 370 healthcare providers were nurses (217); the others were physicians (52), psychotherapists (18), physiotherapists (23), and medical and dental students (78) (Table 1). Eleven studies were included in the single-group meta-analysis of healthcare providers, and nine were used for group comparisons (Cheng et al., 2017, 2007; Coll et al., 2017; Corradi-Dell'Acqua et al., 2019, 2021; Dirupo et al., 2021; Ellingsen et al., 2020; Jackson et al., 2017; Jensen et al., 2014; Olalde-Mathieu et al., 2022; Said Yekta-Michael et al., 2019; Tei et al., 2014; Watanabe et al., 2019).

### 3.2. Meta-analytical results of dispositional assessments

Meta-analyses of IRI scores showed a similar trend in the two subscales: healthcare providers scored higher on the IRI-EC and IRI-PT than did their counterparts. Both the IRI-EC and IRI-PT reached statistical significance, with SMDs between healthcare providers and controls of 0.17 [0.002, 0.33] ( $p = 0.047$ ) and 0.22 [0.10, 0.33] ( $p = 0.001$ ), respectively (Table 2; Fig. S1, S2). For the results of the other two subscales, IRI-PD and IRI-FS, please see Table 2.

### 3.3. fMRI meta-analytical results

#### 3.3.1. Healthcare providers

The fMRI meta-analyses of healthcare providers revealed that the right inferior frontal gyrus ( $x = 48, y = 30, z = 8$ ;  $\text{SDM-Z} = 4.121$ ), extending to the vlPFC ( $x = 48, y = 46, z = 8$ ;  $\text{SDM-Z} = 3.937$ ) and anterior insula (AI:  $x = 36, y = 22, z = 2$ ;  $\text{SDM-Z} = 3.477$ ), were the most spatially convergent regions in response to empathy-eliciting stimuli. The area in the bilateral postcentral gyrus, anterior mid-cingulate cortex (aMCC), left inferior frontal gyrus and left vlPFC also converged (Table 3 and Fig. 2). A sensitivity test using a meta-regression approach was further conducted to examine whether the effect of demographic variables of age and

gender was significantly associated with the meta-analytical results. There was no suprathreshold cluster related to the demographic variables of age and gender when the threshold was set at  $\text{FWE } p < 0.05$ , extent  $> 40$  voxels (Supplementary Table s1).

#### 3.3.2. Group comparisons between healthcare providers and controls

There was no suprathreshold cluster for group comparison (9 studies) when the threshold was set at  $\text{FWE } p < 0.05$ , extent  $> 40$  voxels. When applying a more-liberal threshold (an uncorrected  $p < 0.005$  with a cluster extent of at least 40 voxels), the results revealed two superior clusters in healthcare providers after thresholding that converged to the bilateral secondary somatosensory cortex (SII) and extended to the rTPJ ( $x = 56, y = -20, z = 12$ ;  $\text{SDM-Z} = 3.207$ ). The aMCC and left AI were areas where controls showed increased convergence compared to healthcare providers (Supplementary Table s2, Fig. s5).

#### 3.3.3. An overlay with the core network of empathy

We reconstructed a 'core network of empathy' by an fMRI meta-analysis of empathy from the general population using BrainMap. Then we overlaid our clinical empathy results with the 'core network of empathy'. BrainMap is a database that archives published coordinate-based results in a standard brain space from neuroimaging experiments (Fox and Lancaster, 2002; Laird et al., 2011). Specifically, after exclusion of duplicates and studies that were not eligible for analysis, 172 experiments from 140 studies between 2004 and 2017 were included. Coordinates were extracted from each study, and the fMRI meta-analysis was performed with GingerALE3.0.2. An initial cluster-forming threshold (uncorrected  $p < 0.001$ ) was implemented followed by a cluster-level threshold FWE of  $p < 0.05$  (Fig. 3).

### 3.4. Functional connectivity

To functionally characterize the vlPFC which exhibits different conditions of emotional regulation of clinical empathy, the Neurosynth decoder function was used to assess its similarity to the reverse inference meta-analysis maps generated for the entire set of terms included in the Neurosynth dataset (Yarkoni et al., 2011). 'Expectancy' and 'Control' appeared to be among the five most relevant features (excluding anatomical terms) ranked by the correlation strengths between the vlPFC and the meta-analytical maps (please see the word cloud, with the size of the font scaled by its correlation strength). Accordingly, we further conducted the psychophysiological interaction (PPI) analysis in

**Table 1**

Details of studies included in the fMRI meta-analysis.

Study	Stim	Task	N (female)		Professionals	Age			Meta-analyses inclusion		
			HP	C		HP	C	Exp.	HP	HP>C	C>HP
Cheng et al. (2007)	b, v	PS	14(7)	14(7)	physicians	35	35	> 2	included	included	included
Cheng et al. (2017)	b, i	PS	100(100)	25(25)	nurses	30.2	30.0	7.6	included	included	included
Coll et al. (2017)	f, i	IN	15(10)	15(10)	nurses, physiotherapists	28.5	25.3	6.3	included	included	included
Corradi-Dell'Acqua et al. (2019)	b, i	PS	33(22)	–	nurses	34	–	9	included	NS	NS
Corradi-Dell'Acqua et al. (2021)	b, i	PS	21(21)	14(14)	nurses	37.3	23.4	11.0	N/A	included	N/A
Dirupo et al. (2021)	f, v	PS	26(17)	26(13)	medical students	24.2	23.7	< 1	N/A	N/A	included
Ellingsen et al. (2020)	f, d	IN	20(15)	20(20)	physicians	44.3*	40.0*	> 3	included	NS	NS
Jackson et al. (2017)	f, v	PS	27(27)	24(24)	nurses	36.4	36.8	11.5	included	included	included
Jensen et al. (2014)	f, d	IN	18(10)	–	physicians	NA	–	3.5	included	NS	NS
Kim et al. (2019)	vn	–	13(7)	–	medical students	20.1	–	< 1	included	NS	NS
Kim et al. (2021)	vn	–	19(6)	19(5)*	medical students	24.5	23.7	> 1	included	included	included
Olalde-Mathieu et al. (2022)	rs	–	18(9)	18(9)	psychotherapists	54.4	54.6	20.0	N/A	included	included
Tei et al. (2014)	b, v	PS	25(20)	–	nurses	26.0	–	1–11	included	NS	NS
Watanabe et al. (2019)	b, v	PS	19(11)	19(12)	physiotherapists	32.4	29.4	8.8	included	included	included
Yekta-Michael et al. (2019)	b, v	PS	20(0)	20(0)	dental students	NA	NA	< 1	N/A	included	included
			388(282)	214(139*)					11	9	9

Abbreviations: Stim, stimuli; N, the number of subjects; HP, healthcare providers; C, controls; b, body part; f, facial expression; v, vignette; i, image; vn, video; vn, vignette; d, direct eye contact; rs, resting-state; IN, patient-provider interaction; PS, passive observation; Exp., years of clinical experience; N/A = data not available; NS, not significant. Asterisks\*: for Ellingsen et al. (2020), there were the mean ages for each group before some participants dropped out; for Kim et al. (2019), the controls might have 3–7 females as the gender of the drop-outs was not available.

**Table 2**  
Details of studies included in the meta-analysis of dispositional empathy (IRI).

Study	N		Effect size SMD [95% CI]
	HP	C	
<b>IRI-EC (Empathic Concern)</b>			
Study	HP	C	
Cameron & Inzlicht (2020)	64	59	-0.12 [-0.47, 0.23]
Cheng et al. (2007)	14	14	0.46 [-0.29, 1.22]
Cheng et al. (2010)	15	15	-0.11 [-0.83, 0.61]
Coll et al. (2017)	37	37	0.16 [-0.29, 0.62]
Dirupo et al. (2021)	116	56	0.26 [-0.06, 0.58]
Dong et al. (2013)	22	22	0.20 [-0.39, 0.79]
Handford et al. (2013)	60	40	0.08 [-0.32, 0.48]
Kaseweter et al. (2020)	69	209	0.28 [0.01, 0.55]
Lamothe et al. (2018)	25	12	0.30 [-0.39, 0.99]
Latimer et al. (2017)	27	24	0.60 [0.03, 1.16]
Ogino et al. (2019)	42	42	-0.20 [-0.62, 0.23]
Olalde-Methieu et al. (2022)	52	92	-0.14 [-0.48, 0.20]
Putrino et al. (2018)	64	32	0.99 [0.54, 1.43]
Spring et al. (2019)	40	40	-0.01 [-0.45, 0.42]
Xie et al. (2018)	16	16	-0.10 [-0.79, 0.59]
	663	710	0.17 [0.002, 0.33]
Test for overall effect: $Z = 1.98, p = 0.048$			
Random-effects model (heterogeneity: $\text{Tau}^2 = 0.05; I^2 = 48\%$ )			
<b>IRI-PT (Perspective Taking)</b>			
Study	HP	C	Effect size SMD [95% CI]
Cameron & Inzlicht (2020)	64	59	0.09 [-0.27, 0.44]
Cheng et al. (2007)	14	14	0.21 [-0.53, 0.96]
Cheng et al. (2010)	15	15	0.22 [-0.50, 0.94]
Coll et al. (2017)	37	37	0.33 [-0.13, 0.79]
Dirupo et al. (2021)	116	56	0.05 [-0.27, 0.37]
Dong et al. (2013)	22	22	0.06 [-0.53, 0.65]
Handford et al. (2013)	60	40	0.19 [-0.22, 0.59]
Kaseweter et al. (2020)	69	209	0.19 [-0.08, 0.46]
Lamothe et al. (2018)	25	12	0.08 [-0.61, 0.77]
Latimer et al. (2017)	27	24	0.71 [0.14, 1.28]
Ogino et al. (2019)	42	42	-0.13 [-0.56, 0.30]
Olalde-Methieu et al. (2022)	52	92	0.67 [0.32, 1.02]
Putrino et al. (2018)	64	32	0.32 [-0.10, 0.75]
Spring et al. (2019)	40	40	0.08 [-0.36, 0.52]
Xie et al. (2018)	16	16	0.31 [-0.39, 1.01]
	663	710	0.22 [0.10, 0.33]
Test for overall effect: $Z = 3.68, p = 0.0002$			
Random-effects model (heterogeneity: $\text{Tau}^2 = 0.00; I^2 = 6\%$ )			
<b>IRI-PD (Personal Distress)</b>			
Study	HP	C	Effect size SMD [95% CI]
Cheng et al. (2007)	14	14	-0.12 [-0.87, 0.62]
Cheng et al. (2010)	15	15	-0.17 [-0.89, 0.55]
Coll et al. (2017)	37	37	-0.84 [-1.32, -0.36]
Dirupo et al. (2021)	116	56	-0.42 [-0.74, -0.10]
Dong et al. (2013)	22	22	-0.18 [-0.77, 0.41]
Handford et al. (2013)	60	40	-0.02 [-0.38, 0.42]
Kaseweter et al. (2020)	69	209	-0.13 [-0.40, 0.14]
Latimer et al. (2017)	27	24	0.45 [-0.11, 1.01]
Ogino et al. (2019)	42	42	0.18 [-0.25, 0.60]
Olalde-Methieu et al. (2022)	52	92	-0.45 [-0.79, -0.10]
Putrino et al. (2018)	64	32	-0.79 [-1.23, -0.35]
Spring et al. (2019)	40	40	-0.18 [-0.62, 0.26]
Xie et al. (2018)	16	16	-0.61 [-1.32, 0.10]
	574	639	-0.26 [-0.45, -0.06]
Test for overall effect: $Z = 2.62, p = 0.0087$			
Random-effects model (heterogeneity: $\text{Tau}^2 = 0.07; I^2 = 57\%$ )			
<b>IRI-FS (Fantasy)</b>			
Study	HP	C	Effect size SMD [95% CI]
Cheng et al. (2007)	14	14	0.32 [-0.43, 1.06]
Cheng et al. (2010)	15	15	-0.06 [-0.77, 0.66]
Coll et al. (2017)	37	37	-0.27 [-0.73, 0.19]
Dirupo et al. (2021)	116	56	0.14 [-0.18, 0.46]
Dong et al. (2013)	22	22	0.15 [-0.44, 0.74]
Handford et al. (2013)	60	40	0.01 [-0.39, 0.41]
Kaseweter et al. (2020)	69	209	-0.36 [-0.64, -0.09]
Latimer et al. (2017)	27	24	-0.20 [-0.75, 0.35]
Ogino et al. (2019)	42	42	-0.59 [-1.02, -0.15]
Olalde-Methieu et al. (2022)	52	92	1.04 [0.68, 1.41]
Putrino et al. (2018)	64	32	0.12 [-0.30, 0.55]

**Table 2 (continued)**

Study	N		Effect size SMD [95% CI]
	HP	C	
Spring et al. (2019)	40	40	0.10 [-0.34, 0.54]
Xie et al. (2018)	16	16	-0.06 [-0.76, 0.63]
	574	639	0.03 [-0.23, 0.28]
Test for overall effect: $Z = 0.20, p = 0.8509$			
Random-effects model (heterogeneity: $\text{Tau}^2 = 0.16; I^2 = 76\%$ )			

Abbreviations: N, the number of subjects; HP, healthcare providers; C, controls; SMD, the standardized mean difference.

previous work (Cheng et al., 2017). When seeded in the right insula, based on fMRI contrasts that showed significant interactions between stimuli (pain vs. neutral) and situational context (work vs. home), negative coupling between the insula and ventromedial PFC was identified. When a new seed in the vlPFC was added to the PPI analysis based on this new framework of emotional regulation of clinical empathy, positive connectivity between the insula and the vlPFC was uncovered. This insula cluster within the functional network of upregulation was adjacent to and with overlapped with the functional network involved in top-down inhibition (Fig. 4).

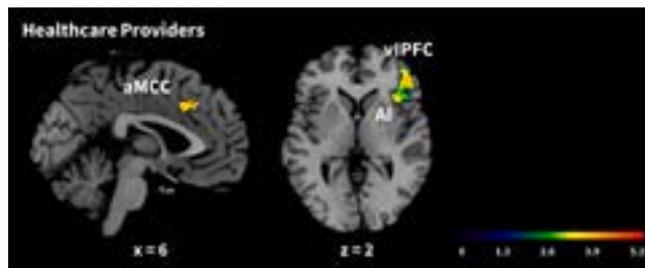
**3.5. Heterogeneity and publication bias statistics**

Heterogeneity between studies, reported as  $I^2$ , ranged from 0.5% to 11.8% among all significant peaks (Table 3, supplementary Table s2). For the main peaks of the meta-analysis of healthcare providers, the vlPFC, right AI, and aMCC exhibited no significant publication bias according to Egger's test (vlPFC:  $p = 0.929$ ; right AI:  $p = 1.000$ ; aMCC:  $p = 0.553$ ). The results are visualized in funnel plots (Fig. S6, S7).

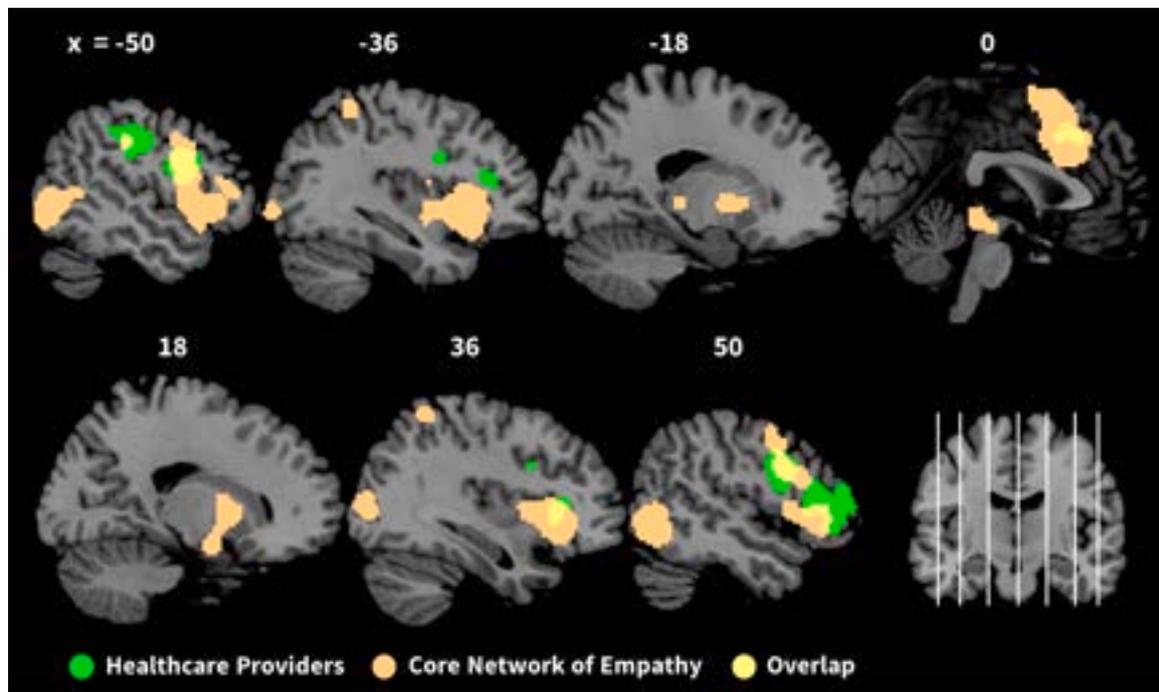
**Table 3**  
fMRI meta-analysis of healthcare providers.

Anatomical areas	L/R	Peak coordinates (MNI)			SDM-Z	voxels	$I^2$
		x	y	z			
Inferior frontal gyrus	R	48	30	8	4.121	987	11.8
ext. vlPFC	R	48	46	8	3.937		6.2
ext. anterior insula	R	36	22	2	3.477		0.5
Postcentral gyrus	L	-54	-26	30	4.903	705	4.7
Inferior frontal gyrus	L	-44	8	28	5.101	530	7.5
Precentral gyrus	R	46	8	34	4.641	469	3.4
Postcentral gyrus	R	64	-16	36	3.833	202	5.8
vlPFC	L	-38	34	16	4.986	97	7.6
aMCC	L	-2	24	40	4.246	79	3.1

Threshold: FWE-corrected  $p < 0.05$ , extent  $> 40$  voxels  
Abbreviations: L/R, left/right hemisphere; vlPFC, ventrolateral prefrontal cortex; aMCC, anterior mid-cingulate cortex; ext., extending to.



**Fig. 2.** Mean activations from meta-analytic maps among healthcare providers (11 studies) thresholded at a family-wise error (FWE) of  $p < 0.05$  with a cluster extent of at least 40 voxels.



**Fig. 3.** Healthcare providers share the ‘core network of empathy’. Green regions are results of the meta-analysis of empathy among healthcare providers (11 studies, family-wise error (FWE) of  $p < 0.05$ ). Beige regions are results of the meta-analysis of empathy from 140 studies, and indicate the ‘core network of empathy’ (FWE of  $p < 0.05$ ). Overlapping regions are in yellow.

#### 4. Discussion

This study attempted to examine empathy in healthcare providers, by integrating dispositional and neuroimaging studies involving this particular population via meta-analytical approaches. We demonstrated that upregulation processes were of the utmost importance in order to give rise to clinical empathy.

Regarding the first hypothesis testing, the meta-analytic results within healthcare providers rejected the null hypothesis. The neuroimaging meta-analysis of healthcare providers (11 studies) identified consistent activations in the neural network of empathy with a strict threshold at FWE  $p < 0.05$  (please see Figs. 2 and 3). For the second hypothesis testing, when applied a stringent FWE criterion, the meta-analytic results of healthcare providers vs. controls comparison (9 studies) did not have any survival cluster and hence rejected the null hypothesis that posited weaker neural responses for clinical empathy. When applied a more lenient threshold, the preliminary results revealed stronger rTPJ but weaker aMCC and AI activity in healthcare providers as compared to controls (please see Table S2 and Fig. S5). As for the third hypothesis testing to examine the functional connectivity, the vIPFC was found to be a pivotal region in emotional regulation of clinical empathy (please see Fig. 4).

Echoing past findings on pain empathy, the most convergent brain regions within healthcare providers exhibited the ‘core network of empathy’ (Fan et al., 2011; Lamm et al., 2011; Timmers et al., 2018), showing consistent activations of the anterior mid-cingulate cortex and anterior insula (aMCC/AI). This is ostensibly contrary to previous research regarding attenuated aMCC/AI activity in physicians as a protective mechanism that prevents them from experiencing personal distress and anxiety (Cheng et al., 2017, 2007). However, in addition to the aMCC/AI, healthcare providers showed the vIPFC activity as well. Compared to controls, healthcare providers were found to have weaker aMCC but stronger rTPJ activity. It is reasonable to infer that cognitive emotion regulation as a characteristic of clinical empathy allows healthcare providers to flexibly shift strategies for coping with changes so that they can be both clinically competent and empathetic towards

patients. In the same vein, the meta-analytical results of dispositional empathy in the aspect of the IRI-EC supported healthcare providers performing better at affective sharing. The IRI-EC was found to be positively associated with ‘compassion satisfaction’, representing happiness obtained after one’s professional performance, in a large-scale study (Gleichgerrcht and Decety, 2013, 2014). The neural underpinning of pain empathy in healthcare providers is modulated by the situational context in relation with the length of their clinical experience (Cheng et al., 2017). Focusing on how healthcare providers display empathy within the context of clinical settings in relation to specialty preference might help clarify previous equivocal findings of clinical empathy (Andersen et al., 2020).

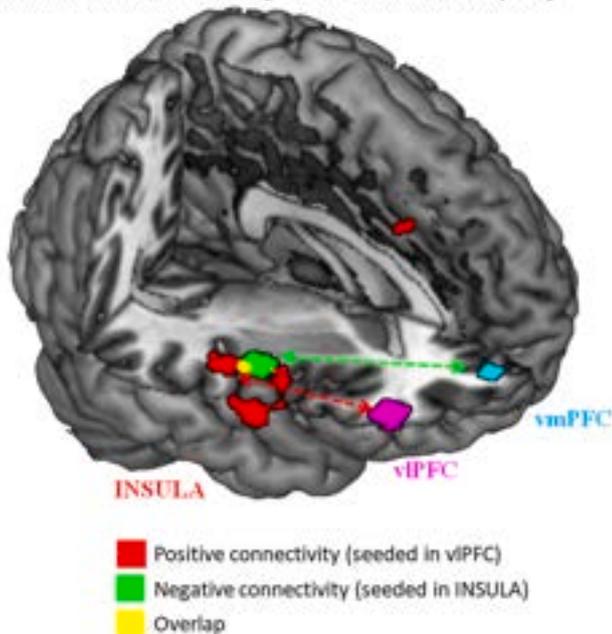
##### 4.1. The vIPFC encodes emotion regulation strategies

Contemporary discussions regarding the neural mechanisms of clinical empathy tend towards a ‘downregulation’ viewpoint. Provided that available neuroimaging studies reveal negative correlations between the aMCC/AI and vIPFC (Cheng et al., 2010; Zaki and Ochsner, 2012), this pattern hinted at the ability of the vIPFC to inhibit affective sharing, especially sentimentality, when encountering emotionally challenging situations in clinical settings. The theorization of the existence of affective strategies employed by healthcare providers, and during which they establish a certain emotional distance—or ‘detached concern’—from patients, is not a surprising one, as it explains the ability of healthcare providers to maintain their objectivity by limiting their exposure to negative emotions habitually experienced by patients. However, the ‘downregulation’ perspective is dominantly based on the concept that brain regions related to empathic arousal represent adverse experiences for professionalism and thus need to be suppressed. Hence, it is essential to clarify the factor which effectively leads to such a reduction in affective empathy. Some researchers argued that it was ‘unreflective’ affective sharing or a failure to recognize the complexity of emotions, meaning that personal distress could be avoided if affective sharing is coupled with adequate executive control (Decety and Svetlova, 2012; Jackson et al., 2005). Notwithstanding, recent research also

### A. Meta-analytic decoding of the vIPFC in clinical empathy



### B. Functional connectivity of PFC in clinical empathy



**Fig. 4.** Prefrontal cortex (PFC) mediates up- and down-regulation of the insula in clinical empathy. **A.** Word cloud showing the top 20 relevant terms (excluding anatomical terms) for the meta-analytic decoding of the ventrolateral prefrontal cortex (vIPFC). The size of the font is scaled to the correlation strength. **B.** When the insula is a seed, based on fMRI contrasts with an interaction between stimuli (pain vs. neutral) and situational contexts (work vs. home), there was a negative connectivity with the ventromedial PFC. When the vIPFC was added as a seed, based on this new framework of emotion regulation in clinical empathy, there was positive connectivity between the vIPFC and insula. This insula cluster within the functional network of upregulation is adjacent to and overlaps with the functional network which is also involved in downregulation.

observed how empathic verbal feedback from others exhibited the capacity to alleviate pain intensity ratings and to increase the functional connectivity of the PFC with the insula (Fauchon et al., 2019). The strategy employed for emotional regulation largely determines whether cognitive resources are primed or drained (Hobson et al., 2014; Moser et al., 2010). We herein challenge the current trend by demonstrating that flexibility in emotion regulation is a characteristic of clinical empathy.

### 4.2. The vIPFC encodes cognitive up- and downregulation

All of the previous findings showed that compared to controls, healthcare providers rendered the vIPFC and aMCC/AI activation to function in an opposite way (i.e., inhibitory regulation). Herein, by incorporating all of the available data via a meta-analytical approach, we observed for the first time that healthcare providers had both increased vIPFC and aMCC/AI activation in a synchronized way when they responded to patients' negative emotions (or suffering). Not only did the results refer to 'upregulation' of clinical empathy instead of an inhibitory effect, but they also indicated a possible role for the vIPFC in adjusting aMCC/AI activity.

Importantly, when it comes to emotional regulation and flexibility incurred by healthcare providers during their clinical practice, a detached perspective can reduce negative emotional reactions or sift out emotional information (Cheng et al., 2017, 2007; Decety et al., 2010). Surgeons, for example, must adjust differential empathy in disparate medical contexts. This detached perspective can be adaptive when performing an operation, but maladaptive when interacting with patients recovering from surgery (Balch et al., 2011). The capability to cognize ongoing situations and decide whether to affectively empathize with the patient or not is a necessity for healthcare providers. In parallel, studies have stated the importance of affective engagement, which aids healthcare providers in fulfilling and improving the patient-physician relationship (Decety et al., 2014; Halpern, 2014).

Interestingly, while shared representations between the self and others as well as self-other discrimination are of critical importance for empathy (Decety and Jackson, 2004; Decety and Sommerville, 2003), it is not surprising that many regions implicated here in clinical empathy were also found to be involved in self-referential processing (Qin et al., 2020). Interacting with patients requires healthcare providers to have empathic understanding and concern; therefore, it demands from them mentalizing and perspective-taking abilities, as well as the motivation to care for someone in need. The rTPJ serves basic functions of differentiation and integration of self-other information during the patient-provider interactions. The vIPFC happens to overlap with meta-analytical results of emotional regulation, especially when monitoring alternative emotional regulation strategies is indicated (Koch et al., 2018).

The role of the vIPFC in emotional regulation is widely acknowledged (Etkin et al., 2015; Levy and Wagner, 2011; Ochsner and Gross, 2005). The capacity to adaptively alternate emotion control behaviors was attributed to the anterior part of the PFC, which allows individuals to reappraise contextual information, monitor alternative options (e.g. emotional engagement or distraction), and meet situational demands (Koch et al., 2018). Verifying the proposed framework that switching between strategies for emotional regulation during clinical empathy should exhibit both up- and downregulation of affective arousal due to vIPFC involvement, we report that the insula indeed has positive connectivity with the vIPFC, but negative connectivity with the ventromedial PFC.

### 4.3. Extending theory to practice

The neuroscientific literature recognizes and underscores top-down inhibition as a key mechanism for eliciting empathic responses in healthcare practitioners (Cheng et al., 2017, 2007; Decety et al., 2010). Conversely, and although the upregulation of cognitive control processes is present in theoretical approaches to clinical empathy, to our knowledge, it has not been totally acknowledged in neuroscientific researching practices. Research using Psychophysiological Interaction (PPI) analyses to investigate and elucidate the neural underpinnings of clinical empathy have highlighted top-down inhibitory processes, which is in line with the previous literature. This is driven by PPI analyses which utilize a seed region in order to identify neural regions whose activation is dependent on an interaction between the psychological

context and the physiological state of the said seed region (O'Reilly et al., 2012). Thus, depending on which brain region, a researcher chooses as a seed, the results may show different types of couplings between the selected brain areas. In clinical empathy research, it is common to use emotion-relevant brain areas (such as the ACC and AI) as seed regions, and this results in findings that top-down inhibition should be the key mechanism behind empathy. Consequently, in order to bridge the gap between theory and practice, it is crucial for future neuroscientific research to delve into the nature of clinical empathy to take into consideration brain regions other than those implicated in emotional regulation (such as the prefrontal cortices).

#### 4.4. Limitations

A few limitations of this study must be acknowledged. First, strict analyses did not reveal robust neural alterations between the groups. Second, a more lenient threshold revealed some neural evidence between the groups, but this finding required confirmation in larger samples and needs to be interpreted cautiously. Finally, the lack of pre-registration limits conclusion of the current analyses. A lack of included studies frustrated our efforts to investigate demographic parameters in meta-analyses of both dispositional empathy and fMRI data. It was suggested that while subjective empathy ratings tend to decline over years of clinical experience (Hojat et al., 2004, 2009), different professions in clinical training and practice may also influence a person's capability to regulate empathy (Andersen et al., 2020). Hence, the findings we hereby delineate should be considered as preliminary evidence. However, the implications shed light on the dynamic and multimodal nature of empathy. We thus urge researchers to continue this line of neuroscientific research in clinical empathy, as to peer into the healthcare providers' various clinical scenarios and their subsequent coping strategies.

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#### Competing Interests

None of the authors have any competing interests to declare.

#### Data availability

Data will be made available on request.

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#### Availability of data and materials

All data needed to evaluate the conclusions in the present paper are included in the manuscript and/or the [Supplementary Materials](#).

#### Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.neubiorev.2022.104874](https://doi.org/10.1016/j.neubiorev.2022.104874).

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