Bachelor Degree Project

UNIVERSITY OF SKÖVDE

# EMPATHIC DISTRESS

The dark side of caring?

Bachelor Degree Project in Cognitive Neuroscience

Basic level 22.5 ECTS

Spring term 2020

Hilda Engelbrektsson

Supervisors: Stefan Berglund & Sakari Kallio

Examiner: Andreas Kalckert

**Abstract**

The current review aims to unravel what is known regarding the neural substrates of empathic distress and compassion fatigue. Empathic distress is a self-oriented feeling of anxiety experienced in response to the suffering of another. It has been related to, and theorized to be a precursor of, compassion fatigue. This is a form of caregiver burnout received by secondary exposure to trauma. In the current thesis, Scopus, Web of Science and PsycINFO were searched identifying 301 articles that were subsequently screened. In the end, five studies were included that measured either empathic distress or compassion fatigue in relation to brain structure or function. Findings are largely inconsistent but areas involved in theory of mind and that are important for the self-other distinction are discussed. A need for more research is identified, together with a desire for conceptual clarification between compassion fatigue and burnout.

*Keywords:* compassion fatigue, empathic distress, personal distress, neural correlates

## Table of Contents

## Introduction

Empathy is crucial to social interaction as well as to the experience of being human (Bernhardt & Singer, 2012). It may be an especially important ability for those working in caring professions. For instance, physician's empathy levels have been positively related to the clinical outcomes of their patients (Del Canale et al., 2012; Hojat et al., 2011). In simple terms, empathy involves experiencing states similar to those of others as well as the ability to put oneself "in the shoes of another" (Baron-Cohen & Wheelwright, 2004). A more thorough description will, however, be given in the background.

Even though empathy can be experienced for both positive and negative states, research has predominantly focused on empathy for other people's negative emotions (Andreychik & Migliaccio, 2015). This form of empathy may also be especially relevant for those working in caring professions, as they are often exposed to the distress or the suffering of others. When empathically responding to someone who is suffering (be it physically or mentally), there are two common responses: an other-oriented response of compassion (also called empathic concern) and a self-oriented response referred to as empathic, or personal, distress (Singer & Klimecki, 2014).

The response of empathic distress is of particular interest in this thesis. It is a response to the suffering of another in which one becomes self-centered and anxious (Eisenberg, 2000) and it has been related to (e.g. Gleichgerrcht & Decety, 2013) and theorized to be a precursor of compassion fatigue (Coetzee & Laschinger, 2018). This is a condition in which one becomes fatigued out of caring for others (Figley, 1995). The term was introduced into the literature by Charles Figley (1995) who saw therapists develop symptoms similar to those they care for only by hearing about their clients' suffering or traumatic experiences. In recent years, the importance of the empathic distress response in developing this condition has been emphasized (Coetzee & Laschinger, 2018). Moreover, due to the differences between empathic distress and compassion, it has even been suggested that the condition should be termed empathic distress fatigue instead of compassion fatigue (Hofmeyer, Kennedy, & Taylor, in press; Klimecki & Singer, 2012).

Despite the considerable amount of literature looking at the prevalence of compassion fatigue in different caring professions (e.g. Cavanagh et al., 2020), much less literature has studied the etiology and neural mechanisms underlying this condition. A greater understanding of the neural mechanisms underlying compassion fatigue and its precursor empathic distress will help us better understand the nature of this phenomenon. This in turn is essential for effectively preventing and treating the condition and thus for promoting well-being among those exposed to the distress of others.

This review aims to investigate what is known regarding the brain's structure and function in relation to compassion fatigue and its precursor empathic distress (see Coetzee & Laschinger, 2018). After giving some general background to empathy and its neural correlates, I will explain the response of empathic distress and discuss its relation to compassion fatigue. Thereafter I will explain my search process and present the results found. These will be discussed in terms of interpretations that can be made from them, as well as in light of the limitations they highlight in the literature. At last, I will outline the most urgent issues for future research to investigate.

# Background

## What is empathy?

Although debates exist in the research literature regarding the definition of empathy (de Vignemont & Singer, 2006), an important distinction should be made between the ability to understand the mental states of others and the ability to understand other people's emotions. Whereas the first is usually referred to as having a Theory of Mind (ToM, e.g. Premack & Woodruff, 1978) (or as "mentalizing" [e.g. Frith & Frith, 2003], or "perspective taking" [e.g. Healey & Grossman, 2018]), the ability to understand the emotions of others is that which is typically termed empathy (Shamsay-Tsoory, 2011). A more thorough description is given below of each of these conce

**Empathy.** To this day, there is no agreed upon definition of empathy (de Vignemont & Singer, 2006). There are broader definitions, such as the one held by Preston and de Waal (2002) in which empathy is seen as "any process where the attended perception of the object's state generates a state in the subject that is more applicable to the object's state or situation than to the subject's own prior state or situation" (p. 4). There are also more narrow definitions such as the one proposed by de Vignemont and Singer (2006) stating that "there is empathy if: (i) one is in an affective state; (ii) this state is isomorphic to another person's affective state; (iii) this state is elicited by the observation or imagination of another person's affective state; (iv) one knows that the other person is the source of one's own affective state." (p. 435).

Traditionally, empathy researchers have fallen into one of two camps: one that views empathy in terms of affect and another that sees it more as a cognitive phenomenon

(Baron-Cohen & Wheelwright, 2004). The affective perspective essentially defines empathy as "an observer's emotional response to the affective state of another" (Baron-Cohen & Wheelwright, 2004, p. 164)**,** however, with the distinction that the other person is the source of that state/with self-other distinction (Preckel, Kanske, & Singer, 2018). Affective or emotional empathy is strongly related to emotional contagion, which entails feeling the pain or stress of the other person (Shamay-Tsoory et al., 2010). This distinction is essentially what differentiates affective empathy from emotional contagion, in which a person's state comes as a result of perceiving the state of another **(**Preston & de Waal, 2002). In this state there is no self-other distinction, rather one experiences the emotion vicariously (Preston & de Waal, 2002) and this can happen without being consciously aware of it (Healey & Grossman, 2018). This self-other distinction is essentially what differentiates affective empathy from emotional contagion (Singer & Klimecki, 2014). Cognitive theories, on the other hand, put emphasis on the understanding of the feelings of others. According to this view, empathy involves taking the role of another and, by so doing, shifting from one's own to the other's perspective. Cognitive empathy is closely related to ToM.

**Theory of mind.** The term ToM was first introduced by Premack and Woodruff (1978) who investigated this ability in the chimpanzee. By saying that someone has a ToM they meant that the individual infers mental states in others - states that are not directly observable, such as their desires, thoughts and beliefs. This they studied by having the chimpanzee watch short videotapes of a human being faced with a problem and then allowing the chimpanzee to choose between different pictures where one was the solution. Having a ToM is what enables us to 'read other people's minds' so to say (Gallagher & Frith, 2003). This underpins our ability to deceive and cooperate, as well as to explain and predict other people's behavior. This is done by mental state attribution where we infer the beliefs, desires, emotions, or intentions of other people. Crucial to ToM is a recognition of other people as agents with personal goals determining their actions. Also vital to ToM is a recognition that other people have a worldview different from ours and the ability to separate and compare their perspective from ours.

Just as with empathy, ToM has also been divided into a cognitive and an affective component (e.g. Shamay-Tsoory & Aharon-Peretz, 2007). Whereas the cognitive component relates to the ability to infer the beliefs and intentions of others, the affective component refers to the capability to infer other people's' emotions and feelings (Shamay-Tsoory, Harari, Aharon-Peretz, & Levkovitz, 2010). The affective component of ToM is closely related to the cognitive component of empathy. See figure 1 for an overview of empathy, ToM and emotional contagion.

**Figure 1.** An overview of the relationship between theory of mind and empathy.

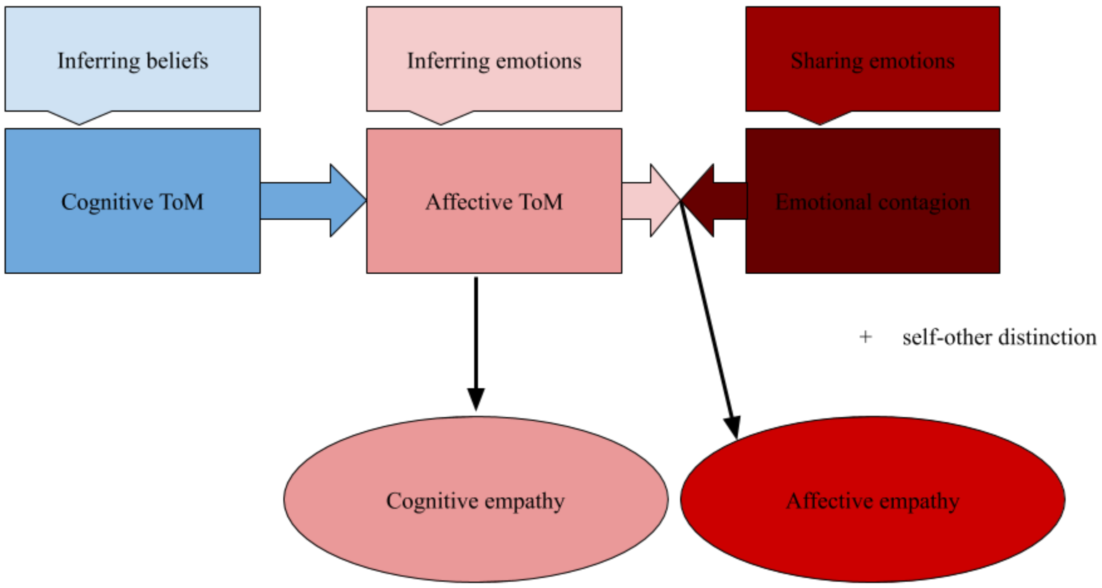


*Figure 1.* Adapted from: "Neural processing associated with cognitive and affective theory of mind in adolescents and adults" by C. L. Sebastian, N. M. Fontaine, G. Bird, S. J. Blakemore, S. A. Brito, E. J. McCrory, and E. Viding, 2012, *Social Cognitive and Affective Neuroscience, 7*, p. 54. Copyright 2011 by The Author. Adapted with permission.

## Neural Correlates of Empathy and Theory of Mind

**Neural correlates of empathy.** So what happens in the brain during empathy? Research indicates that, to some extent, empathizing activates brain regions similar to those recruited during the first-hand experience of the corresponding state (Bernhardt & Singer, 2012). As to brain regions more generally activated in empathy, a recent meta-analysis (Timmers et al., 2018) found a core neural empathy network involving the bilateral anterior insula (AI), bilateral mid-cingulate cortex (MCC), postcentral gyrus (or primary somatosensory cortex, SI), inferior parietal lobe (IPL), thalamus, amygdala, and the brainstem (at the level of the midbrain). The AI and MCC were recognized as the most central parts of this network.

Going into the subcomponents of empathy, a meta-analysis of 40 whole-brain studies (Fan, Duncan, de Greck, & Northoff, 2011) compared what they termed the ‘affective-perceptual’ form of empathy to the ‘cognitive-evaluative’ form. Studying the affective-perceptual form of empathy does not require participants’ knowledge of the experiment goal. Rather, an empathic response can be evoked automatically without any explicit instruction to empathize. In contrast, when empirically testing the cognitive-evaluative form of empathy, participants are asked to attend to the feelings of a target through explicitly imagining or evaluating their feelings. This process is thought to substantially influence the empathic response in the observing participant.

When conducting their meta-analysis, Fan et al. (2011) found the two forms of empathy to be largely dissociable. The only region active in both forms of empathy was the left AI. Other than that, the affective-perceptual form of empathy was linked to activity in the right dorsal anterior cingulate cortex (dACC), the right AI, the right dorsal medial thalamus (DMT), and the midbrain whereas the cognitive-evaluative form was related to activity in the left orbitofrontal cortex (OFC), the left anterior mid-cingulate cortex (aMCC), and the left DMT.

Further support for the dissociation of these two systems comes from a lesion study (Shamay-Tsoory et al., 2009) including 30 neurological patients with different brain lesions. Based on the location of the lesion, patients were divided into three groups defined by having lesions to: (1) the ventromedial prefrontal cortex (vmPFC), (2) the inferior frontal gyrus (IFG), and (3) the posterior cortex (PC). There was also a group of 34 healthy controls (roughly equal to the size of the lesion groups combined).

To measure empathy, a multidimensional self-report measure called the Interpersonal Reactivity Index (IRI; Davis, 1983) was used (Shamay-Tsoory et al., 2009). This is undoubtedly the most widely used instrument for measuring empathy (Pulos, Elison, & Lennon, 2004). The instrument has four subscales; two measuring cognitive empathy and two measuring affective empathy (Davis, 1980). The cognitive subscales are Perspective Taking and Fantasy. The Perspective Taking subscale measures the tendency to adopt the perspective of other people whereas the Fantasy subscale measures the tendency people have to identify with fictional characters. The affective subscales are Empathic Concern and Personal Distress. The aforementioned measures feelings of warmth, compassion, and concern for other people, whereas the Personal Distress measures “personal feelings of anxiety and discomfort that result from observing another's negative experience.” (Davis, 1980, p. 2).

Shamay-Tsoory et al. (2009) performed a one-way analysis of variance (ANOVA) revealing that the group with a lesion in the vmPFC differed significantly from the other groups in the two cognitive subscales of the IRI, namely the Perspective Taking and Fantasy subscales. The ANOVA also revealed a significant difference between the group with IFG damage and the rest of the groups in the PD subscale, which is one of the affective subscales. The authors further emphasized the dissociation between cognitive and affective empathy by performing a repeated measures analysis. This analysis revealed a significant interaction between groups and the sort of empathy (cognitive vs. emotional).

**Neural correlates of ToM.** As to the neural correlates of ToM, a core neural network has been identified involving the medial prefrontal cortex (mPFC) and the bilateral temporoparietal junction (TPJ; Schurz, Radua, Aichhorn, Richlan, & Perner, 2014). Further, when differentiating between cognitive and affective ToM (or perspective taking as they referred to it), Healey and Grossman (2018) found that cognitive ToM activated the dorsomedial and the dorsolateral prefrontal cortex (dmPFC and dlPFC) whereas affective ToM led to activations in the amygdala, the basal ganglia, the vmPFC, and the IFG. The TPJ and the precuneus were found to be active in both cognitive and affective ToM.

## Empathic Responses: Empathic Distress and Compassion

Empathically sharing the suffering of another may result in either compassion or empathic distress (Preckel et al., 2018). Compassion, which is also referred to as empathic concern or sympathy (Singer & Klimecki, 2014), is an other-oriented feeling characterized by feeling *for*, rather than *with* (as is the case in empathy), another person (Singer & Lamm, 2009). It is associated with feelings of warmth and concern (Preckel et al., 2018) and may motivate prosocial behavior (Singer & Lamm, 2009). Empathic distress, on the other hand, can be defined as “a strong aversive and self-oriented response to the suffering of others, accompanied by the desire to withdraw from a situation in order to protect oneself from excessive negative feelings” (Singer & Klimecki, 2014, p. R875). Empathic distress is also referred to as personal distress (Singer & Klimecki, 2014). Goetz, Keltner, and Simon-Thomas (2010) suggest that what determines whether one responds to the suffering of another with empathic distress or compassion is the ability to cope. From their view, feeling that one has adequate resources is essential in order to respond with compassion. If one feels unable to cope, either physically or psychologically, the response of distress is, according to them, more likely. This is similar to the view of Coetzee and Laschinger (2018) who suggest that feeling one has inadequate resources (e.g. lack of skills or energy, inadequate staffing, etc.) leads one to experience the other person as a threat and therefore become self-oriented, leading, in part, to the experience of personal distress. Personal distress may also result from an inability to distinguish between whether an affective experience originates in ourselves or in someone else, or in other words from a failure to maintain a self-other distinction (Singer & Lamm, 2009). What empathic response is given has also been shown to be affected by the perspective one adopts (Lamm, Batson, & Decety, 2007). Lamm and colleagues (2007) demonstrated this by instructing participants to adopt two different perspectives when watching videos of patients undergoing painful treatment. Whereas imagining how they themselves would feel if they were in the place of the other was coupled with high empathic distress and low empathic concern, imagining how the other feels was coupled with low empathic distress and high empathic concern.

The response of empathic distress has several negative consequences. Apart from the personal stress and anxiety that comes with it (Eisenberg, 2000), it has predicted expressions of verbal aggression to both fair and unfair others in an inequality game (Klimecki, Vuilleumier, & Sander, 2016). It has also been related to compassion fatigue (Gleichgerrcht & Decety, 2013), and theorized to be an important precursor of that condition (Coetzee & Laschinger, 2018).

**Compassion fatigue**

Compassion fatigue is a term mainly introduced into the literature by Charles Figley (1995) who studied the costs of caring. Noticing that therapists developed symptoms similar to those they cared for he started speaking of a kind of "secondary traumatization" where one develops symptoms of post-traumatic stress disorder by merely learning about the traumatic experiences of another. The term compassion fatigue was first used in print by Joinson in 1992 (as cited in Figley, 1995) when he was discussing burnout among nurses. Figley posited that the terms compassion stress and compassion fatigue could be used interchangeably with the terms secondary traumatic stress (STS) and secondary traumatic stress disorder (STSD), as he found these terms to be more favored among nurses. He further justified this terminology by explaining that those terms are more in line with the causes and manifestations of STS symptoms in the work nurses and therapists perform; a work where they often experience the stress, and sometimes the fatigue, that comes from caring for others.

The Professional Quality of Life Scale (ProQOL; Stamm, 2010) is today the most commonly used instrument for measuring compassion fatigue (Cavanagh et al., 2020; Stamm, 2010). It is an updated version of the original measure developed by Figley and measures both the positive and the negative effects of working with people, namely compassion satisfaction and compassion fatigue (Stamm, 2010). The positive aspects are called compassion satisfaction and refer to "the pleasure you derive from being able to do your work well" (Stamm, 2010, p. 12). One may derive this pleasure in various ways; for instance from helping others through the work you do. It may also come from having positive feelings about your colleagues or your ability to contribute to the work setting or to the greater good of society. Compassion fatigue, on the other hand, refers to the negative aspects of professional life quality and is measured by two subscales: burnout and STS. Burnout involves feelings of hopelessness and difficulties in handling work and effectively doing one's job. These negative feelings can be associated with a lack of support in the work environment, or with having a very high workload. It can also be a reflection of the feeling that your efforts make no difference. STS, on the other hand, has to do with being exposed to people who have been through very traumatic or stressful events. Negative effects of this condition involve avoiding things that might remind you of the person's traumatic experiences, as well as intrusive images and difficulties sleeping. Whereas burnout is usually gradual in its onset, STS typically involves a rapid onset and an association with a particular event (Stamm, 2010). Important to know about the ProQOL is that it is not a diagnostic test; rather it is a continual measure used to bring awareness to potential issues that would be good to address.

**Empathic Distress and Compassion Fatigue**

In recent years, the term compassion fatigue has received critique and it has been argued that a more appropriate name for the condition would be empathic distress fatigue (Hofmeyer et al., in press; Klimecki & Singer, 2012). The reason for this lies in the different definitions of empathic distress and compassion discussed earlier. Furthermore, recent research suggests that compassion can be seen as an emotion regulation strategy that, through the generation of positive emotions, counteracts negative emotions elicited by experiencing the suffering of others (Preckel et al., 2018).

Further highlighting the role of empathic distress in compassion fatigue, a recent review (Coetzee & Laschinger, 2018) of different models of compassion fatigue recognized the response of personal distress (which is another word for empathic distress) as an important precursor to developing compassion fatigue. In their model, this self-aversive response leads to uncompassionate care, which results in negative feedback from self and others, of which the outcome is compassion stress. Chronically experiencing compassion stress, due to the continual response of personal distress in response to the suffering of others, will eventually lead to compassion fatigue.

Further supporting the relation between empathic distress and compassion fatigue, regression analyses have found personal distress to be related to compassion fatigue in both physicians (Gleichgerrcht & Decety, 2013) and in clinical social workers (Thomas, 2013).

# Method

## Literature Search

A data search was conducted on March 18th, 2020. Three databases were used in the search, namely PsycINFO, Scopus, and Web of Science. No limits were put on publication years included in the search. Search terms relating to empathic distress and compassion fatigue were combined with terms relating to brain structure and function by the use of the Boolean operator "AND"**.** Search terms for empathic distress and compassion fatigue were as follows: ("empathic distress" OR "empathic distress fatigue" OR "compassion fatigue" OR "empath* distress" OR "empath* fatigue" OR "empathy fatigue" OR "empathy-induced distress" OR "vicarious traumatization" OR "secondary traumatization" OR "compassion exhaustion" OR "secondary traumatic stress" OR "secondary trauma" OR "vicarious trauma" OR "work-related trauma"). The search terms used relating to brain structure and function were: ("neural correlates" OR neuroimaging OR fmri OR "functional magnetic resonance imaging" OR mri OR "magnetic resonance imaging" OR "neural substrates" OR "neural bases" OR "brain mapping" OR "brain mechanism" OR "brain mechanisms" OR brain OR "pet scan" OR "positron emission tomography" OR neur* NOT "neuroticism"). The search terms were all adjusted according to the database being used. No related terms were included in PsycINFO and results were limited to neuroscience in Scopus.

**Inclusion/Exclusion Criteria**

To be included, studies had to measure either compassion fatigue or its precursor empathic distress. This had to be coupled with measurements of brain structure or function. Furthermore, data had to be presented to show the relationship (or lack of relationship) between the behavioral measure and brain structure or function. The studies also had to be performed on human subjects and be published in peer-reviewed journals. Studies in languages other than English or Swedish were excluded. Any papers that were not original articles, such as reviews, editorials, and conference papers, were also excluded.

**Data Extraction and Synthesis**

Due to a lack of resources, only one person (the author of the paper) was able to screen the articles and assess them for eligibility. Studies the author was unsure about including during the first sifting (i.e. when screening by titles/abstracts) were investigated a second time after the clear inclusion cases had gone through a second sifting. If uncertainty remained at that time, the author strived for sensitivity rather than specificity and thus included studies if, after careful weighing back and forth against the inclusion and exclusion criteria, there was any remaining uncertainty. During the second sifting (i.e. the assessment of full-text articles), borderline cases were discussed with the supervisor of the author and a decision was thereafter made about whether or not to include the articles of concern.

# Results

## Search Results

A total of 323 records were identified through the databases (for flowchart, see figure 2). After removal of duplicates, 301 remained. Those were all screened by title/abstract, leading to 269 excluded articles and 32 articles included for the second sifting. During the second sifting, the full texts of those 32 articles were assessed for eligibility. 27 were excluded and 5 included. Reasons for exclusion included: no measure of empathic distress/compassion fatigue (n = 8), no relevant neural correlates being reported (n = 8), no measure of brain structure or function being used (n = 1), wrong publication type (n=8), and wrong language (n = 2).

**Figure 2.** Flowchart outlining the study selection process.

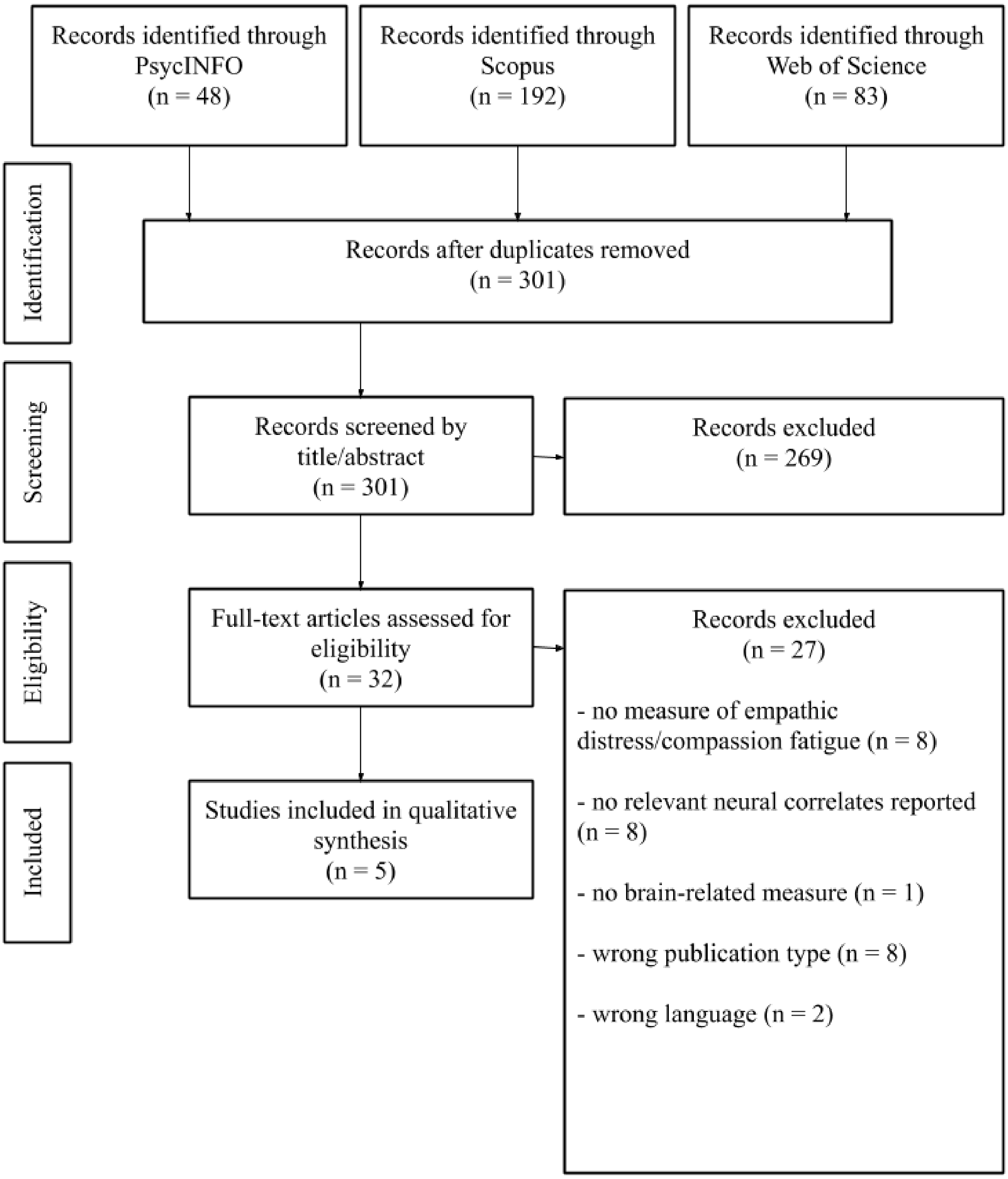


*Figure 2.* Flowchart outlining the study selection process. Based on the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA statement" by D. Moher, A. Liberati, J. Tetzlaff, D. G. Altman, & The Prisma Group, 2009, *PLoS Medicine, 6,* p. 3. Copyright 2009 by Moher et al.

**Descriptives of Studies**

The included studies were performed in a variety of countries including China (n=2), Japan (n=1), Spain (n=1), and the United States (n=1). All studies were performed on healthy adults. Two of them (Li et al., 2019; Luo et al., 2018) were performed on students, one (Uribe et al., 2019) on young adults (defined as 18-35 years old), one (Tei et al., 2014) on nurses (counting into the young adults range of 18-35 years old), and one (Ashar, Andrews-Hanna, Dimidjian, & Wager, 2017) on adults between 23-55 years old. A total of 212 participants were included from all studies. Samples typically included less males (79 total) than females (133 total), with the biggest difference found in the sample of nurses (20 females, 5 males; Tei et al., 2014) and the most equal sample being that of young healthy adults (20 males and 22 females; Uribe et al., 2019). See table 1 for a summary of main components of the studies.

**Table 1**

***Descriptives and measures of the different studies***

| Source | Luo et al. (2018) | Uribe et al. (2019) | Tei et al. (2014) | Li et al. (2019) | Ashar et al. (2017) |
|---|---|---|---|---|---|
| # Participants (male) | 53(14) | 42(20) | 25(5) | 26(14) | 66(26) |
| Population | college students | young healthy adults (defined as 18-35 years old) | nurses (1-11 years of experience) | right-handed students (or recruited from the University of Electronic Science and Technology of China) | healthy right-handed adults |
| Age | M (SD): 21.79 (1.6) | Median (IQR): 19.0 (5.0) | M (SD), range: 26.0 (3.14), 22-34 | M (SD): 22.8 (2.1) | M age = 30.1 and age range = 23 – 55 |
| CF component + | trait personal | trait empathic | trait personal | trait personal | state empathic |

| | | | | | |
|---|---|---|---|---|---|
| definition | distress<br>*def: a self-oriented feeling of personal unease to another's state* | distress<br>*def: the ability of sharing others' negative emotions, such as pain* | distress<br>*def: the tendency to experience negative feelings in response to the distress of others*<br><br>CF defined as burnout, measured by emotional exhaustion (i.e. *feelings of being emotionally exhausted and overextended by one's work*) and depersonalization (i.e. *emotional detachment toward the person receiving one's care*) | distress<br>*def: a tendency toward self-oriented affective empathy* | distress<br>*def: a feeling of discomfort or suffering for you, as someone listening to these stories.* |
| Measure/key conceptualization | Interpersonal Reactivity Index (IRI) | The Cognitive and Affective Empathy Test (TECA) | Interpersonal Reactivity Index (IRI)<br><br>Maslach Burnout Inventory (MBI) | Interpersonal Reactivity Index (IRI) Chinese version | single question: "How distressed do you feel right now?" |
| Brain-related measures | *Structural MRI assessing GMV<br>*Resting-state FC | *Structural MRI assessing cortical thickness and subcortical volumes<br><br>*Resting-state FC | fMRI (with an empathy for pain paradigm) | *Structural MRI assessing GMV<br>*fMRI (with an empathy for pain paradigm) | *fMRI with predictive brain markers (with an empathy for pain paradigm) |
| Main strengths | *whole-brain analysis was performed<br>*ROI in FC analysis was based on structural whole-brain | - | *compassion fatigue is measured | *whole-brain analysis | *a neural network is identified that *predicts* empathic distress |

| | | | | | |
|---|---|---|---|---|---|
| | analysis | | | | |
| Main limitations | *only healthy individuals were included but no people with compassion fatigue or similar conditions that might make them have more extreme levels of personal distress | *Empathic distress scores were just classified as low or high (low</=55<high)<br><br>*only predefined ROIs in the FC analysis | *only predefined ROIs were used, no pain localizer (they just drew on previous research findings)<br><br>*compassion fatigue is viewed as the same thing as burnout<br><br>*no control group<br><br>*averaged neural activity across hemispheres within each participant | *compassion fatigue is not measured directly<br><br>*although whole brain analysis was done for the contrast pain>no pain, IRI scores were only correlated with BOLD responses in bilateral insula but none of the other regions identified to be active during the pain tasks | *only a single-item measure of empathic distress |

***Note.*** CF = Compassion fatigue. MRI = Magnetic Resonance Imaging. fMRI = functional MRI. GMV = Gray matter volume. VBM = Voxel-based morphometry. FC = Functional connectivity. M=Mean. SD=Standard Deviation. N/A=Not applicable.

## Study Methodology

**Definitions and measures of compassion fatigue.** Only Tei et al. (2014) measured compassion fatigue. They viewed it as synonymous with burnout which justified the use of the Maslach Burnout Inventory (MBI; Maslach, 1982) to measure it. This is the most common tool used for measuring burnout (Halbesleben & Demerouti, 2005). It includes three subscales, namely emotional exhaustion, depersonalization, and accomplishment (Maslach, Jackson, Leiter, Schaufeli, & Schwab, 1986). Emotional exhaustion, which is characteristic of burnout, entails a feeling of depleted resources accompanied by the feeling of not being able to give of oneself psychologically. Depersonalization refers to the development of cynical attitudes and feelings about one's clients. Finally, reduced accomplishment entails negative evaluations about oneself, especially in regard to the work one does with clients. Despite the existence of three MBI subscales, only two were used in the study by Tei et al. (2014), namely emotional exhaustion and depersonalization. Apart from that, all studies that were included measured empathic distress (also called personal distress), which has been viewed as a precursor to developing compassion fatigue (Coetzee & Laschinger, 2018).

**Definitions and measures of empathic distress.** Three studies (Li et al., 2019; Luo, et al., 2018; Tei et al., 2014) measured trait personal distress using different versions of the Interpersonal Reactivity Index (IRI; Davis, 1980, 1983; Davis, Luce, & Kraus, 1994). One study (Ashar et al., 2017) defined empathic distress as “a feeling of discomfort or suffering for you, as someone listening to these stories” (Ashar et al., 2017, p. 2). Stories indicated biographies in which true stories of suffering individuals were described**.** It was measured with a single question, namely “How distressed do you feel right now?” (p. 2). Lastly, one study (Uribe et al., 2019) measured empathic distress with the Cognitive and Affective Empathy Test (TECA; López-Pérez, Fernández-Pinto, & García, 2008**)**. In this measure, empathic distress is defined as “the ability of sharing others’ negative emotions, such as pain” (Uribe et al., 2019, p. 3). Just as in the IRI, empathic distress in this measure is one of the two subcomponents of affective empathy. However, unlike the PD subscale of the IRI, the empathic distress scale of the TECA measures the ability of sharing negative states with others and does not specify this as a self-oriented reaction per se. Hence, what in the IRI is divided into a self-oriented feeling of personal distress and an other-oriented feeling of empathic concern is in the TECA (López-Pérez et al., 2008) measured as the same component. This can be seen as a weakness as there is support for the notion of empathic distress being differentiated from compassion (e.g. Hofmeyer et al., in press), and this is foundational for the study of empathic distress and compassion fatigue. However, one could speculate that the other-oriented feeling of empathic concern (which is the other subscale of the IRI) is not so much about sharing negative states of others, but rather about feeling for others (Singer & Lamm, 2009). Indeed, the EC and PD subscales of the IRI might indicate empathic responses rather than a mere sharing of feelings.

**Measures of brain structure and function.** Structural magnetic resonance imaging (MRI) was used in three studies (Li et al., 2019; Luo et al., 2018; Uribe et al., 2019). Two of them (Li et al., 2019; Luo et al., 2018) assessed gray matter volume (GMV) with the use of voxel-based morphometry (VBM) whereas Uribe et al. (2019) measured cortical thickness. That study also looked at subcortical volumes. Two of the mentioned studies (Luo et al., 2018; Uribe et al., 2019) also investigated resting-state functional connectivity (FC) using the seed-based FC analysis.

Three studies (Ashar et al., 2017; Li et al., 2019; Tei et al., 2014) used fMRI with an empathy for pain paradigm, i.e. participants were exposed to the suffering of another. Two of these studies (Li et al., 2019; Tei et al., 2014) used the typical task-related fMRI design and compared the pain>no pain contrast in specific brain regions with trait PD as measured by the IRI. The painful stimuli in both studies were images of painful situations (e.g. someone placing their finger between the scissor instead of the paper they're holding in their hand). The neutral conditions were identical except for that the painful aspect of the picture was removed (e.g. someone simply cutting a paper with a scissor). Neither of the two studies (Li et al., 2019; Tei et al., 2014) included results from a whole-brain analysis when correlating the activity with PD scores. Li et al. (2019) performed a whole-brain analysis to find regions involved in pain. However, although several regions were found to be activated in the pain>no pain contrast, they only correlated pain-related activity of the bilateral AI with trait

PD. Tei et al. (2014) did not perform any whole-brain analysis. Rather they defined ROIs based on previous research. They chose the AI, the inferior frontal gyrus (IFG) and the anterior cingulate cortex (ACC) as ROIs, with the argument that those have been commonly recruited during empathy for pain and because they have been discussed as major affective components of the pain matrix. The AI and the IFG were coupled as a single ROI due to their vicinity to each other. The authors also defined the temporoparietal junction (TPJ) as a ROI as it has been noted to be crucially involved in physicians' brain response to empathy for pain, which was relevant for their study as their sample consisted of nurses. To be noted is also that they averaged the brain activity across hemispheres within each participant, something that could potentially be seen as a weakness since there is a possibility of lateralization. In addition to correlating the activity found in the ROIs in the pain>no pain contrast to scores of PD, Tei et al. (2014) also correlated them with scores of emotional exhaustion and depersonalization, as measured by the MBI (Maslach, 1982).

Although Ashar et al. (2017) also used fMRI with an empathy for pain paradigm, they did not report clusters of activation during specific tasks. Rather, they developed two whole-brain patterns (with the use of machine-based learning) to predict empathic care and distress respectively. While undergoing fMRI, participants listened to true biographies of suffering individuals. The stories were audio-recorded by a member of the research team and an authentic face photograph was shown of the individual while their story was played. Following each biography, participants made ratings of either overall empathic care or distress (each for half of the biographies). After being removed from the fMRI, participants listened to the full 24 biographies a second time, this time providing moment-by-moment ratings of either empathic care or empathic distress. Using machine learning-based regression techniques, the researchers then identified two whole-brain patterns (‘‘brain markers’’) quantitatively predicting the intensity of moment-by-moment ratings of empathic care and empathic distress.

## Study Results

**Structural correlates.** For the structural studies, that all performed whole-brain analysis, (Li et al., 2019; Luo et al., 2018; Uribe et al., 2019), no positive correlates were found between empathic/personal distress and GMV or whole brain cortical thickness. However, negative correlates were found between personal distress (i.e. the tendency to experience a self-oriented feeling of personal unease in response to the distress of others) and the dorsomedial prefrontal cortex (dmPFC; Luo et al., 2018), as well as the right middle frontal gyrus (MFG), the right angular gyrus (AG), the right supplementary motor area (SMA), the right precuneus, and the left supramarginal gyrus (SMG; Li et al., 2019). The study using the broader definition of empathic distress (i.e. defining it as the ability of sharing the negative emotions of others, not specifying whether the reaction is self- or other-oriented; Uribe et al., 2019) did not report any negative correlates either. The slightly broader definition might be a reason for this but even more likely is the dichotomous division of empathic distress; scores were simply classified as high or low with a cut-off between the T-scores of 55 and 56. This might make it harder to differentiate between extremes while instead differentiating between people who are not that different in levels of empathic distress. This study did, however, also investigate six subcortical volumes (amygdala, hippocampus, nucleus accumbens, thalamus, caudate, and putamen). Participants that were high in empathic distress (i.e. with T-scores of 56 or more) had significantly higher bilateral thalamus volumes than those low in empathic distress (i.e. those with T-scores of 55 or less). In other words, people who had a higher ability to share the negative emotions of others (remember that the measured used does not distinguish between this as a self- or other-oriented response) had a bigger thalamus than those with a lower ability to do so. See table 2 for a summary of the structural correlates of empathic/personal distress.

**Table 2**

***Correlates between personal/empathic distress scores and brain structure***

| Source | Luo et al. (2018) | Uribe et al. (2019) | Li et al. (2019) |
|---|---|---|---|
| Measure of personal/empathic distress | Interpersonal Reactivity Index (IRI; Davis et al., 1994) | The Cognitive and Affective Empathy Test (TECA; López-Pérez et al., 2008) | Interpersonal Reactivity Index (IRI) Chinese version (Zhang, Dong, Wang, Zhan, & Xie, 2010) |
| Whole-brain analysis | yes<br>GMV | yes<br>Whole brain cortical thickness | yes<br>GMV in cortical regions |
| Regions of interest | no | Six subcortical volumes: *amygdala, *hippocampus, *nucleus accumbens, *thalamus, *caudate, *putamen | no |
| Covariates of no interest | *age<br>*gender<br>*total GMV | - | *age<br>*total GMV |
| Positive correlates | none | high Empathic distress with:<br>*bilateral thalamus | none |
| Negative correlates | personal distress with:<br>*dmPFC | none | personal distress with:<br>*right MFG<br>*right AG<br>*right SMA |

| | |
|---|---|
| | *right precuneus<br>*left SMG |

*Note.* Summary of results from the studies investigating structural correlates of personal/empathic distress. Abbreviations: GMV = Gray matter volume. dmPFC = dorsolateral prefrontal cortex. MFG = middle frontal gyrus. AG = angular gyrus. SMA = supplementary motor area. SMG = supramarginal gyrus.

**Correlates of functional connectivity.** Two studies (Luo et al., 2018; Uribe et al., 2019) reported correlates between empathic/personal distress and resting-state functional connectivity (FC). Based on the relation they found in the dmPFC between GMV and personal distress, Luo et al. (2018) defined this area as a ROI in their FC analysis. They found personal distress to be positively correlated with functional connectivity between the dmPFC and the left posterior insula and between the dmPFC and the bilateral occipital gyrus. They also found personal distress to be significantly negatively correlated with FC between the dmPFC and numerous areas, including the anterior midcingulate cortex (aMCC), the left dorsolateral prefrontal cortex (dlPFC), and the left inferior parietal gyrus. Uribe et al. (2019), on the other hand, found no significant correlates between empathic distress and FC. Part of the reason for this might be that they only looked at six ROIs defined based on previous literature. Those included the bilateral orbitofrontal, cingulate, and insular cortices, as well as the amygdala, hippocampus, and thalamus. Another explanation for their lack of significant correlations might be the same as mentioned earlier; their dichotomous division of empathic distress.

**Table 3**

***Correlates between personal/empathic distress scores and resting-state functional connectivity***

| Source | Luo et al. (2018) | Uribe et al. (2019) |
|---|---|---|
| Whole-brain analysis | yes but with a seed in dmPFC | no |
| Regions of interest (ROIs) | *dmPFC | *orbitofrontal cortex<br>*cingulate cortex<br>*insular cortex<br>*amygdala<br>*hippocampus<br>*thalamus |
| Reason for chosen ROI | because this region was identified in the VBM analysis | defined based on previous literature |
| Positive correlates | dmPFC with:<br>*left posterior insula<br>*bilateral occipital gyrus | none |
| Negative correlates | dmPFC with:<br>*aMCC<br>*left dlPFC<br>*left inferior parietal gyrus | none |

***Note.*** Abbreviations: dmPFC = dorsomedial prefrontal cortex; aMCC = anterior mid-cingulate cortex; dlPFC = dorsolateral prefrontal cortex.

**Functional correlates.** Three of the studies (Ashar et al., 2017; Li et al., 2019; Tei et al., 2014) used fMRI with an empathy for pain paradigm. Both Tei et al. (2014) and Li et al. (2019) used it in a task-related fashion, comparing the activity during painful and neutral tasks and investigating the correlation between that and trait personal distress. Tei et al. (2014) looked only at predefined ROIs, namely AI, IFG, ACC, and the TPJ. They purposefully applied a more conservative analysis when investigating the latter, with the argument that the TPJ, unlike the other areas, is not considered a part of the pain matrix (Tei et al., 2014). Li et al. (2019), on the other hand, did perform a whole-brain analysis when investigating the pain>no pain contrast. However, they only correlated bilateral AI activity (during the pain>no pain contrast) with personal distress scores. This was defined based on the multisubject statistical maps. Neither Tei et al. (2014) nor Li et al. (2019) found any significant correlations between pain-related brain activity and trait PD. Tei et al. (2014) did, however, find a significant negative relation between pain-related brain activity and scores on the emotional exhaustion subscale of the MBI (Maslach, 1982). More specifically emotional exhaustion was negatively related to activity in the AI/IFG ($r = -0.590$, $p=0.002$) and in the TPJ ($r = -0.550$, $p=0.004$).

**Predictive brain markers.** Ashar et al. (2017) developed two brain markers, or whole-brain patterns, predicting self-reported empathic care and distress respectively. The authors first assessed the extent to which each marker tracked the emotion it was intended to track (i.e. marker sensitivity) and the extent to which it did not track the other emotion (i.e. marker specificity). Whereas the marker trained on care predicted empathic care with high accuracy and did significantly worse at predicting distress, the marker trained on empathic distress predicted both distress and care with a high level of accuracy. Thus, both markers were sensitive to the emotion they were developed to predict but only the care marker exhibited specificity. Based on significant correlations between predicted and reported emotion intensity, both markers were, however, deemed successful at predicting moment-by-moment fluctuations of empathic care and distress. Areas common to the two markers (i.e. where they had overlapping positive weights) were the anterior medial prefrontal cortex (mPFC), orbitofrontal cortex (OFC), ventral striatum (VS), supplementary motor area (SMA) precuneus, and bilateral mid- and posterior insula. To identify regions selective for empathic care and distress respectively, brain regions were identified that, in the multivariate patterns, had significantly more positive weights for the one marker, compared to the other, and that were significantly positively correlated with the related emotion in univariate voxel-by-voxel analyses, both when controlling and not controlling for the other emotion. Using this method, Ashar et al. (2017) found empathic distress was preferentially related to activity in the left ventral premotor cortex, bilateral inferior parietal lobe (IPL), and bilateral somatosensory cortex (SI and SII) as well as to activity in the left mid-insula and a right hemisphere cluster spanning the mid-insula, claustrum, and putamen. By comparing their results with reverse inference meta-analytic maps from Neurosynth, the authors confirmed their interpretation of the regions specific for distress as related to mirroring processes (52% overlap with the word “mirror”). Areas whose activity was preferentially related to empathic care were the medial OFC (mOFC), vmPFC, VS, septal area, and precuneus/posterior cingulate cortex.

## Discussion

The aim of this review was to gain a greater understanding of compassion fatigue by investigating the neural correlates of its precursor, empathic distress, as well as the neural correlates of the condition itself. Thus, studies were included that investigated either compassion fatigue or its precursor empathic distress. From the review, it is clear that research regarding the neural correlates of compassion fatigue is lacking. Indeed, only one study (Tei et al., 2014) was found that investigated it. This study viewed compassion fatigue as synonymous with burnout and therefore used the MBI (Maslach, 1982) to measure it. In order to understand how brain structure and function are affected by this condition, more research is needed.

Five studies were found that investigated the neural correlates of empathic distress. These studies lend important insights into the neural mechanisms involved in empathic distress and potentially in the development of compassion fatigue. However, even though there are more studies on this precursor to compassion fatigue, it is clear that more research is needed on this subject as well. Furthermore, the heterogeneity of study methodology and results makes it hard to draw any clear conclusions. There are, however, some interesting connections to highlight.

## Neural correlates

**Compassion fatigue.** The only study that measured compassion fatigue (Tei et al., 2014) did so with the MBI (Maslach, 1982), viewing it as synonymous with burnout. This in itself may be seen as a weakness since the degree to which these conditions are related remains unclear. Even though symptoms of compassion fatigue (as measured by the ProQOL) have been highly correlated with those of burnout (as measured both by the burnout subscale of the ProQOL [$r = .819$, $p < .001$] and the emotional exhaustion subscale of the MBI [$r = .72$, $p < .001$]; Deighton, Gurris, & Traue, 2007), differences have been noted between the terms (Powell, 2020). Indeed, Figley (1995) contrasted the terms from each other already in 1995, explaining that compassion fatigue has a more rapid onset than burnout, as well as a faster recovery rate. The most prominent feature of burnout, he explained, is client problems "that are perceived to be beyond the capacity of the service provider" (Figley, 1995, p. 24). A distinction he noted between the conditions is that compassion fatigue, in contrast to burnout, is coupled with a sense of helplessness and confusion, with symptoms often being disconnected from real causes. The current version of the ProQOL (Stamm, 2010) brings even more confusion as it measures compassion fatigue with two subscales; burnout and STS. In the previous version of the test the STS scale was called the compassion fatigue scale (Stamm, 2010). In other words, burnout and compassion fatigue were previously seen as two separate negative effects that may result from working with those who are suffering. However, Stamm (2010) now views burnout as a subcomponent of compassion fatigue. This brings with it certain confusion as to the terminology, leaving it unclear whether burnout is a subcomponent of compassion fatigue or distinct from, yet related to, it. This points to a need for conceptual clarification on the subject, which, for instance, could be achieved by comparing definitions and measures of burnout to those of compassion fatigue. It also reveals a need for more studies on compassion fatigue in relation to brain structure and function.

Tei et al. (2014) found significant negative correlations between scores on the MBI subscale emotional exhaustion and activity in the AI/IFG. A recent activation likelihood estimate meta-analysis (Timmers et al., 2018) identified both these regions to be part of a core neural empathy network. Indeed, the AI and the IFG represented two of the largest clusters found, the third cluster found in the MCC. When looking specifically at empathy for pain and non-pain negative affective states, the AI and the IFG still showed robust activation. Thus it is no surprise that Tei and colleagues (2014) identified activations in these regions, as they were using an empathy for pain paradigm. What should be noted, however, is that Timmers et al. (2018) revealed differences in activation between the two hemispheres when looking at empathy for pain and non-pain negative affective states. More specifically, the left AI (extending to the IFG) and the right mid insula were two of the largest clusters found when examining empathy for pain. Furthermore, the left AI and the right IFG were activated for both empathy for pain and empathy for non-pain negative affective states. This highlights the downside of averaging brain activity across hemispheres, as was done by Tei et al. (2014). Thus it is possible that important differences between the hemispheres remained unrevealed in this study.

The authors (Tei et al., 2014) interpret the reduced activity in the AI/IFG, which is associated with increased scores of emotional exhaustion, as reduced empathy-related brain activity. This interpretation is over simplistic. Indeed, the AI seems to be important for much more general processes than empathy. For instance, Menon and Uddin (2010) suggest that the AI, which receives multimodal sensory input, plays a key role in the detection of salient stimuli and that it has a causal, perhaps even critical, role in cognitive control. From this perspective, the findings by Tei et al. (2014) might indicate that increased emotional exhaustion brings with it a reduced ability to detect important sensory cues, whether internal or external, as well as a reduced capacity for cognitive control.

Scores of emotional exhaustion were also negatively related to pain-related activity in the TPJ (Tei et al., 2014), an area situated at the posterior border of the temporal and parietal lobes (Carter & Huettel, 2013). Although the area lacks a clear cut anatomical location, it has been suggested to consist of the more ventral part of the SMG, the ventral part of the AG, the most dorsal region of the superior temporal gyrus (STG) and the most posterior part of the STS (Quesque & Brass, 2019). It is an area that, together with the mPFC, forms a core neural network for ToM (for meta-analysis, see Schurz et al., 2014) and that is activated both in cognitive and affective ToM (Healey & Grossman, 2018).

The TPJ has also been proposed to play an important role in distinguishing between self and other, both at the perceptual level (e.g. body, body parts, ownership), at the action level (e.g. motor actions, imitation control) and at the mental-state level (e.g. beliefs, knowledge, goals, emotions, feelings; for a review, see Quesque & Brass, 2019). Uddin and colleagues (Uddin, Molnar-Szakacs, Zaidel, & Iacoboni, 2006) demonstrated the importance of the TPJ in the ability to distinguish between self and other by using repetitive transcranial magnetic stimulation (rTMS). Participants were exposed to rTMS to the IPL prior to their engagement in a self-other discrimination task. The task involved viewing images representing themselves or a highly familiar, gender-matched other to varying degrees. The pictures were a morphed combination of the two faces (without hair and ears) with varying degrees of self in them (0%, 20%, 40%, 60% and 80%, & 100%). Upon seeing the pictures, participants were asked to indicate whether it looked more like 'self' or 'other'. rTMS to the right, but not left, IPL disrupted participants' performance on this task, indicating a vital role of the right IPL (dorsal TPJ; Quesque & Brass, 2019) in the self-other distinction (Uddin et al., 2006).

From this viewpoint, the fact that more emotionally exhausted individuals tended to exhibit less TPJ activity, as induced by viewing painful compared to neutral stimuli (Tei et al., 2014), might indicate a reduced ability to differentiate between self and other. This ability is key to empathy and is what separates it from emotional contagion (Singer & Lamm, 2009). The inability to maintain this distinction may cause the experience of personal distress. Lamm et al. (2007) demonstrated the importance of the self-other distinction in an fMRI study by asking participants to adopt either a self-perspective or an other-perspective when viewing soundless video clips of individuals listening to aversive sounds as a form of treatment. They found that, whereas adopting an other-perspective led to more empathic concern and less personal distress (as measured by the IRI; Davis, 1996), adopting a self-perspective, when viewing the other person in pain, led to more personal distress and less empathic concern. These results indicate that a failure to maintain the self-other distinction might lead a person to experience increased feelings of personal distress and reduced feelings of empathic concern, something that may be harmful both to the person in pain (due to a lack of care from the empathizer) and the one empathizing (due to the experience of personal distress). Further supporting the importance of the TPJ in the self-other distinction, Lamm et al. (2007) found that the other>self contrast revealed a significant cluster in the right IPL (which might be seen as part of the dorsal TPJ; Quesque & Brass, 2019).

In summary, to the extent that compassion fatigue can be conceptualized as emotional exhaustion, it might bring with it a reduced ability to detect salient sensory cues, a diminished capacity for cognitive control, and a reduced capability to maintain the self-other distinction. The latter two might in turn increase the tendency to experience personal distress in response to the suffering of others. However, it remains unclear whether emotional exhaustion makes people more vulnerable to experiencing personal distress or if a higher tendency to experience personal distress in response to the suffering of others puts one at higher risk for becoming emotionally exhausted and thus, potentially, also for developing compassion fatigue. A possibility is also that the relationship goes both ways, having the potential to cause a downward spiral of decreasing health.

**Empathic distress.** The first thing to be noted regarding the neural correlates of empathic distress is the variety of findings. Considering the small amount of studies included and their methodological variety, the inconsistency in findings is not a surprise. Rather, it highlights the fact that more research is needed in order to draw any meaningful conclusions regarding the brain mechanisms underlying empathic distress and compassion fatigue. However, there are some interesting connections to highlight.

Before going into the brain regions identified in the different studies, I will discuss the methodological variety of the studies. Only three of them (Li et al., 2019; Luo et al., 2018; Tei et al., 2014) used the same measure of empathic distress, namely the IRI. Of those, both Li et al. (2019) and Luo et al. (2018) performed their study on college students in China and investigated relations between GMV and personal distress. They both performed whole brain analysis and correlated GMV with personal distress scores, with age and total GMV as covariates of no interest. Luo et al. (2018), who had a more unequal sample when it comes to gender, also used gender as a covariate of no interest. Despite these highly similar methods, the authors received differing results. What should be noted is that neither found any positive correlates, showing that there is some degree of consensus among the findings. Yet the negative correlates differed completely. The reason for this can only be speculated. However, it makes clear the need for future research to truly establish what areas are involved in the experience of empathic distress.

Whereas Luo et al. (2018) coupled their structural analysis with a seed-based FC analysis, Li et al. (2019) performed an fMRI study in addition to it. Although performed on college students in China instead of nurses in Japan, their fMRI design was similar to that of Tei et al. (2014). Neither of the fMRI studies yielded any significant results as to the relation between trait personal distress and pain-related brain activity. Reasons for this might be they both looked at only a few ROIs, namely the AI, IFG, ACC, and TPJ for Tei et al. (2014) and the bilateral insula for Li et al. (2019).

One could speculate that the reason no significant clusters were found in the TPJ in relation to personal distress was the more conservative threshold that was applied to this ROI. Were this the case, the alterations in activity may simply be more prominent in those who have become emotionally exhausted, which would explain why a correlation was indeed found with scores on that subscale of the MBI. However, what should be noted is that emotional exhaustion also was found to be significantly negatively related to activity in AI/IFG, an area that did not have as a conservative threshold applied to it.

Either way, the predefined ROIs should be seen as a major flaw in the fMRI studies, especially because of the frail ground on which they were based. Correlating only one of the regions found implemented in empathy for pain, as Tei et al. (2014) did, is inconclusive when seeking to understand the neural correlates of empathic distress. There is also a lack of evidence to justify the specific regions defined as ROIs by Li et al. (2019). Even though they based them on regions involved in empathy for pain, a recent meta-analysis (Timmers et al., 2018) has indicated that more (and slightly different) areas are active during empathy for pain. For these reasons, future studies should be careful when defining ROIs and would do well in employing whole-brain analyses in order to find clusters to correlate with personal or empathic distress.

Resting-state FC was investigated both in relation to personal distress (Luo et al., 2018) and in connection to empathic distress (Uribe et al., 2019). The studies gained quite different results. Whereas Uribe et al. (2019) did not find any FC to be related to empathic distress at all, Luo et al. (2018) found several areas of connectivity to be related to scores of personal distress as measured by the IRI (Davis et al., 1994). The explanation may lie in their different methods: whereas Uribe et al. (2019) only looked at certain predefined ROIs, Luo et al. (2018) looked at the whole brain but with a seed in the dmPFC, an area which they, by structural analysis, had identified as related to personal distress. Uribe et al. (2019) defined their ROIs based on previous literature. However, they do not state what that literature is, something that can be viewed as a weakness in and of itself. Nevertheless, it is possible to speculate. For instance, four of their ROIs (specifically, the insular and cingulate cortices, the amygdala and the thalamus) have been identified in the experience of empathy (Timmers et al., 2018). The other two are the OFC and the hippocampus (Uribe et al., 2019). The OFC is important for the processing of rewards and punishments (Kringelbach & Rolls, 2004). It has also been associated with the empathic response of compassion (Preckel et al., 2018). Thus, the lack of significant findings in this area is in line with the idea of empathic distress and compassion as separate responses (e.g. Singer & Klimecki, 2014). What should be noted is the fact that these studies investigated FC. Thus, a lack of significant findings in the areas mentioned only means there were no significant relations between those areas. The flaw in defining those ROIs might indeed be that the regions are connected to other areas of the brain. A likely explanation for the lack of FC related to empathic distress in the study by Uribe et al. (2019) is the dichotomous division of the empathic distress scale of the TECA.

**Combined analysis of findings**

In line with the idea that the TPJ is vital for maintaining the self-other distinction and that failure to do so may be coupled with empathic distress, GMV in right AG and the left SMG were both negatively related to trait personal distress (Li et al., 2019). These regions form the dorsal part of the TPJ (Quesque & Brass, 2019). The reduced volume in these areas in people with a higher tendency to experience negative states in response to the distress of others, in combination with the reduced activation seen in people that are more emotionally exhausted (Tei et al., 2014), may be interpreted as tentative support for the notion that empathic distress would be an important precursor to developing compassion fatigue, at least to the extent that compassion fatigue can be conceptualized as emotional exhaustion. However, this hypothesis needs to be investigated further. It would be of particular interest to perform longitudinal studies on the subject since such a design would have the potential of finding causal relationships between empathic distress and compassion fatigue.

Contradicting the interpretation made above, the bilateral IPL was one of the areas whose activity was preferentially associated with empathic distress in the study by Ashar et al. (2017), in which machine-based learning was used to identify brain markers predicting self-reported empathic distress and care. Once again, this points to the need for additional research being made on the topic. However, lending further support for the notion, Luo et al. (2018) found FC between the dmPFC and the left IPL to be negatively related to trait personal distress (as measured by the IRI).

GMV of both the dmPFC and of the right precuneus were negatively related to personal distress. These are both areas that have been linked to ToM. Whereas the precuneus is active in both cognitive and affective ToM, the dmPFC is specific to cognitive ToM (Healey & Grossman, 2018). Both of these areas have been activated when participants make judgments about themselves and others (Ochsner et al., 2004).

**Future directions**

It is evident that more research is needed on the neural correlates of empathic distress and, especially, on the neural correlates of compassion fatigue. It would be of particular interest to study individuals over time, looking at brain structure and function in relation to both state/trait empathic distress and symptoms of compassion fatigue. This would be a way of testing the hypothesis that empathic distress acts as a precursor to the development of compassion fatigue (see e.g. Coetzee & Laschinger, 2018).

Furthermore, definitions and measures of compassion fatigue should be contrasted with those of burnout, in order to bring clarity to the degree of overlap that exists between the two conditions. Apart from specifically comparing definitions and measures, studies including measures of burnout (e.g. the MBI), compassion fatigue (e.g. the ProQOL) and empathic distress (e.g. the IRI) all in the same study, while also investigating brain structure and function, would be beneficial. Such studies would allow for a thorough comparison of the conditions which in turn would aid in gaining a more comprehensive understanding of both conditions. This knowledge will be important for directing prevention and treatment of these conditions, as well as in directing policy for those who care for others, whether doing so professionally (e.g. nurses, therapists, etc.) or not (Wang et al., 2016).

Lastly, it would be of great importance to explore relations to empathic control or emotion regulation. Results from an event-related potential (ERP) study indicated that counselors distinguished between self and other at an earlier stage than controls (Luo et al., 2013). Assuming this is related to their occupation rather than to personality differences, this might indicate that distinguishing between the self and the other is a skill that can be developed. Finding ways to use such emotion regulation strategies is important to help improve the health of those that care for others. One such method is compassion training, which has recently been suggested as an effective emotion regulation strategy that hinders the development of compassion fatigue (Preckel et al., 2018).

## References

Andreychik, M. R., & Migliaccio, N. (2015). Empathizing with others' pain versus empathizing with others' joy: Examining the separability of positive and negative empathy and their relation to different types of social behaviors and social emotions. *Basic and Applied Social Psychology*, *37*(5), 274-291. https://doi.org/10.1080/01973533.2015.1071256

Ashar, Y. K., Andrews-Hanna, J. R., Dimidjian, S., & Wager, T. D. (2017). Empathic care and distress: Predictive brain markers and dissociable brain systems. *Neuron, 94*(6), 1263-127. http://dx.doi.org/10.1016/j.neuron.2017.05.014

Baron-Cohen, S., & Wheelwright, S. (2004). The empathy quotient: An investigation of adults with Asperger syndrome or high functioning autism, and normal sex differences. *Journal of Autism and Developmental Disorders*, *34*(2), 163-175. https://doi.org/10.1037/12061-001

Bernhardt, B. C., & Singer, T. (2012). The neural basis of empathy. *Annual Review of Neuroscience*, *35*, 1-23.

Carter, R. M., & Huettel, S. A. (2013). A nexus model of the temporal–parietal junction. *Trends in Cognitive Sciences*, *17*(7), 328-336. https://doi.org/10.1016/j.tics.2013.05.007

Cavanagh, N., Cockett, G., Heinrich, C., Doig, L., Fiest, K., Guichon, J. R., ... & Doig, C. J. (2020). Compassion fatigue in healthcare providers: A systematic review and meta-analysis. *Nursing Ethics*, *27*(3), 639-665. doi: 10.1177/0969733019889400

Coetzee, S. K., & Laschinger, H. K. (2018). Toward a comprehensive, theoretical model of compassion fatigue: An integrative literature review. *Nursing & Health Sciences*, *20*(1), 4-15.

Davis, M. H. (1980). A multidimensional approach to individual differences in empathy. *Journal of Personality and Social Psychology, 10*(85), 1-19.

Davis, M. H. (1983). Measuring individual differences in empathy: Evidence for a multidimensional approach. *Journal of Personality and Social Psychology*, *44*(1), 113. https://doi.org/10.1037/0022-3514.44.1.113

Davis, M. H. (1996). *Empathy: A social psychological approach.* Madison, WI: Westview Press.

Davis, M. H., Luce, C., & Kraus, S. J. (1994). The heritability of characteristics associated with dispositional empathy. *Journal of Personality*, *62*(3), 369-391. https://doi.org/10.1111/j.1467-6494.1994.tb00302.x

Deighton, R. M., Gurris, N., & Traue, H. (2007). Factors affecting burnout and compassion fatigue in psychotherapists treating torture survivors: Is the therapist's attitude to working through trauma relevant? *Journal of Traumatic Stress*, *20*(1), 63-75. doi: 10.1002/jts.20180

Del Canale, S., Louis, D. Z., Maio, V., Wang, X., Rossi, G., Hojat, M., & Gonnella, J. S. (2012). The relationship between physician empathy and disease complications: an empirical study of primary care physicians and their diabetic patients in Parma, Italy. *Academic Medicine*, *87*(9), 1243-1249. doi: 10.1097/ACM.0b013e3182628fbf

de Vignemont, F., & Singer, T. (2006). The empathic brain: How, when and why? *Trends in Cognitive Sciences, 10*(10), 435-441.

Eisenberg, N. (2000). Emotion, regulation, and moral development. *Annual Review of Psychology*, *51*(1), 665-697.

Fan, Y., Duncan, N. W., de Greck, M., & Northoff, G. (2011). Is there a core neural network in empathy? An fMRI based quantitative meta-analysis. *Neuroscience & Biobehavioral Reviews*, *35*(3), 903-911. doi:10.1016/j.neubiorev.2010.10.009

Figley, C. R. (Ed.) (1995). *Compassion fatigue: Coping with secondary traumatic stress disorder in those who treat the traumatized.* New York, NY: Brunner/Mazel.

Frith, U., & Frith, C. D. (2003). Development and neurophysiology of mentalizing. *Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences*, *358*(1431), 459-473.

Gallagher, H. L., & Frith, C. D. (2003). Functional imaging of 'theory of mind'. *Trends in Cognitive Sciences*, *7*(2), 77-83.

Gleichgerrcht, E., & Decety, J. (2013). Empathy in clinical practice: How individual dispositions, gender, and experience moderate empathic concern, burnout, and emotional distress in physicians. *PloS One*, *8*(4). doi: 10.1371/journal.pone.0061526

Goetz, J. L., Keltner, D., & Simon-Thomas, E. (2010). Compassion: An evolutionary analysis and empirical review. *Psychological Bulletin, 136*(3), 351-374. doi: 10.1037/a0018807

Halbesleben, J. R., & Demerouti, E. (2005). The construct validity of an alternative measure of burnout: Investigating the English translation of the Oldenburg Burnout Inventory. *Work & Stress*, *19*(3), 208-220.

Healey, M. L., & Grossman, M. (2018). Cognitive and affective perspective-taking: Evidence for shared and dissociable anatomical substrates. *Frontiers in Neurology, 9*. doi: 10.3389/fneur.2018.00491.

Hofmeyer, A., Kennedy, K., & Taylor, R. (in press). Contesting the term 'compassion fatigue': Integrating findings from social neuroscience and self-care research. *Collegian*. https://doi.org/10.1016/j.colegn.2019.07.001

Hojat, M., Louis, D. Z., Markham, F. W., Wender, R., Rabinowitz, C., & Gonnella, J. S. (2011). Physicians' empathy and clinical outcomes for diabetic patients. *Academic Medicine*, *86*(3), 359-364. doi: 10.1097/ACM.0b013e3182086fe1

Klimecki, O. M., & Singer, T. (2012). Empathic distress fatigue rather than compassion fatigue? Integrating findings from empathy research in psychology and social neuroscience. In B. Oakley, A. Knafo, G. Madhavan, & D. S. Wilson (Eds.), *Pathological altruism* (pp. 368–383). New York: Oxford University Press. doi: 10.1093/acprof:oso/9780199738571.003.0253

Klimecki, O. M., Vuilleumier, P., & Sander, D. (2016). The impact of emotions and empathy-related traits on punishment behavior: introduction and validation of the inequality game. *PLoS One*, *11*(3).

Kringelbach, M. L., & Rolls, E. T. (2004). The functional neuroanatomy of the human orbitofrontal cortex: Evidence from neuroimaging and neuropsychology. *Progress in Neurobiology*, *72*(5), 341-372.

Lamm, C., Batson, C. B., & Decety, J. (2007). The neural substrate of human empathy: Effects of perspective-taking and cognitive appraisal. *Journal of Cognitive Neuroscience, 19*(1), 42–58.

Li, Y., Zhang, T., Li, W., Zhang, J., Jin, Z., & Li, L. (2019). Linking brain structure and activation in anterior insula cortex to explain the trait empathy for pain. *Human Brain Mapping 41*(4), 1030–1042. doi: 10.1002/hbm.24858

López-Pérez, B., Fernández-Pinto, I., & García, F. J. A. (2008). *TECA: Test de empatía cognitiva y afectiva*. Tea.

Luo, P., Qu, C., Chen, X., Zheng, X., Jiang, Y., & Zheng, X. (2013). A comparison of counselors and matched controls in maintaining different brain responses to the same stimuli under the self-perspective and the other-perspective. *Brain Imaging and Behavior*, *7*(2), 188-195. doi 10.1007/s11682-012-9214-z

Luo, S., Zhong, S., Zhu, Y., Wang, C., Yang, J., Gu, L., … & Wu, X. (2018). Brain structural and functional substrates of personal distress in empathy. *Frontiers in Behavioral Neuroscience, 12*(0), 1-7. doi: 10.3389/fnbeh.2018.00099

Maslach, C. (1982). *Burnout: The cost of caring.* Englewood Cliffs, NJ: Prentice Hall Trade.

Maslach, C., Jackson, S. E., Leiter, M. P., Schaufeli, W. B., & Schwab, R. L. (1986). *Maslach burnout inventory* (Vol. 21, pp. 3463-3464). Palo Alto, CA: Consulting psychologists press.

Menon, V., & Uddin, L. Q. (2010). Saliency, switching, attention and control: A network model of insula function. *Brain Structure and Function*, *214*(5-6), 655-667. doi: 10.1007/s00429-010-0262-0

Ochsner, K. N., Ray, R. D., Cooper, J. C., Robertson, E. R., Chopra, S., Gabrieli, J. D., & Gross, J. J. (2004). For better or for worse: Neural systems supporting the cognitive down-and up-regulation of negative emotion. *Neuroimage*, *23*(2), 483-499.

Powell, S. K. (2020). Compassion fatigue. *Professional Case Management, 25*(2), 53-55. doi: 10.1097/NCM.0000000000000418

Preckel, K., Kanske, P., & Singer, T. (2018). On the interaction of social affect and cognition: Empathy, compassion and theory of mind. *Current Opinion in Behavioral Sciences*, *19*, 1-6. https://doi.org/10.1016/j.cobeha.2017.07.010

Premack, D., & Woodruff, G. (1978). Does the chimpanzee have a theory of mind? *Behavioral and Brain Sciences, 1*(4), 515-526.

Preston, S. D., & de Waal, F. B. (2002). Empathy: Its ultimate and proximate bases. *Behavioral and Brain Sciences*, *25*(1), 1-20.

Pulos, S., Elison, J., & Lennon, R. (2004). The hierarchical structure of the Interpersonal Reactivity Index. *Social Behavior and Personality*, *32*(4), 355-360.

Quesque, F., & Brass, M. (2019). The role of the temporoparietal junction in self-other distinction. *Brain Topography*, 1-13. https://doi.org/10.1007/s10548-019-00737-5

Schurz, M., Radua, J., Aichhorn, M., Richlan, F., & Perner, J. (2014). Fractionating theory of mind: A meta-analysis of functional brain imaging studies. *Neuroscience & Biobehavioral Reviews*, *42*, 9-34.

Shamay-Tsoory, S. G. (2011). The neural bases for empathy. *The Neuroscientist*, *17*(1), 18-24.

Shamay-Tsoory, S. G., & Aharon-Peretz, J. (2007). Dissociable prefrontal networks for cognitive and affective theory of mind: A lesion study. *Neuropsychologia*, *45*(13), 3054-3067. doi: https://doi.org/10.1016/j.neuropsychologia.2007.05.021

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

Shamay-Tsoory, S. G., Harari, H., Aharon-Peretz, J., & Levkovitz, Y. (2010). The role of the orbitofrontal cortex in affective theory of mind deficits in criminal offenders with psychopathic tendencies. *Cortex*, *46*(5), 668-677. doi:10.1016/j.cortex.2009.04.008

Singer, T., & Klimecki, O. M. (2014). Empathy and compassion. *Current Biology, 24*(18), R875–R878. doi:10.1016/j.cub.2014.06.054

Singer, T., & Lamm, C. (2009). The social neuroscience of empathy. *Annals of the New York Academy of Sciences*, *1156*(1), 81-96. doi: 10.1111/j.1749-6632.2009.04418.x

Stamm, B. H. (2010). The Concise ProQOL Manual, 2nd Ed. Pocatello, ID: ProQOL.org.

Tei, S., Becker, C., Kawada, R., Fujino, J., Jankowski, K. F., Sugihara, G., ... & Takahashi, H. (2014). Can we predict burnout severity from empathy-related brain activity?. *Translational Psychiatry*, *4*(6), e393-e393. doi:10.1038/tp.2014.34

Thomas, J. (2013). Association of personal distress with burnout, compassion fatigue, and compassion satisfaction among clinical social workers. *Journal of Social Service Research*, *39*(3), 365-379. doi: 10.1080/01488376.2013.771596

Timmers, I., Park, A. L., Fischer, M. D., Kronman, C. A., Heathcote, L. C., Hernandez, J. M., & Simons, L.E. (2018). Is Empathy for pain unique in its neural correlates? A meta-analysis of neuroimaging studies of empathy. *Frontiers in Behavioral Neuroscience, 12*, 1-12. doi: 10.3389/fnbeh.2018.00289

Uddin, L. Q., Molnar-Szakacs, I., Zaidel, E., & Iacoboni, M. (2006). rTMS to the right inferior parietal lobule disrupts self–other discrimination. *Social Cognitive and Affective Neuroscience*, *1*(1), 65-71.

Uribe, C., Puig-Davi, A., Abos, A., Baggio, H. C., Junque, C., & Segura, B. (2019). Neuroanatomical and functional correlates of cognitive and affective empathy in young healthy adults. *Frontiers in Behavioral Neuroscience, 13*(0), 1-8. doi: 10.3389/fnbeh.2019.0008520

Wang, Y., Song, J., Guo, F., Zhang, Z., Yuan, S., & Cacioppo, S. (2016). Spatiotemporal brain dynamics of empathy for pain and happiness in friendship. *Frontiers in Behavioral Neuroscience*, 10, 1-17. doi: 10.3389/fnbeh.2016.00045

Zhang, F., Dong, Y., Wang, K., Zhan, Z., & Xie, L. (2010). Chinese version interpersonal reactivity index (IRI-C): A study of reliability and validity. *Chinese Journal of Clinical Psychology, 18*, 155–157.