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Contesting the term 'compassion fatigue': Integrating findings from social neuroscience and self-care research

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ABSTRACT

Background: Nurses describe work-related distress and exhaustion as compassion fatigue and burnout. However, neuroscientists confirm compassion does not cause fatigue.
Aim: This discussion paper explains contemporary social neuroscience evidence about empathy, emotion regulation, and compassion, then discusses evidence-informed strategies to cultivate effective self-care practices and compassion.
Methods: The argument draws on relevant empirical evidence and literature to raise awareness, improve understanding, and spark dialogue and reconceptualisation of these critical issues within the nursing context.
Findings and discussion: Functional magnetic resonance imaging studies show the debilitating condition known as compassion fatigue should be called 'empathic distress fatigue'. This distinction matters because the strategy to ease empathic distress fatigue is compassion training. The capacity to remain clear about the 'self-other' distinction is called emotion regulation. Without emotion regulation skills, our 'self-other' distinction is blurred so we absorb another's suffering and negative emotions as our own and experience empathic distress fatigue. Yet, much of this knowledge is not implemented within the nursing context. On the contrary, the topic of compassion fatigue continues to dominate education and research. This knowledge gap is significant because healthcare leaders cannot address the distress of its workforce and strengthen cultures without understanding its causes.
Conclusion: Evidence from social neuroscience and self-care studies offers promising new knowledge to design strategies to foster self-care, self-compassion, emotion regulation, and ease empathic distress fatigue. These strategies and practices for renewal support the raison d'être of nursing which is to provide quality, safe, compassionate care for patients and their families by resilient nurses.

Summary of Relevance
Problem or issue
Nurses describe work-related stress and exhaustion as compassion fatigue and burnout. Fatigued nurses may provide depersonalised care that lacks compassion and fails to meet patients' needs.
What is already known
Compassion fatigue cannot be empirically validated or measured. Neuroscientists confirm the term 'compassion fatigue' should be replaced by the term 'empathic distress fatigue'. Inadequate emotion regulation is associated with blurring the 'self-other' distinction and leads to empathic distress fatigue. Neuroplasticity studies confirm compassion can be learned.
What this paper adds
We explain social neuroscience evidence and behavioural processes underlying empathy, empathic distress, emotion regulation, and compassion. Empirical evidence about self-care and self-compassion is explained. This evidence can readily be applied within nursing to ease empathic distress fatigue, improve emotion regulation, effective self-care, self-compassion, and compassionate care.

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1. Introduction

Work-related stress is the most common occupational health problem among nurses after musculoskeletal disorders (Bernal et al., 2015). Compassion fatigue and burnout are terms used by nurses to describe work-related stress and physical and mental exhaustion (Sinclair, Raffin-Bouchal, Venturato, Mijovic-Kondejewski, & Smith-MacDonals, 2017; Vachon, Huggard, & Huggard, 2015). Nurses who experience these deleterious consequences "are more self-judgmental and have more psychological inflexibility" (Duarte & Pinto-Gouveia, 2017). Fatigued, burnt-out nurses typically provide depersonalised, sub-optimal care that lacks empathy and compassion and fails to meet the needs of patients (Bauer-Wu & Fontaine, 2015; Bramley & Matiti, 2014). Organisational and systemic failure, negative values and behaviours have culminated in patient neglect, abuse, and unsafe outcomes (Francis, 2013; Lown, Rosen, & Marttila, 2011). In response, there are calls to cultivate cultures of compassion to improve quality of care and educate providers to be compassionate (Christiansen, O'Brien, Kirton, Zubairu, & Bray, 2015; Francis, 2013).

But compassion fatigue continues to be the dominant topic in the nursing literature and education initiatives. For this reason, it makes no sense to nurses to participate in programs to foster compassion because they believe being too compassionate is the root cause of their fatigue.

What is not clear, however, is how nursing can respond to the critical problem of a burned-out health workforce that has negative consequences for patients and clinicians alike. It is time to integrate knowledge from other disciplines to create new perspectives that are better equipped to respond to complex problems and answer questions not originally possible to answer (Boyer, 1990).

The social psychology and neuroscience disciplines offer different and relevant evidence about empathy, compassion and related concepts. Neuroscientists confirm compassion does not cause fatigue and said the term should be replaced by 'empathic distress fatigue' (Klimecki & Singer, 2012). Functional magnetic resonance imaging (fMRI) studies show that 'empathic distress fatigue' is triggered when the 'self-other' distinction is blurred, so clinicians experience the distress of others as their own (Klimecki & Singer, 2012).

The purpose of this paper is to spark dialogue about cutting-edge social neuroscience evidence regarding empathy, compassion and related concepts for nursing education, practice and research. This promising body of work is a breakthrough and taken together with empirical self-care evidence, can inform strategies to cultivate compassion to ease empathic distress fatigue. First, we discuss compassionate practice in healthcare cultures and define burnout and compassion fatigue. Next, we explain the social neuroscience evidence and behavioural processes underlying empathy, empathic distress, emotion regulation, and compassion. Finally, we present empirical evidence about self-care and self-compassion. This evidence informs strategies and practices designed to ease empathic distress fatigue, improve emotion regulation, cultivate effective self-care, and compassion.

2. Background

Our ability to develop social competencies and emotions, such as empathy and compassion, is essential for our wellbeing, successful communication, and cooperative interactions in society (Klimecki, Leiberg, Lamm, & Singer, 2013; Preckel, Kanske, & Singer, 2018; Valk et al., 2017). The benefits and vital role of empathy and compassion to improve healthcare, patient satisfaction and outcomes, and clinician wellbeing is well-documented (Bauer-Wu & Fontaine, 2015; Duarte & Pinto-Gouveia, 2017; Lown, 2014; Seppala, Hutcherson, Nguyen, Doty, & Gross, 2014). When empathic communication and compassion exist in healthcare cultures, clinical teams are more

resilient, effective, morale and quality care are higher, and patient complaints are fewer (Christiansen et al., 2015; Lown, 2014). Joan Halifax confirms, "The practice of nursing is grounded in clinical competence and also deeply embedded in the experience of relationship and the cultivation and expression of compassion" (2014, p. 121). Having compassion for others has inspired many to become nurses (Schantz, 2007). Nurses who believe they relieve the suffering of others experience compassion satisfaction (Burridge, Winch, Kay, & Henderson, 2017).

Patients and families say the manner in which they are listened to and cared for matters *just as much* as the quality of health care (Bramley & Matiti, 2014; Lown et al., 2011). Compassionate care addresses the patient's need for "connection and relationships and is based on attentive listening and a desire to understand the patient's context and perspective" (Lown et al., 2011, p. 1772). Compassion is not only essential for high-quality patient-centred care, but also for reducing burnout and improving health outcomes, wellbeing, and resilience in clinicians themselves (Bauer-Wu & Fontaine, 2015; Seppala et al., 2014). It is essential to maintain the 'self-other' distinction (emotion regulation) and not absorb others' suffering or negative emotions as our own (Vachon, 2016). This can lead to burnout or compassion fatigue (Duarte & Pinto-Gouveia, 2017).

2.1. Definitions

The constant exposure to others' suffering can predispose nurses to similar feelings of distress and negative consequences of care-giving such as compassion fatigue and burnout (Duarte & Pinto-Gouveia, 2017). Burnout was defined by Maslach (1979) as a response to chronic job-related stressors and can develop without exposure to trauma. The World Health Organization included burn-out in ICD-11 as "a syndrome resulting from chronic work stress that has not been successfully managed" (World Health Organization WHO, 2019). Burnout is characterised by emotional exhaustion, cynicism, negativity, depersonalization of patients, inefficacy, and lack of perceived accomplishment (Bauer-Wu & Fontaine, 2015; Maslach, 1979; Vachon et al., 2015). Other factors include low job satisfaction and morale, toxic relationships, incivility, and emotional and cognitive detachment (Bauer-Wu & Fontaine, 2015; Maslach, 1979). Burnout can affect any professional, whereas compassion fatigue is experienced by professionals who witness the suffering of others (Duarte & Pinto-Gouveia, 2017).

Figley (1995) described compassion fatigue as an acute onset of personal suffering linked to an intense sharing of another's negative emotions. The term has been investigated in countless research studies, and embraced by clinicians. It results from stress when working in traumatic situations or witnessing others' distress (Figley, 1995). Symptoms include lack of empathy, anxiety, irritability, anger, persistent arousal, dread of work, and avoidance (Figley, 1995). Concerns have been raised about the tools used to measure compassion fatigue. Ledoux (2015) argued the tools either do not measure compassion fatigue or lack construct validity. Sinclair et al. argued: "empirical studies primarily measure compassion fatigue using the Professional Quality of Life Scale (ProQOL), which does not assess any of the elements of compassion" (2017, 9). Patients can describe care that is technically correct but lacks compassion, resulting in negative experiences and poor health outcomes (Bramley & Matiti, 2014; Lown, 2014).

Culture is a term to explain 'how we do things around here' in workplaces (West, Lyubovnikova, Eckert, & Denis, 2014). Establishing positive 'cultures of care' where nurses feel hopeful, experience job satisfaction, and where compassionate care can flourish is an urgent policy concern (Rafferty, Philippou, Fitzpatrick, Pike, & Ball, 2017).

3. Defining key neurological concepts

Research into the neural processes of empathy and compassion began in the late twentieth century (Singer & Klimecki, 2014). Empathy is the overarching concept. Our ability to feel empathy and to understand the perspective of others is essential for cooperative personal and work relationships, effective communication, compassion and personal wellbeing. There are two distinct empathy-related responses or pathways: socio- affective (empathy) and socio-cognitive (compassion) that are not in opposition. This is because empathy and compassion differ on a neural level - each activates different independent brain networks (Klimecki et al., 2013; Preckel et al., 2018; Valk et al., 2017).

3.1. Socio-affective path: empathy

Empathy is the ability to 'feel with' others when we are exposed to their distress and suffering, while recognising that the emotions we experience are external to oneself, and are initiated by the other person (Klimecki, 2015; Klimecki & Singer, 2012; Singer & Klimecki, 2014; Surguladze, Jaafari, & Chikovani, 2017; Vachon, 2016; Vrticka, Favre, & Singer, 2017; Wright & Pendry, 2016).

Neuroimaging studies using fMRI show the neurological areas activated by empathy include the anterior medial cingulate cortex and anterior insula (Klimecki & Singer, 2012; Klimecki, 2015; Surguladze et al., 2017; Wright & Pendry, 2016). fMRI studies show empathy is driven by mirror neurons and shared networks. Thus empathic experiences are caused by activation of similar neural networks that process the first-person (our own) experiences (Singer & Klimecki, 2014; Vrticka et al., 2017). This means when we empathise with a person who is in pain our brain will show activation of similar circuits as the brain of the person with whom we are empathising. Empathy is essential for understanding others' emotions, but when sharing the suffering of others too much, our negative emotions and distress increases.

3.2. Socio-cognitive path: compassion

Compassion is 'feeling for' others who are in pain with warmth, empathic concern, capacity to understand their perspective and intentions, and having prosocial behaviours such as the motivation to act with compassion to relieve their pain (Klimecki, 2015; Klimecki & Singer, 2012; Singer & Klimecki, 2014; Surguladze et al., 2017; Wright & Pendry, 2016).

In healthy empathic responses, three steps occur: taking another person's perspective which is called mentalising or Theory of Mind (ToM), self-awareness (self-other distinction) and emotion regulation (Klimecki, 2015). These steps allow us to distinguish between the unconscious sharing of a painful situation and cognitively processing it. Mentalising or ToM is the capacity to see another's situation from their perspective through imagination (Valk et al., 2017). This process of perspective-taking yields abstract, propositional knowledge about the other's mental state. This knowledge can motivate our compassion to improve their wellbeing (Klimecki, 2015; Klimecki & Singer, 2012; Surguladze et al., 2017; Wright & Pendry, 2016).

Self-awareness (self-other distinction) is the ability to distinguish between our own and the emotional or mental state of others and is a critical element in empathy and mentalising (or ToM). This capacity is called emotion regulation and is essential to manage the 'self-other' distinction (Klimecki, 2015). Cultivating emotion regulation and self-compassion are critical to being empathic, compassionate and resilient (Singer & Klimecki, 2014; Vachon, 2016).

Contemporary fMRI studies show the neurological areas activated with compassion include the medial orbitofrontal cortex and ventral striatum (Klimecki, 2015; Klimecki & Singer, 2012; Surguladze et al., 2017; Vrticka et al., 2017). These areas are linked to reward and affiliation processing with oxytocin and vasopressin receptors that stimulates positive affect towards those who are suffering (Klimecki & Singer, 2012). Importantly, compassion activates networks that provide a protective action from stress (Vachon et al., 2015). Neuroimaging findings are complemented by results from behavioural studies that show compassion is linked to helping, reward, and forgiveness behaviour, whereas empathic distress fatigue decreases helping behaviour and is associated with increased aggressive behaviour (Klimecki, 2015).

In sum, fMRI studies show that exposure to the distress and suffering of others can activate two different emotional empathic reactions. These reactions lead to either: prosocial behaviour and compassion via the socio-cognitive path or empathic distress if the 'self-other' distinction is blurred due to poor emotion regulation (Klimecki, 2015; Klimecki & Singer, 2012; Preckel et al., 2018; Singer & Klimecki, 2014).

4. Emotion regulation

As explained, the capacity to remain clear about the 'self-other' distinction is called emotion regulation (Klimecki, 2015). Without emotion regulation skills, our 'self-other' distinction is blurred so we absorb another's pain and negative emotions and suffer empathic distress fatigue (Singer & Klimecki, 2014). These painful emotions can trigger an intense neurological response that fMRI studies show becomes overwhelming pain and distress (Klimecki & Singer, 2012; Surguladze et al., 2017; Vrticka et al., 2017; Wright & Pendry, 2016) which many clinicians have experienced. This experience triggers withdrawal behaviours to protect oneself, empathic distress, and poor role performance (Vachon, 2016; Vrticka et al., 2017). It is vital that nurses regulate their emotions when empathising with patients so their response does not hinder their ability to care or threaten their personal wellbeing.

Nurses with inadequate emotion regulation do indeed feel the negative emotions and distress of others to an unbearable degree, leading to physical and emotional exhaustion, disengagement, apathy and anger (Vachon et al., 2015). However, fMRI studies confirm the debilitating experience is empathic distress fatigue, so the term compassion fatigue should be replaced by the term 'empathic distress fatigue' (Klimecki & Singer, 2012, p. 368). As aforementioned, research confirms compassion fatigue cannot be empirically validated or measured (Sinclair et al., 2017). This distinction matters because the alleviating strategy for 'empathic distress fatigue' is compassion training.

5. Empathic distress fatigue

Empathic distress "refers to a strong aversive and self-oriented response to the suffering of others, accompanied by the desire to withdraw from a situation, disconnect from those who are suffering, and adopting depersonalising behaviours in order to protect oneself from excessive negative feelings" (Singer & Klimecki, 2014, p. R875). As explained, in empathic distress, a person feels with the other by sharing and internalising their suffering and emotions to such an extent that the distress experience becomes overwhelming (Klimecki, 2015; Vachon, 2016). fMRI studies show empathic distress can be reversed by turning empathy into compassion through compassion training (Klimecki & Singer, 2012). Compassion can be viewed as an emotion-regulation strategy that buffers negative affect (Preckel et al., 2018, p. 4). These capacities of empathy, emotion regulation, and compassion, taken together with dignity and respect, are critical to nurses' compassionate responses when witnessing the suffering of others (Preckel et al., 2018; Rushton, Kaszniak, & Halifax, 2013). These behaviours, experience, and neural function are illustrated in Fig. 1.
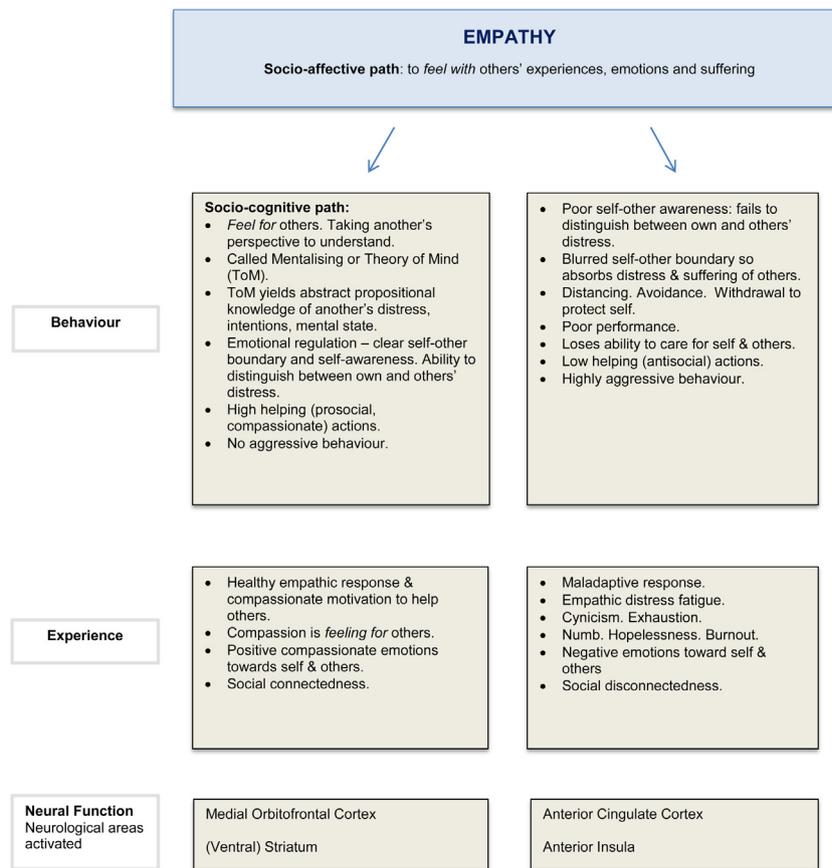
Fig. 1. Empathy Pathways.
(Adapted from Klimecki, 2015; Klimecki & Singer, 2012; Rushton et al., 2013; Vrticka et al., 2017).

6. Strategies to ease empathic distress and cultivate compassion

Contemporary empirical evidence regarding empathy, emotion regulation, compassion and self-care must be implemented in nursing to address persistent problems such as empathic distress fatigue. Few nurses understand that self-care is not selfish, so most would benefit from developing compassion literacy to: 'understand compassion, identify the barriers that impact upon the delivery of compassionate care and develop strategies to address such barriers effectively' (Burridge et al., 2017, p. 90). Compassion literacy involves a "healthy balance of compassion for others and compassion for oneself" (Mills, Wand, & Fraser, 2018a, p. 10). Professional nursing organisations and higher education institutions need to prioritise training programs aimed at cultivating compassion literacy and mindfulness practices (Australian College of Nursing, 2019; Mills et al., 2018a). Nurse educators have a key role to teach nursing students about empathic distress and improving emotion regulation, and empathy (Levett-Jones, Cant, & Lapkin, 2019). There is increasing evidence that compassion can be taught, so training must include self-care practices (Mills, Wand, & Fraser, 2018b), self-compassion, psychological flexibility (Duarte & Pinto-Gouveia, 2017), and compassionate practice (Adam & Taylor, 2013). Researchers can use integrated knowledge translation frameworks to evaluate the impact of strategies in local contexts to tackle these critical issues. Researchers would examine the 'evidence' to be implemented, the 'context' and the way the evidence is 'facilitated' (Harvey & Kitson, 2016).

This paper offers a promising approach to translate new knowledge into practice contexts through implementing evidence-based strategies to foster emotion regulation, self-care practices, and self-compassion to renew and protect nurses in their career and personal life. Compassion is also being responsive to our own suffering and acting to alleviate or prevent it. To that end, we present four strategies to foster:

- Compassion;
- Self-care practices;
- Self-compassion;
- Compassion leadership in healthcare cultures.

6.1. Compassion

Our brains are trainable (plastic). Neuroplasticity studies into training social emotions show measurable changes in neural functioning (Klimecki, 2015). These findings confirm compassion training can build capacity to regulate emotions and increase resilience. Effective emotion regulation is crucial to being less vulnerable to the repeated exposure to others' suffering (Singer & Klimecki, 2014). Compassion training increases altruistic behaviour, improves emotion regulation, and strengthens positive affect that leads to better coping and cultivates self-compassion (Rushton et al., 2013; Halifax, 2014; Vachon, 2016; Klimecki, 2015). Compassion training does not reduce or remove negative emotions. Rather, it increases activation in the brain areas associated with love, affiliation, positive emotions, hope and reward. This is why compassion training acts as a protective factor to empathic distress. The positive reward pathways act as a buffer to negative emotions, allowing one to be motivated to help without becoming overwhelmed by constant negative emotions (Klimecki, 2015; Surguladze et al., 2017; Vrticka et al., 2017). As little as five minutes per day has a positive effect and can lead to measur-

able changes in neural functioning (Klimecki, 2015; Vachon, 2016; Wright & Pendry, 2016). fMRI shows mindfulness meditation "regulates anterior insula activity" when we empathise with others' suffering, so reduces negative affect and stress, enhances emotion regulation, and increases our prosocial, compassionate behaviour (Laneri et al., 2017, p. 4034). Loving-kindness meditation (LKM) is a form of meditation practice that improves compassion and self-compassion (Seppala et al., 2014). LKM is distinct from mindfulness meditation. Compassion training may or may not include the use of LKM or mindfulness meditation. Numerous resources are available, for example:

- Australian College of Nursing (2019) Nurse Strong Initiative in association with Mindful Innovative Actions https://www.acn.edu.au/nursestrong http://miaonline.co/
- Loving-Kindness Meditation developed by Emma Seppala. https://emmaseppala.com/gift-loving-kindness-meditation/ (Seppala et al., 2014).
- Chris Germer: http://www.mindfulselfcompassion.org/
- Schwartz Center for Compassionate Healthcare: http://www.theschwartzcenter.org/
- Free eBook: Compassion. Bridging Practice and Science by Singer and Bolz describes compassion training programs and empirical research. http://www.compassion-training.org/

6.2. Self-care practices

An Australian study defined self-care as "a proactive, holistic, and personalised approach to the promotion of health and wellbeing through a variety of strategies, in both personal and professional settings, to enhance capacity for care of patients and their families" (Mills et al., 2018b, p. 1). Effective self-care is any strategy practised regularly both within the workplace and the personal setting to improve wellbeing (Mills et al., 2018b). Developing a self-care plan is more likely to be effective than an ad hoc approach (Mills et al., 2018b). Self-care is not just about pursuing pleasurable activities. Self-care incorporates self-discipline, self-awareness, accountability and motivation to make better life choices so we are better for others. Personal self-care practices can include getting more rest, eating healthier food, decluttering personal space, spending time alone or in reflection, seeking professional therapy, life coaching, or any activity that supports, energises, soothes or inspires. Meditation practice is effective self-care strategy in both personal and professional setting (Mills et al., 2018b).

Self-care practice is proposed as a shared responsibility between staff and healthcare services (Mills et al., 2018b). Organisational leaders can provide supportive structures and adequate resources to foster positive cultures and enhance opportunities for staff to practise self-care (Mills et al., 2018b). A simple example is to provide adequate staffing so nurses can take breaks. Managers can provide compassion training for nurses that could have a positive flow-on effect for those they serve (Bauer-Wu & Fontaine, 2015; Klimecki & Singer, 2012; Seppala et al., 2014). Effective professional self-care strategies include maintaining clear boundaries and networking with trusted colleagues (Mills et al., 2018b). The term 'work-life balance' is a misnomer in contemporary society. A better goal is the idea of "work-life harmony" that was identified in a recent study as an important aspect of effective self-care (Mills et al., 2018b, p. 9).

6.3. Self-compassion

Self-compassion is treating self with the same kindness and compassion that we would give a good friend (Neff, 2011). Psychologist Kristin Neff was the first researcher to measure and define the term self-compassion. She describes self-compassion as being kind, supportive and understanding toward oneself (particularly when we fail) rather than being harsh or judgmental. We may talk to ourselves in ways we would never talk to a friend when we make an error. Self-compassionate talk is kind, respectful and recognises everyone makes mistakes. Self-compassion is the opposite of self-criticism and self-loathing (Seppala et al., 2014). Neff (2011, p. 41) said three elements are required to be self-compassionate:

(a) Self-kindness: being understanding with ourselves, rather than harshly critical or judgmental;
(b) Common humanity: recognise that pain, feeling inadequate and making mistakes is part of being human and is experienced by everyone. Feel connected with others in that experience rather than feeling isolated by our suffering.
(c) Mindfulness: keep our experience in perspective rather than ignoring or exaggerating it.

Self-compassion has psychological and social benefits including greater life satisfaction and social connectedness. It also includes psychological flexibility that is essential for wellbeing (Duarte & Pinto-Gouveia, 2017). Self-compassion can be learned and may foster more secure attachment with self and others and strengthen resilience (Vachon, 2016). Self-compassion can be practised when feeling upset by taking deep breaths and putting a hand on your heart. Caring touch releases oxytocin, a hormone that makes people feel safe and connected (Neff, 2011). Self-compassion guided meditation practices developed by Kristin Neff are available at: http://self-compassion.org/.

6.4. Compassion leadership in healthcare cultures

Lown noted, "employee engagement emerges from their satisfaction and wellbeing; however, it is difficult for an individual to engage when she or he feels depleted and unsupported" (2018, p. 217). The nurse shortage is taking its toll on nurses' psychological wellbeing and is a barrier to job satisfaction and cultivating compassion in healthcare cultures (Christiansen et al., 2015). Policy makers have an urgent responsibility to address nurse shortages. Leaders and managers work in contexts that are not ideal, but must do what they can to support their staff and encourage recruitment and retention of the right skill mix in their local context. They can, however, 'role model' compassion and provide mindfulness training to strengthen nurses' compassion, emotion regulation and self-compassion (Bauer-Wu & Fontaine, 2015; Lown, 2018; Rushton et al., 2013). Promoting wellness practices enhances clinicians' hope, confidence, reduces stress, and improves compassion (Burridge et al., 2017). Finally, professional development / training budgets must be protected; often viewed as dispensable when organisational cuts are made. These are key ingredients in cultivating 'cultures of care' in which nurses experience job satisfaction and provide compassion in teams (Rafferty et al., 2017). At best, healthcare cultures must be a synergy of safety, quality, competence and compassion. Too little of any ingredient will negatively impact patients and caregivers alike.

7. Conclusion

This paper explained social neuroscience evidence about empathy, emotion regulation, compassion and related concepts, then discussed evidence-informed strategies and practices to cultivate self-care and compassion. We urge nurses to revise their thinking about compassion fatigue and understand promising neuroscience evidence regarding empathic distress fatigue. We explained how improving emotion regulation, cultivating self-care and self-compassion are strategies to become compassionate and resilient. Compassion has a positive impact on patients and caregivers alike. This paper offers new insight to support nurses to

intentionally think and act differently to foster their compassion satisfaction and make their work cultures (and their personal lives) better.

CRediT authorship contribution statement

AH conceived the study whilst KK contributed to its refinement and finalisation. KK conducted the data collection, extraction, analysis, synthesis with AH. AH drafted the manuscript. KK and RT made critical revisions to the paper for intellectual content. All authors approved the final manuscript.

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