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Review article

The neuroscience of sadness: A multidisciplinary synthesis and collaborative review

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ABSTRACT

Sadness is typically characterized by raised inner eyebrows, lowered corners of the mouth, reduced walking speed, and slumped posture. Ancient subcortical circuitry provides a neuroanatomical foundation, extending from dorsal periaqueductal grey to subgenual anterior cingulate, the latter of which is now a treatment target in disorders of sadness. Electrophysiological studies further emphasize a role for reduced left relative to right

Abbreviations: ACC, Anterior Cingulate Cortex; ACG, Anterior Cingulate Gyrus; ALE, Activation Likelihood Estimation; ALFF, Amplitude of Low Frequency Fluctuation; ANPS, Affective Neuroscience Personality Scales; ANS, Autonomic Nervous System; BA, Brodmann Area; BDI, Beck Depression Inventory; BDNF, Brain-Derived Neurotrophic Factor; CEN, Central Executive Network; CNS, Central Nervous System; COMT, Catechol-O-Methyltransferase; dACC, dorsal Anterior Cingulate Cortex; DBD, Disruptive Behaviour Disorders; DBP, Diastolic Blood Pressure; DBS, Deep Brain Stimulation; dlPFC, dorsolateral Prefrontal Cortex; DMN, Default Mode Network; dmPFC, dorsomedial Prefrontal Cortex; EEG, Electroencephalography; EMG, Electromyogram; ERPs, Event-related Potentials; fALFF, fractional Amplitude of Low Frequency Fluctuation; fMRI, functional Magnetic Resonance Imaging; GABA, Gamma-Aminobutyric Acid; GAD, Generalized Anxiety Disorder; HR, Heart Rate; HRV, Heart-Rate Variability; ICA, Independent Component Analysis; IS, Interoceptive Sensitivity; LMGP, Left Medial Globus Pallidus; LMIC, Low-Middle Income Countries; MAO, Monoamine Oxidase; MDD, Major Depressive Disorder; MFG, Medial Frontal Gyrus; MoBI, Mobile Brain/Body Imaging; mOFC, medial Orbitofrontal Cortex; MPCA, Multivariate Pattern Classification Analysis; MRI, Magnetic Resonance Imaging; MTG, Middle Temporal Gyrus; MVPA, Multivariate Pattern Analysis; NE, Negative Emotionality; OFG, Orbitofrontal Gyrus; OXTR, Oxytocin Receptor; PCC, Posterior Cingulate Cortex; rACC, rostral Anterior Cingulate Cortex; RH, Regional Homogeneity; RR, Respiratory Rate; RSFC, Resting-State Functional Connectivity; rs-fMRI, resting-state functional Magnetic Resonance Imaging; rtfMRI-nf, real-time functional Magnetic Resonance Imaging neurofeedback; SBP, Systolic Blood Pressure; SCA, Seed-based Correlation Analysis; SCG, Subcallosal Cingulate Gyrus; SCL, Skin Conductance Level; SFG, Superior Frontal Gyrus; sgACC, subgenual Anterior Cingulate Cortex; SN, Salience Network; SNP, Single Nucleotide Polymorphism; SST, Socioemotional Selectivity Theory; STG, Superior Temporal Gyrus; tDCS, transcranial Direct Current Stimulation; TMS, Transcranial Magnetic Stimulation; tr-fMRI, task-related functional Magnetic Resonance Imaging; vmPFC, ventromedial Prefrontal Cortex; vrACC, ventro-rostral Anterior Cingulate Cortex

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Psychological constructionism
Genetics
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Neuroimaging
Affective neuroscience
Heart rate variability
GENIAL model
Health and wellbeing
Vagal function

frontal asymmetry in sadness, underpinning interest in the transcranial stimulation of left dorsolateral prefrontal cortex as an antidepressant target. Neuroimaging studies – including meta-analyses – indicate that sadness is associated with reduced cortical activation, which may contribute to reduced parasympathetic inhibitory control over medullary cardioacceleratory circuits. Reduced cardiac control may – in part – contribute to epidemiological reports of reduced life expectancy in affective disorders, effects equivalent to heavy smoking. We suggest that the field may be moving toward a theoretical consensus, in which different models relating to basic emotion theory and psychological constructionism may be considered as complementary, working at different levels of the phylogenetic hierarchy.

When I go musing all alone, Thinking of divers things fore-known, When I build castles in the air, Void of sorrow and void of fear, Pleasing myself with phantasms sweet, Methinks the time runs very fleet. All my joys to this are folly, Naught so sweet as Melancholy.
"A dialogue between pleasure and pain"
(Burton, 1857)

1. Introduction

1.1. Background and context

Sadness is a commonly experienced emotion, impacting on body and mind, which may last anywhere from a few seconds to several hours. It is an adaptive emotion that may have been conserved by evolution along the phylum as it has an adaptive function, allowing us to cope with losses such as losing resources, status, friends, children or romantic partners (Nesse, 1990). In humans, sadness is characterised by specific behaviours (social withdrawal, lower reward seeking, slow gait), a typical facial expression (drooping eyelids, downcast eyes, lowered lip corners, slanting inner eyebrows), physiological changes (heart rate, skin conductance) as well as cognitive/subjective processes. Sadness may also sometimes be described as a psychological pain accompanied by additional feelings of loneliness, distress, depression, anxiety, grief and anguish (we discuss the linguistic complexity of sadness further in section 1.5). Paradoxically, the experience of sadness may also lead to pleasant affective states. For instance, listening to sad music is often described as an enjoyable and a 'moving' experience (Sachs et al., 2015), especially when perceived as non-threatening and aesthetically pleasing.

In its mild form, sadness may afford considerable benefits including a more accommodating, vigilant and externally-focused response style (Forgas, 2017). By contrast, depressive rumination (Nolen-Hoeksema et al., 2008) may lead to more prolonged mood states associated with a broader syndrome consisting of negative views about the self, the world, and the future (Beck, 2008), characteristic of depressive disorders, which have no clear evolutionary value. It is acknowledged however, that sadness is distinct from depressive disorders, as these are heterogeneous and involve other features including anhedonia, feelings of worthlessness or guilt, suicidal ideation, fatigue, changes in sleep, appetite and weight, and cognitive impairment (Malhi and Mann, 2018). Some researchers have characterised sadness - especially in humans - as a constructed emotion (Barrett, 2017a) arising from domain-general systems in the brain, once information from the body and the external environment has been contextualised by representations of prior experience. This constructionist perspective may be attributable in part, to the wide application of functional magnetic resonance imaging to understand the emotions in human beings, a technique that imposes limitations on conclusions able to be drawn relating to the neurobiological basis of emotions. For instance, it is not clear whether typically weak emotional stimuli used in the scanner evoke sufficiently strong and specific emotional states. By contrast, sadness has also been described as a 'basic emotion' with a strong evolutionary basis (Panksepp, 1982a). This ongoing debate is one which we pay particular attention to in our paper (see section 6). Our own view is that the field may be moving toward a theoretical consensus, in which different models may be considered as complementary, working at different levels of phylogenetic hierarchy.

The emotion of sadness impacts on the body as well as the mind. Historically, it has been considered to be one of six 'basic' emotion facial expressions, along with happiness, anger, surprise, fear, and disgust. The characteristic facial expression of sadness contribute to what Charles Darwin described as the 'grief muscles', including the "omega melancholicum" and Veraguth's folds (Greden et al., 1985). These expressions were provocatively captured by the camera lens of Dorothea Lange in 1932 as she photographed the 32-year old 'Migrant Mother', on which Fig. 3 in this paper has been based. While such expressions may be characteristic of sadness, recent data suggest that faces often fail to reflect self-reported experience (Russell and Fernandez Dols, 2017) (see also Gendron et al., 2018). The experience of sadness is also associated with a slumped posture and slowed walking speed (Johannes Michalak et al., 2009a, 2009b) and may or may not co-occur with crying. Crying-related sadness is associated with increased heart rate and increased skin conductance (Gross et al., 1994), while noncrying sadness is associated with a reduction in heart rate, reduced skin conductance, and increased respiration (Gross et al., 1994; Rottenberg et al., 2003). Chronic sadness is often (mis)diagnosed as a depressive disorder (Horwitz and Wakefield, 2007), and parallel bodies of literature linked psychological distress and depressive disorder to higher risk of chronic physical conditions (Bhattacharya et al., 2014) and premature mortality (Russ et al., 2012), with effects comparable to or larger than the effects of heavy smoking (Chesney et al., 2014). Readers interested in underlying mechanisms are referred to recent theoretical work that has characterised potential pathways from chronic negative emotions to future morbidity and mortality from a host of conditions and disorders (Kemp, 2019; Kemp et al., 2017b, 2017a; Kiecolt-Glaser and Wilson, 2016; Penninx, 2017; Stapelberg et al., 2019; Wulsin et al., 2018). This work including ongoing debate reinforces a need for an up-to-date review of the neuropsychobiological correlates underpinning the emotion of sadness. This is the aim of the current paper.

Consistent with the neuroevolutionary origins proposed by Jaak Panksepp, the emotion of sadness has been described in animals as well as humans. In his latest book (de Waal, 2019), primatologist Frans de Waal describes how different animals grieve, admittedly a more complex emotion than sadness that also encompasses surprise, fear, anger, and denial. After losing a mate, the prairie vole becomes passive in the face of danger, not caring whether they will live or die. The dog lays near her dead best friend with 'meltingly sad eyes and furrowed brow'. The adolescent wild female chimpanzee gazed at the body of a dead male for over an hour without interruption. Elephants gather the bones of a dead herd member, holding pieces in their trunks, and passing them around to other members of the herd. Even the humble rodent is believed to "express anguish through narrowed eyes, flattened ears, and swollen cheeks." It is also interesting to observe that affective states beyond freedom from fear and distress are now included in scholarly discussions about animal welfare (Mellor, 2017). These authors emphasise that there is now good neuroscientific evidence to cautiously distinguish between states of depression, anxiety, fear, panic, frustration, and anger in animals. Also relevant here is the application of this knowledge to better understand the pathogenesis of depressive disorders and mechanisms for

antidepressant action using a variety of paradigms including social defeat, behavioural despair, and learned helplessness (Krishnan and Nestler, 2011; Planchez et al., 2019). While detailed discussion of the issues around these intriguing accounts of the emotional lives of animals is beyond the scope of the present paper, we note them here to emphasise the importance of neurobiological accounts that extend beyond human egocentricity. These considerations further highlight the need to discuss the ongoing debate between basic emotion theorists and the psychological constructionists, which we do in section 6.

Our paper is organized as follows: In the next section, we briefly report on key milestones in emotion theory with implications for the neuroscience of sadness, focusing on the current debate between two major theories: Basic Emotion Theory and Psychological Constructionism. We then consider the role of interoceptive awareness and embodiment before proceeding to explore the linguistic properties of sadness (linguistic framework - Siddharthan et al., 2020). Following this, we begin our multidisciplinary synthesis and collaborative review of the neuroscience of sadness. Specifically, we address the role of genetics and epigenetics that may in part underpin the emotion of sadness, as well as the physiology, neural correlates, and individual differences. We conclude by drawing some conclusions on the reviewed literature and identify opportunities for future research activity. While a detailed review of the literature in each of these domains is beyond the scope of the current paper, we hope that our contribution will provide a reasonably comprehensive review on the topic of sadness that will provide useful guidance to future researchers.

1.2. A brief history of milestones in emotion theory

We now briefly describe the development of emotion theory and summarize key milestones in Fig. 1 to help provide the historical background and context within which our present review paper was written. This section also provides some context to the ongoing theoretical debate over emotions (and sadness specifically), which we pick up in detail in the next section as well as section 6 of the current paper. The topic of emotion has received considerable attention from modern science, including the disciplines of psychology and human neuroscience. In the 19th century, Charles Darwin initiated the debate over the physiological basis of emotional life with the publication of 'The Expression of Emotions in Man and Animals' (Darwin, 1872), emphasizing the origins of human emotions in human behavior; an emphasis that contrasted with the philosophical separation of body and mind that was characteristic of western philosophy at the time. This publication concentrated on six core human emotions, including sadness. In his chapter on low spirits, anxiety, grief, dejection and despair, Darwin notes: "*the most conspicuous result of the opposed contraction of the [orbiculars, corrugators, and pyramidals of the nose] is exhibited by the peculiar furrows formed on the forehead. These muscles, when thus in conjoint yet opposed action, may be called, for the sake of brevity, the grief-muscles*" (p.179). It is interesting to note that the debate over mind-body separation remains a topic of much debate, as characterized by David Chalmers' so-called 'hard problem' (Chalmers, 1995).

In 1884 and 1885 respectively, William James and Carl Lange independently developed what is now called the 'James-Lange Theory', which presents 'emotion' as an experience of physiological arousal. Eliciting stimuli lead to a complex bodily response that is interpreted as an emotional feeling, in which the "*object-simply-apprehended*" is transformed into an "*object-emotionally-felt*" (James, 1884). Following stimulus perception, currents run down to the muscles and organs, creating a complex response that subsequently courses back to the cortex where it is transformed from simple perception into an emotional feeling. Soon after, Walter B. Cannon (1871–1945) and Philip Bard (1898–1977) severed afferent nerves from the sympathetic branch of the autonomic nervous system in cats which – according to the James-Lange theory – should result in loss of emotional experience. However, the cats continued to display characteristic signs of rage, including retraction of the ears, showing of teeth and hissing in the presence of a barking dog, indicating that visceral feedback from the periphery was unnecessary for the production of emotional responses (Cannon, 1927; Cannon et al., 1927). Cannon and Bard then conducted a series of experiments in which "*animal brains were longitudinally sectioned in the diencephalon in consecutive inferior anatomical planes*" (Roxo et al., 2011, pp. 2433–2434), resulting in the identification of the thalamic region and caudal half of the hypothalamus as relays for external information and essential regions for the emotional brain (LeDoux, 1987). These experiments led to the proposal of the Cannon-Bard Theory, with later developments in the theory also establishing a pivotal role of the neocortex for inhibitory control (Cannon, 1931).

In 1937, James Papez (1883–1958) subsequently proposed the 'Papez Circuit' theory of emotion, arguing that sensory inputs are

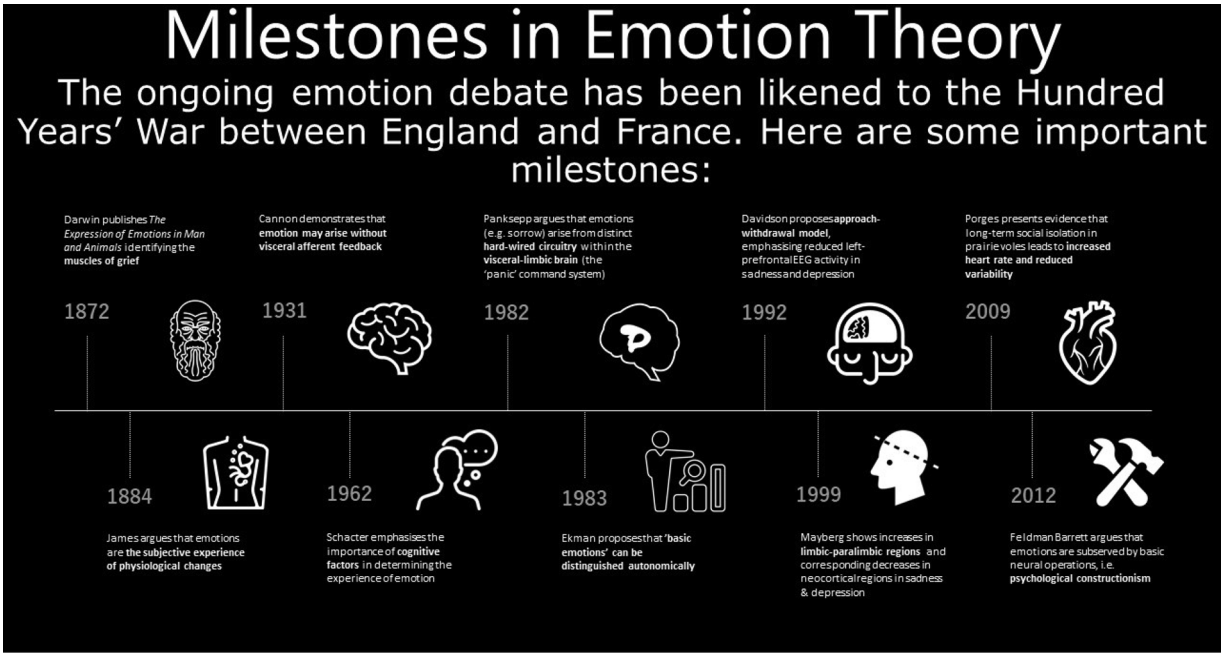

Fig. 1. A brief history of emotion theory with implications for sadness.

processed by the thalamus, which are subsequently transmitted to the sensory cortices through one of two processing streams: one for 'thought' and one for 'feeling' (Papez, 1937). According to this model, the cingulate cortex integrates information from the hypothalamus and sensory cortices, with projections from the cingulate cortex towards the hypothalamus allowing for the cortical regulation of emotion. Despite its limitations, we now know that several regions, including the hypothalamus and the cingulate cortex, are important contributors to emotional processing (Franklin and Mansuy, 2013). In 1949, Paul MacLean (1913–2007) proposed his model of the triune brain, a model of brain evolution and functioning which distinguishes three brain regions: an evolutionary primitive "reptilian brain", responsible for the behaviours directly related to survival (e.g. dominance, competition…) and other basic physiological functions (e.g. breath, heartbeat…) ; a "paleo-mammalian or limbic brain", responsible for emotional experiences such as the expression of emotional states that promote procreation, feeding, parental caring, and further cognitive processes such as memory consolidation; and a "neo-mammalian brain", comprised of the neocortex and responsible for integrating emotion-cognition processes, top-down regulation of emotional responses and the use of highly complex mechanisms such as language, abstraction, and conceptualization (MacLean, 1973, 1949). MacLean proposed that sensory information from the outside world leads to physiological changes which subsequently provoke the experience of emotion (Dalgleish, 2004). MacLean hypothesized that this integration was carried out by the visceral brain, which he then named "the limbic system". Although a widely used term in the twentieth century, MacLean did not establish criteria to determine what regions should be included in the limbic system, and therefore, its relevance to modern neuroscience has been questioned (Franklin and Mansuy, 2013).

Schachter and Singer (1962) proposed that emotional states are a function of two processes: physiological arousal and an associated cognitive state that helps to contextualize experience. According to this perspective, we search the environment for emotionally relevant cues in order to label and interpret otherwise undifferentiated physiological arousal, resulting in an emotional experience. In 1982, Jaak Panksepp (1982) proposed that emotions arise from deep subcortical neural circuitry, the basis for Basic Emotion Theory (explained further in the next section). Subsequently, Ekman proposed that certain 'basic emotions' including sadness, can be distinguished autonomically regardless of cultural influences (Ekman et al., 1983). Other authors argue for alternative approaches built upon principles of evolutionary theory (e.g. Behavioral Ecology Theory), highlighting the importance of social context to the facial representation of emotion (Crivelli and Fridlund, 2018; Fridlund, 2014). In this regard, Lisa Feldman Barrett (2006) has argued that 'basic emotions' do not exist, suggesting instead that emotions are context-dependent and created from domain-general systems in the brain, a proposal labelled as 'Psychological Constructionism". This fascinating topic is one to which we return to in more detail in section 6 of our paper.

On the basis of a series of electrophysiological studies highlighting the role of anterior cerebral asymmetries in emotion reactivity, Richard Davidson (1992) proposed the 'Approach-Withdrawal Model'. These ideas have since led to alternative treatments for major depressive disorder such as stimulation of left prefrontal cortex by transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) (Boggio et al., 2008; Pascual-Leone et al., 1996). Building on these insights, Helen S. Mayberg et al. (1999) examined interactions between limbic and neocortical regions in individuals with normal sadness and depressive disorders using positron emission tomography techniques, finding that sadness was associated with increases in paralimbic blood flow and decreases in dorsal neocortical blood flow. Concurrent inhibition of overactive paralimbic regions and normalization of hypofunctioning dorsal cortical sites characterized remission of clinical depression.

In 1994, Antonio Damasio proposed the 'somatic marker hypothesis', the proposal that "marker signals" influence responses to stimuli at multiple operational levels (Damasio and Sutherland, 1994). The reason why these markers are termed "somatic" is because they arise from the brain's representation of the body (Damasio et al., 1996). Markers arise from bioregulatory processes including, but not limited to, processes which express themselves as emotions and feelings. Importantly, Damasio differentiates between an emotion and the feeling of an emotion, with the latter interpreted as a cognitive response to the stimuli or thought that elicits the emotion, combined with the realization of this cause-effect relationship (Franklin and Mansuy, 2013). According to this hypothesis, somatic responses to thoughts may trigger an unconscious "gut reaction", supporting decision-making, (Franklin and Mansuy, 2013) (for a discussion, see Dunn et al., 2006).

Building on the role of visceral afferent contributions to emotional experience, Stephen Porges proposed his polyvagal theory (Porges, 1995) which highlights a role for the (myelinated) vagal nerve in individual sensitivity to stress. This model has now been further developed and expanded, highlighting roles for the vagus nerve in emotion and social communication (Porges, 2011), and its clinical implications (Porges and Dana, 2018). In 2009, Porges (2009) presented evidence of changes in cardiac function after long-term social isolation, highlighting an important relationship between mental wellbeing and physical health. While the autonomic nervous system is one of several response systems that contribute to stress-related mood disorders, the vagus may play a regulatory role over many of these including the sympathetic nervous system (Deuchars et al., 2018; Porges, 2011), hypothalamic-pituitary-adrenal (HPA) axis (Porges, 2011), inflammatory pathways (Kolcun et al., 2017; Tracey, 2007, 2002), metabolism including glucose regulation (Berthoud, 2008; Dienel, 2019; Malbert et al., 2017; Pavlov and Tracey, 2012), brain-gut interactions (Bonaz et al., 2018), and even neurogenesis and epigenetic mechanisms (Biggio et al., 2009; Follesa et al., 2007). Such findings have led to theoretical frameworks spanning the life course, including the '*n*euro-visceral *i*ntegration *a*cross the *c*ontinuum of *t*ime' (or NIACT) model (Kemp et al., 2017b) and the GENIAL [*g*enomics-*e*nvironment-vagus *n*erve-social *i*nteraction-*a*llostatic regulation-*l*ongevity] model (Kemp et al., 2017a), both of which explicitly link emotional states and well-being, mediated by the vagus nerve. For more comprehensive reviews on the history of emotion theory, readers may wish to consult the

Table 1
Fundamental differences between Basic Emotion Theory and Psychological Constructionism.

	BASIC EMOTION THEORY	PSYCHOLOGICAL CONSTRUCTIONISM
Location of Emotion	Emotional processes are the reflection of activity in specific neural systems.	A category of emotion has no distinct brain location. Instances of emotion are constructed through domain-general networks.
Categories of Emotion	Humans exhibit primitive emotional processes which are similar to the ones present in non-human mammals and some other vertebrates.	Variation is norm. Emotion categories lack a biological fingerprint as each emotion category is a diverse population of situated instances.
Number of Emotions	There is a limited number of fundamental emotional circuits, yet their intertwined activity along with social learning produce richer phenomenology.	Emotions are not inborn and if they are universal, it is due to shared concepts.
Sources of Insights	The scientific understanding of how emotional processes work must be based on the human and non-human brain.	Emotion is a product of social reality and context. Language also affects mental representations of emotions.

recently published book by Boddice (2018). Interested readers are also referred to section six, which describes the debate between basic emotion theorists and psychological constructionists.

1.3. Ongoing debate

Recent and ongoing debate has focused on Basic Emotion Theory versus Psychological Constructionism (see Table 1). Heavily influenced by the work of ethologist Jaak Panksepp (Panksepp, 1998, 1989), Basic Emotion Theory (or Natural Kinds Theory) presents emotions as natural entities preserved by evolution, ingrained in mammalian nervous systems. From this perspective, emotions are essentially natural entities that emerge from ancient sub-neocortical neural systems (Ekman et al., 1969; Panksepp, 1982b) that respond to major environmental challenges (MacLean, 1990; Panksepp, 1998). For this reason, Panksepp (2003a, 1998) argued that subcortical organization (and in turn, functionality; Panksepp, 1992, 1982a, 1982b) in humans and other mammals are strikingly similar, with differences most evident at cognitive levels (Hauser, 2001). Furthermore, Panksepp (2005, 2000) described seven emotional action systems characterizing the emotional apparatus of mammals, including: SEEKING, RAGE, FEAR, LUST, CARE, PANIC/GRIEF, and PLAY (in capital letters to differentiate them from the common words they are named after). Even though few action emotion systems are proposed, their interaction with social learning processing is hypothesized to result in much richer phenomenology.

From a basic emotion approach, sadness is described as an emotion resulting from the activity of the PANIC/GRIEF system, a system which has presumably evolved from more general pain mechanisms (Panksepp, 2003b). Sustained activation of the PANIC/GRIEF system provokes a cascade of psychological despair that, if persistent, leads from normal sadness to depressive disorders. In this context, the first acute phase of the PANIC/GRIEF system includes SEEKING arousal, and if this were to continue, a “despair phase” characterized by diminished SEEKING activity and emotional shutdown may follow (Panksepp and Watt, 2011a). Studies in comparative neurobiology show that while areas crucial for sadness are present along the phylum in vertebrates (Paxinos and Franklin, 2012; Paxinos and Watson, 2014; Vogt and Paxinos, 2014), areas enabling conscious experience are only present in mammals, or even in primates (Elston, 2007). In any case, studies show that the behavior, function, and neural systems of sadness are adaptive and conserved by evolution. Such is the case for regions involved in sadness, including the amygdala and hippocampus (Abellan et al., 2014; Herold et al., 2014; Janak and Tye, 2015; Martínez-García et al., 2002; Reiner et al., 2004), supporting the basic emotion theoretical framework.

In contrast, psychological constructionism differs from Basic Emotion Theory in several ways. First, variation is the norm; emotion categories have no biological fingerprint per se. Thus, one instance of sadness does not necessarily feel or present like another (Barrett, 2017b, 2013). Second, constructionists argue that categories of emotion cannot be localized and that specific emotions have no single, dedicated brain region. In line with the concept of degeneracy, constructionist theory argues that the same instance or experience of the same emotion category can be produced in multiple ways (Clark-Polner et al., 2016a). Third, construction argues that emotion results from the activity of domain-general systems combining in complex ways. According to this approach, an instance of emotion is constructed when physical changes in the body are made psychologically meaningful, and it is only when we perceive these sensations as being causally related to our changing external environment that an emotional episode is constructed (Barrett, 2013; Clore and Ortony, 2013). In other words, emotions are constructions of the world; not reactions to it.

One of the most essential of these domain-general systems is the core ‘affective’ system – consisting of “*neurobiological states that can be described as pleasant or unpleasant with some degree of arousal*” (Barrett, 2011, p.363). This system integrates sensory information from the external world with homeostatic and interoceptive information from the body. In order to make sense of this integration, affect needs to become meaningful through the use of concepts. This occurs by means of the ‘conceptual’ domain-general system, which is created and shaped by our prior experience, allowing fluctuating core affect to be categorized into a discrete emotional experience. Therefore, sadness involves categorization of core affect using conceptual knowledge of sadness. For instance, sadness involves frowning, crying, moping, a monotonous tone of voice and so forth, and whilst every instance and experience varies, these descriptors are nevertheless inherent to sadness. Simulations of an emotion such as ‘sadness’ are engrained in the mental concept of what ‘sadness’ is, and therefore, ‘sadness’ is arguably a collection of neural patterns in the brain (Barsalou, 2008; Barsalou et al., 2003). The ability to form emotion concepts to make physical sensations meaningful may be universal, but theories specific concepts are learnt from culture. Therefore, emotional concepts are hypothesized to be determined by social reality.

In addition to core ‘affect’ and ‘conceptual’ systems, additional ‘ingredients’, including attentional and language domain-general core systems, shape the experience of emotion (Barrett, 2009; Barrett et al., 2004) as well as a perceiver’s goals, values, desires, and intentions (Cunningham et al., 2007).

1.4. Visceral contributions to the experience of sadness

Pivotal to emotional experience is the ability to integrate information from the external world with interoceptive information from the body, including a range of sensations which provide an integrated sense of the body's physiological condition (Craig, 2003). This internal body state modulates emotional experience (Couto et al., 2015a, 2015b) via visceral-interoceptive signals which interact with emotional mechanisms (Adolfi et al., 2017; Garfinkel and Critchley, 2013). Some of the key sources of interoceptive signals related to emotion are the heartbeat (Couto et al., 2015a, 2015b), autonomic changes (e.g. increases in heart rate), and other interoceptive processes (Adolfi et al., 2017). Sadness has been directly linked to interoceptive abilities. For example, individuals with higher IS, as measured by a heartbeat detection task, have been shown to be more sensitive to other's emotions, especially for expressions of sadness (Terasawa et al., 2014). Additionally, IS has been shown to moderate the effect of social rejection on affect, with Pollatos et al. (2015) finding higher IS scores to be associated with lower levels of distress and sadness, and positively associated with better emotion regulation abilities. Therefore, IS may modulate the intensity of the subjective experience of sadness and facilitate the down regulation of affect-related arousal (Fustos et al., 2013; Goldin et al., 2008). Converging evidence from lesion studies of stroke and neurodegeneration have shown that selective insular damage is associated with impairments in negative emotion recognition (including sadness), interoceptive dimensions, and related networks (Adolfi et al., 2017; Baez et al., 2015; Blas Couto et al., 2015a, 2015b; Couto et al., 2013; García-Cordero et al., 2016, 2015; Ibañez et al., 2010; Ibáñez et al., 2013; Sedeño et al., 2017, 2016; Terasawa et al., 2015). Many of the neurobiological substrates thought to underpin sadness have also been implicated in interoception, including the insula and the anterior cingulate cortex (Paulus and Stein, 2010).

In addition to interoceptive awareness, internal body states can also influence human emotion through the process of “embodiment”. This term refers to the notion that knowledge is "embodied" or grounded in bodily states and in the brain's modality-specific systems (García and Ibáñez, 2016; Ibáñez and García, 2018; Niedenthal, 2007). As reported by Rouby et al. (2016): “*these theories suggest that perceiving and thinking about emotion involve perceptual, somato-visceral, and motor re-experiencing of the relevant emotion in the self*” (p. 76). Thus, individuals process emotion-related information by reactivating neural states involved in their own prior perceptual and affective experiences (Niedenthal, 2007). Some studies have tested such theories of emotion applied to sadness. For instance, Duclos et al. (1989) tested whether multiple

facial expressions could elicit specific emotions, covertly manipulated with instructions from the experimenter. After forming each facial expression for six seconds, participants filled out a questionnaire to assess their emotional state, with results finding significantly higher sadness ratings compared to other emotion conditions. Consistent with this, as well as Ekman and Friesen's (1978) research on prototypical facial expressions of emotion, more recent research has shown that both hearing and reproducing vocalizations of emotions, including sadness, results in congruent self-reported emotions and specific facial behaviors. For instance, Hawk et al. (2012) found that 'lip corner depressor' facial behaviour was significantly more likely to occur in the sadness block, with additional research showing how motor execution, observation, and imagery of movements when expressing sadness can also enhance the corresponding affective state (Shafir et al., 2015, 2013). In other words, motor execution and imagery, as well as the observation of whole-body dynamic expressions of sadness, increase the subjective feeling of sadness in the observer (Shafir et al., 2013).

Furthermore, studies have also demonstrated how body posture may impact upon emotional states. Adopting an upright seated posture in the face of stress can maintain self-esteem and increase positive affect (Nair, Sagar, Sollers, Consedine, & Broadbent, 2015; Wilkes et al., 2017). In contrast, slumped individuals show increased negative mood and use more words associated with sadness (Nair et al., 2015). These findings are consistent with theories of embodied cognition, which argue that muscular states influence, and are influenced by, emotional responses. In line with this, some gait patterns have been associated with sadness (e.g., reduced walking speed, arm swing, and vertical head movements), supporting the notion that sadness is embodied in the way people walk (Michalak et al., 2009a, 2009b). Nevertheless, theories of embodied emotion have been subject to heavy criticism. For instance, Carney et al. (2010) concluded that high-power nonverbal bodily displays produce characteristic neuroendocrine and behavioral changes (i.e., increases in testosterone, decreases in cortisol, higher levels of subjective self-confidence), a pattern which was the opposite of low-power nonverbal displays. However, despite enormous public familiarity with this publication, subsequent attempts to replicate the findings have been unsuccessful (e.g. Ranehill et al., 2015).

1.5. The linguistic complexity of sadness

We now review the feelings allocated to the General Wellbeing category by the Human Affectome Taskforce, exploring the language people use to convey sadness in particular. Specifically, we examined whether, and if so, how different aspects of sadness have been addressed by neuroscientists. A total of 95 words relating to sadness were identified by the linguistic task team, raising the question of whether these are simply synonyms for sadness or whether these words refer to distinct variants. As noted previously, sadness is typically considered one of the six basic emotions recognizable from the face, facilitating the receipt of emotional support from attentive others. The feelings associated with the emotion of sadness (see Annex 1) vary considerably in intensity, ranging from "low" and "dreary", to more intense states such as "distress" and those associated with sadness in its extreme form (e.g. "miserable", "grief", "anguish"). These words also refer to feelings that vary in duration, spanning brief emotional states (e.g. "displeased") to longer term mood states (e.g. "somber", "dour"), including those that may coincide with clinical depression (e.g. "melancholic").

Based on findings from animal research, Jaak Panksepp made a distinction between primary-, secondary-, and tertiary-process emotions, which refer to primary-process action tendencies – the 'ancestral tools for living' – that are then refined by learning (i.e., secondary-process) and higher-order cognitions (i.e., tertiary-process) (Panksepp, 2010). In this hierarchy of emotional states, primary-process emotions are capitalized to reflect fundamental or basic emotional states arising from direct electrical or chemical stimulation of the brain. Some of the identified words in our list (e.g. "dysphoric", "distress", "lonely") may arise directly from primary-process emotions (e.g. SEEKING/desire system, GRIEF/separation distress). For instance, dysphoria may arise from reduced activity in the medial forebrain bundle (the SEEKING/desire system), while loneliness and distress may arise from neural circuitry extending from the dorsal periaqueductal gray (PAG) to anterior cingulate (GRIEF/separation distress system). In recent papers (Davis and Panksepp, 2011) Panksepp has even labelled the GRIEF/separation distress system using the capitalized word, SADNESS, highlighting the evolutionary foundations on which states commonly labelled as 'sadness' and 'depression' may arise. According to Panksepp, the primary emotional system of SADNESS is responsible for generating separation distress, loneliness, and crying.

Other words in our list reflect tertiary-process emotions, such as "displeasure", "homesickness", and "being unsatisfied"; all of which involve higher psychological processes including thought and awareness. According to Panksepp, psychologists and human neuroscientists typically focus on higher-level emotional issues (tertiary-process emotions) affected by cognitive attributions and appraisals. This is an especially important consideration in regard to the longstanding debate between basic emotion theorists and psychological constructionists, and is especially relevant here given that Panksepp himself claimed that "*with regard to the construction of higher mental functions,* [I am an] *ultraconstructivist.*" (Jaak Panksepp, 2015, p. 2).

Based on the above, we consider the neurobiological correlates of sadness and its disorders, focusing on major depressive disorder in particular as an expression of sadness in an extreme form. According to Panksepp, clinical depression may involve the manifestation of changes in other primary emotional systems including reduced action within the brain's PLAY and SEEKING networks, in addition to SADNESS. Specific neural substrates for PLAY include the parafascicular complex and posterior dorsomedial thalamic nuclei, while the SEEKING/desire system is subserved by the medial forebrain bundle, traditionally described as the "brain reward system". Deep brain stimulation in humans for clinical depression specifically targets the subcallosal cingulate gyrus (SCG), including Brodmann area 25 (Choi et al., 2015; Hamani et al., 2009). This region is considered to be the command centre of a vast network of regions (Insel, 2010), including the hypothalamus and brain stem (implicated in appetite, sleep and energy), amygdala and insular (motivation and interoception), hippocampus (memory and attention) and prefrontal cortex (thought, action, and the regulation of emotion), all of which are affected in clinical depression.

Whilst sadness is often conceptualized along a continuum, we emphasize here that those feelings typically associated with clinical depression, such as mental "anguish" and psychological "pain", may often be features of normal sadness. Take, for example, the loss of a valued job or the ending of a passionate romantic relationship. The extent to which "anguish" and "pain" are aspects of extreme normal sadness or symptoms of a clinical disorder is typically dependent on context or the circumstance within which these feelings arise. This is the argument made by Allan Horwitz and Jerome Wakefield in 'The Loss of Sadness' (Horwitz and Wakefield, 2007). Since the release of the DSM-5 in 2013, major depressive disorder now includes what used to be an important exclusion to a diagnosis of major depression: bereavement. Proponents for the elimination of the bereavement exclusion criterion emphasized the need for patients to receive appropriate clinical attention, treatment and strategies to prevent possible suicide (e.g. Ajdacic-Gross et al., 2008; Stroebe et al., 2005). It remains very possible therefore, that the neurobiological findings reported in studies of clinical depression, including those described in our review (sections 3 and 4), overlap with those for normal sadness. Indeed, Helen Mayberg and colleagues have demonstrated exactly this (e.g. Helen S. Mayberg, 2009; Helen S. Mayberg et al., 1999).

It is also interesting to observe the link between sadness and words such as "anguish", which refers to mental or physical pain. Intriguingly, Naomi Eisenberger (Eisenberger, 2012) demonstrated that the neural correlates of social pain – defined as the unpleasant experience

associated with social disconnection resulting from social exclusion, rejection, negative evaluation or loss – overlap with the neural correlates associated with the affective component of physical pain. Key regions include the dorsal anterior cingulate cortex (involved in social motivation) and anterior insula (feelings and consciousness). Studies have also demonstrated that the subgenual anterior cingulate cortex (ACC) (including BA25) – a region now targeted in treatment resistant depression using deep brain stimulation – is also activated during social exclusion. Although, responses are higher in adolescents and decrease with age, perhaps reflecting increased capacity for regulation of this region by prefrontal circuitry, at least in non-depressed individuals (Eisenberger, 2012; Gunther Moor et al., 2012). It is especially relevant to emphasize here that psychological distress is associated with increased risk of premature mortality in a dose-response relationship regardless of clinical diagnosis (Russ et al., 2012), highlighting the consequences of not learning to appropriately regulate ones emotions.

We would like to emphasize the utility of the word list identified in our linguistic categorization task for sadness. The word list has facilitated our review of the literature, enabling different aspects of sadness as an emotion, mood state (i.e., "depression"), and features of psychiatric illness ("melancholic") to be reviewed and described. It also allowed us to consider potential interactions with other domains identified by the linguistic categorization workgroup. While focusing on all twelve topics presented in this special issue is beyond the scope of the current section – this is the focus of the Human Affectome capstone paper – we now turn our attention to examining the words related to sadness and their interaction with three topics that have been addressed extensively in the literature; fear, happiness, and anger.

When sadness is both intense and prolonged, impairment in the social and occupational sphere may lead to disorders of sadness (e.g., MDD) when other characteristic features of the disorder are also present. A common clinical observation in depressed individuals is co-occurring anxiety, present in as many as 60 % of individuals with depression (Kessler et al., 2005). For instance, generalized anxiety disorder (GAD), characterized by anxious "apprehension" as well as uncontrollable and persistent "worry", frequently presents alongside MDD. Anxiety, apprehension and worry all overlap with the words "anguish", "distress", and "haunted", highlighting important interactions with the "fear" topic area, especially for when sadness is more intense or extreme.

The primary-process emotion of FEAR is another one of Panksepp's seven basic emotions from which anxiety, worry, difficulty making decisions, rumination, feeling tense, and losing sleep may arise. The neural substrates underpinning these feelings include the central and lateral amygdala, medial hypothalamus, and dorsal PAG (Panksepp, 2011). Electrical stimulation of these regions elicits a variety of symptoms including vigilance, startle, increased heart rate, as well as decreased salivation and freezing behaviors (Panksepp et al., 2011). According to theoretical models (e.g., Watson et al., 1995b, 1995a), "distress" is a non-specific feeling that links feelings of "depression" and "anxiety", while depression is distinguished by feelings of "anhedonia", while "anxiety" is distinguished by heightened arousal. Neurobiological models (e.g., Davidson, 1992; Heller, 1993), including approach-withdrawal and valence-arousal, further highlight a role for left-right asymmetry and rostral-caudal activation, findings largely derived from research using scalp electroencephalography. Although Panksepp has criticized such models as "experimental convenience" based on the diverse languages of emotion (i.e., tertiary processes) (Panksepp, 2010), these models have nevertheless led to specific treatments such as stimulation of the left dorsolateral prefrontal cortex of individuals with major depressive disorder using TMS and tDCS (Boggio et al., 2008; Pascual-Leone et al., 1996). While the role of the left prefrontal cortex in positive emotion has been questioned, modern variants of approach-withdrawal and valence-arousal models continue to be proposed (e.g. Bud Craig's the homeostatic sensorimotor model of emotion; Strigo and Craig (2016)), highlighting a role for brain asymmetry in controlling affective behavior and associated autonomic nervous system function.

The relationship between sadness and happiness has also been the subject of investigation, with important implications for our understanding of mental health and the treatment of emotion disorders. Emotions have been defined using various conceptual frameworks, including basic emotion theory in which sadness and happiness are viewed as discrete individual emotions (Ekman et al., 1969; Panksepp, 1998, 1989), and dimensional models which conceptualize sadness and happiness as lying on a single dimension of pleasantness (i.e., the valence-arousal model) (Russell, 1980) or on independent dimensions (i.e., positive affect and negative affect) that implicitly communicate activation or arousal (Watson and Tellegen, 1985b). Further, basic affective neuroscience research in animals has identified distinct primary-process emotional systems subserving happiness (i.e., PLAY, involving the ventral striatal dopamine system in particular) as well as sadness (i.e., SADNESS) (Davis and Panksepp, 2011). While the SADNESS system is considered to underpin feelings of separation distress and loneliness, the PLAY system appears to give rise to laughter, humor, and social joy. Although studies on human emotions have been characterized by contradictory reports and the observation of overlapping neural correlates, it remains uncertain whether neuroimaging technology – especially functional magnetic resonance imaging (fMRI) – is capable of capturing basic emotion experience due to use of often weak emotional stimuli and artificial recording environments leading to suppression of emotional responses (Harmon-Jones et al., 2011), as well as the involvement of secondary (i.e., learning) and tertiary-processes (i.e., emotion regulation). Nevertheless, it is important to appreciate the major impacts human affective neuroscience has had on the development of treatments in psychiatry such as TMS and tDCS of left dorsolateral prefrontal cortex (PFC) and deep brain stimulation (DBS) of subgenual ACC in major depressive disorder.

The relationship between sadness and anger has also been subject to considerable research. Based on Bud Craig's (2011) research proposing that the posterior insula encodes primary bodily feelings while the anterior insula represents integrated feelings, Zhan et al. (2018, 2015) tested the hypothesis that sadness could counteract anger as a homeostatic mechanism. Their results showed that the posterior insula, superior temporal gyrus, superior frontal gyrus, and medial prefrontal cortex were more significantly activated during sadness induction, and that the level of activation in these areas could negatively predict subsequent feelings of subjective anger in a simulated provocation. Psychological research exploring this relationship by studying children facing a blocked goal, suggests that sadness may serve to shift attention away from goals that cannot be attained (Tan and Smith, 2018).

In summary, our review of the linguistic framework above highlights numerous interactions between sadness and other topics under review for the Human Affectome Project. While we only touch on three topics here (fear, happiness, and anger), these interactions are addressed in further detail in the capstone paper. We now turn our attention towards recent research on the emotion of sadness while considering its implications with regards to the conflict between Basic Emotion Theory and Psychological Constructionism. With this aim, the following sections present an interdisciplinary review of findings coming from different fields, including genetics, epigenetics, psychophysiology, affective neuroscience, cognitive neuropsychiatry, and cultural psychology.

2. Role of genetic and epigenetic factors in sadness

Sadness is a complex psychobiological state whose subjective experience relies on the activity of one or more brain networks. Measuring the transient experience of sadness is difficult, thus, it should come as no surprise that genetic studies have been unable to identify a "sadness gene". Instead, a more fruitful approach has been to investigate the predisposition to feeling sad, which is likely to be associated with the structure and function of the – to be reviewed – brain circuits whose development and activity is largely under genetic control (Bishop and Forster, 2013).

2.1. The heritability of sadness

Two lines of research potentially offering important insights concerning the genetics of sadness are: (1) negative emotionality (NE), referring to the tendency to be quickly and easily aroused, and conceptualized as the opposite of emotional stability (Ormel et al., 2012), and (2) neuroticism, encompassing cognitive and behavioral tendencies associated with the experience of negative emotions (e.g., pessimism, withdrawal, and avoidance). Closely related to NE, neuroticism is also strongly associated with the tendency to experience negative emotions (e.g. sadness) (Stewart et al., 2005; Watson and Clark, 1992) and with a number of internalizing psychopathologies (e.g. MDD, social anxiety disorder, GAD, obsessive-compulsive disorder, and panic disorder) (Barlow et al., 2014).

Neuroticism is also thought to underpin high levels of comorbidity between internalizing disorders such as depression and anxiety, with one study finding a correlation of $r = 0.98$ between trait neuroticism and a measure of internalization (Griffith et al., 2010). Therefore, rather than a specific tendency to experience sadness, such evidence suggests that a broader proclivity towards experiencing negative emotions may be inherited. In support of this, sadness, fear, and anger have been found to load onto a single NE factor (Clifford et al., 2015), with estimates of the precise heritability of this NE factor ranging from 40 %–70 % (Mullineaux et al., 2009; Singh and Waldman, 2010; Tackett et al., 2011). In addition, when employing the NEO PI-R which includes separate subscales for anxiety, hostility, and depression, heritability estimates for neuroticism range from 41 %–50 % (Jang et al., 1996; Lake et al., 2000). Taken together, these findings suggest that while there may be a genetic component to sadness, it may be non-specific, related instead to a tendency to experience negative emotions in general. Thus, in cases of psychopathology, it is likely that environmental factors are crucial for shaping whether sadness becomes the dominant negative emotion experienced compared to other emotions such as fear or anger. For example, an environment characterized by learned helplessness is known to predispose individuals to prolonged and intense sadness in the form of depressive disorders (Maier and Seligman, 2016).

Nevertheless, numerous attempts have been made to identify specific genes that may underlie the propensity to experience sadness, including examination of the Brain-Derived Neurotrophic Factor (BDNF); a growth factor that regulates synaptic plasticity and neurogenesis and whose segregation is encoded by the *BDNF* gene (Leal et al., 2014; Lu et al., 2014; Poo, 2001). For example, a number of studies have investigated a specific single nucleotide polymorphism (SNP) at codon 66 of the *BDNF* gene and its relationship with NE. A point mutation at this coding sequence results in a valine-to-methionine substitution, with the Val allele associated with increased degradation of BDNF mRNA, reduced transport of mRNA to dendrites, and reduced secretion of BDNF (Baj et al., 2013). Hayden et al. (2010) found that children with at least one Met allele exhibited higher levels of NE (i.e., greater emotional liability and proclivity towards experiencing negative emotions) when a parent had a history of depression or when relationship discord was reported by a parent. In contrast, when parental depression and relationship discord was absent, children with at least one Met allele reported particularly low levels of NE (i.e., greater emotional stability and decreased proclivity towards experiencing negative emotions). Although perplexing at first, these results suggest that the Met allele may increase child environmental sensitivity to both positive and negative familial influences, impacting in turn on their tendency to experience emotions in daily life. In other words, the Met allele of the *BDNF* gene may predispose individuals to display increased sadness and negative emotionality generally under environmental conditions that foster and elicit such feelings.

In addition, Sen et al. (2003) found that the BDNF genotype was particularly associated with the depression facet of neuroticism. However, and similar to findings in NE, inconsistent findings have been reported. Frustaci et al. (2008) found some evidence that the Met allele is associated with *lower* levels of neuroticism in a dose-dependent manner, whereas Willis-Owen et al. (2005) observed no significant association between BDNF genotype and neuroticism. Such inconsistency could be attributable to interactions between *BDNF* and other genes associated with neuroticism (i.e., serotonin transporter *SLC6A4;* see Outhred and Kemp, 2012; and Outhred et al., 2012), as well as gene-environment interactions and epigenetic mechanisms affecting gene transcription (see below and Booij et al. (2013)). Equally, it is also important to acknowledge that BDNF is known to be involved in many other cognitive, emotional, and pathophysiological processes than those referenced above (Baker-Andresen et al., 2013; Makhathini et al., 2017; Ortiz et al., 2018; Xu et al., 2018).

Other studies have focused on the serotonin transporter, a protein responsible for the reuptake of serotonin from the synaptic cleft which is expressed in a number of brain regions implicated in emotion regulation (Booij et al., 2015). Research on the serotonin transporter has focused predominantly on a particular polymorphism in the promoter region (*5-HTTLPR*), the binding site of transcription factors. Two potential alleles at this SNP have been commonly studied; a Short allele (S) and a Long allele (L), with the short allele associated with decreased transcriptional activity and decreased protein production as a result (Lesch et al., 1996). Interestingly, Wang et al. (2012) found that carriers of at least one *5-HTTLPR* S allele or one BDNF Met allele exhibited stronger amygdala activation to sad stimuli, with BDNF carriers also exhibiting decreased activation in the dorsolateral and dorsomedial prefrontal cortices in response to attentional targets. In addition, carriers of both the S and Met allele showed increased activation to sad stimuli in the subgenual and posterior cingulate, suggesting that *5-HTTLPR* S and *BDNF* Met allele may increase reactivity to sadness individually or in combination. However, findings are inconsistent, raising the possibility that other genes and environmental factors may further interact with the *BDNF* genotype to determine one's predisposition towards sadness and other negative emotions. For instance, Terracciano et al. (2010) found that *5-HTTLPR* carriers scored lower on a measure of neuroticism when the BDNF Val variant was present, but scored higher in the presence of the BDNF Met variant. In contrast, another study found that LL carriers of the *5-HTTLPR* gene with at least one Met allele display decreased cognitive reactivity to a sad mood provocation in healthy adults. Although longitudinal data are needed, this latter finding suggests that the LL phenotype may be associated with an enhanced tendency to think more negatively when in a sad mood, with the BDNF Met variant serving to protect LL homozygotes from dysfunctional thinking after a sad mood provocation (Wells et al., 2010). Further, another study suggests that both 5-HTTLPR and BDNF Val gene variants might mediate the relationship between life stress and rumination (Clasen et al., 2011), which is known to be a risk factor for the development of sadness-related disorders. Taken together, these studies suggest that further research on how multiple candidate genes interact is necessary before a more complete understanding of the genetic basis of sadness and associated traits can be achieved.

The oxytocin receptor (*OXTR*) gene is another candidate which might contribute to sadness. The oxytocin receptor is an endogenous receptor for oxytocin, a neurohormone released during positive social interactions which is thought to be important for social bonding (Bartz et al., 2011). One research group found that a specific combination of alleles at 3 SNPs in the *OXTR* gene (rs53576, rs2254298 m, rs2228485) was associated with increased negative affect and emotional loneliness (Lucht et al., 2009). Further, Montag et al. (2011) found a significant interaction between the *OXTR* and *5-HTTLPR* genotypes, with individuals homozygous for the L allele at the serotonin transporter promoter and the T variant at the rs2268498 polymorphism at the *OXTR* gene displaying lower sadness scores and lower NE more broadly. This suggests that variation in the *OXTR* genotype, like the *SLC6A4* and *BDNF* genes, may also be associated with NE.

It is also possible that the Catechol-O-methyltransferase (*COMT*) and Monoamine oxidase A (*MAOA*) genes may also drive neuroticism,

as both code for proteins involved in the degradation of neurotransmitters relevant to the biological systems thought to relate to neuroticism (i.e., norepinephrine, dopamine, and serotonin). However, only relatively weak associations have been found between polymorphic variation in the *COMT* and *MAOA* genes and neuroticism (Eley et al., 2003; Kotyuk et al., 2015; Samochowiec et al., 2004; Stein et al., 2005; Wray et al., 2008). In addition, the *G-703T* polymorphism of the gene that codes for the rate-limiting enzyme for the synthesis of serotonin - tryptophan hydroxylase 2 (*TPH2*) - (Ottenhof et al., 2018), the serotonin 1A receptor *HTR1A* gene variant C-1019 T (Strobel et al., 2003), the Dopamine Receptor D4 gene (*DRD4*) (Ellis et al., 2011), and genes regulating gamma-aminobutyric acid (GABA) (Arias et al., 2012) have also been associated with traits linked to sadness. However, given the limited number of studies focusing specifically on neuroticism, negative emotionality, and/or sadness, further discussion goes beyond the scope of this review.

Finally, a number of genome wide association studies have also been conducted (Amin et al., 2012; De Moor et al., 2012, 2015; Okbay et al., 2016; Smith et al., 2016), and even though the results of these studies have so far been inconclusive, a number of genes warrant further attention. For example, the *MAGI1* gene and other genes involved in glutamate and corticotrophin-releasing hormone receptor activity (De Moor et al., 2015; Smith et al., 2016). These genes require further study before their association with negative emotions, and sadness in particular, can be better understood. However, it should again be acknowledged that such genes are also associated with many other emotional, cognitive, physiological, and brain processes; highlighting the complexity of potential associations with the emotion of sadness. Lastly, genome-wide association studies investigating disorders characterized by persistent feelings of sadness, such as depression, also inform our understanding. For example, in a recent genome-wide association meta-analysis of 135,458 individuals with MDD and 344,901 controls, 44 risk variants were associated with major depression. This included genes coding for the dopamine D2 receptor as well as neuronal growth regulator 1 (NEGR1), a protein implicated in synaptic plasticity in the cortex, hypothalamus, and hippocampus (Wray et al., 2018). However, it is important to distinguish between mechanisms which might underlie a prolonged state of low mood compared to normal variation in sadness.

2.2. Epigenetics of sadness

Although the genetic code may be immutable, the rate at which gene products are formed can be regulated by environmental factors through a series of processes referred to as epigenetics (Szyf, 2009). Epigenetics have been defined as the study of inheritable changes in gene expression that do not involve alterations in the DNA sequence (Meaney and Ferguson-Smith, 2010). The most commonly studied epigenetic mechanism is DNA methylation, a process which leads to an alteration of gene expression by changing the 3-D structure of chromatin and thus inhibiting the binding of transcription factors; the proteins responsible for reading the genetic code. This process can alter gene expression in a way that is stable, but also reversible, allowing for long-term programming and re-programming of gene expression (Bestor, 1998; Bird, 2002).

In addition to findings that individual genotypic variation is linked to the experience of sadness as well as negative emotionality broadly, it might also be expected that DNA methylation at these same genes could be related to such constructs. An increasing number of studies have examined this process in relation to *SCL6A4* and *BDNF* genes (Januar et al., 2015). For instance, variation in *SLC6A4* methylation has been associated with variation in depressive symptoms as measured by the Beck Depression Inventory (BDI) (Zhao et al., 2013). Specifically, a 10 % increase in the mean difference in *SLC6A4* methylation levels in monozygotic twin pairs was associated with a 4.4 point increase in the difference in BDI score. A number of other studies have found statistically significant positive associations or trends between peripheral SLC6A4 promoter methylation and depressive symptoms (e.g., van der Knaap et al., 2015). However, specific links to sadness are unknown.

BDNF methylation also appears to be associated with depressive symptoms, with peripheral *BDNF* methylation profiles capable of distinguishing individuals with major depression from healthy controls (Fuchikami et al., 2011). Similarly, in a sample of older women, Chagnon et al. (2015) found higher levels of *BDNF* methylation in depressed/anxious individuals compared to controls, but only in those with the AA genotype rs53576. Together, these studies suggest that the variation in both *SLC6A4* and *BDNF* methylation might account for variation in depressive symptoms, including sadness.

Further evidence for epigenetic regulation of sadness comes from epigenetic imaging studies where participants undergo an fMRI scan while completing an emotion processing task and DNA methylation is assessed. For instance, differences in *SLC6A4* methylation have been linked to differences in frontal-limbic responses to sad faces, as well as to fearful faces, in healthy non-depressed monozygotic twins (Ismaylova et al., 2018). In contrast, Ismaylova et al. (2017) did not find any association between *SLC6A4* methylation and sad stimuli or other types of emotional stimuli in a sample of healthy adults. Collectively, such evidence suggests that DNA methylation in specific genes is likely associated with depressive symptomatology, including sadness, as well as the neural processes that likely underlie it. However, further research is needed in order to fully elucidate how these interactions might work. Specifically, large-scale genome-wide (epi)genetic approaches are needed to confirm proposed candidate (epi)genetic variants and to identify which other (epi)genetic variants may be involved in sadness and related depressive symptomatology.

3. Physiology of sadness and its disorders

In this section, we review physiological responses to sadness and its associated disorders based on data collected from numerous techniques, including facial electromyogram, electrodermal activity, cardiac function, respiration, and electroencephalogram. We will also examine whether physiological responses collected from these techniques are able to distinguish between different categories of emotion.

3.1. Facial electromyogram

Studies using electromyogram (EMG) show that imagining negative emotional events are associated with increased activity in the corrugator supercilii (a small and pyramidal muscle located in the medial end of the eyebrow known as the “frowning muscle”), whereas imagined positive emotional events are associated with increased zygomatic major activity (Lundqvist, 1995). Increased EMG activity at the corrugator region has also been observed while individuals are acting out expressions of sadness (Hu and Wan, 2003). In addition, studies reveal that when people are exposed to emotional facial expressions, they spontaneously react with distinct facial EMG reactions in emotion-relevant facial muscles. Specifically, sad faces evoke significantly larger reactions from the corrugator region (Hess and Blairy, 2001; Lars-Olov, 1995) and lower activity of the orbicularis oculi muscle (Hess and Blairy, 2001). However, increased corrugator supercilii activity has also been observed when viewing fearful and angry faces (Lars-Olov, 1995; Lundqvist, 1995) or portraying such emotional expressions (Hu and Wan, 2003). However, angry faces also elicit increased activity in the depressor supercilii (Lundqvist, 1995) and negative emotions, including disgust, seem to be characterized by additional EMG reactions (e.g., increased activity in the levator labii region; Hu and Wan, 2003; Lundqvist, 1995).

Changes in facial EMG reactions to sadness have also been observed in numerous clinical groups. For example, individuals suffering from MDD have been found to show less EMG modulation during affective

imagery in the horizontal corrugator and zygomatic muscles (Greden et al., 1986), and less facial reactivity in response to expressive facial stimuli compared to their non-depressed counterparts (Wexler et al., 1994). Furthermore, even when self-reported emotion does not differ across groups, reduced facial muscle activity has been observed in depressed versus non-depressed individuals (Gehricke and Shapiro, 2000).

Similarly, individuals with Parkinson's Disease show weaker corrugator and medial frontalis reactions in response to sad faces, and almost no reactions from the orbicularis and the zygomaticus in response to happy faces (Livingstone et al., 2016). Such facial reactions could be linked to hypomimia, a term used to capture the decreased facial expressivity commonly observed in Parkinson's (Jankovic, 2008). Finally, boys with disruptive behaviour disorders have also been reported to display a smaller increase in corrugator activity during sadness-inducing film clips compared to controls (De Wied et al., 2009).

3.2. Electroencephalography

Electroencephalogram (EEG) has also been employed to measure physiological responses to sadness (Ibanez et al., 2012), with evidence suggesting specific temporal profiles for basic emotions (Costa et al., 2014). Balconi and Pozzoli (2003) found that while all emotional faces elicited a negative deflection that peaks around 230 ms (N230), event-related potential (ERP) responses varied according to the affective valence and arousal properties of the stimulus. Very similar potentials were observed for fear, anger, and surprise, but a more positive peak characterized happiness, low-arousal expressions (i.e., sadness), and neutral stimuli. Batty and Taylor (2003) also observed global emotion effects from 90 ms (P1) and amplitude and latency differences across emotion categories from around 140 ms (N170). However, compared to both positive and neutral emotional facial expressions, N170 s were longer for negative emotional facial expressions such as sadness. Overall, the authors argued that slower N170 latencies may reflect activation of a sub-cortical pathway for negative emotions, "*sending information rapidly to different levels of the central pathway*" (p. 617). Similar findings have also been reported by Hot and Sequeira (2013), and Costa et al. (2014) found further evidence to suggest that sadness triggers an ERP response "*with one long sequence of contiguous time segments*" (p. 4), for which "*the putative neural generators for this response are thought to be located in occipitotemporal visual areas, the left inferior parietal lobe, left insula, right paracentral lobule, left supplementary motor area and right dorsolateral prefrontal cortex*" (p. 7).

Preliminary evidence also suggests that ERP responses to sadness may differ according to gender. When asked to judge the emotion shown on a face, Luo et al. (2015) found significantly increased P2 amplitudes in response to sad than neutral facial expressions in women compared to men. This finding might suggest an improved ability to recognize and share the emotions of others in women. In contrast, when asked to evaluate their own affective emotions in response to facial expressions of emotion, only men exhibited larger P2 amplitudes to sadness, suggesting the possibility of an earlier distinction between the processing of self-versus others' emotions in men.

Cortical responses to sadness may also be affected by clinical disorders. Deveney and Deldin (2004) found that non-depressed individuals displayed a marked reduction in slow wave amplitude to sad facial stimuli compared to those with depression. In contrast, individuals with MDD exhibited equivalent slow wave amplitudes for both happy and sad facial stimuli. In addition, MDD has also been associated with task-relevant increased attention toward negative information and reduced attention toward positive information. In a sample of young adults with risk factors for depression (i.e., past depression, current dysphoria), Bistricky et al. (2014) found that previous depression was associated with greater P3 amplitudes following sad targets, and that individuals with dysphoria inhibited responses to sad distractors in an oddball task less effectively. Individuals with recurrent MDD have also been reported to exhibit both lower N170 amplitudes and longer latencies when identifying happy and neutral faces compared to controls, but higher N170 amplitudes and shorter latencies when identifying sad faces (Chen et al., 2014). Furthermore, a significant negative relationship has been observed between the severity of reported depression and N170 amplitudes. As summarized by Chen et al. (2014), such evidence suggests "*that having recurrent depressive episodes are likely to aggravate the abnormal processing of emotional facial expressions in patients with depression*" (p. 1). In addition, it seems feasible to suggest that the N170 amplitude for sad face identification could be viewed as a potential biomarker for recurrent MDD.

While relatively less left frontal and right parietal activity has been reported in depressive disorders (Allen et al., 2004), there have been inconsistent findings pointing to the importance of mediating variables such as gender, comorbidity with anxiety disorders, and methodological differences (see Bruder et al., 2017 for a review). For instance, depressed patients with a comorbid anxiety disorder (i.e., social phobia or panic disorder) were found to differ from those with a depressive disorder alone in their frontal and parietal alpha asymmetry (Bruder et al., 1997). Findings in depression have also been more consistent when EEG is measured during emotional tasks (Stewart et al., 2014), such that individuals with current and past depression display less left frontal activity than healthy controls across several emotions (anger, fear and sadness). Consistent with this finding, Zotev et al. (2016) combined real-time fMRI neurofeedback training (rtfMRI-nf) with simultaneous and passive EEG recordings, to investigate the effects neurofeedback on frontal EEG alpha asymmetry in patients with depression. Average individual changes in frontal EEG asymmetry during the rtfMRI-nf task showed a significant positive correlation with depression severity. Moreover, temporal correlations between frontal EEG asymmetry and amygdala activity enhanced during the rtfMRI-nf task. These findings demonstrate an important link between amygdala activity and frontal EEG asymmetry during emotion regulation (Zotev et al., 2016).

In addition, behavioral and ERP studies have provided evidence for right brain involvement in emotional processing and its dysfunction in MDD. For instance, a study using emotional dichotic listening tasks (Bruder et al., 2015) found that individuals with a lifetime diagnosis of MDD had a smaller right hemisphere advantage than healthy controls. Notably, the left ear (right hemisphere) advantage for emotional recognition in individuals without a lifetime diagnosis of MDD was present for angry, sad, and happy emotions, but it was largest for the negative emotions and not present at all for neutral items. Individuals having a lifetime diagnosis of MDD had markedly smaller left ear advantage for sad items compared to those without MDD. Consistent with this finding, several studies using EEG measures of hemispheric asymmetry have reported evidence of abnormal brain laterality in patients with depressive disorders. Specifically, it has been shown (Deldin et al., 2000; Kayser et al., 2000) reduced right-lateralized responsivity to emotional stimuli in parietotemporal cortex in depressed patients. A study (Kayser et al., 2000) investigating ERPs during passive viewing of negative pictures in patients with depression and healthy controls, also showed that controls exhibited greater amplitude of late positive P3 potential to negative stimuli, and this enhancement was more evident over right parietal regions. Patients with depression failed to show this increased late P3 over either hemisphere.

Additional evidence supporting the hypothesis of right parietotemporal hypoactivation in MDD has been provided by multigenerational studies. Kayser et al. (2017, 2000) found that distinct ERPs reflecting different stages in processing of emotional stimuli are affected by risk of depression. Enhanced activation of right occipitotemporal cortex to negative emotional stimuli, peaking at around 200 ms after stimulus onset (N2), is less evident in high risk than low risk individuals and this right-lateralized reduction was even stronger in individuals with lifetime history of MDD. Furthermore, there was a bilateral emotion-related activation of posterior cingulate cortex, peaking around 400 ms (P3 source), which was weaker in high-risk

individuals and those with lifetime MDD. During a subsequent processing stage (around 600 ms), there was also a bilateral reduction of emotion-related activation in inferior temporal cortex and anterior insula in high-risk individuals. Consistent with this evidence, magnetoencephalographic responses in right parietotemporal cortex related to emotional arousal were markedly reduced in depressed patients. This reduction w most evident in depressed patients with at least one parent with MDD (Moratti et al., 2015). Overall, the above findings are consistent with the hypothesis of right parietotemporal hypoactivation in MDD patients and individuals at risk of depression, which is related to difficulty activating attention-related brain regions during processing of emotionally arousing stimuli (Kayser et al., 2017, 2000; Moratti et al., 2015).

3.3. Autonomic responses

Regarding autonomic nervous activity, different techniques have been employed to elicit and investigate sadness, with mixed outcomes across studies depending on the mood induction methodology employed. Biographical and personalized recall of sadness has been shown to result in increased heart rate (HR), along with increased (Ekman et al., 1983; Rainville et al., 2006; Rochman et al., 2008) or unchanged (Marci et al., 2007) skin conductance level (SCL), increased systolic and diastolic blood pressures (Neumann and Waldstein, 2001; Prkachin et al., 1999), unchanged or reduced finger temperature (Prkachin et al., 1999; Rochman et al., 2008), and increased respiration and variability in respiration period (Rainville et al., 2006). The effect of sadness over heart rate variability (HRV) is more equivocal (Marci et al., 2007; Rainville et al., 2006; Rochman et al., 2008), with different outcomes between crying-related and non-crying sadness (Gross et al., 1994; Rottenberg et al., 2003).

Video-clips to induce sadness similarly result in increased SCL (Vianna et al., 2006), respiration rate (Kunzmann and Gruhn, 2005; Rottenberg et al., 2005), or increased/unchanged HR (Kunzmann and Gruhn, 2005; Vianna et al., 2006), with increased blood pressure (Averill, 1969; Kreibig et al., 2007) and decreased finger pulse amplitude and temperature also observed (Kreibig et al., 2007; Kunzmann and Gruhn, 2005). However, such physiological changes differ across genders (Fernandez et al., 2012), with additional evidence suggesting that sadness reactivity may increase with age (Seider et al., 2011) even though such changes are often unaccompanied by parallel increases in expressive behaviour (Kunzmann and Gruhn, 2005).

Sadness elicited through the use of standardized imagery also appears to be related with decreased or small increases in HR (Gehricke and Fridlund, 2002), unchanged SCL (Gehricke and Fridlund, 2002; Witvliet and Vrana, 1995), as well as decreased respiration rate, ventilation, and oxygen consumption (Van Diest et al., 2001). In addition, unchanged HR and decreased SCL in response to sadness has been observed during an emotion self-generation task (Hess et al., 1992). Finally, sadness induced by music is reported to be characterized by decreased HR (Etzel et al., 2006) and decreased (Krumhansl, 1997) or unchanged (Khalfa et al., 2008) respiration rate. Picture viewing for sadness induction has been reported to lead to increased respiration rate, as well as both decreased finger temperature and SCL (Collet et al., 1997).

Some autonomic responses appear to be specific to the experience of sadness. For instance, systolic and diastolic blood pressure during sadness was found to be greater than during other negative emotions (i.e., anger and fear) (Prkachin et al., 1999). Increased SCL is higher in sadness compared to anger, fear, and disgust (Ekman et al., 1983). Decreased HRV has been reported in sadness, but no changes have been observed in anger (Rainville et al., 2006). Respiration period and variability in respiration period are increased in sadness, while they decrease in fear and anger (Rainville et al., 2006). In addition, a more recent study (Kreibig et al., 2007) assessing responses to fear- and sadness-inducing films showed that HR accelerated in fear and decelerated in sadness, and that diastolic blood pressure was elevated in fear and did not deviate from baseline in sadness. However, other reported autonomic changes during sadness are similar to other negative emotions. Specifically, increased HR in sadness may be similar to fear and anger (Ekman et al., 1983), whereas reduced finger temperature seems to be characteristic of both sadness and fear (Krumhansl, 1997).

3.4. Summary of the evidence

The evidence presented above suggests that physiological responses to sadness may vary depending on the method employed to elicit sadness. However, variable findings may also reflect the observation that researchers often consider sadness as a homogeneous emotion, rather than related emotions and features (e.g., dejection, depression, personal failure). For example, Shirai and Suzuki (2017) investigated physiological responses to sadness using an imagery task across two conditions: the loss of someone and failure to achieve a goal. Even though SCL increased during the imagery task in both conditions, restoration to baseline SCL took longer in the loss condition. Furthermore, tear ratings correlated with blood pressure ratings in the loss condition, while sadness intensity correlated with blood pressure ratings in the failure condition. Similarly, Davydov et al. (2011) found evidence for different physiological responses depending on the affective content of films that led to sadness. Specifically, they found increases in HR and SCL when film content was related to avoidance, but decreases when related to attachment/tenderness.

In summary, autonomic nervous system activity associated with sadness appears to be characterized by a "*heterogeneous pattern of sympathetic-parasympathetic coactivation*" (Kreibig, 2010, p. 404) that can be captured through two broad classes of physiological activity: (1) an activating sadness response characterized by increased cardiovascular sympathetic control and changed respiratory activity, and (2) a deactivating sadness response characterized predominantly by sympathetic withdrawal. However, few studies have considered mediating variables and many have not examined response patterns according to cry-status (see Kreibig, 2010, for a full review).

4. Neuroimaging of sadness and its disorders

Here we review findings from neuroimaging studies of sadness and its disorders. We focus on MDD as an exemplar of extreme sadness for at least six reasons. First, Jaak Panksepp's work emphasizes the primary neurobiological emotional system of SADNESS as the neural source from which states such as sadness and depression both arise (Panksepp, 1982a). Second, according to the depressive continuum hypothesis, chronic sadness may be considered an intermediate state between wellbeing and MDD (Tebeka et al., 2018), and a marker of psychiatric vulnerability (Mouchet-Mages and Baylé, 2008). Third, research has shown that 'sadness rumination' – a maladaptive affect regulation strategy that involves repetitive thinking about sadness – predicts depressed mood even in a non-clinical sample (Peled and Moretti, 2010), highlighting a specific link between the transient experience of sadness and depressed mood. Fourth, the work of Jerome Wakefield (Horwitz and Wakefield, 2007) suggests that many individuals meeting DSM criteria for MDD present with uncomplicated depression, an intense extreme version of sadness. Fifth, the pioneering work of Helen Mayberg (Mayberg et al., 1999) demonstrated considerable overlap in patterns of activity in healthy sadness and MDD, involving limbic metabolic increases and neocortical decreases. Finally, the groundbreaking work of Richard Davidson (summarised in: Begley and Davidson, 2012) and others (Allen and Reznik, 2015) emphasize a role for reduced left relative to right in sadness, leading to transcranial stimulation of left dorsolateral prefrontal cortex as an antidepressant target (Fitzgerald and Daskalakis, 2012). It is important to emphasise however that MDD is a heterogeneous condition (Quinn et al., 2012) that requires one of two core symptoms (i.e., depressed mood or loss of

interest) and the presence of five or more symptoms relating to eating, sleeping, and cognition. There are multiple potential combinations of clinical features that do not necessarily represent distinct biological subtypes (but see, Drysdale et al., 2016; Maglanoc et al., 2019; Williams, 2016).

4.1. Normal sadness

In a recent meta-analysis, Wager et al. (2015) sought to account for the heterogeneity of reported findings, both in terms of study population (e.g., age, sex, ethnicity) and methodology (e.g., visual, auditory, imagery, and memory recall) – and formulated highly generalizable brain-emotion associations. Using novel statistical learning techniques that probe for provisional relationships (i.e., machine learning), unique and prototypical patterns of activity (and connectivity) across multiple brain systems were revealed for five basic emotions – sadness, fear, anger, disgust, and happiness. While all basic emotions were characterized by involvement of domain-general brain networks, including the salience, default mode, frontoparietal control, and visceromotor networks, sadness was uniquely represented by functional patterns that prioritized interoceptive and homeostatic information processing (see Fig. 2 & Table 2).

Sadness involves pronounced and preferential recruitment of cingulate, insular, and somatosensory nodes of the Salience network (Wager et al., 2015), which among other things, serve as target regions for interoceptive pathways conveying information on the internal milieu and somatovisceral sensations (Barrett and Satpute, 2013; Seeley et al., 2007). As the salience network, and its cingulate and insular nodes in particular, can orient the brain's processing capacity and network configuration towards the most motivationally relevant information (Bressler and Menon, 2010; Menon, 2011; Seeley et al., 2007), a general bias for internally-directed neurocognitive processes seems to arise (Wager et al., 2015). On a network-level, this is best illustrated in recruitment of default mode network nodes (i.e., ventromedial prefrontal cortex, hippocampus) that mainly serve self-related sociocognitive processes (internal reflection, autobiographical memory, emotional inferences/awareness) (Andrews-Hanna, 2012), which further amplifies the internal focus during sadness (Wager et al., 2015). Second, and perhaps more pertinent, sadness also seems to involve largely isolated brain networks, with reduced connectivity between major systems (Wager et al., 2015). Specifically, sadness includes dramatically reduced co-activations within the cortex, between cortical and subcortical as well as cerebellar systems, while co-activations within the cerebellar/brainstem systems were maintained, a finding that was distinct from other emotions (Wager et al., 2015). This pattern may reflect reduction of cortical control over evolutionarily ancient hindbrain systems mediating visceroaffective responding and learning, resulting in highly localized, inflexible, and context-ignorant affective processing (Grau, 2014; Roy et al., 2014; Wager et al., 2015).

This may explain why psychopathologies involving chronic feelings of sadness, including MDD, often coincide with impaired ability to describe emotional experiences in a fine-grained, contextualized manner (Demiralp et al., 2012; Wager et al., 2015). It may also partly clarify therapeutic effects (e.g., reduced sadness) associated with stimulation of subgenual anterior cingulate in chronic depression (Mayberg et al., 2005), as this region comprises the densest projections from the cortex to the cerebellum/brainstem territory (Price, 1999; Vogt, 2016; Wager et al., 2015). The profound isolation of cerebellar/brainstem systems in sadness may also help to explain why sadness is often accompanied by somatomotor inactivity and de-energization (Nummenmaa et al., 2014), as these hindbrain systems govern adaptive somatomotor function through interactions with cortical and limbic systems (Buckner, 2013).

Other studies with substantially smaller samples, heterogeneous paradigms and imaging methodology (see Table 3) are similarly characterised by functional patterns across distributed brain systems that collectively prioritize interoceptive information processing (Harrison et al., 2008). For instance, sad mood induction via movies and mental

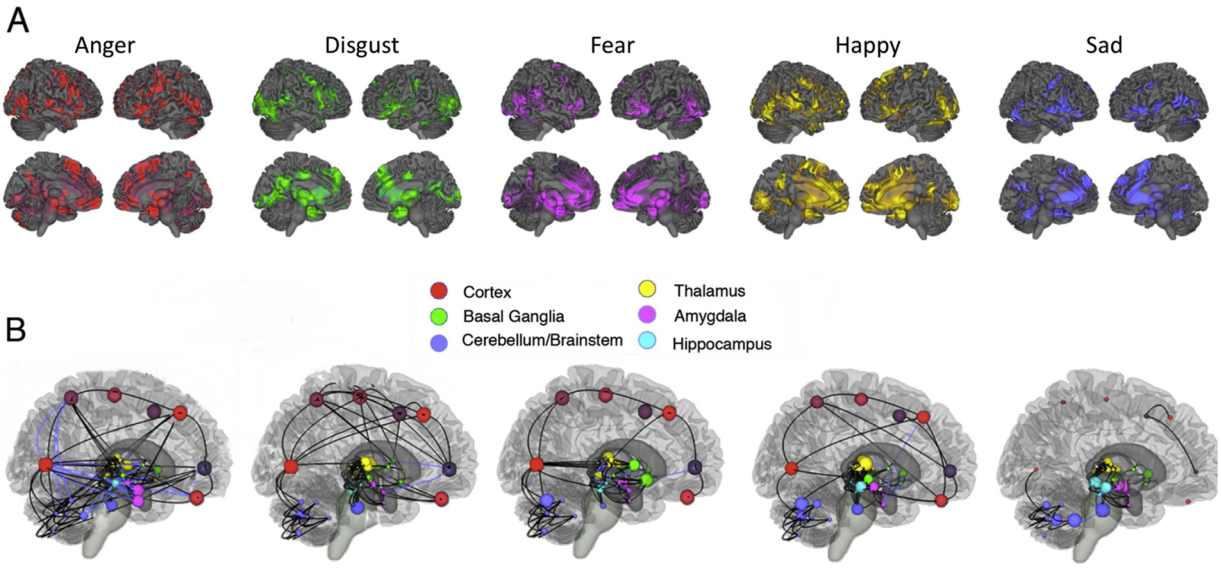

Fig. 2. Neurocircuitry of basic emotions. (A) Lateral and medial views of the unique and prototypical representation of sadness in comparison to other basic emotions across multiple brain regions, including those associated to Salience (e.g., anterior cingulate and insula), Default Mode (e.g., medial prefrontal and hippocampus), Frontoparietal (e.g., lateral prefrontal and dorsal anterior cingulate), and Visceromotor (e.g., cerebellum/brainstem) systems. (B) Connectional profiles associated to each emotion category in anatomical space of the brain. The nodes (circles) are regions or networks, color-coded by anatomical system. The edges (lines) reflect co-activation between pairs of regions or networks. The size of each circle reflects its betweenness-centrality, a measure of how strongly it connects disparate networks. One location is depicted for each cortical network for visualization purposes, though the networks were distributed across regions (see A). Compared to other emotions, sadness involves largely isolated brain networks, with large-scale connectivity among major systems essentially lacking. Specifically, sadness includes dramatically reduced connectivity within the cortex, and between cortical and subcortical systems, while connectivity within cerebellar/brainstem systems seems rather exaggerated. These network functional patterns seemingly link sadness to a neurocognitive profile inclined/biased towards interoceptive and homeostatic information processing. Reprinted with permission from PLoS Publishing: PLoS Computational Biology (Wager et al., 2015).

Table 2
Meta-analysis derived brain network features specific to sadness.

Network	Brain Regions Included	Network Configuration	Neurocognitive Effect
Salience	Anterior Cingulate Cortex Anterior Insular Cortex Somatosensory Cortices	Preferential recruitment of Salience network nodes that serve as interoceptive pathways conveying information on the internal milieu and somatovisceral sensations.	General bias for internally-directed neurocognitive processes.
Default Mode	Ventromedial Prefrontal Cortex Hippocampus Medial Temporal Lobe	Salience network-mediated recruitment of Default Mode network nodes that mainly serve self-related sociocognitive processes (internal reflection, autobiographical memory, emotional inferences/awareness)	Further amplifies the internal focus
Frontoparietal	Lateral Prefrontal Cortex Anterior Cingulate Cortex	Diminished recruitment of frontoparietal control system governing executive control and exogenously-cued information processing.	Suggestive of decreased goal-directed attention towards the external environment.
Visceromotor	Cerebellum Brainstem	Exaggerated connectivity between cerebellar/brainstem nodes of the visceromotor system, along with decoupling of these nodes from cortical regulatory systems.	Highly localized, inflexible, and context-ignorant visceroaffective processing.

imagery in healthy participants impacts salience and default mode function, with particularly strong effects on key network nodes implicated in interoceptive awareness (Harrison et al., 2008; Saarimäki et al., 2016). High levels of self-reported sadness in healthy volunteers also predict diminished recruitment of frontoparietal brain networks supporting executive functions and exogenously-cued information processing, ostensibly suggesting decreased goal-directed attention towards the external environment (Petrican et al., 2015). This pattern is even more pronounced in healthy volunteers with subclinical levels of depression, which lends further support to the apparent neurocognitive inclination/bias towards the internal environment, as a function of increasing sadness (Petrican et al., 2015).

4.2. Clinical depression as an exemplar of a disorder of sadness

We now describe neuroimaging findings reported for clinical depression – and MDD in particular – which we present as an exemplar of a disorder of sadness. Owing to the vast number of published meta-analytic and systematic reviews, a detailed overview of the literature is beyond the scope of this section. Instead, we focus on synthesizing the outcomes from a representative selection of key reviews and published studies. In particular, we pay attention to reported common and distinct patterns of activity in normal sadness and clinical depression, and emphasize the potential impact of disorder heterogeneity on marker profiles.

First, it is intriguing to note that heightened activity in the subgenual prefrontal cortex (sgPFC) has been observed across the spectrum of sadness severity under a wide-range of experimental conditions. This region is also referred to as Broadman's Area 25 (BA25) or the subcallosal cingulate (SCC) and has a role in affective state shifting (Fellows, 2003; Lane et al., 2013) as well as in regulating cardiac vagal control during emotional and cognitive tasks (Thayer et al., 2012). Heightened activity has been observed in non-depressed persons following sad mood induction using autobiographical scripts (Mayberg et al., 1999) and inflammation challenge (Harrison et al., 2009) as well as clinically depressed patients during resting state (Drevets et al., 1997; Mayberg et al., 1999) and negative affective challenge (Laxton et al., 2013). The sgPFC is also a major target of deep brain stimulation for treatment-resistant depression (Holtzheimer et al., 2012; Johansen-Berg et al., 2008; Lozano et al., 2012; Mayberg et al., 2005). Based on the work of Helen S. Mayberg et al. (1999) sadness is associated with increases in paralimbic blood flow and decreases in dorsal neocortical

Table 3
Key evidence on neural substrates of sadness in healthy individuals.

Authors	Methodology	Key Finding
Barrett (2017)	Literature review	Large-scale functional brain networks performing basic psychological operations interactively produce affective states, including sadness.
Harrison et al. (2008)	Mood induction & resting-state fMRI	Sad mood impacts Salience and Default Mode network connectivity patterns, prioritizing interoceptive information processing.
Kragel et al. (2016)	Literature review	Pattern analyses of neuroimaging data show that affective dimensions and emotion categories are uniquely represented in the activity of distributed neural systems that span cortical and subcortical regions.
Kassam et al. (2013)	Task fMRI	Machine learning techniques reveal brain network signatures for sadness, which are reliably activated across episodes and individuals.
Lindquist and Barrett (2012)	Literature review	Large-scale functional brain networks performing basic psychological operations interactively produce affective states, including sadness.
Lindquist et al. (2012)	Meta-analysis	Little evidence that discrete emotion categories can be consistently localized to distinct brain regions. Affective states arise from large-scale brain networks performing basic psychological operations.
Murphy et al. (2003)	Meta-analysis	No consistent and specific correspondence between sadness and neural activity in a particular brain region or circuit. Though some association for other negative emotions are reported.
Petrican et al. (2015)	Resting-state fMRI	Self-reported sadness predicts diminished recruitment of frontoparietal brain networks supporting exogenously-cued information processing. May point to neurocognitive bias towards the internal environment.
Saarimäki et al. (2016)	Mood induction & task fMRI	Sad mood impacts Salience and Default Mode network connectivity patterns, prioritizing interoceptive information processing.
Touroutoglou et al. (2015)	Resting-state fMRI	Specific networks for each emotion do not exist within the architecture of the human brain. Instead, interactions within and between domain general networks are deemed to spur affective states.
Vytal and Hamann (2010)	Meta-analysis	Neural activity patterns associated with sadness were labeled as "discrete", but this was not a consistent and specific correspondence.
Wager et al. (2015)	Meta-analysis	Machine learning techniques reveal that emotion categories such as sadness are not contained within any region or system, but are represented as configurations across multiple, domain general brain systems.

blood flow, while remitted clinical depression is associated with concurrent inhibition of overactive paralimbic regions and normalization of hypofunctioning dorsal cortical sites. This work has led to brain-based models of depression characterized by impaired coordination of interactions within and between segregated limbic and cortical neural circuits (Mayberg, 2003, 1997), and deep brain stimulation of key regions within this circuitry including sgPFC in particular (Holtzheimer et al., 2012; Johansen-Berg et al., 2008; Lozano et al., 2012; Mayberg et al., 2005).

Another body of work on depression has focused on the default mode network (DMN), a region including the medial prefrontal cortex, the posterior cingulate cortex and anterior precuneus, and the tempro–parietal junction (TPJ). The DMN is characterised by higher levels of activity during relative rest, mind-wandering and inward-directed mental activity (Northoff et al., 2006), and depressed relative to non-depressed persons have displayed heightened activity within this region, underpinning features like negative self-focus and ruminative tendencies (Hamilton et al., 2011; Northoff et al., 2006) [but see also (Hamilton et al., 2015)]. It is especially noteworthy here that depressive rumination may facilitate the transition from transient sadness to more intense and prolonged sad mood states including depression (Bonanno et al., 2008; Nolen-Hoeksema et al., 2008; Peled and Moretti, 2010). Disrupted DMN functioning in depression, including findings of heightened activity and failure of deactivation, may be related both to overactive internally directed processes of pathological introspection and rumination and the difficulties displayed by depressed patients when attempting to perform externally focused tasks (Park et al., 2019; Rayner et al., 2016). A systematic review (Kerestes et al., 2014) on resting state fMRI (rs-fMRI) studies (n = 4) in adolescents and young adults with depression reported a consistent pattern of abnormally increased activity in DMN components, including the pregenual ACC, subgenual ACC (sgACC), dorsomedial PFC (dmPFC), and ventromedial PFC (vmPFC) in comparison to healthy controls. These rs-fMRI studies of depression in youth have reported findings generally aligned to those obtained in adult samples. Research (Knyazev et al., 2016) has even demonstrated that non-clinical depression symptoms – based on the Beck Depression Inventory (Beck et al., 1996) – is associated with a predominance of DMN over the fronto-parietal attention system, a 'task-positive network' (TPN). These findings were interpreted as reflecting the 'hijacking of higher cortical functions' such as medial PFC (mPFC) by subcortical emotional systems including temporal lobe and insula. It is noteworthy that although heightened activity within the DMN has not been replicated in other studies (e.g., Hamilton et al., 2015), research reviewed by Mulders et al. (2015) generally supported the notion that pharmacological treatments for depression act towards the normalization of resting-state functional connectivity (RSFC) in the DMN.

Extending on this body of work, meta-analysis has demonstrated that increased functional connectivity between sgPFC and DMN is predictive of higher levels of depressive rumination (Hamilton et al., 2015). Additional meta-analysis in this study further demonstrated that although reliable increases in regional cerebral blood flow were observed in sgPFC, these patterns were not observed in DMN. Together, findings from studies highlighting a role for sgPFC and the DMN in sadness and negative self-focus, as well as results from the reported additional meta-analysis (Hamilton et al., 2015) led to a neural model of depressive rumination (Hamilton et al., 2015), in which the DMN is functionally united with sgPFC, brain function that contributes to depressive rumination. Another meta-analysis (Kaiser et al., 2015) on 25 resting-state functional connectivity studies has characterised MDD with large-scale brain-network dysfunction including hyperconnectivity within the DMN, and hypoconnectivity between regions involved in top-down regulation. These findings provide further evidence for brain dysfunction that may underpin depressive biases towards internal thoughts as well as patients' difficulties in regulating mood, overlapping with research described above in the previous section on the neuroimaging of sadness.

Another line of enquiry in the clinical neuroscience of depression has employed task-related fMRI (tr-fMRI). In their review of 64 tr-fMRI studies exploring neural activity in MDD during affective information processing tasks (e.g., facial expression, film clips), Jaworska, Yang, Knott, & MacQueen (2015) concluded that depressed patients have increased activation to emotive, particularly negative, visual stimuli in regions involved in affective processing. However, notable heterogeneity in the direction of functional abnormalities across separate brain regions was also observed. Increased ventro-rostral/subgenual ACC (vrACC/sgACC) activity was observed during negative emotion processing, with some evidence of decreased dorsal ACC activity during emotional processing of negative, neutral, and fearful stimuli. Increased amygdala activation was also found to occur after negative and arousing stimuli, with increased/decreased basal ganglia/thalamic activity in response to negative and positive emotions, respectively.

Remarkable heterogeneity in the localization and direction of altered activity has typically been reported in prefrontal areas, with both frontal hypo- and hyperactivity reported in MDD (e.g., Diener et al., 2012; Fitzgerald et al., 2006; Hamilton et al., 2012). Such ambiguous neural responding seems to be driven, at least in part, by the emotional valence of stimuli. For example, in their coordinate-based analysis of 44 tr-fMRI studies, Groenewold, Opmeer, de Jonge, Aleman, & Costafreda (2013) found that individuals with MDD displayed reduced activity in the dorsolateral PFC (dlPFC) during negative, but greater activity in the medial orbitofrontal cortex (mOFC) during positive, emotional processing. Activation in the right amygdala, striatum, dorsal ACC (dACC) and parahippocampal/fusiform gyri was found to differ depending to the affective valence of stimuli, with negative and positive emotional processing associated with increased and decreased activation, respectively. Similarly, Hamilton et al. (2012) also found hypoactivation in the dlPFC in response to negative stimuli, as well as hyperactivity in the amygdala, dACC, and insula/superior temporal gyrus (STG) in individuals with MDD relative to controls.

In addition to emotional valence, Diener et al. (2012) found hypo- and hyperactivity in frontal regions, with activity patterns differing depending on the emotional and cognitive demands of the task, as well as medication status. Frontal hyperactivity was evident in medicated (right inferior frontal BA9, right superior frontal BA6) as well as non-medicated MDD patients (left middle frontal BA9) during both executive control and induced sadness and negative mood congruent processing. In contrast, frontal hypoactivity was found in non-medicated MDD patients during affective switching (left inferior frontal/precentral BA9) tasks and those capturing mood-congruent processing towards negatively valenced emotional stimuli (left medial frontal BA6, right paracentral lobule, left inferior frontal/paracentral BA9). The authors argued that hypersensitivity to negatively valenced stimuli is associated with a lack of prefrontal control in the left hemisphere, enhancing attention to negative stimuli and impairing approach related processing towards appetitive stimuli. They also found hyperactivation in the left middle frontal BA9 during executive processes in MDD subjects compared to controls, an effect driven by non-medicated subjects. In contrast to previous research (e.g., Delaveau et al., 2011; Fitzgerald et al., 2008), hyperactivity in inferior (BA9) and superior (BA6) prefrontal regions highlight their involvement in negative emotional states and reduced mental adaptation during emotional-cognitive tasks.

In contrast to the findings of Hamilton et al. (2012); Groenewold et al. (2013), and Jaworska et al. (2015); Diener et al. (2012) also reported no hyperactivation of the hippocampus or amygdala directly, possibly because they combined data from both emotional and cognitive stimuli, rather than prioritizing the investigation of emotional responses. Even so, their analysis generally confirmed a predominantly hypoactive cluster in the anterior insular and rostral anterior cingulate cortex linked to affectively biased information processing and poor cognitive control. For instance, they found generalized hypoactivity in the right insula in both medicated and non-medicated patients with MDD in response to tasks involving negatively biased information processing, attention, and cognitive control.

To synthesize these tr-fMRI findings, while methodology differs substantially across neuroimaging studies, the literature reveals a disruption of emotional processing among individuals with MDD, possibly due to a failure of prefrontal, ACC, and insular areas to down-regulate hyperactivity of caudal limbic areas, such as the amygdala. Again, this is consistent with contemporary limbic-cortical network models for sadness and depression, which emphasize characteristic patterns within and between segregated limbic and cortical neural circuits (Mayberg, 2003, 1997).

Task-related activity involving ACC and insular areas may also be related to brain-body abnormalities involved in depression. These two brain regions are involved in the mapping of bodily responses related to emotional reactions (Craig, 2002; Critchley, 2005; Drevets et al., 1997). While the ACC is relevant to the generation of autonomic arousal, the insula modulates internal visceral responses that accompanies emotional processing (Bechara et al., 1997). Somatic markers generated in the context of emotional processing are thought to be relevant to decision-making in complex situations (Del-Ben et al., 2005; Harmer et al., 2006; Norbury et al., 2007), a process known to be disturbed in MDD (Bell and D'Zurilla, 2009; Lee et al., 2012; Rock et al., 2014; Trivedi and Greer, 2014). Also, the tr-fMRI studies reviewed herein indicate that the neural correlates of negative and positive emotional processing are distinct from one another in MDD. Finally, the existing resting state and tr-fMRI literature point to a core involvement of the ACC in MDD. This is consistent with findings of reduced volume in ACC among depressed groups reported in structural magnetic resonance imaging (MRI) studies (Bora et al., 2012), as well as with models that highlight the role of the ACC in emotion dysregulation in MDD (Northoff et al., 2011). The salience of findings involving the ACC in studies of MDD also converge with therapeutic effects of neuromodulation in this region for treatment of depression (Milev et al., 2016).

In summary, there are clear overlaps between the neural features of sadness and the neural correlates in clinical depression, including characteristic patterns of activation within fronto-limbic circuitry and the default mode network. Although we present MDD as an exemplar of the disorders of sadness, it is important to emphasize that MDD is heterogeneous, and this heterogeneity has implications for marker profiles (Kemp et al., 2014). In this regard, recent work (Drysdale et al., 2016; Maglanoc et al., 2019) has employed a data-driven clustering approach on symptom profiles and identified differential brain-connectivity patterns within limbic and frontotemporal networks. However, the extent to which such 'biotypes' are able to be replicated, remains a matter of debate (Dinga et al., 2019). Another clarification is that mood and anxiety disorders are often comorbid (Kessler et al., 2010b; Lamers et al., 2011), although common and distinct perturbations have been observed (Beesdo et al., 2009; Demenescu et al., 2011; van Tol et al., 2010) [See also Kemp and Felmingham (2008) for discussion]. Interested readers are also referred to outcomes from The Netherlands Study of Depression and Anxiety (NESDA) (see: https://www.nesda.nl/nesda-english/), which is investigating the specific overlap between depression, anxiety, and its comorbidity. Similarly, there is also evidence pointing towards distinct and specific connectivity patterns for fear and anxiety (Cohodes and Gee, 2017). Other authors have proposed taxonomies for mood and anxiety disorders that cut across traditional diagnostic boundaries, consistent with a transdiagnostic approach and Research Domain Criteria (RDoC) framework (Nusslock et al., 2015; Williams, 2016). Given the focus of the current review it is noteworthy that these approaches have emphasized biological signatures for rumination, anhedonia, and depressed mood, all of which have clear relationships with the emotion of sadness.

5. Individual differences and contributors to the experience of sadness

Individual differences can modulate the perception and experience of sadness, and may contribute to contradictory findings. Here we focus on the evidence-base relating to sex, age, culture, and social environment, in particular.

5.1. Sex differences

Epidemiological studies almost universally indicate that risk of depression in females is double that of males (Kessler, 2003). Indeed, the prevalence of internalizing symptoms has been found to be higher in girls compared to boys from a young age (Bask, 2015; Chaplin and Aldao, 2013), although other research suggests that levels of internalizing symptoms in females, including symptoms of depression, do not begin to exceed symptom levels in males until early to mid-adolescence (de Ruiter et al., 2007; Natsuaki et al., 2009). Increased long-term risk amongst females is likely attributable to a combination of biological and environmental factors (Albert, 2015; Kessler, 2003). Fluctuations in estrogen across the female lifespan may also play a role in increasing depressive symptoms (Albert, 2015), which may interact with BDNF, hippocampal, and cerebellum functioning to increase vulnerability to mood disorders (McEwen and Milner, 2017). However, it is also worth noting that feelings of sadness or depression may more readily manifest as external behaviors in males, such as poor impulse control and greater risk for alcohol or substance use (Cavanagh et al., 2017). Consistent with this, males have been found to report greater rates of externalizing disorders than females (Boyd et al., 2015). Females are also exposed to greater environmental vulnerabilities, including socioeconomic factors like lower education and income, as well as traumatic events such as abuse, which may increase risk. Interestingly however, being female poses less risk in lower-income countries compared to high-income countries (Rai et al., 2013). Other factors will further moderate these sex differences, including ruminative regulation styles (Nolen-Hoeksema, 2012), and degree of neuroticism, behavioural inhibition, mastery, and physical health (Leach et al., 2008).

There has been surprisingly little empirical investigation of sex differences in relation to the perception, processing, and experience of sadness. However, from the limited literature that is available, females appear to exhibit stronger corrugator muscle activation (i.e., frown muscle) during the experience of negative emotions in particular, but these findings are not specific to sadness (Schwartz et al., 1980). This is supported by neuroimaging research reporting over-engagement in corticolimbic circuitry, including the amygdala, thalamus, anterior cingulate, and medial PFC, to all emotional stimuli in females relative to their male counterparts (Kemp et al., 2004; Stevens and Hamann, 2012).

During the perception of masked sad faces (relative to masked happy faces), stronger activation in subgenual anterior cingulate and right hippocampus regions have been reported in females, suggesting implicit emotion processing biases that may increase vulnerability to depression (Victor et al., 2017). Female adolescents also display more empathetic sadness than male adolescents, with males showing more empathy towards the other-sex, while females display more towards the same-sex (Stuijfzand et al., 2016). In addition, an ERP study (Luo et al., 2015) found sex differences during empathic neural responses to others' sadness in which females displayed increased P2 amplitudes to sad expressions compared with neutral expressions, relative to males. This finding might be associated with an improved ability in females to recognize and share the emotions of others.

Finally, studies exploring physiological reactivity to emotional stimuli (including sadness) have provided some evidence that females may respond more intensely than males, evidenced by significantly greater SCL and heart rate (HR) responses (Fernandez et al., 2012). Similarly, previous research has reported greater corrugator EMG activity to unpleasant and arousing pictures in females compared to males (Bradley and Lang, 2020), but increased reactivity (SCL) to pleasant pictures (e.g. erotica) in males. McManis et al. (2001) found that prepubescent girls were generally more reactive to unpleasant pictures than boys as captured by a variety of physiologically based measures

(i.e., skin conductance, HR, EMG activity). However, a more recent investigation (Deng et al., 2016) exploring gender differences in both emotional experience (measured by HR) and expressivity (valence, arousal, motivation), found that gender differences appear to depend on emotional valence. For example, with the exception of arousal ratings, no significant gender differences were found for sadness. In contrast, when watching videos eliciting feelings of anger, amusement, and pleasure, males showed larger decreases in HR whereas females reported higher levels of arousal. Thus, when watching videos to induce an emotional experience, the authors argued that males often have a more intense emotional experience, whereas females tend to have high emotional expressivity.

5.2. Age differences

Affective experiences change over the lifespan in accordance with life challenges and developmental stage, and it is possible therefore that there are effects of aging on sadness (Kunzmann and Gruhn, 2005; Seider et al., 2011). However, findings differ markedly across the literature, with contradictory evidence reported. Population studies have shown that the number of sad, depressed or 'blue' days are less frequent in older groups (aged 60–84 years) (Kobau et al., 2004). Prevalence rates for depression reduce with older age (Hasin et al., 2005; Jorm, 2000), with older adults being less likely to endorse clinically significant sadness or mood disturbance symptoms than younger adults (Fiske et al., 2009; Thomas et al., 2016), suggesting that the capacity to effectively regulate sadness may be an important protective factor. By contrast, longitudinal work conducted in Germany found that while the frequency of anger diminishes between young adulthood and older age, the prevalence of sadness increases in older age (Kunzmann et al., 2013). A number of empirical studies in older adults have demonstrated equal or higher reactions to sadness-inducing films, scenarios or memories, relative to younger groups (Charles et al., 2001; Kunzmann et al., 2017; Kunzmann and Gruhn, 2005; Seider et al., 2011), as well as linear increases in sadness with age (Kunzmann and Richter, 2009). It is important to distinguish between normal and disordered sadness experience here, and that older individuals may be more able to effectively regulate affective experience. Indeed, empirical studies have reported increased medial prefrontal cortical engagement during negative information processing with age, indicative of more effective emotion regulation (Williams et al., 2006). Specific effects of age on sadness may also depend on life experiences.

The most prominent theoretical model for understanding the effects of aging on the experience of sadness is the socioemotional selectivity theory (SST) (Carstensen, 2006). This theory posits that it is not chronological age that impacts on affective shifts per se, but rather changes in the perception of time, which shapes goals and motivations and regulation of emotional states. For instance, younger adults hold future-oriented goals, with a focus on acquiring new skills with a high perception of control; as such, barriers to achieving these goals may be met with anger. By contrast, older adults may be more oriented towards present-focused goals that have emotional significance because they perceive themselves as having less control over life events. Moreover, the experience of irrevocable loss is more common – including loss of loved ones, social connections, physical abilities, which may increase the incidence of sadness. While events may be appraised as more sad as one gets older, this may also be met with greater ability to disengage from emotionally-affecting situations (Charles and Carstensen, 2008); suggesting more successful emotion regulation – particularly positive reappraisal and attentional manipulation strategies (Lohani and Issacowitz, 2014). This is supported by evidence that sad autobiographical memories are retained less over the life span (Berntsen and Rubin, 2002), showing a positive bias in favor of remembering more positive events(Carstensen and Mikels, 2005). Therefore, while sadness may become more prevalent as we age, it may exert less impact on our wellbeing. We note however, that although the rate of depression is lower in older cohorts in high-income countries (Thomas et al., 2016), higher rates have been reported in low-middle income countries (LMIC) (Jorm, 2000; Kessler et al., 2010a; Liddell et al., 2013). Cultural differences in the progression of sadness and depression across the lifespan may help to explain some of the inconsistencies reported in the literature, a topic we turn to next.

5.3. Cultural differences

Culture is a critical determinant of the emotional lives of humans, shaping psychological functioning, cognition, and the brain (Han and Ma, 2014; Markus and Kitayama, 2010). Models suggest that culture is central to self-identity and deriving meaning from the external world, including social relationships (Kitayama and Uskul, 2011). Most cultural psychology and neuroscience studies have investigated cultural differences by comparing groups from diverse cultural backgrounds – predominantly those with Western-Caucasian and East Asian backgrounds. Such studies indicate that Western groups value an independent self, individual achievement, high self-esteem, and autonomy; whereas East Asian groups place stronger values on interdependence and collectivistic self-representation, highlighting the importance of social harmony and the group. According to the situated-cognition model, humans instinctively adapt their self-representation to their sociocultural context. This means that specific cultural environments reinforce particular social, emotional, and cognitive patterns of behavior (Oyserman, 2011). This is consistent with a psychological constructionist approach to emotion, which recognizes that emotions are constructions of the world around us, including the influence of cultural practices and value systems (Barrett, 2013).

Consistent with this, numerous studies have shown substantial cultural group differences in the operation and underlying mechanisms of emotion perception, expression, and regulation processes (Ford and Mauss, 2015; Liddell and Jobson, 2016; Tsai et al., 2006). It is unlikely however, that there are specific effects on sadness per se.

Although mental representations of the six basic emotional facial expressions have long thought to be universal, recent evidence suggests that emotion perception may be shaped by cultural influences. The visual extraction of information from facial cues – including sad faces – differs across cultural groups, with East Asian cohorts focusing on the eye region, and Western-Caucasian groups adopting an inverted triangle eye gaze pattern that incorporates the mouth (Adams et al., 2010; Blais et al., 2008). Western-Caucasian groups may exhibit more distinct patterns relating to facial muscles and the temporal unfolding of events when deciphering facial expressions compared to East Asian groups, where there is greater similarity between emotions, particularly sadness, fear, anger, disgust, and surprise (Jack et al., 2012). These may be partially related to dialectical variations across cultural groups, where there is an in-group advantage to discerning ambiguous in-group expressions (Elfenbein et al., 2007).

Use of more contextual cues may also differentiate cultures in terms of emotion perception, including sadness. For example, Japanese participants were found to draw more on background social cues to inform their judgment of target sad faces compared to American participants (Masuda et al., 2008). Another study (Kafetsios and Hess, 2015) reported that sad expressions were judged as less sad in a 'collectivistic' priming condition, and that neutral expressions were judged as more sad in an 'individualistic' priming condition, thus supporting the view of culture as situated cognition (Oyserman, 2011).

Cultural groups also differ in the experience of emotions. For instance, East Asian cultural groups exhibit a preference towards low-arousal emotional states (e.g. calmness, quiet stillness) (Tsai et al., 2006) and socially engaging emotions (e.g. shame) (Kitayama and Markus, 2000). In contrast, Western cohorts appear to prefer high-arousal emotions (e.g. excitement, distress) and social-disengaging emotions (e.g. anger). Interestingly, the discrepancy between ideal and actual affect observed in both cultural groups was smaller for low-

medium arousing emotions like sadness and loneliness, compared to high arousing negative and positive emotions (Tsai et al., 2006). Cultural groups may differ on which negative events are perceived to be more distressing, consistent with dominant self-representations. For example, one study found that that a group of Asian American participants reported greater distress when reflecting on a personal experience of social rejection, relative to European Americans – suggesting greater cultural sensitivity to interpersonal failures (Tsai and Lau, 2013). In a study that induced feelings of social exclusion, Japanese participants who were more collectivistic than the American group in the study, reported more negative affect following the exclusion which was specific to feelings of sadness (Kitayama and Park, 2010). Other studies have found that levels of collectivism are associated with stronger emotional complexity, such as the capacity to either experience multiple affective states simultaneously (e.g. happy and sad) or with stronger differentiation between affective states (Grossmann et al., 2016). Cultural groups also appear to differ in the use of emotion regulation strategies, particularly in the regulation of strong negative or distressing states (Butler et al., 2007; Ford and Mauss, 2015; Matsumoto et al., 2008; Mesquita and Albert, 2007). Taken together, these findings suggest that culture has an important influence on the contexts in which sadness is experienced.

5.4. Social environment and structural factors

Social factors are also critical determinants of a person's emotional state, behavior, health, and wellbeing. Features of the social environment in which individuals are immersed, such as connectedness to others, community cohesion, socioeconomic status, and social equality, have a particularly important impact and contribute to overall mortality risks. Individuals with supportive social relationships are reported to have a 50 % greater likelihood of survival than those with less supportive relationships (Holt-Lunstad et al., 2010); findings that remained consistent across age, sex, health status, cause of death, and follow-up period. Despite some contradictory evidence (e.g., Uchino et al., 2012), social ties and social support buffer, alleviate and protect from stressful experiences (Cohen, 2004). On the contrary, loneliness and social isolation have been linked to a variety of health complications, including alterations in systemic inflammation levels (Yang et al., 2016), increases in coronary heart disease and stroke (Valtorta et al., 2016), and increased risk for mortality over a 7-year period (Steptoe et al., 2013).

Early work emphasized a relationship between loneliness and a variety of psychopathological symptoms. For instance, after controlling for possible confounding variables, Jackson and Cochran (1991) reported associations between loneliness, self-esteem, and signs of depression. More recent publications from cross-sectional and longitudinal analyses of middle-aged to older adults suggest a causal relationship between loneliness and depressive symptomatology (Cacioppo et al., 2006) that persists after controlling for a host of variables including age, gender, ethnicity, education, income, marital status, self-reported stress levels, and social support networks. These findings are consistent with investigations in smaller populations, such as the results published by Heikkinen and Kauppinen (2004) regarding psychological health in older Finish populations, as well as other investigations on the causes of depressive symptomatology carried out on cohort studies (Cacioppo et al., 2010; Richard et al., 2017).

Occupational status has also been linked to differential health outcomes, indexing social inequality due to differences in salary, subjective ratings of an occupation's prestige, and income. Using data from the Wisconsin Longitudinal Survey, the Whitehall II Study, and the National Survey of Families and Households, Marmot et al. (1997) found that scores in the Duncan Socioeconomic Index – a commonly used measure of occupational status combining subjective and objective measures – were associated with self-reported wellbeing and depressive symptomatology. Specifically, individuals from lower social classes exhibited higher levels of depression and reduced health and wellbeing. These results highlight the potential for socio-economic factors relevant to education and occupational status to mediate the experience of sadness and its disorders. Similar findings have been reported by other research groups focusing on the effects of inequality over psychological health outcomes – including depressive disorders – in large cohort studies (Frank et al., 2003). The ubiquitous conclusion of these publications is that lower socio-economic status decreases psychological wellbeing, and increases risk of morbidity and mortality from a host of conditions and disorders (Godoy et al., 2006; Marmot et al., 1997). Other authors have focused on the implications of inequality for human health, highlighting the necessity of improving what has been called "Environmental Justice" (Wilson, 2009) – a term that refers to the need to reduce exposure of disadvantaged populations to environmental and socioeconomic hazards, reducing social inequality to promote psychological wellbeing.

Features of the social environment are critical determinants of mental and physical health, and available evidence has led to life course models such as the GENIAL model (Kemp et al., 2017a), spanning the domains of psychological science, epidemiology, and public health. According to this model, the function of the vagus nerve plays a regulatory role over the functioning of allostatic systems, which subsequently contribute to individual health and wellbeing. Genetic, environmental, and socio-structural factors modulate vagal tone, which underpins capacity for social engagement, itself impacting on health outcomes. Socio-structural factors including community cohesion, low socioeconomic status, and poverty will therefore have major repercussions on vagal functioning, with implications for social relationships, allostatic systems, and ultimately, health outcomes. The influence of social ties on the reduction of mortality risk cannot be underestimated, and is in fact comparable to smoking cessation and its influence has greater impact than that of moderate alcohol consumption and physical activity (Holt-Lunstad et al., 2010).

Despite the impacts of one's social environment on human emotion with clear implications for human health and wellbeing, western culture is characterized by increasing individualism and self-interest (Twenge and Foster, 2010). National census data from the United States (Vespa et al., 2013) and the United Kingdom (Statistics, 2012) reveal a situation in which a quarter of households are comprised of people living alone, and the European Quality of Life survey report that more than 1 in 10 people feel lonely all, most, or more than half of the time (Beutel et al., 2017; Siegler, 2015). In response, researchers in health and social care are now advocating for the implementation of preventive solutions, including for example, social prescription, task shifting, and partnership with social enterprise. Major initiatives including the 'Down to Earth' project (https://www.downtoearthproject.org.uk/), the 'Happy City Initiative' (http://www.happycity.org.uk/), and the Transition Network (https://transitionnetwork.org/) are examples of local, regional, and international commitment to tackling the increasing burden of common mental disorders on society - including the disorders of sadness - by promoting positive social environments to improve mental wellbeing and physical health at scale.

6. Is sadness a basic or constructed emotion?

We now consider the question of whether sadness is a basic or constructed emotion. Recent debate initiated by Barrett (2006), has questioned the previously accepted theory of Basic Emotions, suggesting that position is characterized by a misinterpretation of the evidence, an error of arbitrary aggregation. This debate continued with Izard (2007), who argued that basic emotions remain a viable research hypothesis, and Panksepp (2007b) who argued that basic emotion approaches do not neglect psychological constructionism, later explaining that both Panksepp and Izard are ultraconstructivists with regard to human higher order cognitive functions (Panksepp, 2015). Barrett et al. (2007) replied to both Izard and Panksepp, arguing that there are no

categories of emotions which "*cut nature at its joints*" and that those approaches had outlived their usefulness. Given this context, we now turn our attention to the most recent research on sadness and examine what insights can be extracted from this ongoing debate.

6.1. Sadness and basic emotion theory

Coenen et al. (2011) proposed that MDD may result from unbalanced activity between two complementary networks: dysregulation of the system subserving positive affect, characterized by chronic under-arousal of the SEEKING system, combined with over-arousal of the GRIEF system. Depression therefore involves dysregulation of the emotional systems underlying wellbeing and emotional homeostasis. Despite limitations with neuroimaging techniques, earlier studies anticipated the existence of a dichotomy between the SEEKING and GRIEF systems (Alcaro et al., 2007), arguing for the potential benefits of DBS as a solution for "rebooting" these systems to bring them back into homeostasis and healthy balance. The work of Coenen et al. (2011) is consistent with a role of predetermined neural networks providing the foundation for emotion generation and its disorders, supporting Basic Emotion Theory.

Furthermore, in a study of twin-sibling design, Christian Montag et al. (2016) investigated the extent to which genetic and environmental factors are critical for individual differences in primary emotionality, as measured by the Affective Neuroscience Personality Scales (ANPS). Based on their analysis of 795 participants, they concluded that every ANPS scale was influenced by genetics, and more specifically, the SADNESS system was associated with heritability estimates ranging from 31 to 40%. Christian Montag et al. (2016) argued that such findings imply a common set of genes influencing different primary emotional systems (single additive genetic component) combined with independent genetic factors which only influence specific emotional systems. The remaining variance is then explained by a set of non-shared environmental factors. Such findings are consistent with Basic Emotion Theory, in which specific genetic variability is considered to influence specific emotion systems. In addition, the findings from this study suggest that psychopathologies derived from dysregulation of these systems (e.g., over-activation of the SADNESS system – separation distress and psychological pain – and the resulting reduction of SEEKING system activity as a major cause of MDD) have an important genetic factor, opening the door to novel psychopharmacological treatments and genetic therapy.

A further example is a meta-analysis conducted by Saarimaki et al. (2016) who used multivariate pattern analysis (MVPA) to explore the results of three experiments using fMRI. In these experiments, emotions were elicited by means of short movies and mental imagery while the subjects' brain activity was recorded. Later, the authors sought to classify brain activity patterns for 6 basic emotions: disgust, fear, happiness, sadness, anger, and surprise, applying MVPA to whole-brain data to search for large-scale cortical and subcortical circuits characterizing concrete emotions. Statistical analysis of each of these basic emotions showed different and characteristic neural "fingerprints" - defined as stable activation patterns of neural networks within specific brain regions - evidenced by high accuracy in the classification process using hemodynamic brain signals. The authors report that brain regions which contributed most to classification accuracy included lateral PFCs, frontal pole, pre- and postcentral gyri, precuneus, and PCC, whose activity would be integrated in the midline frontal and parietal regions, acting as a structural link between changes derived from emotion and changes on self-awareness. Authors argue that the results of this meta-analysis provide support for the existence of characteristic and discrete neural signatures of different instances of emotion, and in turn, also support the fundamental principles of Basic Emotion theory. Nevertheless, supporters of theories of constructed emotion countered that these conclusions are flawed and that the obtained results are actually in line with psychological constructionist views (Clark-Polner et al., 2016).

In another meta-analytic study of neuroimaging data from the BrainMap database (Kirby and Robinson, 2017, activation likelihood estimation ALE maps displayed activation within the right inferior frontal gyrus for all emotions and within the amygdala for five out of seven emotions analyzed. For sadness, the analysis drew on data reported in 54 publications across 1078 individuals, 139 experiments, and 840 nodes, with results showing a remarkable amount of prefrontal activity compared to other emotions. Specifically, cortical activation patterns for sadness in the right inferior frontal gyrus BA 45, left middle frontal gyrus BA9/47, the left medial frontal gyrus BA 9, the right precentral gyrus BA 44, and the bilateral frontal gyrus were observed. In addition, activation of subcortical regions, including the left anterior cingulate cortex BA 32, the right insula BA 13, the left medial globus pallidus LMGP, right putamen, and the left thalamus was also observed. The authors interpreted these findings as providing strong support for a multi-system model of emotion basic emotions approach, including primitive subcortical components for emotion processing as well as more specific networks for each different emotion analyzed. However, the authors also acknowledged the need for more extensive meta-analysis and for specific connectivity analysis of identified areas in order to create reliable functional profiles of each basic emotion.

6.2. Sadness and the psychological constructionism theory

We now turn our attention towards reviewing the most recent publications supporting constructionist approaches.

Jastorff et al. (2015) investigated functional brain connectivity in response to viewing a walking avatar presenting four emotions: anger, happiness, fear, and sadness. They identified a general emotion network connecting core affect, conceptualization, language, and executive control networks that was identical for all four emotions. Several nodes of this general network contained information capable of discriminating between the four individual emotions, although twenty-eight additional domain-general pathways were required for successful differentiation. Findings were interpreted as providing support for psychological constructionism, as several regions (e.g., amygdala, anterior dorsal cingulate cortex) appeared as common features in fundamental processes associated with the construction of emotions. The authors also reported a lack of specificity in the activation of certain regions such as insula activation, which was not unique to any one emotion. Interestingly, the connection between the insula and subgenual anterior cingulate was specifically associated with the processing of sad facial expressions.

In a similar study, Raz et al. (2016) examined the dynamic interactions between domain-general neural networks known to be implicated in emotion generation and processing (i.e., salience network and amygdala-based networks) in four samples of healthy volunteers with no known psychiatric or neurological history. Participants were instructed to passively view a series of film clips (sadness, fear, and anger) and pay attention to cinematic events whilst their brain activity was recorded using fMRI. Once completed, participants were then asked to provide a detailed account of their emotional experience by completing a detailed emotion category label inventory. Raz et al. (2016) hypothesized that emotions would be the result of interactions between domain-general networks implicated in processes which are not specialized in emotional processes (i.e., brain networks supporting the experience of different processes and not emotion alone). In accordance with this, they found that enhanced connectivity between the medial amygdala network and dorsal salience network was associated with more intense ratings of emotional experience across all six instances of the three emotions explored. In addition, enhanced connectivity between the ventrolateral amygdala network and the dorsal salience network was also associated with more intense ratings of emotional experience across five of the six emotion exemplars. Thus, such findings are consistent with psychological constructionism as a

variety of emotional experiences were associated with dynamic interactions of domain-general networks. However, several considerations have to be made regarding the efficiency and specificity of the imagery and movie sets with regards to eliciting single emotions, such as the influence of contextual parameters, the variability among the subjects' sensitivity to selected stimuli, stimuli validity, and so on (Coan and Allen, 2007). It is not our intention to undermine a well-stablished tool that is regularly used by affective neuroscience researchers, but to highlight the potential limitations, and also to prompt the reader to cautiously consider research whose conclusions are based on eliciting responses by means of passive observation, which may not be sufficient to induce specific emotional states.

We have already mentioned that the identification of "neural fingerprints" corresponding with specific instances of emotions (i.e., anger, fear, disgust, happiness, sadness, and surprise) by Saarimaki et al. (2016). However, these results were questioned that same year by Clark-Polner, Johnson, & Barrett (2016) who argued that the paper contained important flaws: "*a pattern that successfully distinguishes the members of one category from the members of another (…) is not a fingerprint*" (p.1945) and that the results of the study were more consistent with a constructionist than basic emotion approach. The constructionist approach argues that changes in central nervous system (CNS) and autonomic nervous system (ANS) activity during the occurrence of an emotion are case-sensitive and dependent on specific circumstances, which led to that emotion, thus lacking a specific "fingerprint". This dichotomy between the fingerprint hypothesis (in line with the Basic Emotion Theory) and the population hypothesis (i.e., activity determined by a population of context-dependent variables, in line with a

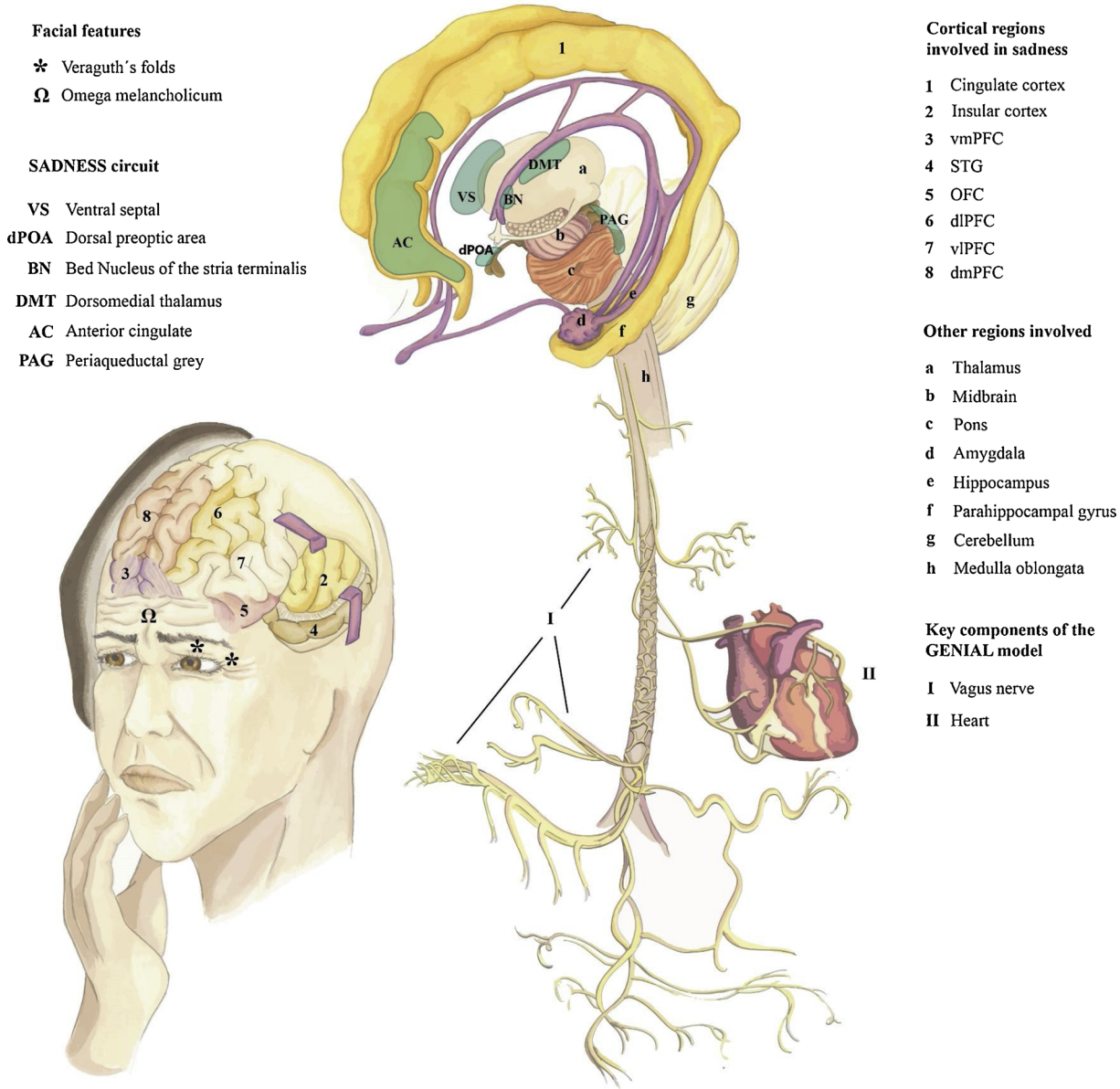

Fig. 3. Integrative illustration of the neurobiology of sadness. **Facial features** include Veraguth's folds (✲) and Omega melancholicum (Ω), also known as Darwin's grief muscles. Key regions identified in animal research and implicated in the **SADNESS circuit** include the VS, dPOA, BN, DMT, AC, and PAG. **Cortical regions** identified in human neuroimaging studies include the cingulate cortex and insular cortex (involved in internally-directed cognitive processes); vmPFC and STG (responsible for further amplifying internal focus); dlPFC and vlPFC (goal-directed attention towards the environment), dmPFC (essential part of the central executive system), and OFC. **Other regions** relevant for the emotion of sadness (thalamus, midbrain, pons, amygdala, hippocampus, parahippocampal gyrus, and cerebellum) are also represented. **The GENIAL model** emphasizes a key role for vagal nerve inhibitory function over the heart – emerging from the medulla oblongata – given its mediation of psychological moments and regulation of downstream allostatic systems, and promotion of longevity or premature mortality if dysregulated (Kemp, Arias & Fisher, 2017). (Illustration by Irene de Diego, 2018; airin.dd@gmail.com).

constructionist approach) was thoroughly tested in a recent meta-analysis (Siegel et al., 2018). This multilevel meta-analysis contained 202 studies exploring ANS activity changes (e.g., heart rate and variability, respiration rate, skin conductance) during the elicitation of different emotions, including anger, fear, happiness, sadness, and disgust. In order to determine whether a consistent and regular set of changes arose during specific emotions, a meta-analytic multivariate pattern classification analysis (MPCA) was performed to determine whether emotion categories could be distinguished by means of ANS activity changes. Results indicated that none of the ANS changes were specific to a particular instance of emotion or could be used to identify an emotion category. More specifically, instances of sadness (87 studies) resulted in increased heart rate (HR), diastolic blood pressure (DBP), systolic blood pressure (SBP), and respiratory rate (RR). However, mean effect sizes were very heterogeneous and only RR showed some evidence of consistency. These results were interpreted as being broadly consistent with the population hypothesis, and therefore, in support of psychological constructionism.

7. Limitations

The neuroscience of sadness is not without limitations. These include small sample sizes that may not be generalizable beyond individual studies, especially for expensive neuroimaging techniques. There is also substantial variability in the methods used even when considering those methods used in human research to induce emotion and mood states in the lab (e.g., processing of various types of emotional stimuli versus script-driven mood states without active rumination), which may lead to discrepant findings. These issues have led to difficulties and disparities in assessing, labelling and measuring sadness in and outside the laboratory. It also impacts on researchers' capacity to formulate widely-accepted and overarching theories of sadness. While large-scale, sophisticated meta-analyses have been conducted on human neuroimaging studies to circumvent some of these issues, conclusions drawn may still be limited to tertiary-level processes, considerably limiting the conclusions able to be drawn by psychological constructionists. Unfortunately, there is limited evidence of partnership working between, for example, researchers conducting 'basic' neuroscientific research in rats and those affective neuroscience researchers focusing on higher level affective processes in humans, highlighting a need for specific funding schemes that encourage transdisciplinary science. Typically, research findings are interpreted from the vantage point of one's own discipline leading to the so-called 'disciplinary dilemma'. Other limitations include issues associated with meta-science, including a lack of successful replication of previously published findings, a general lack of support from competitive funding bodies for replication science as well as limited recognition by institutional promotion pathways of such efforts. There is a need for a multi-pronged approach to better understand the emotion of sadness and its disorders including greater recognition of the structural challenges imposed on researchers that contribute to various limitations. Innovative funding schemes are needed to facilitate partnership working between animal and human researchers as well as collaborative science that draws on contributions from multiple laboratories, facilitating recruitment of larger samples.

8. Discussion

We have summarized the neuroscientific evidence related to sadness and its disorders, commenting specifically on developments in the "Big Debate on Emotion". We have provided an extensive, multidisciplinary synthesis spanning findings from fields including genetics and epigenetics, psychophysiology, affective and cognitive neuroscience, neuropsychiatry, and cultural psychology. The question over whether sadness is a 'natural kind' or a psychological construct that is dependent on domain general neural systems remains a matter of heated debate. Initial neuroimaging studies on humans were viewed as evidence supporting a basic emotion approach, with sadness underpinned by activity in the subgenual anterior cingulate, and to some extent by insular, orbitofrontal, and amygdalar activation (Murphy et al., 2003; Vytal and Hamann, 2010). However, more recent studies have shown key brain regions to be activated in response to other emotions (e.g., fear, disgust, anger) as well as non-affective processes (Barrett, 2017b; Kragel and LaBar, 2016; LeDoux, 2012; Lindquist et al., 2012; Lindquist and Barrett, 2012; Wager et al., 2015; Yarkoni et al., 2011). Recent meta-analyses of human neuroimaging studies have also failed to demonstrate a specific correspondence between basic emotions like sadness and neural activity in a particular brain region or circuit (Lindquist et al., 2012; Lindquist and Barrett, 2012; Wager et al., 2015).

These developments contrast with more convincing data from animal research in which basic emotions have been more easily mapped onto specific brain regions (Panksepp, 2016, 2010; Panksepp et al., 2017), including the emotion of sadness, whose PANIC/GRIEF system has been comprehensively described in several articles (Jaak Panksepp, 2003; Panksepp and Watt, 2011a) (see also Fig. 3). In recent papers (Davis and Panksepp, 2011) Panksepp has even labelled this distress system using the capitalized word, SADNESS, highlighting the evolutionary foundations on which states commonly labelled as 'sadness' and 'depression' may arise. Bearing in mind the complexity of human emotion and associated methodological difficulties in identifying underlying networks, further dialogue and collaboration between human and animal affective neuroscientists is required, as has been argued on multiple occasions (Panksepp, 2015, 2003a, 1992). We recommend a need for innovative funding schemes that facilitate cross-disciplinary working, with an eye towards establishing a transdisciplinary science of sadness.

Basic emotion theorists have proposed that the subcortical structures that we share with other mammals are the neural foundations for all emotional life (Panksepp, 2007; Panksepp and Watt, 2011b). Animal neuroanatomy indicates stratification in which ancient systems are located in a medial-caudal position, while more recently developed systems are located laterally and rostrally. This organization leads to a three-level system of consciousness formed by: (1) a primary-process system arising from ancient subcortical regions, (2) a secondary-process system responsible for emotional learning, and (3) a tertiary-process system responsible for complex cognitive-affective synergies emerging from the interaction between neocortical regions and paralimbic and limbic structures (Panksepp, 2005, 1992, 1982b). Basic Emotion approaches support the existence of networks which conform to the primary level of emotion elaboration (i.e., SEEKING, RAGE, FEAR, LUST, CARE, PANIC/GRIEF, and PLAY systems), while most of the research supporting psychological constructionism focuses on the processes belonging to the higher tertiary level. Interactions between the primary-process system and higher networks contribute to a richer emotional experience that will be case-sensitive and dependent on circumstance and context, as argued by the psychological constructionists. It is somewhat surprising that the animal literature and the nuanced arguments of Jaak Panksepp are often dismissed by human neuroscientists, highlighting the 'disciplinary dilemma' that arises as a result of working in disciplinary silos. Critically, Panksepp repeatedly emphasized that Basic Emotion Theory does not neglect constructionist assumptions (see, for example: Panksepp, 2007a), instead placing importance on the complex contextual and sociocultural features associated with the emotional life of the human species, emphasizing that "*those developmental/epigenetic cortical achievements are built upon cross-mammalian, subcortical, primary-process, affective homologies*" (Panksepp, 2015, p. 1). In the present review, we do not consider it desirable, nor even necessary to claim the victory of either theory. Instead, like Panksepp, we view both theories as simultaneously correct, although on different levels of a phylogenetic hierarchy (Chiao, 2015; Panksepp, 2015). Consequently, basic emotion and constructionist approaches may be considered as complementary, facilitating a better understanding of

human affective processes (e.g., normal sadness) and its disorders (e.g., major depressive disorder). In light of evidence reviewed, we agree with Panksepp and Watt (2011b) who argued that remaining ambiguities are the result of "*(…) nonsubstantial differences among investigators working at different levels of analysis.*" (p. 1). We suggest that the conflict between Psychological Constructionism and Basic Emotion Theory may now be scientifically sterile, and that the hundred-year war on emotion may be moving toward its end. This does not neglect the need for further cross-disciplinary collaborative research in this area as there remains an urgent need to better understand the link between the emotion of sadness and its disorders.

Animal researchers have argued that sadness emerges from activity within the PANIC/GRIEF system (Panksepp, 2003b), a network that includes the dorsomedial thalamus, the anterior cingulate, and the periaqueductal gray among other regions (see Fig. 3). Sustained activation of the PANIC/GRIEF system may lead to chronic negative emotionality, transforming normal sadness into a clinical disorder, associated with loneliness, despair, avoidance, persistent negative cognitions, and behavioural disruption (Bonanno et al., 2008; Leventhal, 2008). But what might trigger the transition from normal sadness to a disorder such as MDD, comorbidity with a host of disorders and conditions, and premature mortality? Transdisciplinary life course models such as GENIAL (Kemp et al., 2017a) and NIACT (Kemp et al., 2017b) spanning the domains of psychological science, epidemiology, and public health (see also Kemp, 2019), highlight a mediating role for vagal function, which if deregulated may lead to adverse effects on downstream allostatic mechanisms ultimately leading to increased risk for morbidity and premature mortality from a host of conditions and diseases (see Fig. 3). A meta-review of the literature concluded that a single depressive episode or recurrent depressive disorder are responsible for reductions in life expectancy of between 7 and 11 years (Chesney et al., 2014), findings equivalent to the effects of heavy smoking. Other research reporting on outcomes from meta-analysis of 293 studies including 1,813,733 participants (135,007 depressed and 1,678,726 nondepressed) from 35 countries (Cuijpers et al., 2014) reported that overall relative risk of excess mortality – after adjustment for publication bias – was 1.52 (95 % CI = 1.45–1.59). By contrast, other research (Steptoe et al., 2015) has demonstrated eudemonic wellbeing – that is, wellbeing associated with meaning and purpose in life – is associated with increased survival. Over an 8.5-year follow-up period, 29.3 % of those in the lowest wellbeing tertile died, while only 9.3 % of those in the highest tertile did so. These findings were based on 9,050 core members of the English Longitudinal Study of Ageing, and were independent of age, sex, demographic factors, and baseline mental and physical health.

Our models emphasize a key mediating role of the vagus nerve – often indexed using heart rate variability – through the cholinergic anti-inflammatory reflex (Sternberg, 2006; Tracey, 2002), which if dysregulated may increase risk for morbidity and premature mortality (Chesney et al., 2014; Penninx et al., 2013, 2001). There is a growing body of evidence demonstrating vagal regulation of downstream allostatic processes known to contribute to important health outcomes. For instance, recent studies have shown that reductions in heart rate variability predict increased level of C-reactive protein four years later (Jarczok et al., 2014), mediate insulin resistance, thickening of the carotid arteries and subsequent cognitive impairment (Kemp et al., 2016) – a marker of ill-being – and has been shown to precede incident depressive symptoms at 10-year follow-up (Jandackova et al., 2016). While the autonomic nervous system is one of several response systems that contribute to stress-related mood disorders, the vagus has a regulatory role over many of these including the sympathetic nervous system (Deuchars et al., 2018; Porges, 2011), hypothalamic-pituitary-adrenal (HPA) axis (Porges, 2011), inflammatory pathways (Kolcun et al., 2017; Tracey, 2007, 2002), metabolism including glucose regulation (Berthoud, 2008; Dienel, 2019; Malbert et al., 2017; Pavlov and Tracey, 2012), brain-gut interactions (Bonaz et al., 2018) and even neurogenesis and epigenetic mechanisms (Biggio et al., 2009; Follesa et al., 2007). It is important to note here that there is also evidence that various response systems such as inflammatory pathways and HPA-axis function may also impact on ANS functioning, thus the vagus nerve affects and is affected by other response systems in a bidirectional relationship, as we have described previously (Kemp et al., 2017a)(Kemp et al., 2017b). Despite increasing evidence for a regulatory role of vagal function, we acknowledge significant debate in the literature, including published correspondence, some of which has been written by authors of the current review (AHK and BWJHP) (e.g. Brunoni et al., 2012; Kemp, 2012; Kemp et al., 2011b, 2011a; Licht et al., 2011b, 2011a). Future research is needed, striving for a more mechanistic and causal description of how discrete patterns of activity and connectivity across the brain give rise to emotions such as sadness, and under what conditions brain and body processes underpinning sadness may trigger its disorders such as MDD, associated morbidity and premature mortality. Finally, recent developments in science – such as the Open Science Framework – provide a platform for collaborative research and partnership working across laboratories and disciplines, laying a foundation for a future transdisciplinary science of sadness and its disorders. We sincerely hope that dedicated funding will become available to facilitate more collaborative and transdisciplinary opportunities.

Contributions

AHK was an advisory board member of the Human Affectome Project and team lead for the sadness topic. JAA managed the writing process, and together with AHK and CW wrote and reviewed successive drafts of the manuscript, supported by RR. All authors contributed original content, helped to further develop the manuscript for publication and approved the final version for publication.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.neubiorev.2020.01.006.

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