Towards a classification of alexithymia: primary, secondary and organic

Verso una classificazione dell'alessitimia in primaria, secondaria e organica

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Summary

Background

Emotion processing is essential for well-being and psychosocial adaptation. Alexithymia is widely viewed as an impairment in emotion processing that includes difficulty identifying and describing emotions. While there is a significant understanding of primary alexithymia, which is thought to be the result of developmental genetic and familial factors, secondary and organic alexithymia are beginning to be focus of research.

Method and results

The present review of the literature suggests the importance of differentiating between primary and secondary alexithymia, and the organic subtype of secondary alexithymia. Secondary alexithymia is thought to be a consequence of psychological stress, chronic disease, or organic processes (e.g. brain trauma or stroke) that occur after childhood (whereas primary alexithymia is a developmental phenomenon). Organic insults to the brain may bring about the organic form of alexithymia by altering cerebral structures involved in emotional processing (e.g. anterior cingulate cortex, frontostriatal networks, callosum corpus, right hemisphere cortex and amygdala). The usefulness of differentiating among alexithymia categories and their relationships with brain structures known to subserve emotional processing is discussed.

Conclusion

We propose that differentiating between primary, secondary and organic alexithymia may potentially serve to develop better treatments for alexithymia.

Key words

Alexithymia • Classification • Brain injury • Emotion

Introduction: origin of the concept of alexithymia

Alexithymia is a psychological construct broadly describing individuals with deficits in emotion processing and awareness [1]. Individuals who score high on measures of alexithymia show difficulty distinguishing emotions from bodily sensations, discriminating between cognition and emotions, and describing and communicating emotions to others [2]. Harvard psychiatrist Peter Sifneos first used the term alexithymia (a = lack; lexis = word; thymos = emotion) to describe individuals who appeared, "different, alien beings, having come from an entirely different world, living in the midst of a society which is dominated by feelings" (Goleman [3], p. 51).

Classically, alexithymia has been defined to include multiple facets including [4]:

1. difficulty identifying and distinguishing emotions from bodily sensations;
2. difficulty describing and verbalizing emotions;
3. poverty of fantasy life;
4. externally oriented thinking style;
5. poor empathizing.

During dynamic psychotherapy, the capacity to symbolize and translate emotions into language is often considered to be critical for improving symptoms. These capacities are greatly reduced or lacking in alexithymia. Sifneos' interest in identifying individuals with alexithymia was motivated by the goal to select individuals who would show improvement with short-term psychodynamic therapy [5]. The negative effect of alexithymia on psychotherapy has been empirically demonstrated in group, psychoanalytic and supportive psychotherapies [6]. The reaction of the therapist to patients with alexithymia may also have a negative effect on treatment [7].

Dating back to earlier research, the body or "soma" was found to play a critical role in alexithymia [8]. The present review will describe the two-way relationship between alexithymia and the body, beginning with a discussion of historical views purporting that emotions are embodied

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experiences. The potential utility of distinguishing between primary, secondary and organic alexithymia based upon aetiology and proposed brain mechanisms will be described.

Some historical views on emotion and the body

Ancient Greeks and Romans traditionally viewed emotions as "pertubationes animi" (literally, disturbances of the soul), or modifications of the mental state of an individual not guided by reason (Cicero I sec. BC) [9]. Today, in light of progress in cognitive and affective neuroscience, the dichotomy between emotion and reason is less tenable [10]. The ability to perceive, modulate and express emotions are core cognitive features of emotional *intelligence* [11]. Knowing one's own emotions is an essential ability that promotes adaptive decision-making and goal-directed behaviour [12]. Emotional awareness has been considered to be a prerequisite for managing bodily drives and delaying gratification, while contributing to the selection of emotionally adaptive behavioural responses [12].

The philosopher and biologist Herbert Spencer (1820-1903) posited that an emotion is a subjective mental state of pain or pleasure associated with bodily manifestations ("the inner and the outer face of the same change" Spencer, 1855, p. 128) [13]. Spencer believed that in the animal kingdom emotions play a role in evolution and adaptation, permitting a comprehensive classification of impressions and inducing adaptive responses to specific situations [13]. Darwin's theory of emotions [14] expanded upon Spencer's ideas and emphasized the concept that an emotion is an automatic response with stereotyped bodily changes. Darwin believed that an emotion was a mental state causing somatic effects and observed similarities between somatic expressions of emotions among humans and other animals (e.g. gnashing teeth in anger) [14]. Darwin distinguished basic emotions including joy, shame, anger, and disgust from social emotions such as love or hate that generally are less stereotyped and more complex [14].

William James and the Danish physician James Lange viewed emotions as a link between the perception of an event and the consequent behaviour: emotion (from Latin *e-moveo* = to move towards) compels to act [15]. According to James, an emotion is the consequence of an activation of the neurovegetative system [15]. The perception of an aroused neurovegetative system generates emotion (Fig. 1). To expand, it is James' opinion that the behaviour that follows a perception *is* the emotion. He wrote: "the bodily changes follow directly the perception of the exciting fact, […] our feeling of the same changes as they occur is the emotion" [15,16].

In contrast with James, Cannon viewed bodily expressions and cognitive appraisal of emotions as parallel processes [17]. This signifies that Cannon believed that the neurovegetative changes were not the cause of the emotion. Cannon highlighted that the perception of an emotional event (e.g. danger) produces activation of subcortical brain structures thus leading to a generalized sympathetic response. Activation of cortical structures is necessary for the conscious representation of the stimulus and its emotional tagging [17]. The late Magda B. Arnold (1903-2002) (American psychologist based at Loyola University, Chicago) thought that emotions are produced during a dialectical process occurring between the mind and external objects. She thought that emotions are products of our evaluation of events (the "appraisal theory of emotions"). In addition she showed that (usually), positive emotions generate approach behaviour while negative emotions generate withdrawal. Hence, emotions are not exclusively inner processes, but are generated by interactions between the subject (with her body) and the object [18].

Conscious representation of an event permits an evaluation of the basic perceptual data and may allow modification of the emotional response [18]. In this model, Arnold posits the pivotal role of emotional awareness in controlling emotion responses and emotion-activated behaviour.

In spite of the critical differences between various theories of emotion, this very brief account of the history of emotion theory demonstrates the importance of the emotion-body connection.

Social role of emotion and alexithymia

Amidst the complexity of human societies and groups, emotions play an important social role. Basic emotions including fear, for instance, often promote affiliation among individuals, as frightened individuals may seek support from the group and utilize these group resources against a real or imaginary enemy [19]. Other emotions (for instance empathy or envy) are eminently social in nature [19]. Decreased levels of empathy have been linked to

EVENT > NEUROVEGETATIVE AROUSAL > EMOTION

FIGURE 1.
James-Lange's theory of emotion. *La teoria delle emozioni di James-Lange*.

greater loneliness [20]. Because of the importance of emotions both for the individual and social groups, the fact that some individuals show a diminished capacity to recognize and describe emotions has been widely regarded as a highly important psychological and clinical issue [21]. Individuals with moderate to high scores of alexithymia show an array of difficulties in their relationships with others, including interpersonal ambivalence, need for social approval and poor sociability [22 23]. Interpersonal difficulties can cause emotional suffering and may prompt individuals with alexithymia to seek psychotherapy. However, individuals with alexithymia may not receive the full benefit from dynamic, supportive, or group, psychotherapy because poorer access and reporting of personal emotions are negative prognostic factors in psychotherapeutic treatment [6].

Alexithymia: cognition, somatic symptoms and disease

Alexithymia and cognition

Individuals with alexithymia typically have difficulties using language to describe their experiences of emotions that are rooted in bodily sensations. This view is consistent with empirical studies showing the association between alexithymia and language difficulties [24]. For instance, Henry et al. [25] observed a significant inverse correlation between difficulty identifying emotions and verbal fluency in patients with a history of traumatic brain injury. Furthermore, Onor et al. [26] showed that alexithymia was associated with weaker functioning (albeit not in the impaired range) in several cognitive domains including language, attention, memory, visual spatial abilities, and working memory. In a different sample of healthy adults, the Paradiso lab showed that the severity of alexithymia was associated with relatively poorer cognition, in particular in the domain of executive function [27]. Thus, the extant literature suggests that one mechanism for alexithymia is cognitive with relative language and abstract reasoning and symbolization deficits [28].

Yet, the mechanisms of alexithymia may be more complex and may extend beyond traditional cognitive functions. As evidenced by research linking alexithymia to awareness of personal emotional and brain regions supporting it (see below) [29], poor emotional self-awareness and poor abstract thinking may underlie a diminished capacity to symbolically express emotions or alexithymia [30].

Alexithymia, disease, and somatic symptoms

The relationship between alexithymia and reported or medically ascertained physical symptoms is complex. Rather than having no emotional life, individuals with alexithymia communicate their emotions using somatic channels [31]. In addition, individuals with alexithymia show an excess of medically ascertained physical illness [32] and alexithymia among individuals with ascertained medical conditions may hinder recovery and delay rehabilitation efforts [33]. Understanding the complex relationship between poor emotion processing and physical symptoms includes understanding that individuals with alexithymia tend to complain of body ailments and disturbances independently from the actual presence of somatic illness [31]. This issue is complicated by evidence of individual differences among people with alexithymia. Bermond [34] separates alexithymia into two types. Type I alexithymia shows affective and cognitive alterations. People with Type I alexithymia display poor awareness and expression of emotions. On the other hand, Type II alexithymia shows normal emotion awareness, but poor emotion expression, and these individuals are more prone to somatization than Type I [35].

Alexithymia is also associated with visceral hypersensitivity. There is evidence relating impaired processing of emotions with functional gastrointestinal disorders [36]. This finding is consistent with the notion that physical symptoms in alexithymia may be related to somatosensory amplification (SA). SA has been defined as: i) excessive attention and hyper-vigilance to somatic symptoms; ii) exaggerated sensitiveness to physical sensations; iii) misinterpretation of physical sensations interpreted as a sign of disease [37]. Somatosensory amplification [38] and somatization [31 39] are generally associated with difficulty identifying and describing feelings (but less so with externally oriented thinking style).

However, not all research supports the association between alexithymia and somatic complaints. Some authors believe that alexithymia and somatization are two different conditions that are only sometimes associated [40]. For example, children in particular show multiple somatic complaints without difficulty in describing or identifying feelings [41].

Alexithymia and psychopathology

Before addressing the differences between primary and secondary alexithymia, a brief account on the association with psychopathology is needed. Alexithymia is a risk factor for suicide in subjects with brain injury [42]. This finding is an important reminder of the vast literature concerning the relationship between alexithymia and depression. This issue has been widely debated in the field. Briefly, researchers now believe that a positive association between alexithymia and depression exists (i.e. the greater the alexithymia scores, the greater the depression scores). Longitudinal studies have also uncovered persistence of some degree of alexithymia following remission of depression [43]. Thus, alexithymia has both state-dependent (e.g. mood but also general psychopathology [22]) and trait-dependent features [44]. Trait dependent features, association with personality traits (including avoidant, schizotypal, dependent and passive-aggressive) [22 45] and lack of association with histrionic features [45] reinforce the notion that the construct of alexithymia captures psychological dimensions related to individual differences. Alexithymia is also found in other psychiatric conditions including autism, eating disorders and schizophrenia, all of which show degrees of deficits in social cognition [20 46 47]. Based on these data, it comes as no surprise that alexithymia together with personality disorders [48] is a predictor of poor outcome in depression [49].

In the end, some have suggested that it may be useful to distinguish between depression with strong and mild alexithymia features [50], but further study in this area is needed. If strong alexithymia prevents a consistent report of emotion changes such that patients admit to sad mood only erratically, depression may take the phenomenological form of depression without sadness (or non-dysphoric depression) [51-53].

Primary *versus* secondary alexithymia

The need for distinguishing between primary and secondary alexithymia emerged rather early in the literature [54], but it took some time before this distinction was widely recognized in the field. Most studies that have contributed to the complex body of knowledge on alexithymia have examined individuals with primary alexithymia. Alexithymia is considered to be primary when emerging "as a life-long dispositional factor that can lead to psychosomatic illness" (Lesser [55], p. 533). Primary alexithymia may derive from a psychic trauma occurring during childhood [56] or from negative primary caregivers interactions [57]. It has been recently suggested that genetic polymorphism of the 5-HT transporter-linked promoter region (i.e. L/L alleles) may influence the occurrence of alexithymia [58]. Hence, primary alexithymia is currently thought of as a more or less stable personality trait that becomes molded during childhood and early adult years. Therefore, primary alexithymia is developmental in nature. It also has no purported organic or psychological risk factors (excluding those occurring in childhood, see discussion below).

Secondary alexithymia is posited to arise not during development, but as a consequence of events occurring later in life. These may be events with psychological significance and/or medical-surgical events (illnesses or disease) [59] that have a direct or indirect effect on brain functioning. Therefore, secondary alexithymia may have both psychological and/or somatic (organic) mechanisms [60]. As evidenced briefly above, in addition to somatic symptoms, alexithymia can also be associated with mental illness. Thus, whereas *primary* alexithymia may play a role as a vulnerability factor for mental illness, *secondary* alexithymia is thought to be a consequence of the illness [60].

If the stressful event is an illness (one that has no obvious direct consequences on brain functioning such as a hip fracture), alexithymia has been seen as a defense mechanism in an attempt to cope with the stress of the medical illness [54]. Based upon the study of alexithymia in 53 inpatients examined in a teaching hospital psychiatric consultation service, researchers suggested that "alexithymia in the medically ill may play a defensive role as a state reaction" (Wise et al. [59], p. 287). In other words, alexithymia secondary to a psychologically significant event may be construed as a defense or protection against highly emotional events. This view is supported by the higher levels of alexithymia found in holocaust survivors [61] and sexual assault victims [62].

In summary, while primary alexithymia is widely thought to be a personality trait, in which affective processing is less developed than normal due to childhood trauma or genetic predisposition (e.g. polymorphism of 5-HT transporter-linked promoter region), secondary alexithymia is a condition occurring later in life either due to psychological trauma, or as a direct insult to brain regions supporting emotion processing and awareness [63]. Note that this proposed sharp dichotomy is useful to frame the field. Clinical experience illustrates that determination of the primary or secondary nature of alexithymia may be in some cases debated. Examples may be youth with severe illness (alexithymia can be seen as secondary because of the illness or primary due to its ensuing during development) or alexithymia resulting from prolonged emotional stress during early development (e.g. hyperprotective parental bonding and specifically excessive maternal protection) mediating development of personality disorders [64]. Therefore, primary and secondary alexithymia may be better viewed as extremes of a continuum, while individual decisions on aetiology are better left to the experienced clinician.

Organic alexithymia

As studies began to examine the hypothesis that alexithymia may be associated with localized brain damage [65], the observation that alexithymia may occur "de novo," as a consequence of brain injury generated extensive interest in the field [63]. The term organic alexithymia refers to a condition in which alexithymia is purportedly caused by organic damage to brain structures involved in emotional processing through indirect or direct insults to the brain. We suggest that it is conceptually useful to categorize organic alexithymia under the rubric of secondary alexithymia, with the understanding that further outcome

TABLE I.
Neuroanatomical substrates of primary, secondary and organic alexithymia. *Substrati neuroanatomici dell'alessitimia primaria, secondaria e organica.*

Brain region	Primary alexithymia	Secondary alexithymia	Organic alexithymia
Anterior cingulate cortex	Borsci et al., 2009 [78] (decreased grey matter volume); Heinzel et al., 2012 [127] (functional impairment)	Messina et al., 2011 [72] (decreased oxygen tension) (purported as for the location)	Sturm et al., 2011 [90]; Paradiso et al., 2008 [89] (decreased grey matter volume)
Corpus callosum	Romei et al., 2008 [108]; Tabibnia and Zaidel2005 [116]; Lumley, et al., 2000 [114]; Parker et al., 1999 [128] (interhemisperic transfer impairment)		TenHouten et al., 1986 [126] (cerebral commissurotomy)
Basal ganglia	Lee et al., 2011 [101] (functional impairment in caudate and frontostriatal circuitry)		Huang et al., 2012 [66] (damage of basal ganglia after carbon monoxide poisoning)
Right temporal lobe	Borsci et al., 2009 [78] (reduced grey matter in right temporal lobe)		
Right hemisphere	Lumley et al., 2000 [114] (functional impairment)		Spalletta et al., 2001 [65] (right hemisphere stroke)

and treatment studies may indicate that this should be considered altogether as a separate category. Organic alexithymia is often more resistant to treatment [66], is not associated with a specific pre-morbid personality and is associated with cognitive impairment.

As briefly mentioned above, alexithymia observed among patients with medical illness represents a clinical puzzle. The question refers to the extent to which in a given patient alexithymia is a primary personality feature or a phenomenon secondary to the stress of the illness or a to direct or indirect brain alteration (induced by the medical condition). Determination of the nature of alexithymia may be inferred from the clinical history (e.g. asking a next of kin on personality features prior to illness or injury), and from characteristics inherent to the alexithymia syndrome (e.g. cognitive impairment).

Studies have examined the possibility that alexithymia stems from direct brain damage. Spalletta et al. [65] observed that alexithymic characteristics were associated with right hemisphere damage among patients with stroke consistently with the role of right hemisphere in emotion processing [67 68]. Becerra et al. [63] reported on a 21 year old man who developed alexithymia after a motor vehicle accident that caused damage to the orbitofrontal cortex, a brain region playing a role in decoding emotional significance of an event and strongly connected with many limbic regions including the amygdala [10 69]. Subsequently, a study examining 54 individuals (67% men) with brain injury (which had occurred about 30 years prior) confirmed the strong association between brain injury and alexithymia (odd ratio = 2.64) [70]. The majority (61%) of subjects with history of traumatic brain injury early in life developed alexithymia, which in turn is a risk factor for suicide in subjects with history of traumatic brain injury [42]. The literature also shows that hypoxic lesions of bilateral globus pallidus provoked by carbon monoxide poisoning were related associated with a severe and resistant form of alexithymia [66]. As reported by the Paradiso lab, a 44-year-old man showed impairment in emotional awareness after anoxic lesion of globus pallidus [71]. Another study that may be relevant for this discussion showed, low levels of haemoglobin in oncologic patients were directly associated with higher level of alexithymia [72]. The authors speculated that low oxygen pressure level may modify the functioning of the anterior cingulate cortex, a region critical for emotional awareness and particularly susceptible to perfusion changes [72].

Whereas the existing literature on treatment of secondary and organic alexithymia remains wanting, it may offer guidance in some cases. For instance, improvement in alexithymia was found when 64 psychiatric patients underwent group therapy [73]. Other studies show efficacy of the serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine (75-150 mg daily) on alexithymia in patients who suffered a stroke [74].

In summary, there may be at least two types of secondary alexithymia. Specifically, one type develops as a consequence of psychosocial stressors and the psychological (e.g. defence) mechanisms set forth to attempt to cope with the stress [75], while the other (organic) occurs due to a direct or indirect insult to the brain. As such, organic alexithymia may follow alterations to brain regions sub-

TABLE II.
Alexithymia: classification based on clinical history. *Alessitimia: classificazione in base alla storia clinica.*

	Primary alexithymia	Secondary alexithymia	Organic alexithymia
Aetiology	Genetically mediated or familial	Subsequent to psychological distress	Subsequent to trauma, vascular or other brain damage
Onset mechanisms	Early onset	Early or late onset	Early or late onset
	Sociocultural education, socio-economic status	Linked to chronic disease (e.g, cancer, diabetes, Parkinson's disease)	Linked to brain damage in regions subserving emotion processing
Treatment response*	Psychotherapy treatment resistance	Somewhat responsive to psychotherapy or pharmacological treatment	Responsive to pharmacological treatment
Outcome*	Poorer	Better	Better

* Based on research studies and personal experience of one of the authors (SP)

serving emotional awareness or participating in linking stimuli from the body to their abstract (language) conceptualization including neurodegenerative disorders (e.g. frontal temporal dementia, semantic dementia, Alzheimer's disease, cortical basal degeneration/progressive supranuclear palsy).

Neuroanatomy of alexithymia

Multiple brain structures have been posited to be involved in the pathogenesis of alexithymia (Table I). There is a broad overlap of brain structures purportedly involved in alexithymia independently whether this may be conceived as primary or secondary (including organic). What appears to be the case is that the involvement of one or another brain region does not allow distinction between primary and secondary or organic alexithymia. The distinction continues to rely on clinical assessment (Table II). Regions purportedly associated with alexithymia have included the anterior cingulate cortex, frontal striatal networks and basal ganglia, insula and amygdala, corpus callosum.

Anterior cingulate cortex

Since Papez's initial postulation (1937), consensus has broadened on the role of anterior cingulate cortex (ACC) in emotion perception and regulation [76-78]. Briefly, the ACC shows at least two functional parts: a rostral region playing a role in emotion processing and interconnected with multiple limbic regions; and a dorsal region connected with the lateral prefrontal, parietal and supplementary motor cortex showing greater specialization for attention and executive functions [79 80]. Rostral and dorsal ACC regions are closely connected allowing integration between the experience and the mental representation of an emotion [81]. "Anatomical and functional continuum rather than segregated operations" between cognition and emotional components of the mind may take place in the ACC (Messina et al. [82], p. 1). The importance of ACC in alexithymia may be attributed to the presence of spindle-shaped Von Economo's neurons. These may represent a *trait d'union* between perception and emotions [83]. Von Economo neurons appeared in late phases of evolution when they took a role in the regulation of social and emotional functioning [84]. The presence of these neurons is related to absolute brain size [85]. Homo sapiens has a larger brain size (about 1500 cc on average) than homo Neanderthal (1400 cc on average) [86].

Von Economo's neurons (VENs) are bipolar neurons allocated in layer V of ACC and frontoinsular cortex in humans [83]. These neurons were also found in animals with high social structure as apes, dolphins [87], elephants [85] macaques monkeys [88]. The importance of Von Economo's neurons in social awareness, empathy and self-referential processing stems from the observation of selective destruction of VENs in early stages of frontotemporal dementia consistent with evidence from functional imaging [83].

The involvement of the ACC as a mechanism of alexithymia in later life was suggested by Paradiso et al. [89] who reported a significant inverse correlation between the grey matter volume of the right ACC and alexithymia, a phenomenon that appeared to be a function of older age. Consistent with this idea, a structural MR imaging study showed that the right pregenual ACC grey matter volume in 7 healthy subjects was negatively correlated with alexithymia [90], but the small sample size is a limitation. Additional regions showing negative correlations with alexithymia were the right middle and superior temporal gyrus, the right postcentral gyrus, the right precuneus and the right inferior parietal lobe. Conversely, homologous regions on the left hemisphere were not correlated with alexithymia [90]. Circuitry connecting temporal, parietal and frontal areas has been posited to support processing of information relating to the self and to emotional events [91]. Consistent with in vivo structural neuroanatomy studies, functional neuroimaging studies have shown reduced activity of ACC in individuals with high alexithymia scores [92] and a reduction of grey matter in anterior cingulate cortex and in middle temporal gyrus in healthy women [78]. Paradiso et al. [93] recently reported that patients with right middle cerebral artery (MCA) stroke show high levels of alexithymia, perhaps as a consequence of distant functional effects of the stroke damage reducing the functioning of the ACC. The ACC is vascularized by MCA and some parts are highly sensible to hypoxia [94].

Functional networks involving the frontal lobe

Over the last decade, the concept of the default mode network (DMN) has gained broad acceptance as a set of functionally interconnected brain regions including the dorsal medial and ventral medial prefrontal cortex, the medial and lateral parietal cortex and the temporal cortex and the posterior cingulate cortex [95-97]. The DMN is active during introspection, while this network is deactivated during "nonself-referential goal-directed tasks in keeping with the folk-psychological notion of losing one's self in one's work" (Sheline et al. [95], p. 1). A recent study showed diminished connectivity within the DMN among participants with alexithymia [98]. The authors studied 20 alexithymic subjects and 18 healthy participants using functional magnetic resonance imaging (fMRI) and observed that brain areas of DMN (medial, frontal, and temporal regions) showed weaker connections in alexithymic subjects than healthy individuals, while connectivity between DMN and sensory-motor areas was higher [98].

This body of work suggests that alexithymia may be related to malfunctioning of brain structures including the cingulate and prefrontal cortex regulating and subserving emotional awareness [77] and self-oriented planning, a mental state often associated with emotion. Hence, it is plausible that when mental functions supported by regions in the DMN fail to work properly, the orderly linkage from body stimuli to emotions and to symbolic language is disrupted [99], leading to poor symbolization of bodily stimuli and alexithymia.

Basal ganglia

Striato-thalamo-cortical circuits support emotional processing [100]. Different basal ganglia structures (globus pallidus, ventral striatum, caudate, subthalamic nucleus) have been associated with primary alexithymia [88] and with organic alexithymia [66]. Lee et al. [101] observed that in 38 healthy subjects with higher levels of alexithymia showed lower activation in right caudate nucleus in response to angry facial stimuli. Six subjects with focal lesions of the left basal ganglia investigated by MRI and PET neuroimaging techniques showed blunted emotions and elevated scores on the assessment of alexithymia [102]. High frequency electrical stimulation of the subthalamic nucleus altered emotional perception of (positive or negative) emotional visual stimuli in patients with Parkinson's disease [103].

Corpus callosum

In homo sapiens, abstract reasoning, symbolization, language, and introspection are highly developed cognitive functions. Emotional processing requires the capacity to translate body language into symbolic (emotional) language. Some authors observed that patients with agenesis of the corpus callosum showed an impairment in paralinguistic information and prosody and concluded that individuals with, "agenesis of [the] corpus callosum appear to lack interhemispheric integration of critical aspects of language" (Paul et al. [104], p. 1). In an observational study performed on 28 healthy women, language and visuospatial abilities were found be linked to dimensions of the corpus callosum measured by inversion recovery magnetic resonance images. Verbal fluency was found directly correlated with splenium of corpus callosum, whereas an inverse correlation was observed between splenium dimension and language lateralization [105]. The importance of the corpus callosum in the pathogenesis of alexithymia has been posited for some time based on the observed dysfunctional transfer of information between right and left hemisphere [106-108].

Frontal lobe

Frontotemporal structures in particular in the right hemisphere play a fundamental role in processing emotions [109] and are involved in frontostriatal circuitry which plays a role in emotional awareness [110]. The orbitofrontal cortex is widely connected with limbic structures and beyond (i.e., parietal, temporal, occipital) [69]. Moreover, the orbitofrontal cortex is crucial in recognizing emotional vocal and facial expressions [111 112].

In a study on 314 alcohol dependent subjects, regression analysis provided evidence that frontal lobe dysfunction, as assessed using the Frontal Systems Behavior Scale, or FrSBe,"mediated the relationship between alexithymia (TAS-20 total score) and risky alcohol use" [113].

The role of the right hemisphere in alexithymia has emerged from studies of patients with right hemisphere stroke [65 114]. Paradiso et al. [115] observed that depressed patients with right hemisphere stroke often presented with an apathetic and nondysphoric depression believed to be the result of reduced emotional processing abilities. In addition, frontal lobe dysfunction may mediate the relationship between alexithymia and risk for drug addiction [113]. The review by Tabibnia and Zaidel [116] suggests that the extant data supports the role of deficit in interhemispheric information transmission and poorer right hemisphere functioning in alexithymia. This view was confirmed in a recent (albeit small) study showing that the grey matter of the right hemisphere (not the left) negatively was associated with alexithymia [90].

Amygdala and insula of Weil

The amygdala is thought be critical for emotional processing [117]. It is made up of several nuclei, including the lateral nucleus that connects with sensory cortical areas, the central nucleus that is the output and connects with brain stem areas subserving the neurovegetative manifestations of emotions, and the basal nucleus that is the relay between lateral and central nucleus [118 119]. The amygdala is a node between the sensory input (to be) labelled with an emotion and the emotional manifestations of the body [120]. Reduced activity in the amygdala can be responsible for an alteration in emotional processing. Because of the key role of amygdala in emotional processing, it is reasonable to speculate that the amygdala can have pathogenetic role in alexithymic subjects.

Difficulty identifying feelings from the faces of others was observed in 21 healthy subjects with a reduced activation of amygdala by fMRI [121]. Difficulty identifying emotions was significantly and negatively correlated with the neural response of the amygdala to sad faces [121]. Alexithymic patients with anorexia nervosa showed poor amygdala activation (as well as cingulate cortex) [122].

Higher levels of activation were observed in right insula and in inferior frontal lobe of alexithymic patients [123]. The insula is connected with the amygdala and ACC and plays an important role as a "prelimbic area" during emotional processing [124]. To the elevated levels of insula activity can be attributed the somatic tendency of individuals with alexithymia.

In summary, several brain regions are purportedly associated with alexithymia. At first glance, alexithymia may appear to be the result of several disparate mechanisms. While this may remain a possibility, a more parsimonious view is that focal dysfunction in differing nodes of emotional processing networks may disrupt the functioning of the entire network. Thus, a pattern of mental and behavioural dispositions consistent with alexithymia may occur in association with dysfunction in differing nodes of the brain supporting emotion processing.

Conclusions

Emotional processing encompasses cortical and subcortical brain mechanisms. Subcortical structures (limbic regions, basal ganglia) may allow for emotional processing to occur at a level below conscious awareness, while the cortex plays a role in (self)-awareness of emotional processing. The interaction between sub-cortical and cortical structures is fundamental for adaptive emotion processing. In the philosophic meditations of ancient Greeks and Romans, emotions were understood as unnecessary passions and were often viewed as *diseases of the mind*. Contemporary views purport that poor recognition and identification of emotions, including personal emotions, may be maladaptive. In this review, we discussed primary alexithymia, understood as a condition arising from various sources including genetic and experiential and distinguished between primary and secondary alexithymia. In addition, we further differentiated secondary alexithymia as deriving either from a psychological stressor or due to an event that indirectly or directly impacts the brain. Thus, we conclude that:

1. recognition and treatment of primary alexithymia is warranted because of its potential as a risk factor for psychiatric disorders [60]. While evidence for a definitive etiological role of alexithymia in physical illness is sparse, alexithymia may exert influence on illness behaviour based on, "physical symptoms, disability, and excessive health care use" [125];
2. secondary alexithymia may be a response to the psychological distress of an organic disease or psychological trauma;
3. organic alexithymia may be considered to be a specific subtype of secondary alexithymia that is a consequence of brain damage (e.g. traumatic or vascular) to specific regions including the anterior cingulate, basal ganglia, amygdala, insula, right hemisphere, and corpus callosum. In vulnerable individuals with brain injury, alexithymia may increase the risk of suicide [42].

In future research, it may be important to distinguish between treatment responses in primary, secondary and organic alexithymia [33].

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