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Goerlich, K.S.; Aleman, A.

*Published in:*  
 Alexithymia

*DOI:*  
[10.1017/9781108241595.015](https://doi.org/10.1017/9781108241595.015)

**IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.**

*Document Version*  
 Publisher's PDF, also known as Version of record

*Publication date:*  
 2018

[Link to publication in University of Groningen/UMCG research database](#)

*Citation for published version (APA):*  
 Goerlich, K. S., & Aleman, A. (2018). Neuroimaging Studies of Alexithymia. In O. Luminet, R. M. Bagdy, & G. J. Taylor (Eds.), *Alexithymia: Advances in Research, Theory, and Clinical Practice* (pp. 207-249). Cambridge University Press. <https://doi.org/10.1017/9781108241595.015>

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# Neuroimaging Studies of Alexithymia

Katharina S. Goerlich and André Aleman

This chapter provides an overview of the current state of neuroscience research on alexithymia. We begin with a review of early and current models of the neurobiology underlying alexithymia, and then describe and discuss the complex interplay between cognition and emotion in the brain. The main section of the chapter is devoted to an overview of brain regions involved in alexithymia, based on evidence from studies using positron emission tomography (PET), transcranial magnetic stimulation (TMS), and functional and structural magnetic resonance imaging (MRI). This section is divided into subsections for functional brain imaging studies and structural brain imaging studies; each subsection is followed by a summary and discussion of the main findings. The chapter concludes with a short section outlining some limitations of neuroimaging studies.

## Early Proposals for a Neurobiology of Alexithymia

In an early attempt to identify the neurobiological mechanism that might underlie the intriguing phenomenon of an inability to verbalize emotional feelings, MacLean (1949) speculated that distressing emotions are expressed through autonomic pathways, rather than finding symbolic expression after being relayed to the neocortex; he hypothesized that this expression could result in physiological changes that would eventually lead to physical disease. MacLean's (1949) theory was based on a "triune" model of the brain (MacLean, 1990), which postulates that over time, the primate brain evolved along a caudal–rostral axis, giving rise to the formation of three hierarchically ordered brains in one: the triune brain, which comprises reptilian (the earliest), paleomammalian, and neomammalian (the latest) structures. Reptilian structures (the brain stem) are responsible for regulating autonomic, endocrine, and instinctive activities of the body, all

of which are important for experiencing emotions. The paleomammalian brain contains the limbic system, comprising the cingulate gyrus, the hippocampus, the fornix, the mammillary body, the septal region, the amygdala, and the dorsomedial nucleus. Extending Papez's (1937) proposal that these structures play a role in the elaboration and expression of emotions, MacLean suggested that the limbic system acts as an analyzing mechanism, which derives information and interprets one's experiences in terms of emotions rather than symbolic thought. The neomammalian brain (or neocortex) mediates cognitive functions and was referred to by MacLean as the "word brain". Extensive neural connections between the neocortex and the limbic system make it possible for emotions to evoke thoughts and an understanding of one's feelings at a cognitive level. In turn, these connections also enable cognitions to have modulating influences on emotions, allowing for some degree of voluntary control of feelings. Based, in part, on MacLean's theoretical model, Nemiah, Freyberger, and Sifneos (1976) proposed that alexithymia might result from a lack of neuronal connections between the limbic system and the neocortex.

## Current Neurobiological Models of Alexithymia

The right hemisphere has traditionally been thought to be more involved in emotion processing than the left hemisphere (Gainotti, 1989; Tucker, 1981), assuming that verbal, analytical, conscious processing takes place predominantly in the left hemisphere (Gazzaniga, 1989), whereas non-verbal, emotional, unconscious processing is mainly lateralized to the right hemisphere (Bear, 1983). Derived from this model, some researchers have proposed that alexithymia may result from a deficit in interhemispheric communication or from a dysfunction of the right

hemisphere, possibly paired with a left hemisphere preference for emotion processing (Larsen et al., 2003; Wingbermühle et al., 2012).

Hoppe and Bogen (1977) proposed that alexithymia might be the result of impaired information transfer between the two hemispheres. This idea of an interhemispheric transfer deficit was based on observations that split-brain patients who had undergone complete commissurotomy (transection of the corpus callosum, which is the main connection between the hemispheres) because of severe epilepsy were found to exhibit features of alexithymia following the surgery, including problems expressing feelings verbally, and that their pre-morbid ability to fantasize, symbolize, and dream decreased (Buchanan, Waterhouse, & West, 1980; Hoppe & Bogen, 1977). The first empirical investigations on the proposed relationship between alexithymia and a deficit in interhemispheric communication were conducted by TenHouten and colleagues (1986), who compared the spoken and written responses of patients who had undergone cerebral commissurotomies with those of neurologically intact participants to an emotion-inducing film. The patients showed a decreased capacity for fantasy and the use of symbols and had difficulty describing feelings expressed in the film. Shortly thereafter, Zeitlin et al. (1989), using a tactile finger localization task, found that alexithymia scores were related to a bidirectional deficit in the interhemispheric transfer of sensorimotor information, which was also observed in a later study by Parker et al. (1999).

Besides the interhemispheric transfer deficit model, several studies provided evidence for a hypoactivity of the right hemisphere and a hyperactivity of the left hemisphere in alexithymia. For instance, right as compared to left hemisphere stroke patients showed a higher prevalence of alexithymia (Spalletta et al., 2001). A PET study identified lower regional cerebral blood flow (rCBF) during the viewing of emotional faces in a distributed right-hemispheric network in individuals with high versus low alexithymia scores (Kano et al., 2003). Furthermore, Jessimer and Markham (1997) investigated the ability of individuals with high levels of alexithymia and individuals with low levels of alexithymia to attribute emotional value to chimeric pictures of faces composed of conjoined emotive and non-emotive halves. Normally, right-handed individuals judge the chimeric face with the emotive half on the left as

being more expressive than those with the emotive half on the right, indicating a leftward bias related to a predominantly right-hemispheric processing of these stimuli (Wirsen et al., 1990). In individuals with high alexithymia scores, however, this left bias was significantly less pronounced, suggesting reduced right-hemispheric lateralization for emotions. Using a lateralized visual-matching task, Bermond, Bleys, and Stoffels (2005) reported that individuals with high alexithymia scores as compared to those with low alexithymia scores showed a left hemisphere preference for the processing of emotional words. Finally, electroencephalography (EEG) studies (see Chapter 14) provided further evidence for a dysfunction of the right hemisphere during emotional processing in alexithymia (Aftanas & Varlamov, 2004, 2007). It should be noted, however, that some neuroimaging studies did not find a stronger involvement of the right hemisphere in alexithymia, and even reported structural abnormalities that were localized to the left rather than the right hemisphere (e.g., reduced left amygdala volume; Goerlich-Dobre et al., 2015a).

Lane et al. (1997) conceptualized alexithymia as the emotional equivalent of “blindsight”, a condition resulting from lesions to the primary visual cortex. Patients with this condition claim to be blind but show intact performance on visual tasks. Thus, these patients perform as if they can see even though they are blind. Based on this, Lane and colleagues hypothesized that the core deficit of alexithymia lies in the conscious self-awareness of emotions, i.e., conceptualizing alexithymia as a disconnection syndrome that results from disrupted transmission of interoceptive emotional information to the anterior cingulate cortex (ACC). Consequently, people with alexithymia show emotional responses but lack conscious awareness of their emotions, much as, in the blindsight phenomenon, people do perceive visual stimuli at some level but are not aware of doing so (Weiskrantz, 1986). Analogously, Lane and colleagues suggested that the apparent lack of the conscious awareness of emotions in alexithymia might be attributable to a dysfunction of the ACC.

Aleman (2005) proposed that impaired interaction between the hippocampus and the amygdala may underlie alexithymia. This hypothesis was based on the notion that learning to verbalize emotions requires the development of associations between particular affective states and particular words. It has been shown that such relational processing depends

on the hippocampus and amygdala (Phelps, 2004). Thus, compromised interactive processing in hippocampal-amygdala circuits during emotional relational memory could foster the development of alexithymia by a lack of strong associations between emotional states and corresponding words. This hypothesis has not yet, however, been directly evaluated.

## Emotions and Cognition: A Complex Interplay

The relation between emotions and cognition has fascinated philosophers for centuries and continues to receive attention in the scientific literature. Over the past several decades, theories on the relation between cognition and emotion have been shaped by evidence from neuroscience. This body of literature has led researchers to appreciate the intimate and closely interacting nature of these processes and is expanding to understand how cognitive and emotional processes are organized in the brain.

Cognition refers to processes such as attention, language, memory, planning, and problem solving. Many cognitive processes are thought to be sophisticated processes that might be unique to humans. With the advent of neuroimaging techniques, a large body of literature has linked a variety of these cognitive processes to cortical brain regions. In contrast, brain structures that have been associated with emotional processes are often subcortical (e.g., amygdala, ventral striatum, and hypothalamus). These structures are considered more primitive as they emerged earlier in evolution and are shared between humans and other animals. Moreover, they are thought to operate in a fast and automatic fashion, and their function in mediating emotional processes is thought to not require conscious awareness.

Based on these differences between cognitive and emotional processes, an appealing approach has been to separate the “emotional brain” from the “cognitive brain”, guided by a scientific endeavor to assign certain functions to particular brain structures (functional localization). However, the past two decades have challenged this approach, as cognitive and emotional processes have been shown to interact in many ways, rendering it difficult to separate emotional and cognitive systems in the brain (e.g., Pessoa, 2008). For example, the amygdala, a core affective region (i.e., involved in emotion processing), also plays a role in

cognitive functions such as attention and associative learning.<sup>1</sup> Moreover, amygdala responses are modulated by attention, indicating top-down control of amygdala activity by cortical areas (Larson et al., 2013; Peck & Salzman, 2014). Conversely, the prefrontal cortex (PFC), a classical cognitive area, comprises several subregions such as the ventromedial PFC, orbitofrontal cortex (OFC), and the ACC that play important roles in the cognitive processing and regulation of emotions.<sup>2</sup> This illustrates that the neural basis of the relationship between emotions and cognition is marked by a complex interplay of brain regions interacting closely and reciprocally to integrate emotional and cognitive processes underlying human behavior.

## Measures of Alexithymia in Neuroscience Research

As reviewed in Chapter 2, there are several available instruments for measuring alexithymia. The most frequently and widely used measure in neuroimaging studies is the self-report *20-Item Toronto Alexithymia Scale* (TAS-20), which comprises three subscales that assess the difficulty identifying feelings (DIF), difficulty describing feelings (DDF), and externally oriented thinking (EOT) facets of the alexithymia construct (Bagby, Parker, & Taylor, 1994; Bagby, Taylor, & Parker, 1994). Very few neuroimaging studies have assessed alexithymia with the observer-rated *Beth Israel Hospital Questionnaire* (BIQ; Sifneos, 1973), or the modified BIQ (Taylor, Bagby, & Parker, 1997); and to date no studies have employed the *Toronto Structured Interview for Alexithymia* (Bagby et al., 2006).

In recent years, some researchers have used the self-report *Bermond–Vorst Alexithymia Questionnaire* (BVAQ; Vorst & Bermond, 2001), which has three subscales that are comparable to those of the TAS-20 and assess the “putative” cognitive facets of alexithymia (DIF, DDF, and EOT), and two subscales that assess the fantasizing and emotionalizing facets that constitute the putative “affective” dimension of

<sup>1</sup> See Schaefer and Gray (2007) for a review on the role of the amygdala in higher cognition.

<sup>2</sup> See Ochsner, Silvers, and Buhle (2012) for a review on the cognitive control of emotions, and Dolcos, Iordan, and Dolcos (2011) for a review on the neural correlates of emotion–cognition interactions.

alexithymia. Studies that use the BVAQ attempt to explore whether the different alexithymia facets and the two proposed dimensions might be associated with separate neurobiological mechanisms. Based on the differentiation between cognitive and affective alexithymia dimensions, Bermond and colleagues (2007; Moormann et al., 2008) proposed different types of alexithymia according to whether scores are high on both dimensions, high on one dimension and low on the other, or low on both dimensions, the last type indicating an absence of alexithymia (i.e., lexithymia; see Chapter 2). However, the existence of different alexithymia dimensions and types is considered controversial and is not yet widely accepted, as most authors refer to four (rather than five) alexithymia facets, as described by Nemiah et al. (1976) and Taylor et al. (1997), and some empirical studies have failed to support the idea of alexithymia types and an emotionalizing facet (Bagby et al., 2009; Waters et al., 2016). More recently, Preece et al. (2017) provided empirical support for an attention-appraisal model of alexithymia in which the construct comprises only the DIF, DDF, and EOT facets, and is operationalized in the TAS-20. Throughout the remainder of the chapter, we use the abbreviations HA (high alexithymia individuals) to refer to individuals who score in the high range on measures of alexithymia, and LA (low alexithymia individuals) for those who score in the low range.

## Neuroimaging Studies on Alexithymia

### Functional Imaging

The identification and functional characterization of regions mediating emotional and cognitive processing in the human brain has been made possible by the advent of neuroimaging techniques such as transcranial magnetic stimulation (TMS), positron emission tomography (PET), and functional magnetic resonance imaging (fMRI). Summaries of the studies that we review are displayed in Tables 13.1 and 13.2.

As noted earlier, Hoppe and Bogen (1977) proposed that alexithymia might result from impaired information transfer between the two hemispheres. Neuroimaging studies subsequently investigated this model using TMS, a method through which certain brain regions can be stimulated by means of a small magnetic field. This method allows researchers to measure directly the time required for information

to travel from one hemisphere to the other (transcallosal transmission time). A study testing transmission times of motor evoked responses reported reduced transcallosal inhibition in HA compared with LA, providing support for the interhemispheric transfer deficit hypothesis (Romei et al., 2008). In contrast, three further studies using similar TMS paradigms found evidence for shorter rather than prolonged transmission times between the hemispheres in HA (Grabe et al., 2004; Lang et al., 2011; Richter et al., 2006). These findings contradict the interhemispheric transfer deficit hypothesis; instead, they support facilitated transcallosal inhibition (via GABAergic fibers) in alexithymia, which may lead to increased inhibitory control of both hemispheres. Taken together, high levels of alexithymia seem to be linked to facilitated transcallosal inhibition, arguing against the hypothesis of an interhemispheric transfer deficit. In contrast, split-brain patients who underwent surgical transection of the corpus callosum probably developed alexithymic characteristics as a consequence of a surgically induced disruption of information transfer between the hemispheres.

During the past 15 years, neuroimaging studies have led to significant insights into the neural mechanisms underlying difficulties in the cognitive processing of emotions linked to alexithymia. Some of these studies have begun to differentiate between the different facets and proposed dimensions of alexithymia. In these studies, individuals with varying (high, low, or continuous) levels of alexithymia are presented with emotional stimuli, and their brain activity is measured while they perform some explicit (focusing on the emotional level; conscious processing) or implicit task (focusing on some other level than the emotional one; unconscious processing). We review these studies in the following sections, and summarize the brain regions and neural activation patterns that have been implicated in abnormalities in the explicit and implicit processing and cognitive regulation of emotions associated with alexithymia.

### The Amygdala and Emotional Attention

The amygdala is a core emotional region of the brain that is functionally closely interconnected with many subcortical and cortical structures. It is an important hub in what MacLean (1949) referred to as the limbic system, which is crucially involved in the elicitation of emotional reactions and in the initiation of autonomic changes and facial expressions (Barrett et al., 2007).

Several fMRI studies have reported a reduced response of the amygdala to emotional stimuli with higher levels of alexithymia, both during the conscious and the automatic (unconscious) processing of emotions. In two priming experiments (i.e., implicit processing), in which neutral faces were masked with emotional ones (happy or sad) for a very short period of time (33 ms), amygdala responses were significantly reduced for sad faces in individuals with higher levels of alexithymia (Kugel et al., 2008; Reker et al., 2010). Indeed, in both studies, amygdala activity was negatively correlated with the DIF subscale of the TAS-20, suggesting that hampered amygdala functioning, occurring already at unconscious processing levels, might underlie the DIF facet of alexithymia. Studies investigating the conscious processing of emotions observed similar results. Leweke et al. (2004) reported a hypoactivity of the amygdala during viewing of emotional faces in patients with high TAS-20 scores, and a further study revealed that the more difficulty individuals had identifying feelings, the lower was their amygdala response while watching videos of fearful bodily expressions, namely, actors reacting to someone or something that had frightened them (Pouga et al., 2010). Moreover, this observed hypoactivity of the amygdala appears to be modality-independent, as reduced amygdala responses were also observed for processing emotional speech prosody, both during the implicit and the explicit processing of such auditory stimuli (Goerlich-Dobre et al., 2013). In addition, Zotev et al. (2011) tested in a neurofeedback study the ability to increase one's own amygdala activity by recalling positive autobiographical memories. They observed that the training effect on left amygdala activity was associated negatively with the DIF facet of alexithymia, indicating that people with a higher ability to identify their feelings were more successful in learning how to regulate activity within their left amygdala than those with a lower ability. These findings are consistent with the observation that labeling affective expressions with words reduces amygdala activity (Hariri, Bookheimer, & Mazziotta, 2000; Lieberman et al., 2007). In HA, particularly those with pronounced DIF, this mechanism may be dysfunctional as the level of their amygdala activity is low to begin with, preventing a further decrease during emotion regulation strategies such as affective labeling.

As the majority of fMRI studies on alexithymia utilized visual emotional stimuli, further research is needed to confirm that these individuals suffer from a

general dysfunction of the amygdala independent of modality. The studies that identified amygdalar dysfunction in relation to alexithymia, and specifically the DIF facet, generally also observed reduced activity in the fusiform gyrus as well as in occipital areas.<sup>3</sup> The amygdala influences activity in the occipital cortex via a feedback loop through the fusiform gyrus (Vuilleumier, 2005), thereby directing attention to emotional stimuli such that those stimuli receive more attention than neutral ones (Hodsoll, Viding, & Lavie, 2011). A dysfunction in that feedback loop (e.g., due to amygdala lesions) leads to a reduction of attention to emotional or novel stimuli (Anderson & Phelps, 2001; Jacobs et al., 2012). Such reduction in emotional attention has been reported repeatedly in alexithymia, showing that HA are less distracted by negative words (Mueller, Alpers, & Reim, 2006), and that alexithymia correlated negatively with the ability to recall emotional distractors (Suslow, Kersting, & Arolt, 2003). The latter study revealed that this impairment in emotional attention was specifically related to DIF, in line with studies reporting amygdalar hypoactivity in relation to the same alexithymia facet (Kugel et al., 2008; Reker et al., 2010). Moreover, a further study found that activity in the fusiform gyrus in response to masked surprised faces correlated negatively with the DIF subscale of the TAS-20 (Duan et al., 2010). Thus, converging evidence suggests that reduced neural activity in an emotional attention system, comprising the amygdala, fusiform gyrus, and occipital cortex, underlies the DIF component of alexithymia. Considering the role of the amygdala in eliciting emotional reactions and initiating changes in one's autonomic state (Barrett et al., 2007), reduced amygdalar responsiveness to (covert and overt) emotional stimuli should lead to limited peripheral physiological and facial responding (low response mobilization) and in turn to poor somatosensory remapping. Therefore, individuals with difficulties identifying their feelings might have less bodily information available for spontaneous emotional reactions (Donges & Suslow, 2017). Amygdala hypo-reactivity might thus underlie the stiff posture and low emotional reactivity often described about individuals with a high level of alexithymia, and the dull and

<sup>3</sup> For a meta-analysis of fMRI studies on alexithymia, see van der Velde et al. (2013); for a review on automatic emotion processing in alexithymia, see Donges and Suslow (2017).

emotionally flat impression they tend to make on others (Taylor et al., 1997).

### The Insula and Emotional Experience

Similar to the amygdala, the insula has long been recognized as an important brain region for the processing of emotions (Craig, 2009; Damasio & Dolan, 1999). Insular cortex functions as a center of multimodal convergence that relays information from unimodal sensory, visual, and auditory cortices to higher-order association cortex, allowing these regions to modify autonomic and visceral outflows (Mesulam & Mufson, 1982, 1985). Posterior portions of the insula receive direct representations of homeostatic afferent information via thalamo-cortical pathways, and project this information onto the anterior insula (Craig, 2002). The posterior insula is therefore directly involved in the representation of bodily states during emotional experience, which are then relayed to the anterior insula, where the bodily signals are integrated into subjective feeling states, generating emotional experience (Craig, 2009). Thus, the insula is a central brain structure in a network underlying the conscious experience and awareness of emotions.

A number of neuroimaging studies on alexithymia have reported abnormalities in insular activity in relation to levels of alexithymia, implicating insular dysfunction in aberrant social and emotional processing in alexithymia. In a study investigating the neural correlates of visceral hypersensitivity (i.e., hypersensitivity to bodily signals), it was found that the right insula was hyperactive during colonic distension in HA (Kano et al., 2007). In addition, the higher the alexithymia scores, the more anxiety that participants expressed during visceral stimulation, which was accompanied by higher adrenaline levels. The authors concluded that HA may become more aroused by the experience of unpleasant feelings, thereby displaying more autonomous responses reflected in increased activity of the right insula. Similarly, Karlsson, Näätänen, and Stenman (2008) observed in a PET study that female HA seem to over-activate their “bodily” brain regions (including the insula) while being exposed to emotional films, implying a different mode of emotion processing that may be related to the tendency of individuals with high levels of alexithymia to experience physical symptoms when processing emotions. In line with these observations is the finding that insula activation is higher when more arousing emotional stimuli are subjectively perceived

(Heinzel et al., 2010). In a sample of patients diagnosed with PTSD, alexithymia levels were associated with increased activation of the right posterior insula and decreased activation of the anterior insula bilaterally in response to trauma-script imagery (Frewen et al., 2008a). In addition, alexithymia scores in the patients correlated positively with emotional neglect scores (see Chapter 8). Together, these findings suggest that the insula is hyperactivated in alexithymia during the experiencing of emotions elicited by exposure to emotion-evoking stimuli or by physical stimuli that are perceived as unpleasant. Increased insula activity during the processing of emotion-evoking and physically unpleasant stimuli likely underlies the hypersensitivity to physical sensations characteristic of alexithymia. This interpretation is further corroborated by research on the embodiment of emotions, which found that alexithymia is associated with a deficit in remapping especially negative emotions, such as fear and disgust that they observe in others, onto their own somatosensory system (Scarpazza, di Pellegrino, & Lådavas, 2014; Scarpazza, Lådavas, & di Pellegrino, 2015).

It is noteworthy that several studies, which employed paradigms requiring cognitive and empathic emotion processing rather than subjectively experiencing feelings, reported reduced insular activity in relation to alexithymia: when watching others in pain, HA activated their (left) insula to a lesser degree than LA. Moreover, the HA behaved less altruistically and reported less distress on watching others in pain (FeldmanHall, Dalgleish, & Mobbs, 2013). Such reduced empathic responses reflected in lower insula activity were also observed in a study in which participants rated the degree of unpleasantness of emotional pictures, requiring interoception (Silani et al., 2008). Similarly, left anterior insula activity was negatively correlated with levels of alexithymia in both a group with an autism spectrum diagnosis and matched control group without any pre-existing neurological or psychiatric disorders, demonstrating that not autism per se but the associated levels of alexithymia predict reduced empathic brain responses (Bird et al., 2010). The finding of reduced left anterior insula activity was corroborated by two further MRI studies that also reported negative correlations between alexithymia and brain activity in the left anterior insula during empathy for pain (Enzi, Amirie, & Brüne, 2016; Feng et al., 2016). Moreover, differences in left anterior insula activity specifically in relation to the DIF facet

of alexithymia distinguished patients with depersonalization disorder from participants without the disorder, during the processing of happy and sad facial expressions (Lemche et al., 2013).

In addition to reduced insula activity at conscious processing levels, a reduced activation of this region has also been observed at unconscious, automatic processing levels in response to masked happy faces (Reker et al., 2010). This suggests that dysfunctional insula activity is already evident during unconscious emotional processing in alexithymia.<sup>4</sup> Given the role of the insula in emotional awareness and empathy, this reduction in insula responsiveness likely underlies the reduced ability to be aware of one's feelings and reduced empathy for others that are associated with alexithymia. A recent lesion study involving 129 brain-injured patients further supports an important role for the anterior insula in alexithymia: increased damage to this region predicted increased levels of alexithymia, indicating that alexithymia was acquired as a consequence of damage to this region, thus confirming a necessary role of the anterior insula in emotional self-awareness (Hogeveen et al., 2016).

Taken together, the present evidence suggests a critical involvement of the insula in aberrant emotion processing in alexithymia. The pattern of insular activation seems bidirectional depending on the emotional processes that the respective task paradigms tap into: hyperactivation of the insula occurs when HA subjectively experience emotions, whereas hypoactivation is observable when they are required to process emotional stimuli cognitively and to empathize with others.

### The Anterior Cingulate Cortex and Emotional Awareness

The ACC is considered a key correlate of alexithymia based on Lane et al.'s (1997) "blindfeel hypothesis", which postulates that the core deficit of alexithymia lies in the conscious self-awareness of emotions. As noted earlier, this hypothesis proposes that alexithymia might involve a neural disconnection such that interoceptive emotional information does not adequately communicate with cortical brain regions including the ACC. The hypothesis was based on the results of a PET study in which levels of emotional awareness correlated with activity in the right dorsal ACC when participants

watched emotional films and when they recalled the emotions shown in the films (Lane et al., 1998).

The ACC is a large structure whose subregions have been proposed to fulfill different functions: ventral portions of the ACC regulate limbic regions involved in the generation of emotional responses, whereas dorsal portions of the ACC, partially overlapping with the middle cingulate cortex (MCC), are implicated in the appraisal and expression of emotions (Etkin, Egner, & Kalisch, 2011). Outcomes from several neuroimaging studies have shown that alexithymia is indeed associated with impairment in ACC activation during emotional processing. In a meta-analysis, van der Velde and colleagues (2013) confirmed a hyperactivation of the dorsal ACC and MCC in alexithymia, which was associated with the processing of positive as well as negative emotional stimuli (i.e., valence-independent) and occurred across a variety of different paradigms. This demonstrates that dysfunction in the cingulate cortex is an important neural correlate of alexithymia, with activation increases representing either an amplification of physical sensations (Kano et al., 2007; Moriguchi et al., 2007) or a recruitment of additional neural resources during the processing of non-physical emotional stimuli (Berthoz et al., 2002; Heinzl et al., 2010; Mériaux et al., 2006; Pouga et al., 2010). Providing further evidence for the latter interpretation, we recently found that levels of alexithymia, specifically the DIF facet, were associated with ventral ACC activation during the anticipation of social rewards, showing that already the expectation of a positive social stimulus elicits increased ACC activation in alexithymia (Goerlich et al., 2017). This mechanism appears to be specific to social rewards, as no alexithymia-related differences in ACC activation occurred during the anticipation of monetary rewards. Moreover, differences in dorsal ACC (dACC) activity specifically in relation to the DDF facet distinguished patients with depersonalization disorder from healthy participants during the processing of happy facial expressions (Lemche et al., 2013). A further study using trauma-script imagery found that a measure of levels of emotional awareness correlated positively with activation of the bilateral ventral ACC in healthy controls, whereas they were negatively correlated with activation in the same region in patients with PTSD (Frewen et al., 2008b).

The relation between alexithymia and ACC dysfunction appears to be non-linear, and the results are

<sup>4</sup> For a meta-analysis of emotion processing studies, see van der Velde et al. (2013).

not consistent across studies – several imaging studies reported increased ACC activation, whereas others found decreased activation of the dorsal ACC in relation to alexithymia (Kano et al., 2003; Karlsson et al., 2008; Moriguchi et al., 2007). Reduced ACC activation (along with reduced activation of the amygdala and insula, amongst other regions) was also observed in a study that required labeling emotional faces in a comparison of HA with LA (Jongen et al., 2014). Furthermore, a study investigating alexithymia in patients with anorexia nervosa reported that subjective ratings indicating how unpleasant negative words were perceived, as well as neural activation in the ACC, PCC, and amygdala, correlated negatively with alexithymia scores (Miyake et al., 2012). The latter studies seem to have in common that they employed paradigms that were relatively high in cognitive demand, such as empathizing with others experiencing pain or introspecting one's own emotional perception, both of which are difficult for people with high levels of alexithymia. Van der Velde et al. (2013) hypothesized that if basic emotion processing tasks, such as passively viewing emotional images, already elicit higher ACC activation in alexithymia, tasks that require even more emotional awareness may become too strenuous. They proposed that ACC activation patterns in relation to alexithymia might be characterized by an inverted U-shape pattern, with ACC activation decreasing again once a certain level of cognitive demand is reached. Such a pattern of ACC activation had previously been observed in patients with obsessive-compulsive disorder: when task difficulty increased, dACC activation increased in the patients compared with healthy controls, presumably representing a compensation mechanism. However, when task difficulty increased even further, dACC activation decreased and was lower in the patients than in the controls (Koch et al., 2012). A similar pattern of ACC response to emotional stimuli depending on task demand might be involved in alexithymia, a hypothesis awaiting verification in future research.

### The Prefrontal Cortex and Emotional Learning and Imagery

The prefrontal cortex (PFC), which occupies almost one-third of the total amount of cortical space, accommodates higher cognitive and affective functions. It can be grossly divided into ventromedial and dorsolateral regions. The ventromedial PFC (vmPFC), a subarea of the medial PFC, is connected with limbic structures (e.g., hypothalamus, amygdala)

and is well situated to integrate cognitive and emotional processes. Both the ACC and the OFC are regions important for emotional functioning, and both are located in the vmPFC. The OFC is involved in emotion-related learning (Jonker et al., 2015) and emotion regulation (Etkin, Büchel, & Gross, 2015). Lesions to the vmPFC, especially the OFC, are associated with a reduction in the subjective experience of emotion and emotional reactivity (Hornak et al., 2003; Jenkins et al., 2018) and with impairment in emotional decision-making (Noonan et al., 2012).

Some studies have implicated a dysfunction of the vmPFC/OFC in alexithymia, although the available evidence is inconclusive. The *Iowa Gambling Task* (IGT) assesses how decision-making is influenced by emotionally biased signals, based on Damasio, Everitt, and Bishop's (1996) theory of somatic markers: decision-making is not just the product of rational calculations of reward and losses, but is also dependent upon positive or negative emotional reactions and emotionally guided evaluation. Lesions to the vmPFC result in decision-making deficits because of an inability to use emotion-based biasing signals generated from the body (i.e., somatic markers) during the appraisal of different response options. Ferguson and colleagues (2009) examined the influence of alexithymia on the IGT in a sample of 326 women and men. LA showed standard learning on the IGT. In contrast, HA learned to avoid disadvantageous decks over the first half of the task, but then showed a change in performance: they shifted from advantageous to disadvantageous and back to advantageous decks again (termed an "explore-learn-change-return" strategy). The authors suggested that this may be due to an inability to fully consolidate earlier learning and a reduced sensitivity to losses. Corroborating these findings, a PET study observed that men with high alexithymia scores failed to learn an advantageous decision-making strategy in the IGT (Kano et al., 2011). Moreover, the men showed lower rCBF in the vmPFC during the learning phases of the IGT. Together, these findings suggest that people with high levels of alexithymia are less capable of using emotion-based signals to achieve advantageous decision-making. Thus, individuals with alexithymia may be unable to use feelings to guide their behavior appropriately.

Furthermore, the PET study by Kano et al. (2003) found that HA activated the OFC to a lesser degree than LA while viewing emotional facial expressions, and OFC activity correlated negatively with

alexithymia scores while participants viewed negative (angry and sad) facial expressions. In a study using trauma-script imagery, alexithymia levels were associated with reduced activity in the vmPFC in patients with PTSD (Frewen et al., 2008b). This negative association between alexithymia and medial PFC activation was also reported in another study using a theory of mind (ToM) task, in which alexithymia was associated with reduced mentalizing and less activation in the right medial PFC (Moriguchi et al., 2006). Notably, the latter study is one of the few that assessed alexithymia with both the self-report TAS-20 and the observer-rated modified BIQ.

A further study reported that activation differences in the orbital gyrus specifically related to the EOT facet of alexithymia distinguished patients with depersonalization disorder from healthy participants during the processing of sad facial expressions (Lemche et al., 2013). However, no alexithymia-related differences in OFC activation were identified in another study employing an imagery task that required the imagination of past and future events (Mantani et al., 2005), nor in a study investigating the influence of alexithymia on emotion regulation (van der Velde et al., 2014). Rather than the OFC, the former study identified the posterior cingulate cortex (PCC), a structure crucially involved in emotional memory (Maddock, 1999), to underlie the deficient emotional imagery characteristic of alexithymia: HA activated the PCC significantly less than LA when imagining past and future happy events (Mantani et al., 2005). Thus, reduced imagery capacities in alexithymia might be related to a dysfunction of the PCC, whereas the role of the OFC remains to be clarified in further studies.

More converging evidence suggests a dysfunction of the dorsomedial PFC (dmPFC) adjacent to the vmPFC, in alexithymia. According to the results of a meta-analysis (van der Velde et al., 2013), the dmPFC was activated to a lesser degree in relation to levels of alexithymia during the processing of negative emotional stimuli. The dmPFC is part of the ToM network, which is important for understanding the mental states of others (Molenberghs et al., 2016). Regions of this network are assumed to have mirror neuron properties, i.e., they are activated during the execution and imitation, as well as during the observation, of motor actions (Molenberghs, Cunnington, & Mattingley, 2009), and also emotional facial expressions (Carr et al., 2003). Consequently, the dmPFC is important

for emotion processing and for empathy for others (Lamm, Decety, & Singer, 2011), implying that the low empathic abilities associated with alexithymia might result from dmPFC dysfunction. Indeed, a study that directly examined the mirror neuron system in groups of students with either high or low alexithymia scores observed increased activation in several areas of this system in the group with high scores during the execution and observation of motor actions (Moriguchi et al., 2009). Yet, behavioral performance did not differ between groups, leading the authors to conclude that increased dmPFC activity reflects a compensatory mechanism in people with high levels of alexithymia, which they assumed to fail during empathic processing and emotion processing in general.

In sum, several subregions of the PFC appear to show dysfunctions in relation to alexithymia. Reduced rCBF in the vmPFC seems to hamper emotional learning during the IGT, leading to failure to learn an advantageous decision-making strategy in HA (Kano et al., 2011), and thus an inability to use feelings to guide behavior. Moreover, rCBF in the OFC was reduced in alexithymia during the viewing of facial emotional expressions and correlated negatively with alexithymia scores during the viewing of negative facial expressions, indicating an altered processing of facial emotions in alexithymia. In contrast, medial PFC activation was correlated positively with alexithymia scores during emotional imagery in trauma-exposed individuals without PTSD (Frewen et al., 2006), whereas no differences in this region were found in another study on emotional imagery (Mantani et al., 2005) and in a study investigating emotion regulation in alexithymia (van der Velde et al., 2014). The role of the OFC in alexithymia therefore needs clarification in future studies.

A role of the lateral PFC is not frequently reported in alexithymia studies, despite its involvement in emotion regulation (Etkin et al., 2015). One study, however, investigated the neural response to masked emotional faces in depressed patients with either high or low TAS-20 scores (Suslow et al., 2016). The authors reported less activation of the right inferior, middle, and superior gyrus and the right caudatus in the patients with high scores than in those with low scores. Lastly, the meta-analysis by van der Velde et al. (2013) identified reduced activation in the dmPFC for negative emotional stimuli in alexithymia, suggesting that dmPFC dysfunction may underlie the low empathic abilities of people with high levels of alexithymia.

### Functional Connectivity between Emotional and Cognitive Brain Areas

Few studies to date have investigated the functional connectivity between cognitive and emotional brain regions in relation to alexithymia, with the aim of shedding light on the influence of alexithymia on the complex interplay between the emotional and cognitive brain systems. Mériaux et al. (2006) compared changes in effective connectivity of the dACC between HA and LA during a perceptual (gender-) decision-making task on emotional facial expressions. They found greater coupling of the dACC with prefrontal regions in LA, whereas HA showed greater coupling of the dACC with the amygdala. These results suggest that reduced communication between limbic and cortical areas impairs the cognitive processing of emotions in alexithymia.

A further study reported that high TAS-20 scores in smokers predicted reduced resting state functional connectivity (rsFC) strength between the right anterior insula (AI) and vmPFC (Sutherland et al., 2013). High TAS-20 scores also predicted more severe tobacco craving during nicotine withdrawal, and the identified AI–vmPFC circuit fully mediated this relation between alexithymia and craving severity: high alexithymia scores predicted decreased AI–vmPFC rsFC, which, in turn, predicted increased craving during withdrawal. These results provide further evidence for the observation that alexithymia levels are associated with altered functional coupling between emotional (AI) and cognitive (vmPFC) brain regions.

Functional connectivity differences in relation to alexithymia were further reported in a study investigating the default mode network (DMN) in participants with high versus low scores on the BVAQ (Liemburg et al., 2012). The group with high scores showed lower connectivity within areas of the DMN (medial frontal and temporal areas) as compared with the group with low scores. In contrast, connectivity in the group with high BVAQ scores was higher for the sensorimotor cortex, occipital areas, and right lateral frontal cortex; this suggests alexithymia may be characterized by a diminished connectivity within DMN brain areas related to emotional awareness and self-referential processing, but a stronger connectivity within DMN brain areas involved in sensory input and control of emotion. A recent MRI study reported DMN alterations in relation to alexithymia in a group of participants with major depressive disorder

(MDD) and in a healthy control group: in the MDD group, alexithymia was linked to reduced functional connectivity in the right precentral gyrus and several right-hemispheric brain regions associated with cognitive regulation. In the healthy control group, alexithymia was correlated with increased functional connectivity between the right inferior frontal gyrus and the right superior occipital lobe, which is associated with emotional responses to external stimuli (Ho et al., 2016). Moreover, alexithymia-related differences were identified within the salience network (a network of brain regions important for the detection of relevant stimuli and subsequent attention allocation) in a group of cocaine users, but not in a healthy control group (Liang et al., 2015).

In conclusion, the current neuroimaging evidence suggests that alexithymia not only affects the activation of several brain regions in isolation during the processing of emotions, but also seems to alter the neuronal crosstalk within the DMN network and the salience network during rest.

### Summary and Discussion of Functional Neuroimaging Findings

To date, findings from neuroimaging studies suggest that differences in neural activity of the amygdala, insula, ACC, and several regions of the PFC constitute the neural basis of alexithymia. Hypoactivity of the amygdala is evident during both conscious and unconscious processing of emotions, and can be considered a core neural marker of alexithymia. Specifically, difficulty identifying feelings (DIF) seems to be associated with reduced neural activity in the emotional attention system comprising the amygdala, fusiform gyrus, and occipital cortex.

Next to the amygdala, the insula seems critically involved in aberrant emotion processing in alexithymia. Its activation pattern depends on the type of emotion processing required: whilst subjectively experiencing emotions, people with high levels of alexithymia hyperactivate the insular cortex. In contrast, when required to process emotions at a cognitive level or to empathize with other people, hypoactivation of the insula occurs.

Furthermore, dysfunction of the anterior and middle cingulate cortex is an important correlate of alexithymia. As was found for the insula, the activation patterns appear to be non-linear and are possibly characterized by an inverse U-shape pattern. Increases

in cingulate activation may represent either an amplification of physical sensations in alexithymia, or a recruitment of additional neural resources when processing non-physical emotional stimuli. In contrast, emotional tasks that exceed a certain level of cognitive demand elicit hypoactivation of the cingulate cortex.

Moreover, dysfunction of several prefrontal brain regions, including the vmPFC, OFC, and dmPFC, seem to be part of the neural basis of alexithymia. Reduced activity in the vmPFC seems to underlie the alexithymic inability to use emotion-based biasing signals for advantageous decision-making, i.e., to use feelings to guide behavior. Specifically, the orbital portion of the vmPFC, the OFC, might underlie problems in recognizing facial emotions and the lack of emotional imagery in alexithymia. However, the evidence regarding the OFC is not yet conclusive; its exact role during emotion processing difficulties in alexithymia needs to be clarified in future studies. Regarding the dmPFC, converging evidence suggests that reduced activity in this region underlies the low empathic abilities associated with alexithymia.

Beyond dysfunctions in these key regions, neuroimaging research has also provided evidence for altered neural crosstalk within entire networks of brain regions, including the DMN and the salience network, in relation to alexithymia. Besides demonstrating that alexithymia alters the functioning of large neural networks, not only of the aforementioned specific key regions during emotional processing, these findings further imply that alexithymia is characterized by differences in neural function already at rest, i.e., when no emotional tasks are performed. Moreover, TMS studies found that alexithymia is associated with facilitated transcallosal inhibition. Taken together, these findings suggest a broader neural basis for alexithymia, which may not be restricted to the processing of emotions, but might include impairment in self-referential processing, decreased self-awareness, and aberrant information transfer between the left and right hemisphere.

## Structural Imaging

### Structural Correlates of Alexithymia and Its Facets

In the past decade, results from structural MRI studies have complemented the pattern of neural activation differences provided by functional imaging

studies on alexithymia. Rather than investigating how alexithymia influences the activity within certain brain regions or networks during the processing of emotions, these studies aim to reveal potential differences in the anatomy of brain regions implicated in this personality construct. Summaries of the studies we review are displayed in Table 13.3. The first studies of this kind used manual tracing techniques in order to identify regional differences in gray matter volume in relation to alexithymia. The first such study was performed by Gündel, López-Sala, and Ceballos-Baumann (2004), who focused on the ACC and the hypothesis of a deficit in the conscious awareness of emotions by examining the relationship between alexithymia and surface areas of the anterior and posterior cingulate gyri in both hemispheres in a sample of 100 university students with a mean age of 25.6 years. Their results indicated that the surface area of the right ACC was positively related to levels of alexithymia in both female and male participants. In contrast to these findings, Paradiso et al. (2008) found that alexithymia in an older sample of healthy participants (mean age 53.7 years) was linked to reduced gray matter volumes in the right rostral ACC. This association was driven by the EOT facet of alexithymia, leading the authors to conclude that deterioration in the rostral ACC contributes to increased alexithymia levels in older age and that this effect may be specifically related to an externally oriented style of thinking.

More recent structural MRI studies employed automated rather than manual techniques to determine brain volume differences in relation to alexithymia. The gold standard method in this field is voxel-based morphometry (VBM), which allows for automatically calculated and thus objective voxel-wise comparisons of regional variations in gray matter volume or density. The first such VBM study was performed by Borsci et al. (2009), who found that TAS-20 scores in female participants were associated with smaller volumes of the ACC. Additionally, alexithymia scores correlated negatively with volumes of the middle temporal gyrus, the anterior insula, the OFC, and the superior temporal sulcus. Confirming the finding of reduced ACC volumes by Borsci and colleagues, Sturm and Levenson (2011) reported reduced gray matter volumes of the right pregenual ACC in healthy controls in association with alexithymia. Gray matter volume reductions in the ACC in relation to alexithymia were also reported by Ihme et al. (2013), who further found reduced volumes of

the amygdala, anterior insula, and middle temporal gyrus in the left hemisphere in HA when compared with LA. However, a VBM study with only a male sample failed to find alexithymia-related differences in gray matter volume (Heinzel et al., 2010).

Comparing gray matter volumes in relation to alexithymia in patients with schizophrenia and a healthy control group, Kubota et al. (2011) reported that TAS-20 scores correlated negatively with volumes of the bilateral ventral striatum and left ventral premotor cortex in healthy controls, and were negatively linked to volumes of the left supramarginal gyrus in the patients. Left insula density differences in relation to levels of alexithymia were reported by Zhang et al. (2011) in a group of smokers, but not in a group of non-smokers, which the authors attributed to the small size of the latter group. Lastly, a recent large-scale study ( $N > 1,600$ ) controlling for possible confounds by levels of anxiety and depression identified reduced gray matter volumes of the bilateral dACC in relation to total TAS-20 scores (Grabe et al., 2014). This study also investigated the three facets of alexithymia separately and found that the DIF facet specifically was associated with less gray matter volume in the dACC, left middle and inferior temporal gyrus, left fusiform gyrus, and cerebellum, with the association between lower fusiform volume and DIF being observed only in women. Grabe and colleagues concluded that lower dACC volume represents a major structural correlate of alexithymia, and that associations with DIF suggest a prominent involvement of left temporal areas involved in language and the cognitive processing and conscious identification of feelings. Moreover, their findings suggest that the different facets of alexithymia might be related to separable morphological correlates.

### Structural Correlates of the Postulated Alexithymia Types and Dimensions

In our laboratory at the Neuroimaging Centre Groningen and in collaboration with colleagues in the Department of Psychology at Harvard University, we set out to investigate the structural basis of the different alexithymia facets more thoroughly. Rather than relying on the TAS-20 alone for assessing alexithymia as was done in the previous VBM studies on alexithymia, we also administered the BVAQ. According to Bermond and colleagues (2007), the five subscales of the BVAQ assess separately the putative affective and cognitive components of alexithymia.

Our group found that the two dimensions were related to differences in gray matter volume in distinct brain regions. Whereas the cognitive dimension was linked to more gray matter volume in the right posterior insula, the affective dimension, specifically the emotionalizing facet indicating low emotional reactivity, was related to more gray matter volume in the right cingulate cortex (Goerlich-Dobre et al., 2014). A further investigation in our lab also identified dissociable morphometric profiles of the two alexithymia dimensions (van der Velde et al., 2014), providing additional support for a structural differentiation between the alexithymia dimensions. Based on these observations, and following the proposal of four different types of alexithymia by Bermond et al. (2007), we then investigated whether individuals who scored either low or high on the cognitive dimension and low or high on the affective dimension (corresponding to the four alexithymia types) would show different patterns of morphometric alterations (Goerlich-Dobre et al., 2015b). Type I (high cognitive, high affective scores = “full-blown” alexithymia) was characterized by gray matter volume reductions in the left amygdala and thalamus in comparison to lexithymics (low cognitive, low affective scores). Individuals with Type II alexithymia (high cognitive, low affective scores) showed a similar but much smaller cluster comprising the left amygdala and thalamus. Type III (low cognitive, high affective scores) was marked by volume reduction in the MCC compared to lexithymics. Moreover, the intermediate Types II and III exhibited reductions in gray matter volume in distinct regions. Thus, the proposed different types of alexithymia seem linked to dissociable morphometric profiles, with impairments in the cognitive processing of emotions showing particularly pronounced effects on regional brain volume in individuals with so-called Type I alexithymia. As we noted earlier, however, it should be kept in mind that the categorization of alexithymia into separate dimensions and subtypes is controversial and is not widely accepted (see Bagby et al., 2009; Watters et al., 2016). Indeed, in a recent factor analytic study, Preece et al. (2017) found that a higher-order “affective factor” (representing difficulties fantasizing and low negative reactivity) correlated strongly and negatively with a higher-order “cognitive factor”, and thus the two factors were not orthogonal or positively related. Moreover, Preece and colleagues noted that the scoring of the emotionalizing subscale of the BVAQ does not take into account the

distinction that emotion reactivity researchers make between reactivity with negative emotions and reactivity with positive emotions, which statistically are separate dimensions that correlate negatively with each other, and that some items appear to measure empathy rather than emotional reactivity. Thus, further empirical research is necessary to evaluate the validity of types and dimensions of alexithymia.

### Summary and Discussion of Structural Neuroimaging Findings

In sum, the structural imaging findings currently available appear to support the neural landscape of alexithymia that has been identified by functional imaging studies. The ACC, particularly its dorsal part, as well as the left amygdala and insula seem to be reduced in volume in relation to alexithymia, presumably underlying their altered functioning during emotion processing. In addition, several VBM studies reported reduced volumes in left temporal areas in alexithymia. Notably, the pattern observed by most morphometric studies performed so far suggests that gray matter volume reductions in HA might be particularly pronounced in the left hemisphere. Considering the hypothesis of a left hemisphere preference in alexithymia, this would imply a particularly pronounced emotion deficit in people with this condition. However, to provide a reliable picture of alexithymia-related alterations in regional brain volume, a systematic synthesis in the form of a quantitative meta-analysis is necessary. Therefore, we performed a parametric coordinate-based meta-analysis including 17 structural imaging studies on alexithymia (Xu et al., 2018). The results demonstrate that alexithymia is associated with reduced gray matter volumes in the left insula and the left amygdala, orbital frontal cortex, and striatum. These areas are important for the conscious as well as unconscious perception and experience of emotions, emotional awareness, and the processing of rewards. Reduced gray matter volumes in these regions likely underlie their aberrant functioning during the processing of social and emotional information, resulting in deficiencies in appropriately identifying and communicating emotional feelings as experienced by individuals with high levels of alexithymia.

Few structural studies so far have taken the different alexithymia facets, dimensions, and proposed subtypes into account. The results of these preliminary studies suggest that, while the effect of the affective

alexithymia dimension on brain morphometry might be less severe in terms of the number of brain regions involved than the effect of the cognitive dimension, the two dimensions and also specific alexithymia facets seem to be related to distinct morphometric profiles, rendering it unfortunate that the majority of VBM studies focused solely on the cognitive dimension and rarely attempted to disentangle the different facets of alexithymia. In light of the recent finding of the proposed types of alexithymia being related to distinct structural correlates, it remains for future research (with larger samples) to further investigate structural markers of the specific alexithymia facets, dimensions, and subtypes. In combination with functional imaging findings, this research could have important clinical implications as the identification of such markers might aid the neuropsychiatric assessment of individuals at risk for psychiatric disorders, and even assist the development of highly targeted pharmacological or psychological interventions.

### Limitations of Neuroimaging Studies

Neuroscientific research has provided important insights into the neural correlates of alexithymia. However, there are several limitations to consider. Most neuroimaging studies use self-report questionnaires to assess alexithymia. Given the greater reliability of a multi-method measurement of personality most generally, future studies would benefit from a combination of self-report and observer-rated or structured interview assessments of alexithymia. Further, there is a wide variety among paradigms employed in imaging research. Given the complexity of emotion processing in the brain and the variety of contributing mechanisms, this complicates comparisons between study results. Alexithymia is associated with other personality dimensions such as neuroticism, and with levels of anxiety and depression symptom severity. Only a few studies have corrected for the influence of these other factors. Furthermore, several studies have indicated sex differences, but many studies did not differentiate between male and female participants. Lastly, because findings from neuroimaging studies are correlational, no causal inferences can be drawn regarding the etiology of alexithymia. Future research would benefit from taking these factors into account in order to arrive at a more comprehensive understanding of the neural correlates of alexithymia.

**Table 13.1** Functional magnetic resonance imaging (fMRI) studies.

Study	Alexithymia measure	Experimental design/paradigm	Sample	Main results	Conclusions
Berthoz et al., 2002	TAS-20	<ul style="list-style-type: none"> <li>Comparison of the groups for their regional cerebral activation in response to the presentation of pictures with validated positive or negative arousal capabilities</li> </ul>	<ul style="list-style-type: none"> <li>8 men HA</li> <li>8 men LA</li> </ul>	<ul style="list-style-type: none"> <li>Men with HA demonstrated less cerebral activation in the left mediofrontal-paracingulate cortex in response to highly negative stimuli and more activation in the anterior cingulate, mediofrontal cortex, and middle frontal gyrus in response to highly positive stimuli than men without alexithymia</li> </ul>	<p>→ Alexithymia plays a role in affect regulation and is associated with differences in anterior cingulate and mediofrontal activity during emotional processing</p>
Bird et al., 2010	TAS-20, BVAQ	<ul style="list-style-type: none"> <li>Measure of empathic brain responses with an "empathy for pain" paradigm assessing empathic brain responses in real-life social setting that does not rely on attention to, or recognition of, facial affect cues</li> </ul>	<ul style="list-style-type: none"> <li>18 male participants with autism spectrum conditions</li> <li>18 male controls matched for alexithymia scores, age, and IQ</li> </ul>	<ul style="list-style-type: none"> <li>Confirming previous findings, empathic brain responses to the suffering of others were associated with increased activation in left anterior insula and the strength of this signal was predictive of the degree of alexithymia in both autistic and control groups but did not vary as a function of group</li> </ul>	<p>→ Empathy deficits observed in autism may be due to the large comorbidity between alexithymic traits and autism, rather than representing a necessary feature of the social impairments in autism</p>
Duan et al., 2010	TAS-20	<ul style="list-style-type: none"> <li>Participants were scanned while viewing surprised faces, which were presented for 33 ms and immediately "masked" by a neutral face for 467 ms</li> <li>In a control situation, they viewed masked happy or neutral faces as well</li> </ul>	<ul style="list-style-type: none"> <li>18 participants (13 females), all right-handed, healthy, young adults</li> </ul>	<ul style="list-style-type: none"> <li>The TAS-20 factor "difficulty identifying feelings" was negatively correlated with the neural response of the areas parahippocampal gyrus and fusiform gyrus to masked surprised faces</li> </ul>	<p>→ Decreased activation in these brain regions may reflect more difficulties in recognizing one's emotions in everyday life</p>

Enzi et al., 2016	<ul style="list-style-type: none"> <li>• Pictures depicting a painful or a non-painful situation, presented for 3 seconds</li> <li>• In total, 60 trials were presented per run, 30 in the painful stimulation condition and 30 in the non-painful condition</li> <li>• After scanning, participants rated each picture used in the paradigm regarding the contained facial emotional expressions, i.e., angry, happy, painful, and neutral</li> </ul>	<ul style="list-style-type: none"> <li>• 20 healthy participants</li> </ul>	<ul style="list-style-type: none"> <li>• After presenting angry faces there was an increased neuronal response in the right mid-cingulate cortex, the left anterior insula (AI), and the left dorsolateral prefrontal cortex (dlPFC)</li> <li>• Alexithymia, particularly the factor difficulty identifying feelings, was negatively correlated with pain-related activation in the left AI</li> </ul>	<p>→ Alexithymia, particularly difficulty identifying feelings, is linked to a reduced neural response in the left AI during empathy for pain</p>
FeldmanHall et al., 2013	<ul style="list-style-type: none"> <li>• Experimental task: participants had to choose how much money they would give to prevent a painful electric stimulation of another person (more money, less pain); participants watched a video of the outcome of their decision</li> <li>• fMRI scanned the distress level of the deciders while watching the video</li> </ul>	<ul style="list-style-type: none"> <li>• 15 participants</li> <li>• those with scores <math>\leq 51</math> on the TAS-20 were LA, those with scores <math>\geq 61</math> were HA</li> </ul>	<ul style="list-style-type: none"> <li>• Individuals high on the alexithymia spectrum reported less distress at seeing others in pain and behaved less altruistically</li> <li>• Individuals who have difficulty recognizing and experiencing others' emotional distress have reduced neural activation within the anterior insula and temporo-parietal junction, key regions in the experience of distress and perspective taking</li> </ul>	<p>→ Evidence of decreasing distress levels suggests that the prototypical emotional blunting seen in alexithymia can translate into diminished prosocial action and self-serving behavior</p>

**Table 13.1** (cont.)

Study	Alexithymia measure	Experimental design/paradigm	Sample	Main results	Conclusions
Feng et al., 2016	TAS-20	<ul style="list-style-type: none"> <li>Photographs of faces receiving painful and non-painful stimulation</li> <li>Participants were scanned with fMRI while watching inferior-status or superior-status targets receiving painful or non-painful stimulation</li> </ul>	<ul style="list-style-type: none"> <li>22 participants with normal or corrected-to-normal vision and no history of neurological or psychiatric disorders</li> </ul>	<ul style="list-style-type: none"> <li>Empathic neural responses to the pain of inferior-status targets in the left anterior insula (AI) inversely correlated with levels of alexithymia</li> </ul>	<p>→ Emotional sharing of others' pain is shaped by relative positions in a social hierarchy such that underlying empathic neural responses are biased toward inferior-status compared with superior-status individuals. With higher levels of alexithymia, empathic responses in the AI decrease while watching others with an inferior status experiencing pain</p>
Frewen et al., 2006	TAS-20	<ul style="list-style-type: none"> <li>Study 1: Participants were administered the TAS-20, the <i>Clinician Administered PTSD Scale</i> (CAPS), the <i>Dissociative Experiences Scale</i> (DES), peritraumatic DES (P-DES), and the <i>Childhood Trauma Questionnaire</i> (CTQ)</li> <li>Study 2: Participants completed a trauma script imagery task during fMRI BOLD scanning</li> </ul>	<ul style="list-style-type: none"> <li>77 patients with PTSD</li> <li>45 controls</li> </ul>	<ul style="list-style-type: none"> <li>TAS-20 scores correlated positively with response in medial prefrontal cortex (mPFC), and negatively with responses in anterior cingulate cortex (ACC) and thalamus</li> <li>In 26 individuals with PTSD, TAS-20 scores correlated positively with activity in insula, posterior cingulate cortex (PCC), and thalamus, and negatively with activity in ACC</li> </ul>	<p>→ In patients with PTSD, levels of alexithymia were associated with activation in areas devoted to emotional self-awareness, executive control and self-regulation, and arousal-related body state mapping</p> <p>→ In controls, higher levels of alexithymia were associated with increased activation in mPFC and reduced activation in left thalamus and bilateral ACC, which might be related to increased self-reference but decreased cognitive control during the recall of traumatic memories</p>

Frewen et al., LEAS 2008a	<ul style="list-style-type: none"> <li>• One week before the fMRI session, participants completed the <i>Levels of Emotional Awareness Scale</i> (LEAS) and diagnostic interviews (DSM-IV &amp; PTSD)</li> <li>• Trauma script-driven imagery fMRI paradigm</li> </ul>	<ul style="list-style-type: none"> <li>• 25 trauma-exposed participants with the diagnosis of PTSD</li> <li>• 16 trauma-exposed participants without a diagnosis of PTSD or any other DSM-IV diagnosis</li> </ul>	<ul style="list-style-type: none"> <li>• Individuals with PTSD exhibited reduced emotional awareness and a significantly less adaptable response to the LEAS situations than controls</li> <li>• LEAS scores correlated positively with BOLD activity during trauma script-imagery in the ventral anterior cingulate cortex (vACC) in healthy non-psychiatric controls, whereas they correlated negatively with activation of vACC in PTSD patients</li> </ul>	<p>→ Patients with PTSD exhibit lower levels of emotional awareness and emotional adaptability relative to non-PTSD trauma-exposed controls</p> <p>→ Levels of emotional awareness are differentially associated with vACC response during trauma script-driven imagery PTSD patients compared to controls</p>
Frewen et al., TAS-20 2008b	<ul style="list-style-type: none"> <li>• Diagnostic interviews (SCID-I and CAPS), followed by CTQ and DES</li> <li>• fMRI scanning of the neutral and traumatic imagery conditions was repeated for three trials within test blocks</li> </ul>	<ul style="list-style-type: none"> <li>• 105 participants with a principal diagnosis of PTSD</li> <li>• 45 controls who met PTSD Criterion A but had no lifetime history of Axis I psychiatric disturbance</li> </ul>	<ul style="list-style-type: none"> <li>• Individuals with PTSD scored higher on alexithymia than the non-psychiatric control group</li> <li>• Functional neural responses to trauma-script imagery were associated with severity of alexithymia, including increased right posterior insula and ventral posterior cingulate activation, and decreased bilateral ventral anterior cingulate, ventromedial prefrontal, anterior insula, and right inferior frontal cortex activation</li> </ul>	<p>→ The findings reveal an association between perceived difficulty in identifying and describing emotional states and severity of PTSD symptoms, dissociation, and retrospectively reported childhood emotional neglect. Levels of alexithymia predicted brain activation associated with exposure to reminders of traumatic memories in areas known to be involved in emotional processing</p>

**Table 13.1** (cont.)

Study	Alexithymia measure	Experimental design/paradigm	Sample	Main results	Conclusions
Goerlich et al., 2017	TAS-20	<ul style="list-style-type: none"> <li>• Social incentive delay (SID) task and monetary incentive delay (MID) task</li> <li>• In both tasks, participants were required to respond to a visual cue within a certain time window to gain a reward. Cues informed the participant whether a reward could be gained</li> <li>• The relationship of alexithymia and empathy with neural activity in several a priori regions of interest (ROIs) was examined by means of partial correlations</li> </ul>	<ul style="list-style-type: none"> <li>• 45 healthy men</li> </ul>	<ul style="list-style-type: none"> <li>• Alexithymia modulated neural activity in several ROIs of the emotion and reward network, both during the anticipation of social and monetary rewards and in response to the receipt of monetary rewards</li> <li>• In contrast, empathy did not affect reward anticipation and modulated ROI activity only in response to the receipt of social rewards</li> </ul>	<p>→ Alexithymia is associated with significant differences in the neural processing of social and monetary rewards, both during reward anticipation and when receiving rewards</p>
Goerlich et al., 2013	TAS-20	<ul style="list-style-type: none"> <li>• Three a priori regions of the prosody network: superior temporal gyrus (STG), inferior frontal gyrus, amygdala</li> <li>• Participants performed an explicit task (emotional prosody categorization) and an implicit task (metrical stress evaluation) on the same prosodic stimuli</li> </ul>	<ul style="list-style-type: none"> <li>• 22 healthy participants</li> </ul>	<ul style="list-style-type: none"> <li>• Alexithymia was associated with a blunted response of the right STG and the bilateral amygdalae to angry, surprised, and neutral prosody</li> <li>• Individuals with difficulty describing feelings deactivated the left STG and the bilateral amygdalae to a lesser extent in response to angry compared with neutral prosody</li> </ul>	<p>→ Alexithymia may be linked to blunted neural responses to speech prosody</p> <p>→ Such restricted prosodic processing may contribute to problems in social communication associated with this personality trait</p>

<p>Heinzel et al., 2010</p> <p>TAS-20</p>	<ul style="list-style-type: none"> <li>50 fearful, 50 happy, and 50 neutral images of facial affect from the Ekman-Friesen inventory as well as 50 positive, 50 negative, and 50 neutral images taken from the International Affective Picture System</li> <li>All images were presented for 4 seconds each</li> </ul>	<ul style="list-style-type: none"> <li>30 HA</li> <li>30 LA</li> <li>All participants right-handed men</li> </ul>	<ul style="list-style-type: none"> <li>Increased activation of the supragenual ACC for different emotional valences as well as for different emotional stimuli in HA compared with LA</li> <li>Positive correlation of the ACC with the individual TAS-20 scores but no correlations with the individual <i>Beck Depression Inventory</i> scores</li> <li>No differences in amygdala activity</li> </ul>	<p>→ Supragenual ACC is activated more strongly in participants with HA</p> <p>→ This activation seems specifically related to alexithymia but not to depression</p>
<p>Ho, Wong, &amp; Lee, 2016</p> <p>TAS-20</p>	<ul style="list-style-type: none"> <li>Diffusion tensor imaging</li> <li>White matter connectivity</li> <li>Resting state functional connectivity</li> </ul>	<ul style="list-style-type: none"> <li>22 females diagnosed with first-episode major depressive disorder (MDD)</li> <li>21 matched healthy controls</li> </ul>	<ul style="list-style-type: none"> <li>A group interaction effect revealed distinct white matter correlations for MDDs versus controls</li> <li>In MDDs, alexithymia was associated with reduced functional connectivity in the right precentral gyrus and several right-hemispheric brain regions of the default mode network implicated in cognitive regulation</li> <li>In controls, alexithymia was correlated with increased functional connectivity between the right inferior-frontal gyrus triangularis and the right superior occipital lobe, associated with emotional response to external stimuli</li> </ul>	<p>→ MDDs and controls have distinct white matter correlates of alexithymia, and these corresponded to the existing proposed neural correlates for the cognitive and affective characteristics of alexithymia, respectively</p> <p>→ Extended impacts of these microstructural changes on remote functional networks might help to explain the distinct behavioral characteristics of alexithymia in these groups</p>

**Table 13.1** (cont.)

Study	Alexithymia measure	Experimental design/paradigm	Sample	Main results	Conclusions
Jongen et al., 2014	TAS-20	<ul style="list-style-type: none"> <li>• <i>Facially Expressed Emotion Labelling</i> (FEEL) Test</li> <li>• Whole-brain analysis and ROI analysis</li> </ul>	<ul style="list-style-type: none"> <li>• 20 HA</li> <li>• 20 LA</li> </ul>	<ul style="list-style-type: none"> <li>• HA showed deficits in the ability to recognize emotions from faces</li> <li>• This deficit was accompanied by reduced activation in the ACC, in areas that are part of the extended system of face recognition (amygdala, insula, striatum) and in other regions implicated in facial emotion recognition (e.g., inferior frontal gyrus, middle temporal gyrus, thalamus, parahippocampal gyrus, and middle frontal gyrus)</li> <li>• HA showed enhanced activity in the left superior parietal lobule</li> </ul>	<ul style="list-style-type: none"> <li>→ Deficits recognizing emotions from faces in HA are associated with reduced activity in a multitude of brain regions involved in emotional awareness and the extraction of meaning from faces</li> <li>→ Enhanced activation of the superior parietal lobule could reflect an involvement of the parietal mirror neuron system as a compensatory mechanism, possibly reflecting a focus on local facial features</li> </ul>
Kugel et al., 2008	TAS-20	<ul style="list-style-type: none"> <li>• Pictures of faces with sad, happy, and neutral expressions, masked by neutral faces</li> <li>• A detection task to assess participants' awareness of the masked emotional faces</li> <li>• ROI of amygdala</li> </ul>	<ul style="list-style-type: none"> <li>• 21 healthy volunteers</li> </ul>	<ul style="list-style-type: none"> <li>• Masked sad and happy facial emotions were associated with greater right amygdala activation than masked neutral faces</li> <li>• Alexithymia facet difficulties identifying feelings was negatively correlated with the neural response of the right amygdala to masked sad faces, even when controlling for depression and anxiety</li> </ul>	<ul style="list-style-type: none"> <li>• Reduced automatic amygdala responsivity may contribute to problems in identifying one's emotions in everyday life</li> <li>• Low spontaneous amygdala reactivity to sad faces with higher levels of alexithymia might implicate less engagement in the encoding of negative emotional stimuli</li> </ul>

Lemche et al., 2013	TAS-20	<ul style="list-style-type: none"> <li>• Happy and sad emotion expressions in increasing intensities from neutral (0%) through mild (50%) to intense (100%) in an implicit event-related fMRI design</li> <li>• Correlations between respective brain activations and scorers on the TAS-20 and its three subscales</li> <li>• Differential regression analyses for each alexithymia facet</li> </ul>	<ul style="list-style-type: none"> <li>• 9 patients with depersonalization disorder (DPD)</li> <li>• 12 healthy controls</li> </ul>	<ul style="list-style-type: none"> <li>• Alexithymia predicted a clinical diagnosis of DPD with a unique variance proportion of 38%</li> <li>• Differential regions of total alexithymia severity for happy emotion (globus pallidus externus) and sad emotion (dorsal anterior cingulate gyrus)</li> <li>• Specific associations between the TAS-20 subscales and brain responses to happy and sad expressions of emotion</li> </ul>	<p>→ Alexithymia plays a substantial role in emotional dysregulation in DPD, presumably based on impairments in interoception</p> <p>→ The alexithymia subscales affect neural responses to happy and sad emotions in different brain regions</p>
Leweke et al., 2004	TAS-20	<ul style="list-style-type: none"> <li>• Picture perception paradigm: emotional stimulation which included pictures evoking anxiety and disgust as well as neutral illustrations</li> <li>• Participants should assess valence, arousal, disgust, anxiety, surprise, sadness, anger, and happiness on a nine-point scale</li> </ul>	<ul style="list-style-type: none"> <li>• 8 patients with HA</li> <li>• 8 patients with LA</li> <li>• All patients were hospitalized for the treatment of psychosomatic diseases</li> </ul>	<ul style="list-style-type: none"> <li>• As response to negative affect arousing visual stimulation, HA vs. LA showed lower activation in the right medial prefrontal cortex and in the right amygdala</li> <li>• Results were significant for disgust</li> </ul>	<p>→ The results support the existence of a complex central feedback circuit consisting of regions of the prefrontal cortex and limbic structures to process negative affects</p> <p>→ The authors suggest that a fundamental factor for the emergence of alexithymia might be an inhibiting process between affect processing (e.g., medial prefrontal cortex, anterior cingulum) and affect generating structures (e.g., amygdala)</p>

**Table 13.1** (cont.)

Study	Alexithymia measure	Experimental design/paradigm	Sample	Main results	Conclusions
Liang et al., 2015	TAS-20	<ul style="list-style-type: none"> <li>Resting state fMRI and modularity network analysis to identify brain modules of a priori interest: default-mode network, salience network, executive control network, medial temporal lobe, and striatum</li> </ul>	<ul style="list-style-type: none"> <li>47 cocaine-dependent participants</li> <li>47 matched healthy controls</li> </ul>	<ul style="list-style-type: none"> <li>Cocaine-dependent individuals with reduced functional connections within the salience network exhibited higher levels of alexithymia</li> </ul>	<p>→ Organizational disruptions within the salience network may give rise to deficiencies in integrating sensations from the internal bodily milieu into coherent emotion experiences (i.e., alexithymia)</p> <p>→ These may in turn contribute to sustaining drug use to alleviate uncomfortable internal sensations without needing to identify negative emotional states</p>
Liemburg et al., 2012	BVAQ	<ul style="list-style-type: none"> <li>Resting state fMRI</li> <li>Independent component analysis was used to identify the default mode network (DMN)</li> </ul>	<ul style="list-style-type: none"> <li>20 HA</li> <li>18 LA</li> </ul>	<ul style="list-style-type: none"> <li>HA showed lower connectivity within areas of the DMN (medial frontal and temporal areas) compared with LA</li> <li>Resting state connectivity in HA was higher for the sensorimotor cortex, occipital areas, and right lateral frontal cortex</li> </ul>	<p>→ HA seem to have a diminished connectivity within the DMN</p> <p>→ This might contribute to lower emotional awareness and reduced self-referential processing in alexithymia</p>
Mantani et al., 2005	TAS-20	<ul style="list-style-type: none"> <li>Imagination task: subjects imagined a past happy (PH) event, a past sad (PS) event, a past neutral (PN) event, a future happy (FH) event, a future sad (FS) event, and a future neutral (FN) event</li> </ul>	<ul style="list-style-type: none"> <li>10 HA (7 males)</li> <li>10 LA (7 males)</li> </ul>	<ul style="list-style-type: none"> <li>Subjective ratings of both the vividness of the imagery and the felt intensity of emotion were higher in LA than in HA during PS and FS</li> </ul>	<p>→ Alexithymia is linked to reduced activation of the PCC during the imagination of (past and future) happy events</p> <p>→ This suggests that alexithymia is associated with a dysfunction of episodic memory</p>

	<ul style="list-style-type: none"> <li>Visual analog scales assessed the vividness of the imagery (range, 0–10), from imagining nothing to imagining extremely vividly; and the intensity of emotion during the imagery (range, 0–10), from feeling nothing to feeling extremely intensely</li> </ul>		<ul style="list-style-type: none"> <li>HA showed significantly less activation in the PCC during the PH and FH imagery conditions compared with REST, and during the FH imagery condition compared with the FN imagery condition</li> </ul>	retrieval regarding positive imagery
Mériaux et al., 2006	<ul style="list-style-type: none"> <li>Pictures of facial affect were presented</li> <li>Emotion decision: participants decided about the emotional expression of a face (fear vs. anger)</li> <li>Gender decision: participants decided about the gender</li> <li>Comparison of task-dependent changes in effective connectivity of dACC in individuals with good and with poor ability to cognitively process emotions using a psychophysiological interaction analysis</li> </ul>	<ul style="list-style-type: none"> <li>23 healthy female participants</li> </ul>	<ul style="list-style-type: none"> <li>Alexithymia covaried with changes in dACC activity during gender decisions; no correlation during emotion decisions</li> <li>Greater coupling of dACC with prefrontal regions in individuals with good ability to identify and communicate their emotional state</li> <li>Subjects with poor ability in this domain showed greater coupling between dACC and amygdala</li> </ul>	<p>→ Individual differences in the ability to identify and communicate one's emotional state are reflected by altered effective connectivity of the dACC with prefrontal and limbic regions</p> <p>→ Evidence for a theoretical model that posits that a discommunication between limbic areas and the neocortex impairs cognitive processing of emotions</p>
Moriguchi et al., 2007	<ul style="list-style-type: none"> <li>Visual perception of pictures depicting human hands and feet in painful situations</li> </ul>	<ul style="list-style-type: none"> <li>16 HA</li> <li>14 LA</li> </ul>		<p>→ Hypofunction in the DLPFC, brain stem, cerebellum, and ACC in combination with subjectively reduced ratings suggest that alexithymia is associated</p>

**Table 13.1** (cont.)

Study	Alexithymia measure	Experimental design/paradigm	Sample	Main results	Conclusions
		<ul style="list-style-type: none"> <li>Subjective pain ratings of the pictures and empathy-related psychological scores were also compared between the two groups</li> </ul>		<ul style="list-style-type: none"> <li>HA showed less activation in the left dorsolateral prefrontal cortex (DLPFC), the dorsal pons, the cerebellum, and the left caudal ACC within the pain matrix</li> <li>Increased activation in this group was observed in the right insula and inferior frontal gyrus</li> <li>Moreover, they scored lower on pain ratings and on scores related to mature empathy</li> </ul>	<p>with cognitive impairments; particularly in executive and regulatory aspects, of emotional processing and support the importance of self-awareness in empathy</p>
Moriguchi et al., 2006	TAS-20, Structured Interview	<ul style="list-style-type: none"> <li>Mentalizing animation task: visual animations for assessing theory of mind (ToM): animations with two triangles acting like humans (ToM) versus animations with two triangles moving randomly (control)</li> <li>Verbal responses to scripts coded for intentionality and appropriateness</li> <li>Mentalizing and <i>Interpersonal Reactivity Index</i> (IRI) scores assessed</li> </ul>	<ul style="list-style-type: none"> <li>16 HA</li> <li>14 LA</li> </ul>	<ul style="list-style-type: none"> <li>HA had lower mentalizing and IRI perspective-taking scores and less activation in the right medial prefrontal cortex</li> <li>Medial prefrontal activity was positively correlated with mentalizing scores and IRI perspective-taking scores</li> </ul>	<p>Individuals with HA seem to have a deficit in mentalizing associated with an inability to take the perspective of others</p> <p>→ This suggests that the skills involved in comprehending the self and others are interrelated and play an important role in emotion regulation</p>
Pouga et al., 2010	BVAQ and its five factors	<ul style="list-style-type: none"> <li>Participants passively observed fearful body expressions</li> </ul>	<ul style="list-style-type: none"> <li>13 men with HA</li> <li>12 men with LA</li> <li>9 men with intermediate levels</li> </ul>		<p>→ Results reveal interaction between ACC and PM in sustaining self-regulation of one's own emotional state in response to threatening social signals</p>

→ On the behavioral level, this neural mechanism could account for the description of the “cold-blooded” personality and “stiff wooden posture” of prototypic individuals with alexithymia

- Right amygdala response to fearful stimuli correlated negatively with facet difficulty identifying feelings
- Activity in premotor cortex was linked to reduced subjective emotional reactivity
- Between-group comparisons revealed greater ACC activity in HA than in LA
- The relationship between ACC and premotor cortex (PM) was in opposite direction in individuals with high (negative link) and low (positive link) alexithymia

→ A reduced automatic reactivity of the amygdala and visual occipito-temporal areas could implicate less automated engagement in the encoding of emotional stimuli in HA

→ The observed low spontaneous insular and amygdala reactivity could be related to an attenuation of basic emotional experiences, which may contribute to problems identifying and differentiating one’s feelings

- Independent from trait anxiety and depression, alexithymia levels correlated negatively with activation to masked sad and happy faces in several regions of interest (in particular, insula, superior temporal gyrus, middle occipital, and parahippocampal gyrus)
- Levels of alexithymia were negatively correlated with response of the left amygdala to masked sad faces

Reker et al., 2010

TAS-20

- Automatic brain reactivity to briefly presented pictures of sad, happy, and neutral facial expression masked by neutral faces
- 33 healthy women

**Table 13.1** (cont.)

Study	Alexithymia measure	Experimental design/paradigm	Sample	Main results	Conclusions
Suslow et al., 2016	TAS-20	<ul style="list-style-type: none"> <li>Brain activation in response to sad, happy, neutral, and no facial expression (presented for 33 ms and masked by neutral faces) was measured</li> </ul>	<ul style="list-style-type: none"> <li>26 MDD patients with HA</li> <li>26 MDD patients with LA</li> </ul>	<ul style="list-style-type: none"> <li>Patients with HA showed less activation in response to masked sad and happy faces (compared with neutral ones) in right frontal regions and right caudate nuclei, compared with LA</li> </ul>	<p>→ Alexithymia has a modulating effect on automatic emotion processing in clinical depression, which could be associated with functional deficits of the right hemisphere</p>
Sutherland et al., 2013	TAS-20	<ul style="list-style-type: none"> <li>Overnight-deprived smokers and non-smokers completed six neuroimaging assessments on different days both in the absence of, and following, varenicline and/or nicotine administration</li> <li>In this secondary analysis of data from a larger study trait alexithymia and state tobacco craving were assessed using self-reports</li> <li>Resting state functional connectivity (rsFC) of bilateral insular subregions (anterior, middle, posterior) and dACC was measured</li> </ul>	<ul style="list-style-type: none"> <li>24 smokers</li> <li>20 non-smokers</li> </ul>	<ul style="list-style-type: none"> <li>Higher alexithymia in smokers predicted reduced rsFC strength between the right anterior insula (AI) and ventromedial prefrontal cortex (vmPFC)</li> <li>Higher alexithymia also predicted more severe tobacco craving during withdrawal</li> <li>The identified AI–vmPFC circuit fully mediated this alexithymia–craving relation</li> <li>Higher alexithymia levels predicted decreased AI–vmPFC rsFC, and, in turn, decreased AI–vmPFC rsFC predicted increased craving during withdrawal</li> <li>This AI–vmPFC mediational effect was not observed following drug administration</li> </ul>	<p>→ A weakened right AI–vmPFC functional circuit confers increased liability for tobacco craving during abstinence from smoking</p> <p>→ Individual differences in alexithymia and/or AI–vmPFC functional coupling may be relevant factors for smoking cessation success</p>

van der Velde et al., 2014	BVAQ	<ul style="list-style-type: none"> <li>Using fMRI, participants were scanned while viewing, reappraising, or suppressing negative emotional pictures</li> </ul>	<ul style="list-style-type: none"> <li>51 healthy participants</li> </ul>	<ul style="list-style-type: none"> <li>Cognitive, but not affective alexithymia was associated with lower activation in emotional attention and recognition networks during emotion perception</li> <li>However, there were no alexithymia-related differences during emotion regulation, neither reappraisal nor suppression</li> </ul>	<p>→ Alexithymia may result from an early emotion processing deficit rather than compromised frontal circuits subserving higher-order emotion regulation processes</p>
Zotov et al., 2011	TAS-20	<ul style="list-style-type: none"> <li>Experimental group: received feedback regarding left amygdala activity, instructed to increase signal by contemplating positive autobiographical memories</li> <li>Control group: same task but received sham feedback from the left horizontal segment of the intraparietal sulcus (HIPS) region</li> </ul>	<ul style="list-style-type: none"> <li>28 healthy men</li> </ul>	<ul style="list-style-type: none"> <li>In the LA, a significant BOLD signal increase due to rtfMRI neurofeedback training was observed in the experimental group versus the control group</li> <li>The training effect in the experimental group on LA BOLD activity was negatively correlated with scores on the difficulty identifying feelings facet of the TAS-20</li> </ul>	<p>→ Healthy subjects can learn to regulate their amygdala activation using rtfMRI neurofeedback</p> <p>→ HA impede people's ability to regulate left amygdala activity via training</p>

**Table 13.2** Transcranial magnetic stimulation (TMS), positron emission tomography (PET), and computed tomography (CT) studies.

Study	Alexithymia measure	Experimental design/paradigm	Sample	Main results	Conclusions
Grabe et al., 2004	TAS-20 (HA $\geq 61$ )	<ul style="list-style-type: none"> <li>Hypothesis of an interhemispheric transfer deficit investigated with a transcallosal inhibition paradigm (TMS)</li> <li>Transcallosal conduction time (TCT) reflects the time that an inhibitory impulse needs to cross the corpus callosum (CC) and reach the corresponding contralateral area of the brain; prolonged TCT would be indicative of CC dysfunction</li> </ul>	<ul style="list-style-type: none"> <li>20 participants (10 women) with TAS-20 scores above the clinical cut-off <math>\geq 61</math> (HA)</li> <li>42 controls (21 women) with TAS-20 scores below the clinical cut-off (LA)</li> </ul>	<ul style="list-style-type: none"> <li>Interaction between alexithymia and gender</li> <li>Men with HA had shorter bidirectional TCTs than controls and a significantly shorter left to right TCT than controls</li> <li>Women: no difference</li> <li>Left to right TCT was not significantly different from the right to left TCT in any group</li> </ul>	<p>→ The results do not support the hypothesis of a dysfunction of the CC in alexithymia</p> <p>→ Instead, transcallosal inhibition seems to be facilitated in relation to alexithymia</p>
Hogeveen et al., 2016	TAS-20	<ul style="list-style-type: none"> <li>Prospective study of male Vietnam war veterans with penetrating traumatic brain injuries (TBI), and non-brain-injured combat veterans</li> <li>Four groups: patients with <math>&gt;15\%</math> damage of anterior insula, <math>&lt;15\%</math> damage, no damage, and healthy controls</li> <li>Non-contrast axial CT</li> </ul>	<ul style="list-style-type: none"> <li>129 TBI patients</li> <li>33 controls</li> </ul>	<ul style="list-style-type: none"> <li>Alexithymia levels varied across groups, with <math>&gt;15\%</math> anterior insula (AI) damage being linked to higher alexithymia relative to all other groups</li> <li>Increased AI damage predicted increased alexithymia after controlling for ACC damage and total lesion volume</li> </ul>	<p>→ AI damage is associated with elevated levels of alexithymia whereas ACC damage is not</p> <p>→ Pronounced AI damage is linked to increased levels of alexithymia, providing critical evidence that this region supports emotional awareness</p>

Kano et al., 2003	TAS-20	<ul style="list-style-type: none"> <li>• PET study</li> <li>• Brain activity measured in HA when viewing a range of emotional face expressions</li> <li>• Regional cerebral blood flow (rCBF) was measured while the participants looked at angry, sad, and happy faces with varying emotional intensity as well as neutral faces</li> </ul>	<ul style="list-style-type: none"> <li>• 12 HA men</li> <li>• 12 LA men</li> </ul>	<ul style="list-style-type: none"> <li>• HA men exhibited lower rCBF in the inferior and middle frontal cortex, OFC, inferior parietal cortex, and occipital cortex in the right hemisphere than LA men, for all three emotions compared to neutral faces</li> <li>• In addition, they showed higher rCBF in the superior frontal cortex, inferior parietal cortex, and cerebellum in the left hemisphere</li> <li>• The ACC and insula were less activated in HA men in response to angry faces than to neutral faces</li> </ul>	<p>→ HA is associated with differences in the processing of facial emotions such that regions important for emotion processing are underactivated in the right hemisphere, while regions in the left hemisphere are more activated than in LA</p> <p>→ These differences may account for the disorder of affect regulation and consequent peculiar behavior in HA</p>
Kano et al., 2007	TAS-20, three subscales, cut-off $\geq 61$	<ul style="list-style-type: none"> <li>• PET study</li> <li>• Hypothesis: Alexithymia is linked to an amplification of unpleasant internal signals resulting in higher sensitivity to visceral stimulation</li> <li>• Brain activity, blood neuroendocrine levels, and subjective perception were measured in response to visceral stimulation induced by a barostat bag inserted into the colon</li> </ul>	<ul style="list-style-type: none"> <li>• 45 healthy participants (11 women)</li> <li>• 10 participants with TAS-20 scores <math>\geq 61</math></li> </ul>	<ul style="list-style-type: none"> <li>• The 10 HA showed higher activation in the pregenual ACC, right insula, and midbrain during colonic distension</li> <li>• Alexithymia scores correlated with activity in the right insula and orbital gyrus and with blood adrenaline levels</li> </ul>	<p>→ Alexithymia is associated with hypersensitivity to visceral stimulation, supporting the hypothesis of somatosensory amplification associated with alexithymia</p>

**Table 13.2** (cont.)

Study	Alexithymia measure	Experimental design/paradigm	Sample	Main results	Conclusions
Kano, Ito, & Fukudo, 2011	TAS-20, cut-off $\geq 61$ , <i>State-Trait Anxiety Inventory</i> (STAI) as confounding factor	<ul style="list-style-type: none"> <li>The colon was stimulated with a bag pressure of 0, 20, and 40 mmHg for 80 s</li> </ul>	<ul style="list-style-type: none"> <li>10 HA</li> <li>13 LA</li> </ul>	<ul style="list-style-type: none"> <li>Especially participants scoring high on difficulty identifying feelings perceived strong pain, urgency for defecation, stress, anxiety, and slight sleepiness</li> </ul>	<p>→ The findings are important to elucidate the influence of alexithymia on brain-gut function, particularly to understand the pathophysiology of functional gastrointestinal disorders</p>
		<ul style="list-style-type: none"> <li>PET study</li> <li>4 trials of <i>Iowa Gambling Task</i> (IGT) (disadvantageous vs. advantageous decks) → choose between high gains with a risk for even higher losses and low gains with a risk for smaller losses</li> <li>Score: number of choices from the advantageous decks (C and D) minus the number of choices from the disadvantageous decks (A and B) for 100 trials</li> <li>2 visuomotor control tasks</li> </ul>	<ul style="list-style-type: none"> <li>HA failed to learn an advantageous decision-making strategy; their performance differed markedly from LA in the fourth IGT trial</li> <li>At the neural level, HA showed lower rCBF in the medial frontal area (BA10) and higher rCBF in the caudate and occipital areas in the first and second IGT trials (learning phase)</li> </ul>	<p>→ BA10 (medial frontal) activity may be associated with using internal signals during affective evaluation, which is crucial for successful decision-making</p> <p>→ Reduced BA10 activity in HA suggests that they may not be able to use emotion-based biasing signals to achieve advantageous decision-making</p>	

Karlsson et al., 2008	TAS-20	<ul style="list-style-type: none"> <li>• PET study</li> <li>• Four films were projected on a video screen to induce each of three emotional conditions (neutral, amusement, sadness)</li> </ul>	<ul style="list-style-type: none"> <li>• 10 HA women</li> <li>• 10 LA women</li> </ul>	<ul style="list-style-type: none"> <li>• In response to emotional stimuli, HA activated more parts of their sensory and motor cortices and insula, especially on the left side, and less of their anterior cingulate, compared with the control group</li> </ul>	<p>→ HA women seem to over-activate their "bodily" brain regions, implying a different mode of emotion processing</p> <p>→ This may be related to their tendency to experience physical symptoms</p>
Lang et al., 2011	TAS-20, three subscales, cut-off $\geq 61$	<ul style="list-style-type: none"> <li>• TMS study</li> <li>• Aim: To reveal whether cortical inhibition is modulated by alexithymia in borderline personality disorder (BPD)</li> <li>• Hypothesis: Higher levels of alexithymia would be associated with deficits in cortical inhibition (as reflected in a shorter cortical silent period) and, possibly, with a less active inhibition in the interhemispheric transfer paradigm (as reflected by prolonged TCTs, i.e., duration of stimulus transfer from one hemisphere to the other)</li> </ul>	<ul style="list-style-type: none"> <li>• 15 women BPD patients with alexithymia scores <math>\geq 61</math> (HA)</li> <li>• 14 women BPD patients with alexithymia scores <math>&lt; 61</math> (LA)</li> </ul>	<ul style="list-style-type: none"> <li>• HA showed a shortened cortical silent period (CSP) compared with LA and controls</li> <li>• Group differences were larger in the left hemisphere</li> <li>• An inverse correlation was found between the TAS-20, the left CSP, and the left transcallosal conduction time</li> </ul>	<p>→ Reduced CSP is not a borderline-specific feature but is rather modulated by levels of alexithymia in patients with BPD</p> <p>→ The findings indicate that alexithymia is associated with facilitated transcallosal inhibition and changes in GABAergic neurotransmission</p>

**Table 13.2** (cont.)

Study	Alexithymia measure	Experimental design/paradigm	Sample	Main results	Conclusions
Richter et al., 2006	TAS-20 (cut-off $\geq 61$ and $< 51$ )	<ul style="list-style-type: none"> <li>TMS study</li> <li>TMS over primary motor cortex to measure transcallosal inhibition, i.e., TMS-induced inhibitory cortical activity that is mediated via the corpus callosum</li> </ul>	<ul style="list-style-type: none"> <li>19 HA psychiatric inpatients (7 men)</li> <li>12 LA psychiatric inpatients (7 men)</li> </ul>	<ul style="list-style-type: none"> <li>HA had shorter bidirectional TCTs than LA (bidirectional; i.e., both right to left TCT and left to right TCT)</li> <li>Neither gender nor depression levels had any significant effects on TCTs</li> </ul>	<p>→ Alexithymia is associated with facilitated (rather than prolonged) bidirectional transcallosal inhibition in psychiatric patients, independent of gender and depression</p>
Romei et al., 2008	TAS-20 (cut-off $\geq 58$ and $< 45$ )	<ul style="list-style-type: none"> <li>TMS study</li> <li>Aim: To test the hypothesis of a transcallosal interhemispheric transfer deficit in alexithymia by means of paired-pulse TMS</li> <li>A first (conditioning) magnetic stimulus was delivered to one motor cortex, followed by a second (test) stimulus to the opposite hemisphere at different interstimulus intervals (2, 4, 6, 8, 10, 12, 14, 16, 18, and 20 ms) for both motor cortices.</li> <li>Motor evoked responses were recorded from the abductor digiti minimi muscles</li> </ul>	<ul style="list-style-type: none"> <li>16 HA (8 men) with alexithymia scores</li> <li>16 age- and gender-matched LA</li> </ul>	<ul style="list-style-type: none"> <li>HA showed reduced transcallosal inhibition as compared with LA at the interstimulus intervals of 10, 12, and 14 ms</li> <li>This reduced transcallosal inhibition was observed in both directions, from the left to the right hemisphere and vice versa</li> </ul>	<p>→ The results indicate functional differences in transcallosal interactions in HA compared with LA and support the hypothesis of an interhemispheric transfer deficit associated with alexithymia</p> <p>→ The observed reduced transcallosal inhibition could be linked to a reduced coordination and integration of the specialized activities of the two cerebral hemispheres with higher levels of alexithymia</p>

**Table 13.3** Structural magnetic resonance imaging studies (MRI).

Study	Alexithymia measure	Methods	Sample	Main results	Conclusions
Borsci et al., 2009	TAS-20 (cut-offs $\geq 61$ and $> 51$ and continuous)	<ul style="list-style-type: none"> <li>Voxel-based morphometry (VBM)</li> <li>Group analysis between participants with alexithymia scores <math>\geq 61</math> (HA) versus those with scores <math>&lt; 51</math> (LA)</li> <li>Correlation of TAS-20 scores on the whole sample</li> <li>Additional group analysis on 14 participants with alexithymia scores <math>\geq 61</math> and 14 with scores <math>&lt; 51</math> matched for age</li> <li>Significance threshold <math>p &lt; 0.005</math> uncorrected</li> </ul>	<ul style="list-style-type: none"> <li>54 women participants: 14 HA (TAS-20 scores <math>\geq 61</math>), 30 LA (TAS-20 scores <math>&lt; 51</math>)</li> </ul>	<ul style="list-style-type: none"> <li>HA had smaller GM volume in the ACC and middle temporal gyrus</li> <li>Additional smaller clusters were located in the anterior insula, OFC, and superior temporal sulcus</li> <li>The correlation analysis confirmed the pattern of results mainly in the left hemisphere</li> </ul>	<p>→ Alexithymia is associated with smaller GM volumes in a specific set of cerebral structures that are known to be involved in decision-making and self-awareness, with the most pronounced differences observed in the ACC</p> <p>→ The ability to process emotional aspects of the self correlates with the morphology of these structures</p>
Goerlich-Dobre et al., 2014	TAS-20 (cut-offs $\geq 61$ and $< 35$ ) BVAQ (continuous)	<ul style="list-style-type: none"> <li>VBM</li> <li>Aim: To reveal neural structures linked to the affective versus the cognitive dimensions of alexithymia</li> <li>Two group analyses, one on the cognitive, one on the affective alexithymia dimension</li> <li>Cluster-level family-wise error (FWE) correction for multiple comparisons</li> </ul>	<ul style="list-style-type: none"> <li>40 participants: 20 (10 men) with TAS-20 scores <math>\geq 61</math>, 20 (9 men) with TAS-20 scores <math>&lt; 35</math></li> <li>Subset of 32 (13 men) tested with the BVAQ (affective dimension)</li> </ul>	<ul style="list-style-type: none"> <li>The cognitive dimension was associated with larger GM volumes in the right posterior insula</li> <li>The affective dimension was associated with larger GM volume in the right dorsal ACC/middle cingulate cortex</li> </ul>	<p>→ Preliminary evidence for a different morphological basis of the cognitive and affective alexithymia dimensions</p>

**Table 13.3** (cont.)

Study	Alexithymia measure	Methods	Sample	Main results	Conclusions
Goerlich-Dobre et al., 2015a	BVAQ (continuous)	<ul style="list-style-type: none"> <li>VBM</li> <li>Comparing differences in GM volumes between the cognitive and affective dimensions of alexithymia and empathy in women and men</li> <li>Empathy: <i>Interpersonal Reactivity Index</i></li> <li>Cluster-level FWE correction for multiple comparisons</li> </ul>	<ul style="list-style-type: none"> <li>125 healthy participants (55 men)</li> <li>18–42 years old</li> </ul>	<ul style="list-style-type: none"> <li>Left amygdala volumes were related to alexithymia and empathy in opposite directions, showing a negative relationship with the cognitive alexithymia dimension but a positive correlation with both empathy dimensions</li> <li>Men – but not women – with difficulty fantasizing, part of the affective alexithymia dimension, had reduced GM volumes in MCC</li> </ul>	<ul style="list-style-type: none"> <li>The left amygdala is a key correlate of both alexithymia and empathy, independent from age</li> <li>Sex plays an important role regarding the structural correlates of the affective alexithymia dimensions</li> <li>The results provide evidence for distinct neuroanatomical profiles of the two alexithymia dimensions, whereas only little structural differences seem to exist between the two empathy dimensions</li> </ul>
Goerlich-Dobre et al., 2015b	BVAQ (median-split)	<ul style="list-style-type: none"> <li>VBM</li> <li>Comparing GM and WM volumes between the alexithymia dimensions and between four alexithymia subtypes, created via a median-split on each dimension: Type 1: both dimensions impaired; Type 2: only cognitive dimension impaired; Type 3: only affective dimension impaired; Type 4 (lexithymics): no impairment on either dimension</li> <li>ROI GM analyses on 13 anatomical a priori regions</li> </ul>	<ul style="list-style-type: none"> <li>118 healthy participants (51 men)</li> <li>18–42 years old</li> </ul>	<ul style="list-style-type: none"> <li>Type 1 and Type 2 alexithymia showed reduced GM in the left amygdala and the thalamus</li> <li>The cognitive dimension was associated with GM volume reductions in the right amygdala, left posterior insula, preuncus, caudate, hippocampus, and parahippocampus</li> <li>Type 3 alexithymia showed GM volume reduction in middle cingulate cortex (MCC)</li> </ul>	<ul style="list-style-type: none"> <li>The two alexithymia dimensions have a differential impact on brain morphology</li> <li>The cognitive dimension is associated with pronounced GM volume reductions in a network of limbic and paralimbic regions, including the amygdala, insula, and preuncus</li> <li>The affective dimension is associated with MCC volume reductions</li> <li>There is evidence for separable neuroanatomical representations of different alexithymia subtypes</li> </ul>

	<ul style="list-style-type: none"> <li>Cluster-level FWE correction for multiple comparisons</li> </ul>		<ul style="list-style-type: none"> <li>The affective dimension was associated with larger subgenual ACC volume</li> <li>The intermediate types 2 and 3 exhibited distinct GM volume reductions and larger corpus callosum (CC) volumes than alexithymics (Type 4)</li> </ul>	
Grabe et al., 2014	<ul style="list-style-type: none"> <li>TAS-20 (continuous)</li> <li>VBM</li> <li>Part of "Study of Health in Pomerania (SHIP)": two-stage stratified cluster sample of adults aged 20–79 years (baseline) of 6,267 participants</li> <li>Baseline and follow-up study 5 years after (SHIP-1), and 10 years after (SHIP-2); concurrent to SHIP-2 a new sample (SHIP-Trend-0) was drawn</li> <li>Participants from SHIP-2 and SHIP-Trend-0 included</li> </ul>	<ul style="list-style-type: none"> <li>1,685 participants</li> <li>≤65 years of age</li> <li>43 participants with TAS-20 scores &gt;60</li> <li>No history of major depression</li> </ul>	<ul style="list-style-type: none"> <li>TAS-20 total scores were associated with less GM volumes of the bilateral dACC</li> <li>The factor DIF was associated with less GM volume in the dACC, left middle and inferior temporal gyrus, left fusiform gyrus (women), and cerebellum</li> <li>Absolute GM volume analyses also revealed associations of the factors DDF and EOT with dACC volumes</li> </ul>	<ul style="list-style-type: none"> <li>Lower GM volume in the dACC represents a major structural correlate of alexithymia</li> <li>Specifically difficulties identifying one's feelings seem associated with GM volume reductions in temporal areas important for language and semantic processing, part of cognitive emotion processing</li> </ul>
Gündel et al., 2004	<ul style="list-style-type: none"> <li>TAS-20 (continuous)</li> <li>Manual tracing</li> <li>Surface area measurements of the anterior cingulate gyrus (ACG) were performed on reformatted sagittal views in both hemispheres</li> </ul>	<ul style="list-style-type: none"> <li>100 healthy students (51 men, mean age 25.6 years)</li> </ul>	<ul style="list-style-type: none"> <li>Right ACG surface area significantly correlated with TAS-20 total score</li> <li>After controlling for the temperament-character dimensions harm avoidance, self-directedness, and self-transcendence, the correlation between TAS-20 total and right ACG became non-significant in women, but was only slightly reduced in men</li> </ul>	<ul style="list-style-type: none"> <li>The size of the right ACG correlates significantly with levels of alexithymia, especially in men. In women, this association may be less specific to alexithymia</li> <li>There may be a partial lateralization of human emotion processing, especially regarding negative emotions</li> </ul>

**Table 13.3** (cont.)

Study	Alexithymia measure	Methods	Sample	Main results	Conclusions
Ihme et al., 2013	TAS-20 (cut-off $\geq 50$ )	<ul style="list-style-type: none"> <li>• VBM</li> <li>• ROI analysis</li> <li>• Whole-brain analysis</li> <li>• Correction for multiple comparisons using clustering (identification of a minimum cluster size by Monte Carlo simulation)</li> </ul>	<ul style="list-style-type: none"> <li>• 17 HA</li> <li>• 17 gender matched LA</li> </ul>	<ul style="list-style-type: none"> <li>• The ROI analysis indicated that HA had less GM volume in the ACC, amygdala, and anterior insula compared with LA</li> <li>• The whole-brain analysis additionally revealed less GM volume in the middle temporal gyrus</li> </ul>	<ul style="list-style-type: none"> <li>➔ HA show GM volume reductions in several emotion-related brain areas</li> <li>➔ These structural differences might contribute to functional alterations in the processing of emotions</li> </ul>
Kubota et al., 2011	TAS-20 (continuous)	<ul style="list-style-type: none"> <li>• VBM</li> <li>• Testing association between alexithymia and regional GM alterations in patients with schizophrenia</li> </ul>	<ul style="list-style-type: none"> <li>• 14 patients with schizophrenia</li> <li>• 24 age-, sex-, and education-level matched healthy controls</li> </ul>	<ul style="list-style-type: none"> <li>• TAS-20 total scores were higher in patient group</li> <li>• Bilateral ventral striatum and left ventral premotor cortex volumes were negatively correlated with alexithymia in the healthy controls</li> <li>• GM volume in the left supramarginal gyrus was negatively correlated with TAS-20 total scores and with DIF in the patient group</li> </ul>	<ul style="list-style-type: none"> <li>➔ Schizophrenia is associated with higher levels of alexithymia</li> <li>➔ GM alterations of the left supramarginal gyrus may constitute a key pathology underlying alexithymia in schizophrenia</li> <li>➔ This association may be related to deficits in self-other distinction, self-disturbance, and language processing in schizophrenia</li> </ul>
Paradiso et al., 2008	TAS-20 (continuous)	<ul style="list-style-type: none"> <li>• Manual tracing</li> <li>• Correlation analyses between functionally distinct ACC subregions, age, and alexithymia features</li> </ul>	<ul style="list-style-type: none"> <li>• 24 healthy volunteers aged 24–79 years</li> </ul>		<ul style="list-style-type: none"> <li>➔ Older age is associated with higher levels of alexithymia</li> <li>➔ Deterioration in the rostral subregion of the ACC may contribute to greater alexithymic features in older age and</li> </ul>



**Table 13.3** (cont.)

Study	Alexithymia measure	Methods	Sample	Main results	Conclusions
Van der Velde, 2014	BVAQ (continuous)	<ul style="list-style-type: none"> <li>VBM</li> <li>Examine whether the affective and cognitive dimensions of alexithymia are associated with different anatomical profiles</li> <li>Cluster-level FWE correction for multiple comparisons</li> </ul>	<ul style="list-style-type: none"> <li>57 healthy participants (29 men)</li> </ul>	<ul style="list-style-type: none"> <li>The cognitive dimension was related to lower dorsal ACC volume</li> <li>The affective dimension was associated with lower GM volume in the medial OFC and lower white matter volume in the superior longitudinal fasciculus near the angular gyrus</li> <li>Total scores on both dimensions were unrelated to regional GM and WM volumes</li> </ul>	<ul style="list-style-type: none"> <li>There may be two separable neural systems underlying alexithymia</li> <li>Cognitive emotion processing difficulties are related to lower GM volume in a region involved in emotion recognition and regulation</li> <li>Affective difficulties appear associated with lower volume in an emotion induction region and lower white matter in a tract connecting regions of a fantasizing network</li> </ul>
Zhang, 2011	TAS-20	<ul style="list-style-type: none"> <li>VBM for GM</li> <li>Fractional anisotropy for WM</li> <li>Whole-brain analysis</li> <li>ROI analysis</li> <li>Nicotine dependence (Fagerström Test of Nicotine Dependence)</li> </ul>	<ul style="list-style-type: none"> <li>48 nicotine-dependent participants</li> <li>48 matched non-smoking controls</li> </ul>	<ul style="list-style-type: none"> <li>Gray matter density was lower in left PFC in high pack-years' smokers and was inversely related to pack-years</li> <li>TAS-20 total scores and DIF factor were associated with higher GM density in left insular cortex in smokers</li> <li>No alexithymia-related GM density differences in the control group</li> </ul>	<ul style="list-style-type: none"> <li>Chronic tobacco use is associated with low prefrontal gray matter density</li> <li>Increased GM density in the anterior insula with higher levels of alexithymia may underlie a greater reliance on bodily sensations during emotion processing</li> <li>Lack of alexithymia-related findings in the control group probably due to the small range of TAS-20 scores in this group</li> </ul>

Notes: GM: gray matter; WM: white matter.

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