ALEXITHYMIA: STATE OF THE ART AND CONTROVERSIES. CLINICAL AND NEUROSCIENTIFIC EVIDENCE

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ALEXITHYMIA: STATE OF THE ART AND CONTROVERSIES. CLINICAL AND NEUROSCIENTIFIC EVIDENCE

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SECTION 3
NEUROBIOLOGICAL CORRELATES OF ALEXITHYMIA

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EDITORIAL
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Editorial: Alexithymia: State of the Art and Controversies. Clinical and Neuroscientific Evidence

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Editorial on the Research Topic

Alexithymia: State of the Art and Controversies. Clinical and Neuroscientific Evidence

The relevance of alexithymia has grown exponentially in the past decades. It is currently considered a relevant concept for several psychological and physical disorders (Taylor and Bagby, 2004; Di Tella and Castelli, 2013, 2016), and increasing attention is paid to its relationships with other psychological constructs. From a neuroscientific standpoint, an increasing number of studies has been aiming at shedding light on the neuro-anatomical/-functional correlates of alexithymia. The studies included in the present research topic reflect this manifold panorama. Specifically, some studies investigated the relationship between alexithymia and other clinical conditions, i.e., gastrointestinal/hepatological disorders, headache, substance use disorders, autism spectrum disorders (ASD), functional blindness and fibromyalgia. A second block of studies focused on the association between alexithymia and other clinically relevant psychological constructs such as type-D personality, self-harm, emotional recognition and awareness, implicit and explicit positive and negative affectivity. Finally, three studies analyzed neurological/neuro-vegetative aspects.

Among those articles that investigate the prevalence and the impact of alexithymia in medical disorders, Carrozzino and Porcelli systematically reviewed the literature investigating the role of alexithymia in "organic" and "functional" gastrointestinal disorders. Alexithymia, and in particular the difficulty identifying and communicating feelings, were found to be more prevalent in functional gastrointestinal disorders (FGIDs) than in organic ones (i.e., inflammatory bowel disease or liver diseases), with a prevalence of 60% or more vs. 30–50%, respectively. Empirical evidence also suggested that alexithymia is mainly associated to the subjective dimension of health perception, including somatization, symptom persistence, and, above all, negative treatment outcomes. Kano et al. confirmed the association between alexithymia and FGIDs, focusing on the possible mechanism underlying this association. Although empirical evidence proposed several contributing factors, such as somatosensory amplification, visceral hypersensitivity or alteration of the stress response system, the specific mechanism linking alexithymia and FGIDs still remains unclear. The fact that alexithymia is mainly associated to the clinical outcomes related to the subjective dimension of health perception was confirmed by a study on a different functional syndrome, i.e., fibromyalgia. Indeed, Tesio et al. found that alexithymia contributes both directly and indirectly, through the mediation of depressive symptoms, to worsen the impact that this chronic pain pathology has on the patients' quality of life, especially regarding their psychosocial functioning. Another rare functional syndrome, a conversion disorder called non-organic vision loss (NOVL), was investigated by the research paper of Scarpina et al. They found that two patients with NOVL judged themselves as competent in emotional processing on the Toronto Alexithymia

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Scale (TAS-20; Bagby et al., 1994a,b), but showed a selective deficit in efficiently recognizing the emotion of fear in a behavioral experimental task. These data suggested a mismatch between the patients' subjective evaluation and their actual emotional processing performance.

Natalucci et al. reviewed the few studies on the relation between alexithymia and primary headache (e.g., migraine and tension type headache) in children and adolescents. A general consensus on high levels of alexithymia in this population emerged. The authors suggested that the association between alexithymia and headache could be moderated by insecure attachment or by an incomplete development of emotive competency, which may result in a deficit in emotional regulation and expression. The difficulties in emotional regulation and the lack of emotional awareness, possibly consequent to alexithymia, could compromise the understanding of others' emotions, giving rise to problems in social interaction. The deficit in social competences of people with ASD prompted several authors to investigate the association between alexithymia and ASD. Aiming to evaluate the state of the art, Poquérusse et al. argued that, in spite of the high amount of studies focusing on emotional, social and cognitive features shared by alexithymia and ASD, the nature of this relationship remains unclear. Nevertheless, the scientific evidence seems to support the "alexithymia hypothesis," i.e., alexithymia, not ASD, would be the main cause of the emotional deficits in ASD. Despite it having been associated with several medical and psychiatric disorders, a recent point of view speculated that alexithymia, rather than characterizing distinct disorders, might be more associated with specific features regarding psychological distress or negative affectivity. Along this line of thought, both the absence of differences between drug-dependent inpatients and psychiatric patients, and the limited ability of alexithymia in predicting treatment outcome led Parolin et al. to question the specificity of alexithymia in substance-dependent patients.

Moving to the articles that focus on the association between alexithymia and other clinically relevant psychological constructs, Suslow and Donges studied its relations with both implicit and explicit positive and negative affectivity. They concluded that there was no substantial relationship between alexithymia and positive affect in healthy adults. However, the difficulties identifying feelings (DIF) factor of the TAS-20 appeared to be associated with an increased conscious experience of negative affect, but not with a heightened disposition for negative affect at an automatic response level. Regarding negative affect, also Epifanio et al. evidenced a strong positive correlation of the negative affectivity factor of the type-D personality with both the DIF and the DDF (difficulty describing feelings) factors of alexithymia. Nevertheless, they confirmed that alexithymia and type-D personality are distinct constructs, with alexithymia being at the base of affect dysregulation underlying the type-D way to cope with emotions. According to Cerutti et al. also non-suicidal self-injury (i.e., the intentional injuring of one's body without apparent suicidal intent) could be regarded as a way to cope with emotions in adolescents with difficulties in identifying and describing feelings. In particular, they proposed a theoretical model in which the difficulty in identifying and describing feelings is a mediator of the associations between non-suicidal self-injury and quality of attachment toward both parents and peers.

Emotional awareness is another construct closely related to alexithymia. Both encompass potential difficulties in identifying and describing one's own and others' feelings, but emotional awareness does not entail limited imaginal ability and externally-oriented thinking. Going further to the partial theoretical overlap, Maroti et al. conducted a meta-analysis of the correlations between the most commonly used measures of alexithymia (TAS-20) and emotional awareness (the Level of Emotional Awareness Scale; LEAS) to explore how the constructs relate to each other empirically. The only small overlap between the two instruments suggested that they measure different aspects of emotional functioning, confirming that alexithymia and emotional awareness are distinct constructs of emotional well-being. The last considered deficit associated with alexithymia is the identification of emotional facial expressions, a crucial mechanism for social interactions. Starita et al. found that participants with high vs. low levels of alexithymia need more emotional intensity to identify static fearful faces, whereas no differences emerged in the identification of dynamic emotional facial expressions. The fact that alexithymia is related to the need for more perceptual information to identify static fearful, but not happy or disgusted facial expressions might be related to partially different brain networks involved.

The latest articles selected for this research topic are focused on the neurobiological correlates of alexithymia. Lischke et al. investigated the association of the vagally mediated heart rate variability (vmHRV) with alexithymia and empathy. vmHRV is a parasympathetical biomarker of the engagement of prefrontal and (para-)limbic brain regions during the regulation of emotional and cognitive processes. Results confirmed that individuals with high vmHRV, which are thus more efficient in recruiting prefrontal and (para-)limbic brain regions implicated in the simulation and interpretation of emotional and mental states, showed more empathy and lower levels of alexithymia than individual with low vmHRV. The introspection-centric simulation theory (IST) predicts that an inability to accurately identify and describe internal affective states may lead to empathy difficulties. Resting on the IST, Valdespino et al. hypothesized that alexithymia may not only be correlated with, but might even cause empathic deficits. Indeed, in their review, they argued that alexithymia and its associated insula pathology could be considered a potential common cognitive and neural marker of empathy deficits across several diagnostic categories. Finally, Goerlich's perspective paper reviewed neuroimaging studies that differentiated the alexithymia facets and dimensions, in order to highlight their dissociable substrates. Results indicated that the DIF and, to a lesser extent, the DDF factors of the TAS-20 usually correlate with emotion-related areas, while the externally oriented thinking factor showed little effect on the function and structure of these brain regions. For example, one large study confirmed a special role of DIF on volumes of the dorsal anterior cingulate cortex, a key region for emotional self-awareness, and other studies linked the DIF factor to a dysfunction

of the amygdala during the processing of emotions with negative valence.

Taken together, the articles included in the present research topic clearly highlight the clinical relevance and the complexity of the alexithymia construct, which can be considered transversal to different medical and psychiatric conditions besides being strongly linked to many relevant psychological constructs, like type-D personality. Since psychological factors are more and more recognized as key predictive factors for therapeutic response to treatments (Castelnuovo et al., 2016), further research should investigate the specific role of alexithymia as a potentially relevant outcome predictor, both for medical and psychological conditions.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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SYSTEMATIC REVIEW
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Alexithymia in Gastroenterology and Hepatology: A Systematic Review

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Background: Alexithymia is a multifaceted personality construct that represents a deficit in the cognitive processing of emotions and is currently understood to be related to a variety of medical and psychiatric conditions. The present review aims to investigate the relationship of alexithymia with gastrointestinal (GI) disorders as functional gastrointestinal disorders (FGID, as irritable bowel syndrome (IBS) and functional dyspepsia) and inflammatory bowel disease (IBD) [ulcerative colitis (UC) and Crohn's disease (CD)] and liver diseases as chronic hepatitis C (CHC), cirrhosis, and liver transplantation.

Methods: The articles were selected from the main electronic databases (PsycInfo, Medline, PubMed, Web of Science, Scopus, Cochrane, and ScienceDirect) using multiple combinations of relevant search terms (defined GI and liver diseases, articles in English, use of the Toronto scales [TAS] for alexithymia). The TAS was selected as inclusion criterion because it is the most widely used measure, thus allowing comparisons across studies.

Results: Forty-eight studies met the inclusion criteria, of which 38 focused on GI disorders (27 on FGID and 11 on IBD) and 10 on liver diseases. Most studies ($n = 30$, 62%) were cross-sectional. The prevalence of alexithymia was higher in FGID (two third or more) than IBD and liver diseases (from one third to 50% of patients, consistent with other chronic non-GI diseases) than general population (10–15%). In functional disorders, alexithymia may be viewed as a primary driver for higher visceral perception, symptom reporting, health care use, symptom persistence, and negative treatment outcomes. Also, it has been found associated with psychological distress and specific GI-related forms of anxiety in predicting symptom severity as well as post-treatment outcomes and is associated with several psychological factors increasing the burden of disease and impairing levels of quality of life. A number of critical issues (small sample sizes, patients referred to secondary and tertiary care centers, cross-sectional study design, use of one single scale for alexithymia) constitutes a limitation to the generalization of findings.

Conclusions: Alexithymia showed to play different roles in gastroenterology according to the clinical characteristics and the psychological burden of the various disorders, with main relevance in increasing subjective symptom perception and affecting negatively post-treatment outcomes.

Keywords: alexithymia, gastroenterology, hepatology, somatization, Toronto Alexithymia Scale

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INTRODUCTION

It is widely recognized that individual health status is only partially explained by the presence of a medically diagnosable disease. Subjective perception, thoughts, emotions, and behaviors associated with one's somatic status are sometimes clinically or more important than the medical diagnosis. Overall, the more the individual perception and behaviors are discrepant from those expected by medical recommendations, the less the course of disease (onset, recognition, presentation, maintenance, and outcomes) can be explained solely by biomedical factors. As documented by a large body of literature, psychosocial factors play a significant role in this regard. In one word, health and disease can be conceptualized and understood best within a biopsychosocial approach. Within this biopsychosocial perspective, each clinical factor is variously inter-connected with the others and has its own specific relative weight (Engel, 1980, 1982; Lipowski, 1984; Fava and Sonino, 2017).

Several authors attempted to explain the complex relationship between the individual illness experience and specific psychological factors when going beyond the misleading dichotomy between functional syndromes and organic diseases. For example, Pilowsky (1993, p. 62) defined abnormal illness behavior as "the persistence of a maladaptive mode of perceiving, experiencing, evaluating, and responding to one's health status, despite the fact that a doctor has provided a lucid and accurate appraisal of the situation and management to be followed." Also, Lipowski's (1970) identified the most frequent meanings given by individuals to their illness (challenge, enemy, punishment, weakness, relief, strategy in interpersonal relations, irreparable loss or damage, and value). These subjective meanings can influence the likelihood to adequately recognize an underlying disease and to promptly seek medical care. Moreover, according to the self-regulatory model of Leventhal et al. (1980), subjective representations of illness determine the coping behaviors adopted and, consequently, the illness outcome. If a certain disease is considered unavoidable and dependent on factors outside of personal control (e.g., inflammation process, viral infection), it is unlikely that preventive measures (e.g., healthy lifestyle) will be adopted. More recently, the DSM-5 (American Psychiatric Association, 2013) dropped the "medically unexplained" criterion from the former diagnostic category of somatoform disorder of the DSM-IV and included positive psychological features (health anxiety, symptom preoccupation, and maladaptive illness behavior) in the new category of somatic symptom disorder. Finally, a recent international consensus recognized the value of patient-reported outcome (PRO) in order to inform shared decision making, clinical guidelines, and health policy. This international consensus provided indeed guidelines for PRO-specific information that should be included in clinical trial protocols (Calvert et al., 2018).

The strict neurohumoral interactions between the brain and the digestive system (referred to as the "brain-gut axis") constitute a continuous bidirectional signaling homeostatic information system. Within this framework, gastrointestinal (GI) disorders are considered as one of the main bodily systems involved in the perception of somatic health. Gut sensations and symptoms emerge as a complex psychobiological process, whereby bottom-up inputs are modulated by top-down cognitive and emotional brain circuits (Van Oudenhove et al., 2016). GI illnesses are traditionally classified according to the biomedical model where causes and symptoms are specifically circumscribed to local organs and pathophysiological patterns. However, a wide body of research, as well as consolidated clinical experience, indicate that psychological factors significantly and negatively influence many clinical aspects such as the individual perception of gut sensations, the reported GI symptoms, as well as other clinically relevant illness-related behaviors. These findings have been reported in many GI conditions, from functional GI disorders (FGID) such as functional dyspepsia (FD) and irritable bowel syndrome (IBS) to chronic diseases such as inflammatory bowel disease (IBD) and liver diseases such as chronic hepatitis C (CHC). Not by chance, the term *hypochondriasis* derives etymologically from the Greek *hypokhondrios* (litteraly, "under the sternum") because the viscera were considered the seat of melancholy.

FGID are functional multidetermined disorders arising from the gut mucosa, microbiota, and GI motility and FGID are caused by dysregulation of the brain-gut axis, with alterations at different levels of the enteric, autonomic and/or central nervous systems or a disturbed interplay between these systems (Ohman and Simrén, 2010). FGID are best understood from a biopsychosocial perspective. Evidence strongly suggest that: (1) there is no single biomarker for a comprehensive diagnosis of FGID, (2) compared to other GI disorders, psychiatric morbidity is more common (40–60%) among patients with FGID, (3) psychological and pharmacological treatments are only partially effective particularly on the long run, and a wax-and-wane temporal course characterized FGID, (4) psychological stress is one of the main triggers for onset and persistence of FGID (Drossman, 2016).

IBD are a group of chronic inflammatory intestinal diseases, the most common forms of which are ulcerative colitis (UC) and Crohn's disease (CD) whose pathophysiology is currently not fully understood. IBD is characterized by intermittent phases of quiescence and unforeseeable acute relapses. IBS and IBD are distinct entities, even though they do share some clinically relevant similarities. Symptom onset and clinical relapses in both IBS and IBD involve multifactorial, yet incompletely understood, triggers that likely include variable combinations of environmental, psychological and biological components such as altered gut microbiota and different grades of pro-inflammatory and immune activation (Spiller and Major, 2016). It is estimated that up to 60% of UC patients and more than one third of CD patients show symptoms that are common to IBS and IBD relapses such as abdominal pain, bloating, diarrhea, and loose stools. These overlapping IBD-IBS symptoms represent a source of considerable psychological distress for IBD patients, as well as a diagnostic and therapeutic conundrum for the physician (Stanisic and Quigley, 2014; Carter et al., 2017). Furthermore, there is consistent evidence of high prevalence of psychological disturbances (76% for anxiety and 41% for depression) during the acute phase of IBD (Fukuba et al., 2014; Neuendorf et al., 2016). Also, it was found that these psychological comorbidities

had a bidirectional association with symptom activity (Sexton et al., 2017) and may predict acute relapses (Mikocka-Walus et al., 2016).

Of interest, IBD is not the only GI organic disease where psychological factors play a relevant role in explaining symptom reporting. Hepatology is a branch of gastroenterology in which patient-related outcomes are receiving increasing attention. Liver diseases such as hepatitis C virus (HCV) infection constitute an interesting paradigm for the biopsychosocial model. Before the availability of the new generation of antiviral drugs that directly inhibit HCV, treatment was largely based on interferon (IFN). However, IFN treatment gave the paradoxical effect of patients who were symptom-free but became ill because of the induced side effects of therapy. Among the most important adverse effects, depression (affecting up to 70% of patients) and common somatic symptoms (e.g., fatigue, insomnia, pruritus, diarrhea, flu-like syndrome, nausea, and headache) may lead to non-compliance and discontinuation of therapy (Schaefer et al., 2012). These drug-induced adverse effects are particularly challenging for clinicians due to their overlap with somatization symptoms. However, they are generally neglected by both physicians (because considered as expected side effects of therapy) and clinical psychologists (because considered as biological-driven symptoms), thereby perpetuating the organic-functional dualism (Sirri et al., 2013; Carrozzino et al., 2017; Fava et al., 2017). Evidence however showed that psychological constructs such as proneness to somatization and higher depressive symptoms may explain not only poorer psychosocial functioning, but also higher perception and the reporting of somatic side effects (Porcelli et al., 2014a; Cozzolongo et al., 2015).

Among the different psychological constructs extensively investigated in several medical settings, alexithymia has received increasingly high attention in the last decades (Nemiah, 1977; Sifneos, 1994). Alexithymia is a multifaceted personality construct that represents a deficit in the cognitive processing of emotions. It is currently conceived as composed by two higher order factors including deficit of affect awareness (difficulty identifying and describing feelings) and operatory thinking [externally oriented thinking (EOT) and poor imaginal processes; (Taylor et al., 1997; Bagby et al., 2006)]. These main characteristics of alexithymia reflect a defective cognitive processing of feelings that is thought to generate an individual inability to regulate affects and emotions (Taylor et al., 1997). Although alexithymia was early considered as one of the core personality determinants of psychosomatic illness (Nemiah and Sifneos, 1970; Nemiah et al., 1976), current evidence shows that the alexithymic deficit in processing feelings is an unspecific vulnerability factor and a trans-categorical dimension rather than a specific category. More specifically, alexithymia is likely to affect health in different ways as follows: (1) by influencing affective states, e.g., altered eating-related behavior; (2) through somatosensory amplification leading to low tolerance to painful stimuli (e.g., chronic pain); (3) through a post-traumatic shutdown of emotions (e.g., acute reactions to illness); (4) by altered autonomic, endocrine, and immune activity leading to tissue damage (e.g., increased vulnerability to inflammatory processes) (Kooiman et al., 2000; Lumley et al., 2007).

Alexithymia has been conceived as the inability to tolerate negative affect by balancing it with positive affect without mostly relying on external reality such as medical reassurance or behavioral actions such as drugs usage (Taylor et al., 1997; Taylor and Bagby, 2012). The concept of alexithymia as a personality construct of affect dysregulation is supported by separate lines of research. One is based on neuroimaging studies suggesting impairment in integration of interhemispheric transfer communication and dysregulation over prefrontal cortex and anterior regions (Moriguchi et al., 2006; Kano et al., 2007; Karlsson et al., 2008). The other is based on the high prevalence rate of alexithymia that has been found in a variety of chronic medical disorders, such as dermatology (Willemsen et al., 2008), cardiology (Tolmunen et al., 2010), pain disorders (Di Tella and Castelli, 2016), and cancer (De Vries et al., 2012), as well as in many psychiatric disorders. Examples are provided by the clinical link between alexithymia and somatization (De Gucht and Heiser, 2003), as well as by the relationship of alexithymia with eating disorders, substance use disorders, and panic disorder (Taylor et al., 1997; Taylor and Bagby, 2012). In sum, evidence suggests that alexithymia is a defective processing of feelings that is likely to affect mental and somatic health through behavioral patterns such as altering the normal regulation of affective states, reactive shutdown of emotions, increased vulnerability to inflammatory processes, somatosensory amplification, adoption of an abnormal illness behavior (Lumley et al., 2007).

The various methods assess the alexithymia construct under different perspectives, each one with merits and limitations. Differences among assessment instruments are related to the nature of the instrument (e.g., self-report scales, interview-based questionnaires, by-proxy assessment, performance-based measures) the evaluation of different facets of the construct (e.g., emotionality, fantasy, interpersonal relationships, and cognitive aspects), the amount of time needed for administration (some scales are brief and easy to use, while others are longer and more time-consuming) specific linkage to the construct (some methods assess core aspects of alexithymia, whereas others are more closely tied to the overall construct). The 20-item Toronto Alexithymia Scale (TAS-20) (Bagby et al., 1994) is the third in the family of TAS scales, after the 26-item version (Taylor et al., 1985) and the less used TAS-Revised (Taylor et al., 1992). The TAS-20 is surely the most popular and used scale for assessing alexithymia. The TAS-20 has been widely supported psychometrically in terms of good reliability and acceptable construct validity. In particular, its 3-factor solution for difficulty identifying feelings (DIF), difficulty describing feelings (DDF), and EOT has been identified as stable and invariant across languages and cultures (Bagby et al., 1988; Taylor, 2000; Parker et al., 2003; Taylor et al., 2003; Taylor and Bagby, 2004). The availability of a reliable, valid, short, not time-consuming, and easy-to-administer measure contributed substantially to the expansion of research on alexithymia over time. In other words, this common single instrument permitted the accumulation of a large body of knowledge, through the use of a single common instrument, as well as a large consensus in considering the TAS-20 as a "gold standard" for assessing the construct of alexithymia. The TAS-20 has been however criticized for not including items that directly assess the reduced fantasy

and imaginal thinking facets, from one side, and for a sort of paradox because of its self-report nature. It is indeed highly controversial that individuals supposed to lack of introspective skills may be able to accurately rate their deficits in affective awareness (Lane et al., 2000; Kooiman et al., 2002).

Other assessment methods have been developed in response to the conceptual limitations of the TAS scales, even though basically the current knowledge on the multiple aspects of alexithymia rests on the TAS-26 and TAS-20 as the other measures have not reached the same level of usage as the Toronto scales. The Bermond-Vorst Alexithymia Questionnaire (BVAQ) (Vorst and Bermond, 2001) is a self-report scale, but the developers included items covering not only the cognitive dimension of alexithymia, but also its fantasizing and emotionalizing components. The Levels of Emotional Awareness Scale (LEAS) (Lane et al., 1990) is an indirect self-report measure as it requires to infer the presence of alexithymia by assessing trait emotional awareness. Other scales provide a direct assessment, but from a different perspective. For example, the Observer Alexithymia Scale (OAS) (Haviland et al., 2001) is a by-proxy measure that asks clinicians, family members, and acquaintances to rate the subject in order to overcome the self-report paradox. Other direct measures not based on self-reporting are structured and semi-structured interviews such as the Toronto Structured Interview for Alexithymia (TSIA) (Bagby et al., 2006) and the Diagnostic Criteria for Psychosomatic Research (DCPR) for alexithymia (Fava et al., 2017). Also, measures for assessing implicit motives such as Rorschach-based scores have been developed (Porcelli and Meyer, 2002; Tibon et al., 2005; Porcelli and Mihura, 2010). They are based on the assumption that this performance-based test is thought to infer the emotional ability (affective awareness and emotional expression) of an individual. However, these last scales have not been widely used because of their theoretical problems, practical difficulty in administration, insufficient statistics, large amount of time required for administration, and required extensive experience from the assessors. At this time, therefore, the substantial body of evidence on alexithymia is based on the TAS that is judged to be the best instrument for balancing sound characteristics and limitations.

To our knowledge no previous report systematically reviewed the body of literature investigating the role of alexithymia in gastroenterology. The present review aims to provide a synthesis of findings and to elucidate the clinical relevance of alexithymia in gastroenterology and hepatology. The inclusion of papers in this review was limited to those assessing alexithymia with the TAS as the use of this single instrument allows comparing prevalence and findings across different settings, population, and disorders.

Based on findings in other medical conditions (Lumley et al., 1996), we expected that alexithymia would be:

(1) more prevalent in functional than organic GI disorders because of the supposed higher impact of psychological factors in medical syndromes whose clinical outcomes are based more on the subjective perception of somatic health.

(2) more clinically relevant, according to Lipowski's view (1970), in illness dimensions related to somatization and/or somatoform-like symptoms.

METHODS

Eligibility Criteria

Eligible articles included only original research studies (e.g., brief research reports, short communications, research letters, research articles, single cases, meta-analytic studies, as well as other studies reporting quantitative data by focusing on a specific experimental design) that were published in peer-reviewed journals and were written in English. As a consequence, qualitative studies (e.g., reviews, commentaries, letters to the editor, books or book chapters) were excluded. Also, studies had:

(1) to investigate a defined GI disorder. The most frequently investigated GI conditions are FGID as IBS, FD, functional abdominal pain syndrome, and other syndromes that are included in the panel of the Rome criteria (Drossman, 2016), and IBD as UC and CD;
(2) to investigate a defined liver disease as HCV infection, cirrhosis, and liver transplantation (LT);
(3) to use one of the three versions of the Toronto Alexithymia Scale, i.e., the TAS-26 (Taylor et al., 1985), the revised TAS (TAS-R) (Taylor et al., 1992), and the 20-item version of the TAS (TAS-20) (Taylor et al., 1992; Bagby et al., 1994) (see Introduction).

Information Sources and Literature Search

The International Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009) were used during the systematic search procedure of literature on PsycInfo, Medline, PubMed, Web of Science, Scopus, Cochrane, and ScienceDirect databases. Each database was systematically searched from inception (1985, i.e., when the TAS-26 was published) to July 2017. In order to further screen for relevant studies that may have been omitted by the systematic search, a manual search of the literature was also performed on Google Scholar. When screening the research literature for titles, abstracts, and keywords, specific search terms were used and combined in the following Boolean string: ("alexithymia" OR "alexithymic") AND ("gastroenterology" OR "ulcerative colitis" OR "irritable bowel syndrome" OR "functional dyspepsia" OR "inflammatory bowel disease" OR "hepatology" OR "liver disease" OR "hepatitis C" OR "cirrhosis").

Selection of Articles and Data Extraction

One of the authors (D.C.) performed the initial data extraction by removing duplicates and all the articles that appeared clearly irrelevant on the basis of the relevance of the title and after reading the specific abstract. The full-text of the remaining studies were independently assessed for eligibility by both authors. After a full-text evaluation of the potentially relevant studies, the two authors reached a consensus regarding eligibility and excluded all the research articles that not meet the inclusion criteria.

Analysis of Articles and Data Synthesis

In view of the highly heterogeneous clinical populations, including patients with different GI disorders and liver diseases, a meta-analysis was not deemed to be fully appropriate from a

psychometric point of view. On this basis, for each of the included studies, we provided a qualitative synthesis of relevant data. More specifically, we analyzed data regarding objective of the study, number and description of participants by reporting the main results obtained with the TAS (e.g., mean scores, and prevalence of alexithymia).

RESULTS

Included Studies

As presented in the PRISMA flow chart (**Figure 1**), a total of 1,101 studies were identified by the systematic search. After removing 599 duplicates and excluding 355 clearly irrelevant studies, the full-text of the remaining 147 articles was evaluated for potential eligibility. Of these studies, 99 articles were further discarded because of the following: (1) alexithymia was not measured with one of the three versions of the TAS; (2) the clinical samples did not include patients with GI disorders or liver diseases; (3) the manuscript was not written in English; (4) the study consisted of a conference paper and only an abstract without full-text was available; (5) the study did not have a quantitative experimental design. Of the remaining 48 full-text articles that were found eligible for inclusion, no unpublished studies were reported. Overall, 27 studies included patients with FGID, of which 21 cross-sectional and 6 longitudinal studies; 11 IBD patients, of which 7 cross-sectional and 4 longitudinal studies; and 10 patients with liver diseases, of which 2 cross-sectional and 8 longitudinal studies. **Tables 1**–**6** showed the characteristics of the included reports.

FGID and Alexithymia

FGID are a multifactorial group of disorders of the GI tract whose pathogenesis remains incompletely understood from a medical point of view (Koloski et al., 2012; Keightley et al., 2015). The etiology of these disorders may result from an altered communication of the bidirectional gut-brain axis that is not fully explained by medically known structural, biochemical or organic abnormalities (Van Oudenhove et al., 2016). From a biopsychosocial perspective, FGID may be considered a consequence of a complex dysregulation of brain-gut and affective systems, involving emotional, cognitive, and neurophysiological functions (Drossman, 2016). More specifically, motility disturbances of the GI tract and alterations in sensory input from the gut have been implicated and, by way of the bidirectional brain-gut axis, functional somatic symptoms may be generated by states of emotional arousal and by mutual interactions of the enteric, nervous, and immune systems (Mayer, 2011).

Prevalence of Alexithymia in FGID

Most studies on FGID had a cross-sectional design (Arun, 1998; Porcelli et al., 1999; Porcelli and De Carne, 2001; Weinryb et al., 2003; Van Oudenhove et al., 2008; Van Oundenhove et al., 2011a; Faramarzi et al., 2012; Mazaheri et al., 2012; Bengtsson et al., 2013) and control groups were formed of healthy subjects (Arun, 1998; Porcelli et al., 1999; Faramarzi et al., 2012; Mazaheri et al., 2012). The first study investigating alexithymia with the original TAS-26 (Taylor et al., 1985) in a sample of 30 IBS patients showed they had higher levels of alexithymia (125.96 ± 11.5) than a control group of 30 matched healthy subjects (108.96 ± 13.29) ($t = 20.04$; $p < 0.01$) (Arun, 1998). In the same period, a similar study compared 121 consecutive patients with FGID with a sample of 116 IBD outpatients and a control group of 112 healthy participants (Porcelli et al., 1999). They found that FGID patients scored significantly higher on the TAS-20 (62.7 ± 13.6) than IBD respondents (54.3 ± 13.9) and healthy subjects (42.9 ± 9.1) [$F_{(2,\ 347)} = 73.30$; $p = 0.001$] FGID patients scored significantly higher (62.7 ± 13.6) than IBD patients (52.6 ± 12.5) on the TAS-20 [$t_{(162)} = 4.21$; $p < 0.001$], even after controlling for education, gender, anxiety, depression, and overall GI symptoms. When considered categorically by using the suggested TAS-20 cut-off scores (Taylor et al., 1997), the prevalence of alexithymia was 66% ($n = 80$) in the FGID, 38% ($n = 44$) in the IBD, and 4.5% ($n = 5$) in the control groups ($\chi^2 = 94.94$, $p < 0.001$). Similarly, it was found that 60 FD patients scored significantly higher than 60 controls on the total (61.58 ± 6.56 vs. 47.50 ± 8.30) as well as the DIF (27.45 ± 4.31 vs. 17.52 ± 4.47) and DDF (17.22 ± 4.10 vs. 13.00 ± 3.74) subscales, even after multiple adjustments ($F = 106.16$; $p < 0.001$) (Faramarzi et al., 2012). By contrast, there was no statistically significant difference between groups on the EOT factor of the TAS (16.92 ± 3.51 vs. 16.98 ± 3.31; *t*-test; $p = 0.915$).

Consistently, a sample of 100 IBS patients (Farnam et al., 2014) scored significantly higher than 587 healthy controls on the TAS-20 total score (59.67 ± 9.92 vs. 43.88 ± 15.06), as well as on all the three subscales (DIF: 18.60 ± 5.90 vs. 16.54 ± 6.55, DDF: 14.66 ± 4.25 vs. 11.44 ± 3.36, EOT:26.41 ± 3.09 vs. 15.88 ± 5.27). Similar findings were reported by Faramarzi et al. (2014) showing that TAS-20 total scale (62.9 ± 4.7 vs. 62.2 ± 10.6; $adj.R^2 = 0.10$; $F = 5.96$; $p = 0.004$), as well as DIF (27.8 ± 3.9 vs. 23.5 ± 6.3; $adj.R^2 = 0.25$; $F = 16.07$; $p < 0.001$), and DDF (17.3 ± 3.6 vs. 16.5 ± 4.4; $adj.R^2 = 0.58$; $F = 3.74$; $p < 0.028$) scores were significantly higher in a group of 30 FD patients than 30 patients with peptic ulcer. These findings were consistent with another study evidencing high prevalence rates of alexithymia at 60% ($n = 114$) in a large sample of 190 FGID outpatients as measured by the TAS-20 and at 47.4% ($n = 90$) as identified by the DCPR alexithymia cluster (Porcelli and De Carne, 2001). These patients also scored significantly higher on the TAS-20 (65.2 ± 10.9) than patients not meeting the DCPR criteria for alexithymia (48.2 ± 11.4) ($t = 9.86$; $p < 0.001$). Similar results were obtained by Portincasa et al. (2003) on 100 patients with IBS who scored significantly higher on the TAS-20 (59.1 ± 1.1) than 100 healthy control subjects (40.5 ± 1.0). Similarly, they found higher prevalence of alexithymia in IBS patients (43%; $n = 43$) than healthy subjects (only 2%; $n = 2$). In this study, frequency of bowel movements was associated less with anxiety ($r = 0.39$; $p < 0.001$) and somatization ($r = 0.34$; $p < 0.001$) and more with alexithymia ($r = 0.52$; $p < 0.001$).

Similar findings of higher prevalence of alexithymia in FGID patients have been shown in other (as in Van Oudenhove et al., 2008; Mazaheri et al., 2012) but not all studies. In one small sample size study, no significant TAS-20 difference was found between 17 IBS (42.3 ± 14.1) and 17 healthy control groups (32.0 ± 8.8) ($F = 3.56$; $p = 0.044$; *effect size* = −0.88) (Weinryb

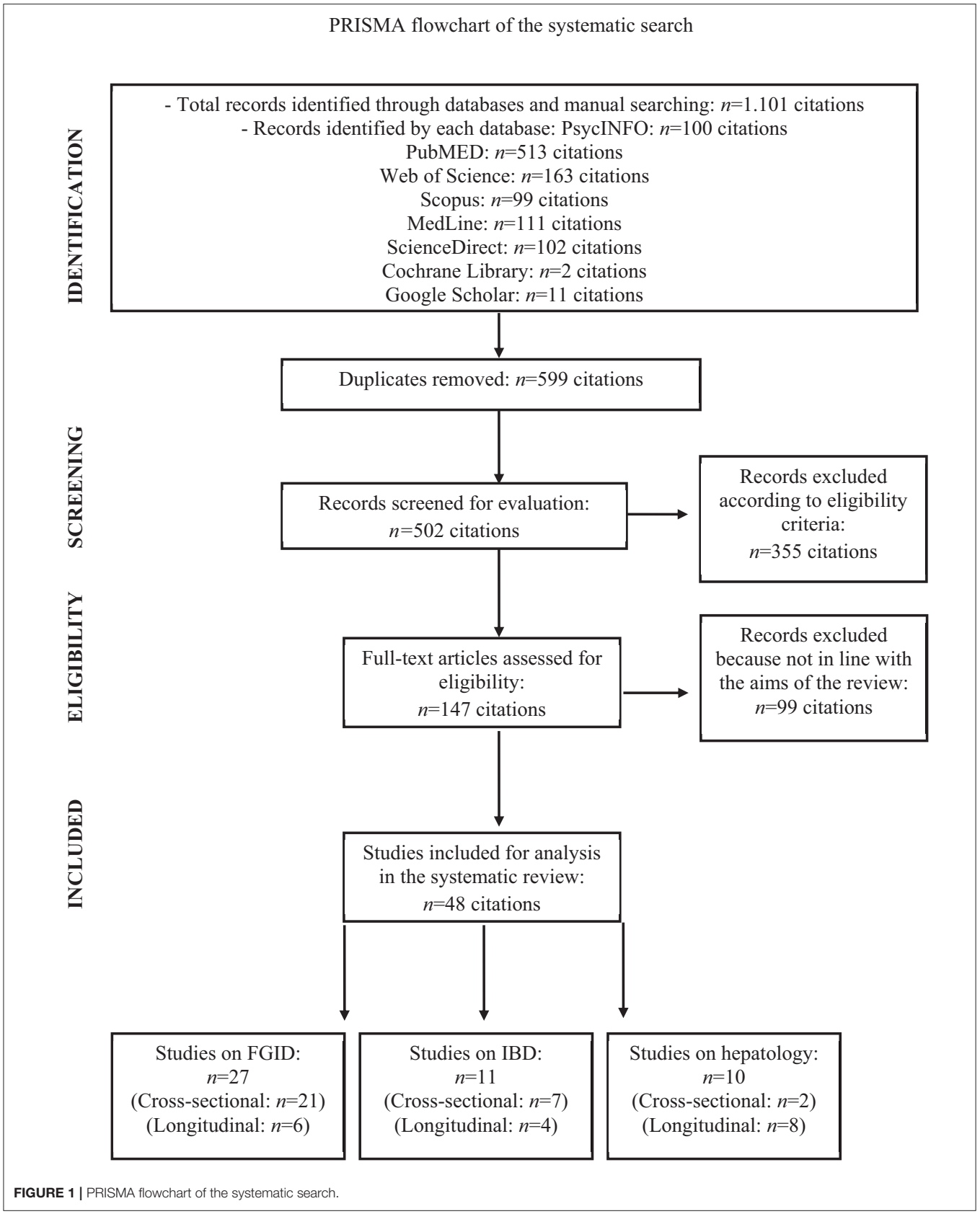

FIGURE 1 | PRISMA flowchart of the systematic search.

TABLE 1 | Cross-sectional studies on alexithymia in functional gastrointestinal disorders.

Authors	Aim	Clinical sample	Control sample	Mean (SD) scores on TAS	Prevalence (%) of alexithymia	Main results
Arun, 1998	Association of alexithymia with neuroticism, depression, and stressful life events	30 consecutive IBS patients	30 healthy individuals	IBS patients: 125.96 ± 11.5** Control sample: 108.96 ± 13.29	–	Compared to subjects with low alexithymia (3.65 ± 2.52), those with high alexithymia reported significantly higher neuroticism scores (8.67 ± 4.75) (*F ratio* = 6.52; $p < 0.01$)
Bengtsson et al., 2013	Comparison of psychological and coping functioning between IBS and IBD patients	81 patients with IBS 74 patients with IBD	None	IBS patients: median (interquartile ranges) = 44 (36-54)* IBD patients: median (interquartile ranges) = 42 (34-50)	–	IBS patients scored higher on the TAS-20 than those with IBD, but no statistically significant difference was found when adjusted for gender and age (*OR* = 1.025; 95% *CI* = 0.993–1.057; $p = 0.123$)
Dibaise et al., 2016	Evaluation of the relationship between psychological dysfunction, gastric emptying, and dyspeptic symptoms	Out of 209 patients undergoing gastric emptying testing, 151 met the Rome III criteria for FD	None	FD patients: 47.62 ± 13.06* Non-FD patients: 45.62 ± 13.32	–	There were no statistically significant differences on the TAS-20 between FD and non-FD patients (*Cohen's d* = 0.14; $p = 0.332$)
Eiroa-Orosa et al., 2015	Evaluation of psychological, subjective functionality	28 FGID patients and 17 patients with gastrointestinal motility disorders	None	FGID patients: 46.16 ± 13.91* Patients with gastrointestinal motility disorders: 48.43 ± 17.15	–	FGID patients were not more alexithymic than those with GI motility disorders ($z = -0.63$; $p = 0.527$)
Faramarzi et al., 2012	Association between psychological symptoms, including alexithymia, and the occurrence of FD	60 consecutive FD patients	60 healthy controls	FD patients: 61.58 ± 6.56* Healthy controls: 47.50 ± 8.30	–	Compared to healthy subjects, FD patients reported significantly higher alexithymia ($F = 106.16$; $p < 0.001$)
Faramarzi et al., 2014	Evaluation of psychiatric problems, including alexithymia	30 FD patients 30 PUD patients	30 healthy individuals	FD patients: 62.9 ± 4.7* PUD patients: 62.2 ± 10.6 Healthy controls: 55.6 ± 10.4	–	FD patients reported significantly more alexithymia than those with PUD (62.9 ± 4.7 vs. 62.2 ± 10.6; *adj* $R^2 = 0.10$; $F = 5.96$; $p = 0.004$)
Farinelli et al., 2007	Prevalence of alexithymia in GERD	69 patients with GERD	None	43.7 ± 9.9*	0%	GERD patients were not alexithymic according to TAS-20 cut-off scores
Jones et al., 2004	Evaluation of alexithymia and somatosensory amplification	111 patients with FD	53 healthy subjects	FD patients: 43 ± 11* Healthy subjects: 38 ± 9	FD patients: 12% Healthy controls: –	FD patients scored significantly higher than controls on TAS-20 (*t*-test; $p < 0.005$) Difficulty in identifying feelings significantly correlated with abdominal discomfort ($r = 0.27$) and bloating ($r = 0.23$)
Jones et al., 2006	Evaluation of coping strategies, social support and psychological factors, including alexithymia	74 IBS patients 48 IBD patients	55 healthy subjects	IBS patients: 42 ± 12* IBD patients: 43 ± 12 Controls: 38 ± 9	IBS patients: 8% IBD patients: 8% Controls: 0%	Alexithymia was detected in 6 patients with IBS, in 4 IBD patients, and in 0 controls ($\chi^2 = 4.78$; $p = 0.09$)
Jones et al., 2013	Association between abuse history, state affect, somatic symptom reporting, trait affectivity, including alexithymia, gastric discomfort threshold and health-related quality of life	259 consecutive FD patients	None	50.9 ± 12.8*	–	Higher levels of alexithymia and trait anxiety were significantly associated with lower mental quality of life (*effect size* = −1.12; *factor loadings/standardized path coefficients* = 0.23; $p < 0.001$)
Mazaheri et al., 2012	Evaluation of alexithymia and severity of GI symptoms	129 FGID patients	109 healthy individuals	FGID patients: 60.26 ± 11.18* Control group: 21.62 ± 3.2	–	FGID patients scored significantly higher on TAS-20 than controls ($F = 1.20$; $df = 1$; $p < 0.001$)

(Continued)

TABLE 1 | Continued

Authors	Aim	Clinical sample	Control sample	Mean (SD) scores on TAS	Prevalence (%) of alexithymia	Main results
Phillips et al., 2013	Evaluation of psychosocial factors, including alexithymia	82 patients with IBS	67 healthy controls	IBS patients: 50.8 ± 12.5* Healthy controls: 43.4 ± 12.2	–	Alexithymia factors as difficulty identifying feelings, and difficulty describing feelings were two significant predictors of IBS symptom severity
Porcelli et al., 1999	Evaluation of alexithymia	121 consecutive FGID outpatients 116 IBD outpatients	112 healthy individuals	FGID patients: 62.7 ± 13.6* IBD patients: 54.3 ± 13.9 Healthy controls: 42.9 ± 9.1	FGID patients: 66% IBD patients: 38% Healthy subjects: 4.5%	FGID patients were significantly more alexithymic than IBD and control groups [$F_{(2,347)} = 73.30$; $p = 0.001$]
Porcelli and De Carne, 2001	Validation of the DCPR diagnostic criteria for alexithymia	190 consecutive FGID outpatients	None	59.6 ± 13.9*	60%	FGID patients meeting the DCPR criteria for alexithymia scored significantly higher on the TAS-20 than those who were negatives ($t = 9.86$; $p < 0.001$)
Porcelli et al., 2004	Evaluation of alexithymia and psychopathology	58 FGID patients of which 38 with psychiatric comorbidities 52 psychiatric patients of which 25 with comorbid FGID	None	FGID patients: 64.6 ± 12.4* Psychiatric patients: 50.8 ± 12.9 FGID patients with psychiatric comorbidities: 66.7 ± 11.2 Psychiatric patients with FGID comorbidities: 52.7 ± 10.4	FGID patients: 75.9% Psychiatric patients: 21.1% FGID patients with psychiatric disorders: 81.6% Psychiatric patients with FGID: 28%	Alexithymia independently predicted which subjects belonged to the subgroup of FGID patients with psychiatric comorbidities (*OR* = 1.14; 95% CI = 1.03–1.26; $p = 0.001$)
Porcelli et al., 2014b	Influence of alexithymia and GSA on IBS severity	177 outpatients with IBS	None	65.33 ± 7.22*	54.2%	Alexithymia explained more unique variance than GSA in predicting IBS symptom severity.
van Kerkhoven et al., 2006	Influence of alexithymia on GI endoscopy outcomes	1141 consecutive FGID patients	None	51 ± 12*	21%	Patients with alexithymia reported more GI symptoms (6 ± 4 vs. 5 ± 3; $p < 0.05$) and higher symptom severity (42 ± 34 vs. 34 ± 30; $p < 0.01$) than those who were not alexithymic
Van Oudenhove et al., 2008	Influence of psychosocial factors, including alexithymia, on gastric symptom severity	201 consecutive FD patients	None	Median (interquartile range): 53 (42-61)*	87%	Out of 201 FD patients, 174 were alexithymic on the basis of the TAS-20 cut-off score
Van Oundenhove et al., 2011a	The role of gastric sensorimotor function, psychological and psychiatric comorbidities, including alexithymia, on comorbid IBS and CF-like symptoms	259 consecutive FD patients of which 70 without comorbidity, 80 with comorbid IBS, 40 with comorbid fatigue, and 61 with comorbid IBS and fatigue	None	FD patients without comorbidity: 15.5 ± 6.0* FD patients with comorbid IBS: 16.4 ± 6.1 FD patients with comorbid CF-like symptoms: 17.7 ± 6.6 FD patients with comorbid IBS and CF-like symptoms: 17.4 ± 6.5	–	When comparing groups according to comorbidity (none, IBS alone, fatigue alone, or both comorbidities), no statistically significant difference was found on the TAS-20 (*one-way ANOVA*; $p = 0.25$)
Van Oudenhove et al., 2011b	Influence of gastric sensorimotor function, psychosocial factors, including alexithymia, and somatization on quality of life	259 consecutive FD patients	None	–	–	The mental component of health-related quality of life was negatively and significantly associated with alexithymia (Spearman's *rho* = −0.42)
Weinryb et al., 2003	Evaluation of psychological factors, including alexithymia	17 IBS patients 17 IBS non patients	17 healthy controls	IBS patients: 42.3 ± 14.1* IBS non patients: 39.6 ± 11.4 Controls: 32.0 ± 8.8	–	Patients with IBS and controls were not-alexithymic and there were no statistically significant differences between groups on the TAS-20 ($F = 3.56$; $p = 0.044$)

*CF, chronic fatigue; DCPR, Diagnostic Criteria for Psychosomatic Research; FD, functional dyspepsia; FGID, functional gastrointestinal disorders, including functional dyspepsia, irritable bowel syndrome, functional abdominal pain syndrome; GERD, Gastroesophageal Reflux Disease; GI, gastrointestinal; GSA, gastrointestinal-specific anxiety; IBD, inflammatory bowel disease, including patients diagnosed with ulcerative colitis or with Crohn's disease; IBS, irritable bowel syndrome; PUD, Peptic Ulcer Disease; TAS, Toronto Alexithymia Scale. *Using TAS-20 for evaluating alexithymia. **Using TAS-26 for evaluating alexithymia.*

TABLE 2 | Longitudinal studies on alexithymia in functional gastrointestinal disorders.

Authors	Aim	Clinical sample	Control sample	Mean (SD) scores on TAS	Prevalence (%) of alexithymia	Main results
Faramarzi et al., 2013	Influence of brief core conflictual relationship theme psychoanalytic psychotherapy on GI symptoms and alexithymia	Out of 49 patients with FD, 24 were randomly assigned to the experimental group	Out of 49 patients with FD, 25 were randomly assigned to the control group	FD patients assigned to the experimental group at baseline: 63.5 ± 5.2* FD patients assigned to the experimental group after treatment: 47.2 ± 9.0 FD patients assigned to the experimental group at follow-up 1: 47.9 ± 10.0 FD patients assigned to the experimental group at follow-up 2: 47.7 ± 9.8 FD patients assigned to the control group at baseline: 60.4 ± 8.1 FD patients assigned to the control group after treatment: 60.9 ± 8.9 FD patients assigned to the control group at follow-up 1: 57.0 ± 10.4 FD patients assigned to the control group at follow-up 2: 60.3 ± 8.5	–	Brief psychodynamic psychotherapy significantly improved all GI symptoms, as well as many psychological symptoms as alexithymia
Farnam et al., 2014	Influence of emotional awareness training on the severity and frequency of pain and alexithymia	100 IBS patients	587 university students	IBS patients: 59.67 ± 9.92* Healthy controls: 43.88 ± 15.06	–	Patients with IBS scored significantly higher than controls on the TAS-20 (t-test; $p < 0.005$)
Porcelli et al., 2003	Influence of alexithymia on treatment outcomes	At baseline: 130 consecutive FGID patients After 6 months of follow-up: 112 FGID patients	None	Baseline: 58.89 ± 13.50* Follow-up: 55.85 ± 12.32	56%	Even after controlling for baseline anxiety and depression, alexithymia emerged as the most powerful predictor of both recovery status and improvement of GI symptoms
Porcelli et al., 2007a	Role of alexithymia on the persistence of gastrointestinal symptoms	Out of 52 gallstone patients judged as also having dyspepsia, 31 patients were categorized as improved and 21 as unimproved	None	Improved patients: 49.32 ± 11.50* Unimproved patients: 66.00 ± 7.79	–	Alexithymia significantly predicted the persistence of GI symptoms more strongly than did psychological distress
Porcelli et al., 2017	Influence of alexithymia and GSA on symptom improvement	150 patients with IBS	None	Improved IBS patients at baseline: 55.97 ± 12.22* Improved IBS patients at follow-up: 51.49 ± 10.18 Unimproved IBS patients at baseline: 63.46 ± 7.35 Unimproved IBS patients at follow-up: 63.92 ± 8.54	Improved IBS patients at baseline: 45.9% Improved IBS patients at follow-up: 24.3% Unimproved IBS patients at baseline: 84.6% Unimproved IBS patients at follow-up: 82%	Alexithymia, but not GSA, significantly predicted post-treatment improvement of GI symptoms
Portincasa et al., 2003	Evaluation of gastrointestinal motility and alexithymia	100 consecutive patients with IBS	100 healthy participants	IBS patients: 59.1 ± 1.1* Healthy controls: 40.5 ± 1.0	IBS patients: 43% Healthy controls: 2%	Alexithymia positively and significantly correlated with dyspepsia symptoms ($r = 0.47$) and frequency of bowel movements ($r = 0.52$)

*FD, functional dyspepsia; FGID, functional gastrointestinal disorders, including functional dyspepsia, irritable bowel syndrome, functional abdominal pain syndrome; GI, gastrointestinal; GSA, gastrointestinal-specific anxiety; IBS, irritable bowel syndrome; TAS, Toronto Alexithymia Scale. *Using TAS-20 for evaluating alexithymia. **Using TAS-26 for evaluating alexithymia.*

TABLE 3 | Cross-sectional studies on alexithymia in inflammatory bowel disorders.

Authors	Aim	Clinical sample	Control sample	Mean (SD) scores on TAS	Prevalence (%) of alexithymia	Main results
Boye et al., 2008a	Influence of some personality factors, including alexithymia, on quality of life of IBD patients	110 IBD patients, of which 56 with UC, and 54 with CD	None	UC patients: 65.5 ± 10.7** CD patients: 67.0 ± 10.1	–	In patients with UC, alexithymia significantly and negatively correlated with the emotional domain of quality of life ($r = -0.26$)
Boye et al., 2008b	Influence of some personality traits, including, alexithymia on general quality of life	109 IBD patients	None	CD patients: 67.0 ± 10.1** UC patients: 65.5 ± 10.7	–	In patients with UC, high levels of alexithymia were significantly associated with low levels in the physical ($r = -0.33$), mental ($r = -0.49$), and social ($r = -0.30$) components of health-related quality of life In CD patients, high levels of alexithymia significantly correlated with increased physical limitations ($r = 0.29$)
Iglesias-Rey et al., 2012	Influence of alexithymia on health-related quality of life	484 IBD patients of which 192 with CD, and 292 with UC	None	Total sample (95% CI): 65.8 (95% CI = 64.6–67.0) ** CD patients: 65.2 (95% CI = 63.1–67.3) UC patients: 66.2 (95% CI = 64.7–67.6)	Total IBD sample: 30.2% CD patients: 30.5% UC patients: 30.0%	Multivariate logistic regression analysis found that alexithymia was a risk factor for poor quality of life ($OR = 3.34$; 95% CI = 1.98–5.65)
La Barbera et al., 2017	Association between IBD and specific psychological factors, including alexithymia	100 IBD patients	66 healthy individuals	R1 community containing 15 CD and 24 UC patients: 40.0 ± 10.3* R1 community containing 47 control participants: 43.2 ± 8.4 R2 community containing 40 CD and 21 UC patients: 53.1 ± 12.3 R2 community containing 19 control participants: 53.5 ± 15.0	–	It has been found a significant correlation between alexithymia and low levels of physical and mental health
Porcelli et al., 1995	Association between alexithymia and IBD	112 IBD patients, of which 89 with UC, and 23 with CD	112 healthy subjects	IBD patients: 53.7 ± 13.6* UC patients: 53.1 ± 13.0 CD patients: 55.5 ± 15.9 Healthy controls: 42.8 ± 8.9	IBD patients: 35.7% Healthy controls: 4.5%	Patients with IBD scored significantly higher than controls on the TAS-20 ($t = 7.02$; $p < 0.001$)
Verissimo et al., 1998	The influence of alexithymia on health-related quality of life	74 IBD patients, of which 49 with CD, and 25 with UC	None	Total sample: 51.2 ± 9.7* CD patients: 51.5 ± 9.3 UC patients: 50.8 ± 10.8	–	Alexithymia correlated negatively and significantly with quality of life ($r = -0.34$), bowel symptoms ($r = -0.28$), systemic symptoms ($r =$ c0.37), and emotional functioning ($r = -0.38$)
Verissimo et al., 2000	Relationship between alexithymia and locus of control	124 patients, of which 74 with IBD	218 medical students	Patients: 56.44 ± 11.66* Controls: 48.68 ± 9.15	–	Patients scored significantly higher than controls on the TAS-20 total scale ($t = 6.82$; $p < 0.001$)

*CD, Crohn's Disease; IBD, inflammatory bowel disease, including patients diagnosed with ulcerative colitis or with Crohn's disease; TAS, Toronto Alexithymia Scale; UC, Ulcerative Colitis. *Using TAS-20 for evaluating alexithymia. **Using TAS-26 for evaluating alexithymia.*

TABLE 4 | Longitudinal studies on alexithymia in inflammatory bowel disorders.

Authors	Aim	Clinical sample	Control sample	Mean (SD) scores on TAS	Prevalence (%) of alexithymia	Main results
Porcelli et al., 1996	Influence of IBD activity on both alexithymia and psychological distress	104 patients with IBD	None	Unchanged IBD patients at baseline: 53.9 ± 13.4* Improved IBD patients at baseline: 55.0 ± 13.9 Worsened IBD patients at baseline: 53.1 ± 14.6	–	TAS-20 scores at baseline significantly and impressively correlated with TAS-20 scores at follow-up ($r = 0.95$) A series of ANOVA measures revealed also that there was no influence of disease activity on alexithymia levels
Porcelli and Meyer, 2002	Evaluation of the construct validity of Rorschach alexithymia variables	92 outpatients with IBD were divided into the following three groups: (1) 32 IBD patients with stable alexithymia; (2) 45 IBD patients without alexithymia; (3) 15 IBD patients with indeterminate alexithymia	None	IBD patients with alexithymia at baseline: 66.4 ± 4.5* IBD patients with alexithymia at follow-up: 66.6 ± 3.2 Not-alexithymic IBD patients at baseline: 41.0 ± 5.5 Not-alexithymic IBD patients at follow-up: 41.2 ± 4.3 IBD patients with indeterminate alexithymia at baseline: 53.5 ± 6.1 IBD patients with indeterminate alexithymia at follow-up: 53.3 ± 7.0	34.8% of IBD patients presented with stable alexithymia 48.9% of IBD patients presented without alexithymia 16.3% of IBD patients presented with indeterminate alexithymia	Compared to IBD patients with indeterminate alexithymia or without alexithymia, those presenting with stable alexithymia showed an impoverished fantasy life, poorly adapted emotional expression, poor coping resources, concrete and stereotypical thinking, as well as social conformity with compromised relationships
Porcelli and Mihura, 2010	Evaluation of the alexithymia Rorschach scale	92 patients with IBD 127 psychiatric outpatients	None	IBD patients: 52.1 ± 12.1* Psychiatric outpatients: 52.2 ± 12.9	Out of 219 patients, 38.8% ($n = 85$) were alexithymic	IBD patients and those with psychiatric disorders had similar levels of alexithymia
Tibon et al., 2005	Evaluation of the construct validity of a new Rorschach index,	92 IBD patients	None	–	34.8%	Compared to IBD patients with indeterminate alexithymia on the TAS-20, those with alexithymia scored significantly higher on the Rorschach Reality-Fantasy Scale

*IBD, inflammatory bowel disease, including patients diagnosed with ulcerative colitis or with Crohn's disease; TAS, Toronto Alexithymia Scales. *Using TAS-20 for evaluating alexithymia. **Using TAS-26 for evaluating alexithymia.*

TABLE 5 | Cross-sectional studies on alexithymia in hepatology.

Authors	Aim	Clinical sample	Control sample	Mean (SD) scores on TAS	Prevalence (%) of alexithymia	Main results
Blomhoff and Malt, 1995	Behavioral styles in non-alcoholic liver transplant candidates	29 patients with advanced liver disease	None	Patients: 64.0 ± 10.5**	–	No one of patients were alexithymic on the basis of TAS-26 mean scores
Rustgi et al., 2010	The association of alexithymia with a variety of GI symptoms	83 consecutive HCV outpatients	None	48.01 ± 12.82*	22%	Compared to not alexithymic patients, those with alexithymia had greater viral loads and reported more subjective appraisal for their illness

*GI, gastrointestinal; HCV, Hepatitis C; TAS, Toronto Alexithymia Scale. *Using TAS-20 for evaluating alexithymia. **Using TAS-26 for evaluating alexithymia.*

et al., 2003). Also Bengtsson et al. (2013) found no statistical differences in the TAS-20 scores between 81 IBS and 74 IBD patients. Specifically, the TAS-20 scores were higher in the IBS sample, but no statistically significant difference was found when adjusted for gender and age ($OR = 1.025$; 95% CI = 0.993–1.057; $p = 0.123$). Similarly, no statistical difference was found by comparing TAS-20 scores of 70 FD patients without comorbidity (15.5 ± 6.0), 80 FD patients with comorbid IBS only (16.4 ± 6.1), 40 FGID patients with comorbid chronic fatigue-like symptoms only (17.7 ± 6.6), and 61 FD patients with comorbid IBS and fatigue (17.4 ± 6.5) (Van Oundenhove et al., 2011a).

Association With Treatment Outcome and Symptom Severity

Only few studies investigating the effects of alexithymia on treatment outcomes and symptom severity with a longitudinal design (Porcelli et al., 2003, 2007a, 2017). All the other studies included in this review (Porcelli et al., 2004, 2014b; Jones et al., 2006, 2013; van Kerkhoven et al., 2006; Farinelli et al., 2007; Van Oudenhove et al., 2011b; Phillips et al., 2013; Eiroa-Orosa et al., 2015; Dibaise et al., 2016) were cross-sectional. Moreover, all but two studies (Jones et al., 2006; Phillips et al., 2013) did not include control samples.

Porcelli et al. (2003) evaluated the stability of alexithymia by analyzing to what extent alexithymia can predict treatment outcomes in 112 patients with FGID after 6 months of as-usual care (various combination of psychological and pharmacological interventions). They showed that unimproved patients ($n = 44$) obtained significantly higher baseline TAS-20 scores (69.25 ± 7.81) than 68 improved patients (52.19 ± 12.10) ($t = 7.89$; $p < 0.001$). However the relative stability of alexithymia (i.e., the degree to which the relative differences of alexithymia among individuals remain the same over time, measured with Pearson test-retest coefficients) was established by correlating baseline and follow-up TAS-20 scores ($r = 0.76$, $p < 0.001$). When performing hierarchical regression models by analyzing the entire FGID sample, the authors were also able to show that baseline TAS-20 scores were significant predictors of follow-up TAS-20 scores even after controlling for baseline and follow-up depression ($R^2_{chg} = 0.23$, $p < 0.001$) and anxiety ($R^2_{chg} = 0.35$, $p < 0.001$) scores. Such findings suggest that the stability of TAS-20 scores over the 6 month treatment period could not be accounted for by their associations with anxiety and depression scores. To further determine the contribution of alexithymia as stable clinical factor in predicting treatment outcomes, a series of logistic and linear regression analyses showed that TAS-20 was the strongest predictor of treatment outcome, after controlling for co-variables, with an accurate prediction rate of 85% for the improved and 82% for unimproved patients. When alexithymia was entered into the regression model at a second step, after including anxiety, depression, and gastrointestinal symptoms at the step one, the overall fit of this model increased significantly, i.e., $\chi^2_{\text{dif}(1)} = 32.51$, $p < 0.001$. The addition of alexithymia increased also the Cox and Snell R^2 from 0.23 to 0.42.

GI-specific anxiety (GSA) (Labus et al., 2004, 2007) is another psychological factor that has been found to influence FGID. GSA refers to the cognitive, affective, and behavioral response stemming from fear of GI sensations or symptoms, and the context in which these visceral sensations and symptoms occur (Jerndal et al., 2010). GSA indeed relates to hypervigilance to, and fear, worry, and avoidance of GI-related sensations. Alexithymia and GSA are likely involved in visceral symptom perception since these psychological factors may indicate difficulty in emotional regulation, biased selective attention to somatic attention, higher negative emotionality, exaggerated symptom reporting, poor coping, avoidant behaviors, higher health anxiety resulting in heightened fear of GI symptoms (GSA) and difficulty identifying and describing feelings (alexithymia) (Labus et al., 2004, 2007). Consistent with these hypotheses, Porcelli et al. (2014b) found in 177 IBS patients that symptom severity was significantly and independently predicted by alexithymia and GSA at a similar degree, either when GSA was forced into the regression model before alexithymia ($R^2 = 0.51$; $\Delta R^2 = 0.14$; $\beta = 0.38$), and alexithymia before GSA ($R^2 = 0.56$; $\Delta R^2 = 0.19$; $\beta = 0.53$). Large effect sizes were found between symptom severity and alexithymia alone ($d = 1.16$) or combined with GSA ($d = 1.45$). However, TAS-20 alone explained 54% of the IBS severity score variance, to which GSA added a smaller although significant amount of 9%. In other words, alexithymia explained much more unique variance in IBS severity when compared with the contribution provided by GSA. Semipartial correlations that measure the proportion of IBS severity associated uniquely with the predictor confirmed that TAS-20 was associated more strongly with illness severity (*semipartial* $r = 0.50$) than GSA (*semipartial* $r = 0.23$). Similar results were previously reported

TABLE 6 | Longitudinal studies on alexithymia in hepatology.

Authors	Aim	Clinical sample	Control sample	Mean (SD) scores on TAS	Prevalence (%) of alexithymia	Main results
Cozzolongo et al., 2015	Role of alexithymia in the quality of life of patients with chronic HCV treated with antiviral therapy	124 HCV patients	None	Male HCV patients: 53.63 ± 13.36* Female HCV patients: 46.71 ± 10.14	33.1%	Poor quality of life was significantly and independently predicted by alexithymia and psychological distress before ($R^2 = 0.60$) and 6 months after the antiviral treatment ($R^2 = 0.69$)
Fukunishi et al., 2002	Evaluation of post-transplant occurrence of psychiatric disorders, including alexithymia	31 recipient-donor pairs who underwent living-related liver transplantation 65 recipient-donor pairs who underwent living-related kidney transplantation	None	–	Pre-living-related liver transplantation recipients: 38.7% Pre-living-related liver transplantation donors: 9.7% Pre-living-related kidney transplantation recipients: 41.5% Pre-living-related kidney transplantation donors: 12.3%	Compared to not-alexithymic recipients, those with alexithymia undergoing a liver ($\chi^2 = 7.2$; $df = 1$; $p = 0.007$) or a kidney transplantation ($\chi^2 = 19.7$; $df = 1$; $p < 0.001$) exhibited significantly more paradoxical psychiatric syndrome
Fukunishi et al., 2003	Evaluation of alexithymia before and after transplantation	116 pairs of recipients and donors who underwent living-related liver transplantation 325 pairs of recipients and donors who underwent living-related kidney transplantation	None	–	–	In recipients undergoing a liver or a kidney transplantation, the severity of alexithymia was significantly higher before than after transplantation
Murri et al., 2017	The role of different biopsychosocial risk factors, including alexithymia, on the onset of depression	55 HCV patients of which 29 classified as depressed, and the remaining 26 as not depressed	None	Depressed HCV patients: 52.3 ± 16.4* Not depressed HCV patients: 48.5 ± 13.9	–	HCV patients developing interferon-related persistent depression had higher TAS-20 scores, but this difference did not reach statistical significance ($t = 1.62$; $p = 0.11$)
Nardelli et al., 2013	Influence of depression, anxiety and alexithymia on health related quality of life	60 cirrhotic patients	None	–	23%	All domains of health-related quality of life, but bodily pain, were significantly impaired in patients with alexithymia
Palmieri et al. (2013)	Evaluation of psychopathological factors, including alexithymia	22 cirrhotic patients 24 patients with hepatocellular carcinoma	20 healthy controls	Cirrhotic patients: 59.6 ± 16.2* Patients with hepatocellular carcinoma: 60.8 ± 15.1 Healthy controls: 36.5 ± 8.9	Cirrhotic patients: 54% Patients with hepatocellular carcinoma: 50%	Both cirrhotic patients and those with hepatocellular carcinoma were significantly more alexithymic than controls
Porcelli et al., 2014a	Influence of somatization and alexithymia on somatic symptom reporting	111 chronic HCV patients	None	50.72 ± 12.37*	–	Alexithymia and somatization significantly and independently predicted somatic adverse events (as fatigue, pain, and skin, digestive, respiratory, and ophthalmological disturbances) both at baseline and follow-up
Porcelli et al., 2015	Role of alexithymia and specific functional gene variants on depression	130 consecutive patients presenting with chronic HCV	None	HCV patients with HTR1A-G/G: 62.08 ± 9.37* HCV patients with 5-HTTLPR-s/s: 48.23 ± 11.45	HCV patients with HTR1A-G/G: 20% HCV patients with 5-HTTLPR-s/s: 17.7%	Alexithymia and the G-variant polymorphism of the HTR1A (a promoter region of the serotonin receptor gene), both separately and jointly, significantly predicted the development of interferon-induced depression

*HCV, Hepatitis C; TAS, Toronto Alexithymia Scale. *Using TAS-20 for evaluating alexithymia. **Using TAS-26 for evaluating alexithymia.*

by Phillips et al. (2013) who showed that symptom severity in 82 IBS patients was significantly predicted by the DIF ($\beta = 0.24$) and DDF ($\beta = -0.37$) factors of the TAS-20, together with gender ($\beta = 0.15$), by accounting for 38.5% of the variance of illness severity ($R^2 = 0.38$; $p < 0.001$). Consistently, a recent follow-up study aimed at investigating whether symptom improvement in 150 IBS patients could be independently predicted by the level of alexithymia and GSA, over and above other clinical and psychological factors (Porcelli et al., 2017). The overtime stability of alexithymia was investigated with hierarchical regression showing that baseline TAS-20 scores significantly predicted TAS-20 scores at follow-up ($R^2 = 0.53$; *semipartial* $r = 0.39$; $p < 0.01$). Baseline alexithymia (*Cox & Snell* $R^2 = 0.15$; $\Delta R^2 = 0.10$; $p < 0.001$) and gastrointestinal symptoms (*Cox & Snell* $R^2 = 0.01$; $\Delta R^2 = 0.01$; $p < 0.009$), but not GSA (*Cox & Snell* $R^2 = 0.05$; $\Delta R^2 = 0.03$; $p < 0.21$), significantly and independently predicted also post-treatment improvement status with an overall classification rate of 74%. Moreover, after controlling for co-variables, alexithymia emerged as the unique significant predictor of symptom improvement by adding 17% of explained variance of change in IBS severity symptoms ($R^2 = 0.23$; $\Delta R^2 = 0.17$; *semipartial* $r = -0.41$; $p < 0.001$). In other terms, although alexithymia and GSA were closely related to IBS symptoms, only alexithymia was to found to be a stable trait and a stronger predictor of treatment outcome than GSA.

The predictive value of alexithymia in GI symptom persistence was investigated in 52 patients with gallstone disease after laparoscopic cholecystectomy (Porcelli et al., 2007a). After assigning patients to either an post-surgery improved or an unimproved outcome group, the authors showed not only that at baseline the unimproved patients scored significantly higher on the TAS-20 (66.00 ± 7.79) than the improved counterpart (49.32 ± 11.50) ($t = 5.80$, $p < 0.001$, $d = 1.70$), but also that alexithymia and psychological distress significantly predicted improvement of GI symptoms [$R^2 = 0.59$, $F_{(2,49)} = 35.72$, $p < 0.001$]. More specifically, TAS-20 total scores added a significant incremental amount of explained variance in predicting GI symptoms [$\Delta R^2 = 0.38$; $\Delta F_{(1,49)} = 45.17$; $p < 0.001$]. A previous study (van Kerkhoven et al., 2006) found similar results in a large sample of 1141 patients referred to endoscopy for upper GI symptoms by showing that high alexithymia patients (21% of the total sample; $n = 245$) reported significantly more GI symptoms (6 ± 4 vs. 5 ± 3; $p < 0.05$) and higher symptom severity (42 ± 34 vs. 34 ± 30; $p < 0.01$) than those with lower levels of alexithymia (79% of patients; $n = 896$). Alexithymia was also related to symptom perception as patients reporting more than 8 GI symptoms had more than 2-fold risk of being classified as alexithymics (*OR* = 2.1; 95% CI = 1.5–2.9). Especially patients with hematemesis (*OR* = 3.7; 95% CI = 1.5–9.2), abdominal pain (*OR* = 1.8; 95% CI = 1.4–2.5), and vomiting (*OR* = 1.9; 95% CI = 1.2–3.0) are indeed frequently identified as subjects with alexithymia. The clinical consequence of alexithymia in FD patients was further underlined in studies reporting that alexithymia and trait anxiety were the main determinants of the mental component of quality of life (Van Oudenhove et al., 2011b; Jones et al., 2013). Specifically, Van Oudenhove et al. (2011b) found that mental quality of life was negatively and significantly associated with alexithymia (Spearman's $rho = -0.42$; $p < 0.001$).

An interesting study investigated the role of alexithymia in comorbid FGID and psychiatric syndromes.

Thirty-eight FGID patients with comorbid psychiatric syndromes recruited in a GI setting were compared with 25 psychiatric outpatients with comorbid FGID recruited in a psychiatric setting (Porcelli et al., 2004). The first group scored significantly higher on the TAS-20 (66.7 ± 11.2) than the latter group (52.7 ± 10.4) ($t = 4.99$, $p < 0.001$), with a prevalence of alexithymia at 81.6% ($n = 31$) compared with a rate of only 28% in the latter group ($n = 7$). Also, TAS-20 total scores independently predicted which subjects belonged to the subgroup of FGID patients with comorbid psychiatric disorders (*OR* = 1.14; 95% CI = 1.03–1.26; $p = 0.001$).

Conflicting results were also found, however. Farinelli et al. (2007) showed that no one of 69 patients with gastroesophageal reflux disease was identified as alexithymic on the basis of the TAS-20 (43.7 ± 9.9). Similar negative results were obtained by Jones et al. (2004) who found that only 12% of 111 FD patients obtained a score of ≥61 on the TAS-20, even though patients with FD scored slightly higher (43 ± 11) than 53 control healthy subjects (38 ± 11) ($p < 0.005$). Similarly, no significant TAS-20 difference was found by Jones et al. (2006) between 74 IBS (42 ± 12) and 48 IBD patients (43 ± 12), even though they were more alexithymic than 55 healthy subjects (38 ± 9) ($p = 0.005$). Same results were reported by other two studies comparing TAS-20 mean scores between 151 FD (47.62 ± 13.06) and 58 non-FD patients (45.62 ± 13.32) (Cohen's $d = 0.14$; $p = 0.332$) (Dibaise et al., 2016), and between 28 patients with FGID (46.16 ± 13.91) and 17 patients reporting GI motility disorders (48.43 ± 17.15) ($z = -0.63$; $p = 0.527$) (Eiroa-Orosa et al., 2015).

Neurobiological Studies

Only two cross-sectional studies on non-patients from one Japanese group performed an assessment of alexithymia and its neurobiological correlates in GI patients. Kano and her colleagues (Kano et al., 2007, 2015) found that in subjects where visceral sensation was induced by distension of the colon or rectum, the DIF alexithymia factor was significantly associated with subjective symptoms as abdominal distension ($r = 0.27$; $p < 0.05$), abdominal pain ($r = 0.34$; $p < 0.05$), urgency for defecation ($r = 0.31$; $p < 0.05$), perceived stress ($r = 0.3$; $p < 0.05$), sleepiness ($r = -0.3$; $p < 0.5$), and anxiety ($r = 0.28$; $p < 0.005$). They found also that alexithymia significantly and positively correlated with both higher activity in the right insula of the brain (*Z-score* = 4.26; $z = 4$; $p < 0.001$) (which is the primary projection area for visceral afferent information and is critically involved in subjective emotional experience and awareness of the internal bodily state) and orbital gyrus (*Z-score* = 4.29; $z = -22$; $p < 0.001$) (which receives robust sensory inputs and acts as an internal environmental integrator that coordinates behavioral, autonomic, and endocrine responses).

Treatment Studies

Only one follow-up study by Faramarzi et al. (2013) investigated the effects of psychotherapy on GI symptoms and alexithymia.

This study aimed to evaluate the effect of short-term psychodynamic psychotherapy on alexithymia in 24 patients with FD and found that the psychotherapy group significantly improved after treatment for both alexithymia and dyspepsia symptoms (as heartburn/regurgitation, nausea/vomiting, post-prandial fullness/early satiety, bloating, upper or lower abdominal pain) and that the improvement was maintained at 1 and 12 months post-treatment. Specifically, the improvement of alexithymia concerned the TAS-20 total scale [$F_{(3, 45)} = 25.80$; $p < 0.001$] and DIF [$F_{(3, 45)} = 16.00$; $p < 0.001$] and DDF [$F_{(3, 45)} = 11.70$; $p < 0.001$] scores but not the EOT factor.

IBD and Alexithymia

UC and CD, the main forms of IBD, are "complex immunologically mediated diseases that arise due to a dysregulated immune response to commensal flora in a genetically susceptible host" in which "diet, lifestyle and behavior, as well as perturbations of the gut microbiota through use of antibiotics, might also have important roles in disease pathogenesis" (Ananthakrishnan, 2015, p. 206). The clinical course of the disease is characterized by intermittent phases of unforeseeable, intermittent acute relapses and symptom-free periods. Acute episodes are characterized by clinical symptoms of severe abdominal pain, bloody stools, and severe diarrhea and endoscopic and histological signs of inflammation and lesions of the gut mucosa. It is a severe GI disease with likely complications at the intestinal (malnutrition, weight loss, colon cancer, fistulas, intestinal perforation, bowel obstruction) and extra-intestinal (arthritis and ophthalmologic, dermatologic, and urinary complications) manifestations (Kucharzik et al., 2006; Sartor, 2006).

Seven studies on alexithymia with IBD patients had a cross-sectional design (Porcelli et al., 1995; Verissimo et al., 1998, 2000; Boye et al., 2008a,b; Iglesias-Rey et al., 2012; La Barbera et al., 2017), and only 4 were longitudinal (Porcelli et al., 1996; Porcelli and Meyer, 2002; Tibon et al., 2005; Porcelli and Mihura, 2010).

Porcelli et al. (1995) conducted the first research study aimed at evaluating the association between alexithymia and IBD. By comparing 112 IBD patients with 112 matched healthy control subjects, they found a prevalence rate of alexithymia of 35.7% ($n = 40$) in the clinical sample that was higher than the 4.5% ($n = 5$) prevalence in control subjects ($\chi^2 = 49.5$; $p < 0.001$). The association between TAS-20 and IBD was further confirmed after controlling for the sociodemographic variables of gender, age, and education ($\chi^2 = 48.12$; $p < 0.001$). Similarly, when comparing a clinical group of 124 patients, of which 74 with IBD, with a control group of 218 medical students, Verissimo et al. (2000) showed that the clinical sample scored significantly higher than controls on the TAS-20 total scale score (56.44 ± 11.66 vs. 48.68 ± 9.15) ($t = 6.82$; $p < 0.001$). Particularly the DIF (20.96 ± 6.88 vs. 17.85 ± 5.30; $t = 4.66$; $p < 0.001$) and EOT (20.82 ± 4.39 vs. 16.18 ± 3.69; $t = 10.42$; $p < 0.001$) factors were significantly higher in clinical sample than controls. In 104 IBD patients investigated longitudinally for 6 months, Porcelli et al. (1996) further supported alexithymia as a stable personality trait through high correlation between baseline and follow-up TAS-20 scores ($r = 0.95$, $p < 0.001$). Another study by Verissimo et al. (1998) confirmed that alexithymia scores were not significantly related to the duration of IBD or the level of disease activity. However, the TAS-20 correlated negatively and significantly with disease-specific quality of life score ($r = -0.34$, $p < 0.01$), particularly with bowel symptoms ($r = -0.28$; $p < 0.05$), systemic symptoms ($r = -0.37$; $p < 0.01$), and emotional functioning ($r = -0.38$; $p < 0.01$). Finally alexithymia ($\beta = -0.27$), emotional control ($\beta = 0.26$), education ($\beta = -0.7$), and socioeconomic index ($\beta = -0.09$),played a significant role in predicting levels of quality of life [$R^2 = 0.21$; $F_{(4,57)} = 3.69$; $p < 0.01$]. Consistently, Boye et al. (2008b) and La Barbera et al. (2017) examined 109 and 100 IBD patients, respectively, and found that high levels of alexithymia were associated with lower scores of physical, mental and social functions. Specifically, in patients with UC alexithymia negatively and significantly correlated with physical ($r = -0.33$), mental ($r = -0.49$), and social ($r = -0.30$) components of health-related quality of life (Boye et al., 2008b). Similar results have been found by Iglesias-Rey et al. (2012) in a large sample of 484 patients showing that alexithymia, particularly the DIF factor ($\beta = -0.02$; $p \leq 0.001$), represents a significant determinant of impaired health-related quality of life in IBD. More specifically, alexithymia was found as a significant risk factor for poor quality of life ($OR = 3.34$, 95% CI: 1.98–5.65). Consistently, another study by Boye et al. (2008a) found that in 56 UC patients alexithymia negatively and significantly correlated with the emotional dimension of quality of life ($r = -0.26$).

Liver Diseases and Alexithymia

Differently from previous studies on FGID and IBD, 8 of the 10 included studies evaluating alexithymia in hepatology had a follow-up study design (Fukunishi et al., 2002, 2003; Nardelli et al., 2013; Palmieri et al., 2013; Porcelli et al., 2014a, 2015; Cozzolongo et al., 2015; Murri et al., 2017). Research investigations focused more on the role that alexithymia might play in the course of disease and medical treatment rather that its prevalence. Prevalence of alexithymia was reported in only 2 studies at 22% ($n = 100$) (Rustgi et al., 2010) and 54% ($n = 22$) (Palmieri et al., 2013).

The first research study investigating alexithymia in hepatology included patients with chronic non-alcoholic liver disease pending for a liver transplantation (Blomhoff and Malt, 1995). The most frequent causes of non-alcoholic liver diseases include primary biliary cirrhosis, primary sclerosing cholangitis, and chronic autoimmune hepatitis, while other potential causes include secondary biliary cirrhosis, CHC, malignant liver cancer, and cirrhosis of medically unknown etiology. In this first study, the authors did not find higher alexithymia levels in their 29 patients who scored in the normal range of TAS-26 (64.0 ± 10.5). Later, Fukunishi et al. (2002) administered the TAS-20 to 31 donor-recipient pairs undergoing living-related liver transplantation and found that pre-transplant alexithymia was significantly related to the manifestation of post-transplant paradoxical psychiatric syndrome (PPS) ($\chi^2 = 7.2$, $p = 0.007$). The PPS is a reactive psychiatric disorder characterized by core symptoms of prominent conflicts associated with transplantation such as guilt regarding the donor's well-being; situational

reactions such as depression, anxiety, somatization; late reaction occurring as a complication following liver transplantation; and favorable medical status of donor and recipient. This psychiatric disorder is defined with the specific term "paradoxical" because such a syndrome occurs despite successful transplantation and without tissue rejection or other medical complication (Fukunishi et al., 2001). The same authors later showed that the severity of alexithymia was significantly higher in 441 recipients before than after transplantation (Fukunishi et al., 2003).

The other liver disease investigated for alexithymia is CHC. It is mainly caused by HCV infection, reaches a worldwide prevalence of about 2% (Shepard et al., 2005), and has been associated to an increased rate of mortality (Lee et al., 2012). HCV is transmitted through exposure to contaminated blood and slowly attacks the liver, advancing to CHC, hepatic cirrhosis or liver cancer (Lauer and Walker, 2001). Before the availability and marketing of new direct anti-viral drugs, standard treatment consisted of a combination therapy with pegylated IFN, a proinflammatory cytokine that modulates the immunologic system, and ribavirin, a nucleoside inhibitor with a broad activity against viral pathogens, for variable periods of 6–12 months. The IFN-based therapy induced patients who were subjectively healthy before starting the treatment to long-lasting (up to 1–2 years after the end of the treatment period) biological adverse events (hematologic, immunologic, infective, cardiovascular diseases, as well as neuropathy, heart, kidney, and lung failures) and subjective somatic symptoms (fatigue, insomnia, pruritus, diarrhea, flu-like syndrome, nausea, and headache). As stated in the Introduction, subjectively reported somatic symptoms are largely overlapped with somatization symptoms. The first study assessing alexithymia in 83 consecutive patients with CHC found that alexithymia was prevalent at 22% ($n = 18$) and significantly associated with the Illness Effects Questionnaire ($r = 0.40$ $p < 0.001$) that measures the individual burden of hepatitis in terms of the subjective appraisal in biologic, emotional, and interpersonal domains (Rustgi et al., 2010). Also after controlling for levels of depression, alexithymia significantly correlated mainly with fatigue ($r = 0.53$; $p < 0.001$) and burden of disease ($r = 0.41$; $p < 0.001$) and less with sleep difficulties ($r = 0.24$; $p < 0.05$). Furthermore, patients designated categorically as alexithymic endorsed significantly greater levels of depression than those that were identified as not alexithymic and alexithymia emerged as the only significant predictor of depression, accounting for 43% of the total variance ($OR = 1.1$; $p < 0.01$).

The predictive value of alexithymia in CHC patients during the standard medical treatment with IFN for 6–12 months that was available at that time was evidenced by Porcelli et al. (2014a). Adjusting for co-factors (lifetime psychopathology, psychological distress, and sustained virological response at follow-up, that is a measure of successful virus eradication), alexithymia and somatizing vulnerability independently predicted IFN-related somatization symptoms while not adverse biological events (as anemia, neutropenia, and thrombocytopenia) during the entire study period, explaining 77– 80% of their variance at both baseline and follow-up evaluations. Specifically, alexithymia ($\beta = 0.26$; $p = 0.001$) and somatization ($\beta = 0.66$; $p < 0.001$) significantly and independently contributed to predict somatic symptoms at baseline ($R^2 = 0.80$; $p < 0.001$) and follow-up ($\beta = 0.43$; $p < 0.001$, and $\beta = 0.68$; $p < 0.001$, respectively; $R^2 = 0.77$; $p < 0.001$). Consistently, the same research group (Porcelli et al., 2015) found that, after a first follow-up of 3 months (T2), as well as at the end of treatment (T3), alexithymia and a gene variant of the 5-HT1A receptor (HTR1A-G/G) polymorphism (i.e., a functional gene polymorphism in the upstream regulatory region of the serotonin transporter coding sequence associated with major depression), both separately (explained variance: from 20 to 22%; T2: $R^2 = 0.22$; $F = 6.83$; $p = 0.01$; T3: $R^2 = 0.20$; $F = 4.34$; $p = 0.03$) and jointly (explained variance: from 14 to16%; T2: $R^2 = 0.16$; $F = 7.39$; $p = 0.007$; T3: $R^2 = 0.14$; $F = 5.53$; $p = 0.03$), significantly and independently predicted the development of IFN-induced depression in a sample of 130 HCV patients. Poor quality of life in patients with HCV ($n = 124$) was also independently predicted by alexithymia (at baseline: *semipartial* $r = 0.24$; at follow-up: *semipartial* $r = 0.39$) and depression (at baseline: *semipartial* $r = 0.24$; at follow-up: *semipartial* $r = 0.31$) before (T0: $R^2 = 0.60$) and at the 6-month post-IFN treatment follow-up (T3: $R^2 = 0.69$) (Cozzolongo et al., 2015). Similarly, a previous study on 60 cirrhotic patients found that all domains of health related quality of life, except bodily pain, were significantly impaired in cirrhotic patients presenting with alexithymia (Nardelli et al., 2013). Specifically, the authors showed that alexithymia particularly altered the mental component of health-related quality of life ($\beta = -0.54$; $t = -2.63$; $p = 0.01$). Finally, Murri et al. (2017) did not detect a significant role of alexithymia in predicting persistent IFN-related depression but the subsample of 12 HCV patients developing persistent depression reported higher TAS-20 scores (56.7 ± 15.9) than 43 patients without depression (48.7 ± 14.8), although not at a statistically significant level ($t = 1.62$, $p = 0.11$).

DISCUSSION

The close bidirectional communication between the central and the enteric nervous systems is referred to as the brain-gut axis. Its role is to monitor and coordinate gut functions as well as to link emotional and cognitive centers of the brain with peripheral intestinal mechanisms. Also, the role of gut microbiota is increasingly emerging as one of the major clinical factor that is able to influence health and disease, as well as the subjective perception of visceral sensations. Although this research topic is in its infancy in humans, alterations in bidirectional brain-gut-microbiota interactions are believed to be involved in the pathogenesis of several functional and organic GI disorders, some brain disorders such as autism spectrum disorders, and Parkinson's disease, and psychiatric disturbances such as mood and affect disorders, and chronic pain (Mayer et al., 2015). Given the strict connections between different organs and systems, upstreaming GI sensations and downstreaming emotional and cognitive perceptions are closely intertwined in affecting individual illness behavior (Fava and Sonino, 2017). Based on theoretical assumptions and a wide dataset of research findings (e.g., Taylor, 2000; Taylor and Bagby, 2004, 2012), it is

conceivable that alexithymia may be seen as playing an important role in the GI setting.

In the present systematic review, for the first time to our knowledge, the link between alexithymia and GI disorders has been investigated. We expected that alexithymic features would be more prevalent in GI disorders based more on subjective perception than organic biomarkers. Regardless of the etiological nature of illness, we expected also that alexithymia would be more relevant in clinical outcomes related to the subjective dimension of health perception. The main findings of our systematic review are generally consistent with our expectations. Specifically, we have found that:

(1) the prevalence of alexithymia was significantly higher in GI patients compared to control subjects and to the estimated prevalence rates in the general population (10–15%; see Mattila et al., 2006; Franz et al., 2008; Tolmunen et al., 2011);
(2) alexithymia was higher in patients with FGID than in those with IBD and liver diseases;
(3) most significant findings concerned the difficulty identifying and communicating feelings (the DIF and DDF factors of the TAS-20), whereas no significant results emerged generally as for the external-oriented thinking facet of alexithymia;
(4) the relevance of alexithymia (i.e., the impact and its main consequences) was significantly more related to somatization, health-related perception, symptom persistence and reporting, and negative treatment outcomes. However, these results should be considered in the light of several limitations of the reviewed studies that will be highlighted later.

Prevalence Rates of Alexithymia

Based on the widely used cut-off scores of the TAS-26 and TAS-20, in the GI clinical setting alexithymia has been found consistently highly prevalent in patients with FGID, with rates ranging from 66% (Porcelli et al., 1999) to 87% (Van Oudenhove et al., 2008). The prevalence of alexithymia in IBD patients, though lower than in FGID, is still higher than the general population, at about 30–35% (e.g., Porcelli et al., 1995; Iglesias-Rey et al., 2012). Unlike FGID, however, conflicting results in IBD patients were reported by some investigations showing prevalence at similar level of general population, if not even lower (Jones et al., 2006; Boye et al., 2008a,b). Hence, currently there is no consensus about the prevalence rate of alexithymia in IBD.

Prevalence of alexithymia in hepatology is based on a lower number of studies. Palmieri et al. (2013) found a high prevalence rate of alexithymia in 54% of cirrhotic patients. This frequency of alexithymia is higher than the prevalence rate of 23% reported in the same population of cirrhotic patients by Nardelli et al. (2013), but it is comparable to the prevalence of alexithymia reported in other chronic disease such as obstructive pulmonary disease (Han et al., 2012), essential hypertension (Jula et al., 1999), psoriasis (Sampogna et al., 2017), and type 2 diabetes (Lemche et al., 2014; Avci and Kelleci, 2016).

Overall, in gastroenterology and hepatology the prevalence of alexithymia was higher than the general population and control subjects. Furthermore, alexithymia was found in more than two third of samples of FGID patients. By contrast, in organic disorders like IBD and liver disease, alexithymia was prevalent only in one third to one half of samples, similar to other non-GI chronic diseases.

Alexithymia and Clinical Outcomes

Associations With Health-Related Issues

In line with the view of alexithymia as a personality dimension associated with affective dysregulation, several studies have found consistently that alexithymic traits negatively influence a series of clinical outcomes, that are strictly related to the subjective perception of health. Specifically, the following were the main results in this regard: (1) in patients with FGID (Arun, 1998; Jones et al., 2004, 2006) and also in those with non-alcoholic liver disease (Blomhoff and Malt, 1995) higher scores of alexithymia were directly associated with higher levels of negative emotional traits such as neuroticism, rigidity, introversion, and perfectionism; (2) there was a significant relationship between alexithymia and depressive symptoms in patients with FGID and peptic ulcer (Faramarzi et al., 2014), as well as in those with HCV and cirrhosis (Rustgi et al., 2010; Nardelli et al., 2013; Murri et al., 2017); (3) alexithymia correlated significantly with insecure attachment relations in patients with IBD (Bengtsson et al., 2013) and gastroesophageal reflux disorder (Farinelli et al., 2007); (4) alexithymia was significantly associated with lower quality of life and impaired psychosocial functioning in patients with HCV (Cozzolongo et al., 2015) and liver carcinoma (Palmieri et al., 2013), IBD (Verissimo et al., 1998; Iglesias-Rey et al., 2012; La Barbera et al., 2017), and FGID as well (Portincasa et al., 2003; Van Oudenhove et al., 2011b; Jones et al., 2013).

Symptom Perception and Persistence

Compared to patients with lower levels of alexithymia, those characterized by higher alexithymia reported more severe GI symptoms. In particular, patients with IBS perceived higher levels of symptom severity even when controlled for GI-specific anxiety (Porcelli et al., 2014b). Similarly, patients with gallstone disease reported persistence of dyspeptic symptoms 1 year after cholecystectomy (Porcelli et al., 2007a), and those with HCV infection had higher somatic symptoms during antiviral treatment (Porcelli et al., 2014a) if scoring higher on alexithymia. However, results are not consistent across investigations and conflicting findings on the association of alexithymia with symptom severity have been reported also (Van Oudenhove et al., 2008; Jones et al., 2013; Dibaise et al., 2016).

Treatment Outcomes

Some studies investigated the role of alexithymia in explaining treatment outcomes. After 6 months of enhanced treatment with medical and psychological interventions, alexithymia showed to be a stable trait over time that influences negatively treatment outcomes, even after controlling for baseline GI symptoms, depression, and anxiety (Porcelli et al., 2003). In IBS patients, alexithymia was found to be a stronger predictor of symptom severity and negative outcomes following enhanced usual care compared to other clinically relevant constructs as visceral sensitivity (Porcelli et al., 2017). Finally, in a randomized

controlled trial, significant improvement of alexithymia and GI symptoms 6 months after short-term psychodynamic psychotherapy (combined with standard medical treatment) was found in FD patients compared to those who received as-usual medical care only (Faramarzi et al., 2013).

Associations With Clinical Issues in Liver Disease

Except for findings on prevalence reported above (e.g., Nardelli et al., 2013; Palmieri et al., 2013), few studies have investigated how much alexithymia may influence clinical issues in hepatology. In patients with CHC undergoing antiviral treatment, alexithymia (particularly the facets of difficulty identifying and describing feelings), alone or together with tendency to somatization, was more prominent in explaining subjective somatic symptoms (i.e., fatigue, insomnia, pruritus, diarrhea, flu-like syndrome, nausea, and headache), but not the biological adverse events (i.e., anemia, neutropenia, and thrombocytopenia) (Porcelli et al., 2014a). Alexithymia contributed also to impair quality of life even when lifetime mood disorders were controlled for (Cozzolongo et al., 2015), at the entry of the study and after 6 months from the termination of treatment with IFN. Of interest, in these patients alexithymia and the presence of the G-variant polymorphism of the HTR1A, a promoter region of the serotonin receptor gene, explained higher vulnerability to depressive symptoms during the antiviral treatment (Porcelli et al., 2015).

Findings on the role of alexithymia in treatment outcomes and liver diseases should be however viewed with caution, as they come from a single research group and therefore cannot be compared with independent research investigations.

Potential Mechanisms of Alexithymia

Alexithymia has been extensively investigated in the last 30 years. There is indeed a lot of evidences that alexithymia is associated with personality traits affecting mental and somatic health. Its several clinical consequences are neuroticism, harm avoidance, low openness to experience and psychological mindedness (Taylor, 2000), insecure attachment (Taylor et al., 2014), implicit mechanisms of emotional recognition in interpersonal relations (Donges and Suslow, 2017), higher somatic symptom reporting (Mattila et al., 2008) and perception (Lumley et al., 1996; Porcelli et al., 2007b), altered immune and inflammation status (Honkalampi et al., 2011), persistence of somatic symptoms and negative outcomes of medical treatments (McIntosh et al., 2014; Baudic et al., 2016; Saariaho et al., 2017), increased genetic susceptibility (Terock et al., 2018), and higher mortality risk over long periods (Tolmunen et al., 2010). In the clinical link between alexithymia and GI disorders, it is not easy to disentangle which co-variate is associated to which. Data suggest that alexithymia is prevalent in high rate in GI disorders and is particularly relevant in modulating the individual perception of symptoms, even after as-usual medical care and independently of the nature of the GI condition.

Several factors may explain the association of alexithymia with GI symptoms and health-related issues.

One is represented by the proneness of alexithymic individuals to experience and to report more functional somatic symptoms because of their tendency to amplify, selectively focus on, and misinterpret the somatic sensations that accompany states of emotional arousal, as well as other normal bodily sensations (Nakao et al., 2002; Jones et al., 2004; Van Oudenhove et al., 2016). It has been hypothesized that the diminished ability of alexithymic individuals to experience emotions as conscious feelings may lead to a significantly amplification of the somatic sensations accompanying emotional arousal (Barsky and Klerman, 1983; Lane and Schwartz, 1987; Lane and Garfield, 2005). The higher prevalence of alexithymia among patients with functional illnesses such as IBS and FD than in those with organic diseases such as IBD and HCV is thought to be due to this perceptual mechanism.

Another pathway is represented by the bidirectional brain-gut axis that allows GI symptoms to be generated not only by motility disturbances or alterations in sensory inputs originating in the gut, but also by unregulated states of emotional arousal that, when mutually interact with somatic sensations of the gut and with other psychological factors, lead individuals to develop visceral hypersensitivity (Mayer, 2011). IBS patients have been found to have lower thresholds for visceral sensations and pain perception, and central alteration of abnormal pain evaluation. This is thought to be attributable not only to bottom-up signals from the gut to the brain, but also to complementary top-down affective disturbances clinically related to functional alterations of prefrontal and cingulate regions (Elsenbruch, 2011; Stabell et al., 2013). Alexithymia, as an individual deficit characterized by difficulties with emotion regulation and reduced emotional awareness, may determine a significantly lower threshold to somatic sensations arising from the gut. A large body of literature repeatedly confirmed the association between alexithymia and increased severity of subjective somatic symptom reporting (Kooiman et al., 2000; Lumley et al., 2007; Tolmunen et al., 2010; Stabell et al., 2013).

Furthermore, alexithymic individuals reported higher activation of processes leading to amplification of visceral states at multiple levels. They have been found to exhibit higher resting or tonic sympathetic activity (Stone and Nielson, 2001; Alkan Härtwig et al., 2013) as evidenced by: (1) altered interoceptive awareness (Herbert et al., 2011); (2) higher activation of pain-related brain areas (e.g., insula, pregenual anterior cingulate cortex, and brainstem); (3) lower awareness of the internal body states (Kano et al., 2007, 2015); (4) higher pro-inflammatory activity (i.e., higher C-reactive protein and altered balance of pro- and anti-inflammatory cytokines) (De Berardis et al., 2008; Guilbaud et al., 2009; Honkalampi et al., 2011). Overall, these findings suggest that difficulties with emotion regulation through reduced emotional awareness via alexithymia may negatively impact the subjective pain experience and increase the likelihood of reporting high somatic symptoms.

A third pathway may be identified in the association with illness behavior (Sirri et al., 2013). The construct of illness behavior refers to the varying ways individuals respond to bodily sensations, monitor internal states, interpret somatic symptoms, and use health care services (Sirri et al., 2013). Alexithymia may prompt a maladaptive and unhealthy lifestyle serving as modulator of unregulated emotional arousal (Kauhanen et al.,

1992; Pinaquy et al., 2003). Unhealthy behaviors such as poor nutritional consumption, poor eating behavior (e.g., fast eating and binging), alcohol and drug use, sedentary lifestyle may be conceived as maladaptive coping strategies and efforts that individuals with alexithymia use to self-regulate distressing emotions that they cannot process at a cognitive level (Kauhanen et al., 1992; Pinaquy et al., 2003). Various combinations of somatic amplification, lower threshold to pain, unhealthy lifestyle, and abnormal illness behavior might be the underlying mechanisms through which alexithymia, as a predisposing or mediating factor, is linked to symptom formation and poor treatment outcomes in FGID and to overlapping somatization symptoms in organic conditions such as IBD and HCV.

The likely role of alexithymia in disorders of the GI system can be viewed within the framework of contemporary theoretical models of the mind-body-brain relations. For example, Damasio (1999) speculated on two different neural pathways of "body loop" and "as-if body loop." In the first model, physiological inputs are relayed into the brain, where they are later transformed in emotions that form somatic markers. The enacted somatic states can then activate regions involved in body mapping, trigger somatic states thus increasing or decreasing thresholds for subsequent somatic states. These somatic states can simultaneously activate working memory thus strengthening or weakening a particular representation in the brain. In the second pathway, instead of having somatic states expressed in the body, cognitive representations of the emotions (e.g., imagining an unpleasant situation "as-if" one were there) may activate representations of somatic states in the brain thus inducing changes in neurotransmitter release but without re-enacting the body. The individual brain might therefore anticipate expected bodily changes without being directly elicited by a sensory stimulus and allows the individual to respond faster to external stimuli without waiting for an event to actually occur. Damasio's "as-if body loop" may serve either the adaptive purpose of planning future behavior in advance and the maladaptive pattern of re-mapping bodily states as perception of somatic illness, particularly if feelings are defectively linked to somatic sensations of autonomic arousal, according to the alexithymia construct.

Another theoretical model that is gaining interest recently conceptualizes somatization as a disorder of perception (Wiech, 2016; Henningsen et al., 2018). In this model, perception of bodily states, including inputs from the enteric nervous system, is co-determined by top-down expectations generated by the central nervous system that is continuously building probabilistic predictions of its environment. Such predictions include the mapping of bodily states, like a coding machine. Higher perception of GI symptoms may arise when downstreaming predictions of distress meet with rougher upstreaming inputs from the gut. Symptoms may be therefore based on this sort of mismatch between expectations and sensations. Several predisposing, triggering, and maintaining factors modulate how individuals would perceive their health status, report the outcomes of their illness, and shape their illness behavior, from spontaneous remission of mild symptoms to denial of being ill to amplification of symptoms to chronicity of disease. Environmental and psychosocial factors may act as triggering (e.g., a viral infection as in post-infective IBS or a stressful event as in many acute episodes of FGID) or maintaining (e.g., frustration stemming from the burden of antiviral treatment in HCV or a persistent low-grade inflammation in post-relapsing phases of IBD). Predisposing or vulnerability factors are powerful variables in paving the way toward different individual pathways of illness behavior. Also, the cultural background (Kirmayer and Sartorius, 2007), childhood traumas, attachment patterns (Maunder et al., 2017), and epigenetic mechanisms play a significant role in this regard (Turecki and Meaney, 2014).

Alexithymia may be considered as one of predisposing psychological factors as well as one of the determinants involved in the Damasio's "as-if body loop." Deficits in processing and regulating affects may constitute indeed a strong personality-related vulnerability aspect in disrupting the matching process between central expectations and peripheral sensations generating emotions. This may explain the high prevalence rate of alexithymia in medical and psychiatric disorders (Taylor et al., 1997) as well as the overlap between alexithymia and mood, anxiety, and somatization symptoms (Porcelli et al., 2013).

Limitations

Caution should be expressed when interpreting the findings of this systematic review because of the limits of the reviewed studies. Overall, studies prevalently involved patients with FGID (27 of the 48 reviewed studies), samples sizes were generally small (under 100 participants), adopted a cross-sectional design (30 studies), and used only one method for assessing alexithymia.

Studies with small sample size constitute a strong limitation for the generalization of results. In the GI setting, as well as in other medical settings, and particularly in patients with functional somatic disorders, patients recruited from secondary and tertiary care centers have been shown to have moderate to severe illness severity (Drossman, 2016). In these patients, representing the most severe end of severity continuum, high level of alexithymia may co-occur—and confounded with—higher psychological distress, psychiatric comorbidity, and abnormal illness behavior. However, the higher prevalence rate of alexithymia in FGID than IBD and liver disease patients than the estimated rate in the general population might be biased by these confounding factors.

Cross-sectional studies do not allow to establish direction of causality or the overtime stability of alexithymia. Patients recruited in secondary and tertiary care settings generally show longer duration of illness, previous tentative treatments, and therefore may be frustrated by the unwanted effects of therapy. Usually these patients are considered by their physicians as "difficult patients," thus limiting the benefits of an effective doctor-patient relationship (Aronson, 2013). Alexithymic features may therefore be a consequence rather than a predisposing factor of the illness status. Furthermore, some studies showed the relative stability of alexithymia within the context of change of symptoms following treatment both in FGID (Porcelli et al., 2003, 2017) and cancer patients (Luminet et al., 2007; Porcelli et al., 2011), but the cross-sectional design of most

reviewed studies does not allow to infer to which extent trait alexithymia may predict the course of illness over time.

Finally, as previously stated in the section of introduction, we selected studies using the Toronto scales. No study assessed alexithymia in a multi-method approach and the TAS was the only used measure. Even though the TAS has shown strong psychometric properties, the results from these investigations are limited by the limits of the TAS (reliance on self-report and ability to self-awareness, and missed core aspects of the construct from the scale contents).

Further studies would be needed for further ascertaining the role played by alexithymia in GI disorders. Sounder investigations should include longitudinal studies on larger samples, and better defined inclusion criteria as baseline illness severity and adjustment for primary vs. secondary/tertiary health care settings. Furthermore, the predisposing or mediating role of alexithymia should be investigated at the light of other likely co-determinants of GI conditions such as the influence of gut microbiota and immune inflammatory processes, as well as lifestyle factors like diet and exercise. Future randomized controlled trials should investigate whether interventions aiming to reduce both alexithymia and symptoms are equally effective on both outcomes and if the improvement of symptoms parallels the improvement of alexithymia, by evaluating also which of the two clinical factors is a stronger predictor of the other.

CONCLUSION

This systematic review suggests that alexithymia is largely present in patients with functional disorder of the GI tract in two third or more patients, potentially reinforcing symptom persistence and reducing the positive effects of standard medical treatments. Furthermore, alexithymia is present in about one third of patients with inflammatory chronic disease of the gut, as well as in patients with liver disorders. Alexithymia is associated with several psychological factors increasing the subjective burden of disease and impairing quality of life.

Clinicians should be alerted to take alexithymia into serious account when evaluating, managing, and planning interventions with GI patients. Even with some limitations in mind, the assessment of alexithymia in these patients during all stages of patient management, from diagnosis to treatment outcome, is recommended by using the TAS-20 in combination with several validated instruments (self-report scales, interviews, and personality tests), according to the clinical and research needs. Also, since some intervention trials showed that reducing alexithymia significantly contribute to ameliorate symptoms in patients with cancer-related pain (Tulipani et al., 2010), FGID (Faramarzi et al., 2012; Porcelli et al., 2017), and multisomatoform symptoms (Probst et al., 2017), clinicians are strongly suggested to treat alexithymia as a solid contribution to improve the clinical condition of their patients. Even if not directly associated with positive symptom change, reduction of alexithymia may greatly improve the capacity to recognize one's feelings and to communicate them to others, thus contributing to positive clinical outcomes by enhancing psychosocial functioning, affective regulation (Cameron et al., 2014), and psychological well-being.

AUTHOR CONTRIBUTIONS

Both of the authors made substantial contributions to the work and approved it for publication. Specifically, DC contributed to the acquisition, qualitative analysis and synthesis of data by drafting the first version of the manuscript. PP contributed to the conception and design of the systematic review and revised the manuscript for intellectual content.

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Association Between Alexithymia and Functional Gastrointestinal Disorders

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The personality construct alexithymia is characterized by the difficulty in identifying and describing feelings with an externally oriented thinking pattern and a limited imaginative capacity (Nemiah et al., 1976). Alexithymia was first described as a specific cognitive and affective style of patients with classic psychosomatic diseases who showed little insight into their emotions and failed to respond to dynamic psychotherapy (Sifneos, 1967). Studies have found that alexithymia contributes to various medical conditions, including gastrointestinal diseases, cardiovascular diseases, obesity, chronic pain, renal failure, eating disorders, panic disorders, and posttraumatic stress disorders (Taylor et al., 1997). Alexithymia has been recognized as a risk factor for various physical and mental health problems; however, the mechanism that links alexithymia with these physical symptoms remains unclear.

Functional gastrointestinal disorders (FGIDs) are one of the conditions associated with alexithymia that has a high prevalence (Porcelli and Todarello, 2007). FGIDs are characterized by chronically recurring gastrointestinal symptoms in the absence of structural or biochemical abnormalities (Drossman, 2016). FGIDs are defined as disorders of the gut-brain interaction, which is a complex interaction that may be dysregulated by microbial dysbiosis within the gut, altered mucosal immune function, altered gut signaling (visceral hypersensitivity), and central nervous system modulation of gut signaling and motor function (Drossman and Hasler, 2016). FGIDs have been studied from a biopsychosocial perspective and shown that psychological and social factors have an impact on FGIDs (Van Oudenhove et al., 2016). Irritable bowel syndrome (IBS) and functional dyspepsia (FD) are the most widely recognized FGIDs with a prevalence of 11.2% (Lovell and Ford, 2012) and 10–30% (Mahadeva and Goh, 2006) worldwide, respectively.

To identify the association between alexithymia and FGIDs, we searched the relevant papers on PubMed from 1985 until September 2017 for full-text articles with a combination of "alexithymia" and "functional gastrointestinal disorders," "irritable bowel syndrome," "functional dyspepsia," or "gastrointestinal" in the title of abstract. The first version of the Toronto Alexithymia Scale was published in 1985 (Taylor et al., 1985).

Alexithymia in FGIDs

The studies of alexithymia in FGIDs are summarized in **Table 1**. A high prevalence of alexithymia has been reported in patients with FGIDs (Porcelli et al., 1999, 2003, 2004b; Mazaheri et al., 2012). Alexithymia was a negative predictor of treatment outcome (failure to improve) in FGIDs (Porcelli et al., 2003, 2004b), while health anxiety (hypochondria) predicted improvement (Porcelli et al., 2004b). Relative to depression, alexithymia was the stronger predictor for poor outcome

TABLE 1 | Alexithymia and FGIDs.

Year first author	Subjects	Alexithymia measure	Diagnosis of FGIDs	Results
FGIDs				
2012 Mazaheri	129 FGIDs (47 m) 108 Controls (39 m)	TAS-20	ROME III GSRS	Mean scores of alexithymia and its subscales were higher in FGIDs than Controls
2004 Porcelli	58 FGIDs (26FD, 12IBS, 9FD&IBS, 10FAP) 52 psychiatric patients	TAS-20	ROME I	FGIDs had higher alexithymia and more severe gastrointestinal symptoms than psychiatric patients.
2004 Porcelli	118 FGIDs	DCPR	ROME I	In unimproved patients, the prevalence of alexithymia and persistent somatization was higher while healthy anxiety was more prevalent in improved patients.
2003 Porcelli	112 FGIDs (25FD, 25IBS, 8FD&IBS, 10FAP)	TAS-20	ROME I	Base-line alexithymia and depression were significant predictors of treatment outcome in FGID patients.
1999 Porcelli	112 FGIDs (37FD, 29IBS, 20FAP, 35FD&IBS) 116 IBD 112 HC	TAS-20	ROME	The FGID group was significantly more alexithymic than the IBD group, and the two gastrointestinal groups were more alexithymic than the normal healthy group
IBS				
2017 Porcelli	150 IBS	TAS-20	ROMEIII	Alexithymia and gastrointestinal-specific anxiety (GSA) were closely related IBS symptoms. Only alexithymia was found to be a stable trait and a stronger predictor of treatment outcome than GSA
2016 Huang	10 adolescents IBS 10 adolescents IBD 10 HC	TAS-20	ROMEIII	TAS-20 score was higher in IBS and IBD than HC. Higher activation within interoceptive brain regions during anticipated pain was observed in IBS compared to IBD and HC subjects. IBD patients demonstrated increased activation in perceptual brain regions during experienced pain as compared to IBS and HC.
2014 Farnam	100 IBS	TAS-20	ROMEIII	IBS patients scored higher in TAS-20 and all three subscales of alexithymia. The level of alexithymia did not influence on the outcome by emotional awareness training.
2014 Porcelli	177 IBS	TAS-20	ROME III	The highest IBS severity scores were obtained by patients with high alexithymia alone or combined with higher GSA.
2013 Phillips	82 IBS 67 controls	TAS-20		Alexithymia and the defectiveness schema related to both IBS and symptom severity.
2011 Endo	256 boys and 335 girls (14 y.o. in 2009)	TAS-20	ROME II Modular Questionnaire	In IBS students (19% of total students), TAS-20 total, DIF, and DDF scores were higher than controls. Alexithymic IBS (TAS-20 $>$ 50) showed higher IBS scores than low alexithymic IBS (TAS20 $\leq$ 50).
2006 Jones	74 IBS 48 IBD 55 HC	TAS-20	ROME II	Patients with IBS and IBD had significantly higher scores for both alexithymia and somatosensory amplification compared with controls.
2003 Portincasa	100 IBS (27M) 100 HCs (30M)	TAS-20	ROME II	IBS patients had increased scores TAS-20 compared to healthy subjects. Higher alexithymia was found in 43% of IBS patients and in 2% of HCs.
1998 Arun	30 IBS 30 HCs	TAS		More IBS patients were higher alexithymia (127 $\leq$ TAS).

(Continued)

TABLE 1 | Continued

Year First author	Subjects	Alexithymia measure	Diagnosis of FGIDs	Results
FD				
2005 Jones	103 FDs 67 HCs	TAS-20	ROME II	TAS-20 and DIF scores were higher in FDs.
2004 Jones	111 FDs 53 HCs	TAS-20	ROME II	Higher levels of alexithymia and somatosensory amplification in patients with functional dyspepsia
FCP				
2011 White	231 NCCP (56% females)	TAS-20		Alexithymia and anxiety sensitivity were both uniquely and independently associated with pain severity and life interference due to pain. Alexithymia may be increasingly stable over time.
1997 Lumley	15 NCCP Ischemia 34 Silent ischemia 68	TAS-20		The patients with NCCP and the patients with silent ischemia had higher TAS-20 total than no ischemia/no chest pain patients. The patients with NCCP had higher score of DIF and DDF than the no ischemia/no chest pain patients.

DCPR, Diagnostic Criteria for Psychosomatic Research; DDF, difficulty describing feelings; DIF, difficulty identifying feelings; F, females; FAP, functional abdominal pain; FCP, functional chest pain; FD, functional dyspepsia; FGIDs, functional gastrointestinal disorders; GSA, gastrointestinal-specific anxiety; GSRS, Gastrointestinal Symptom Rating Scale; HC, healthy controls; IBS, Irritable bowel syndrome; IBD, inflammatory bowel disease; M, males; NCCP, non-cardiac chest pain; TAS, Toronto alexithymia scale.

(Porcelli et al., 2003). In a comparison between FGID patients with comorbid psychopathology and psychiatric outpatients with comorbid FGIDs, gastrointestinal symptoms were not significantly different between groups, but the FGIDs patients with psychopathology were more alexithymic and visited a gastroenterologist (Porcelli et al., 2004a). Alexithymia may contribute to the onset or maintenance of FGIDs independent of psychiatric disorders such as anxiety or depression, and illness behavior to seek medical help.

In patients with IBS, the prevalence of alexithymia or alexithymia level was high (Arun, 1998; Jones et al., 2006; Endo et al., 2011; Phillips et al., 2013; Farnam et al., 2014; Huang et al., 2016) and IBS severity was positively associated with alexithymia (Endo et al., 2011; Phillips et al., 2013; Porcelli et al., 2014). Furthermore, alexithymia and gastrointestinal-specific anxiety (GAS) were closely related to IBS symptoms (Porcelli et al., 2014, 2017), and the highest IBS severity was associated with alexithymia alone (Porcelli et al., 2014); only alexithymia was found to be a stable trait and a stronger predictor of treatment outcome of IBS (Porcelli et al., 2017). In addition to alexithymia, the same study found that somatosensory amplification, which refers to the tendency to experience somatic sensation as intense, was also higher in patients with IBS (Jones et al., 2006). In one randomized clinical trial to evaluate the therapeutic effect of emotional awareness training, alexithymia did not correlate with the overall outcome of pain severity or pain frequency (Farnam et al., 2014). Thus, alexithymia may be a more reliable trait than GAS and is associated with the severity of IBS.

In two functional dyspepsia studies from the same group, a high level of alexithymia was found in patients with FD (Jones et al., 2004, 2005). Level of somatoform amplification was also higher in patients with FD than in controls, but there was no correlation between somatosensory amplification and alexithymia (Jones et al., 2004).

The alexithymia score was high (Lumley et al., 1996) in patients with non-cardiac chest pain (NCCP), which is now categorized as functional chest pain as part of esophageal disorders of FGIDs (Drossman, 2016), and alexithymia and anxiety sensitivity were both uniquely associated with pain severity (White et al., 2011).

Alexithymia in Other Gastrointestinal Conditions

Inflammatory bowel disorders (IBD) are classic psychosomatic diseases (Sifneos, 1967; Taylor et al., 1981), and several studies have demonstrated that patients with IBD have high alexithymia (Porcelli et al., 1999; Jones et al., 2006; Huang et al., 2016). In these cases, alexithymia was associated with a poor quality of life (Mazaheri et al., 2012). One study reported that the FGID group was significantly more alexithymic than the IBD group (Porcelli et al., 1999), while another study found that patients with IBS and IBD did not differ from one another in terms of alexithymia severity (Jones et al., 2006). Alexithymia levels were related to the abdominal symptoms, but not with upper endoscopy findings (van Kerkhoven et al., 2006). On the other hand, a previous study demonstrated that alexithymia was higher in the peptic ulcer group than in the erosive gastritis group (Fukunishi et al., 1997), and both adenoma and adenocarcinoma patients had higher alexithymia scores than controls (Lauriola et al., 2011). Interestingly, in a 3-year prospective study with 60 colorectal cancer patients who underwent elective cholecystectomy, the high alexithymia group showed a significantly higher health related quality of life than did the lower alexithymia group during the postoperative period (Ripetti et al., 2008). Alexithymia predicted

better outcomes of postoperative psychosocial adjustment several years after pelvic pouch surgery for ulcerative colitis (Weinryb et al., 2003). These studies indicate that alexithymia might be advantageous for psychosocial adaptation after surgery.

Alexithymia Measurement

Most of studies which listed in **Table 1** used 20-itemToronto alexithymia scale (TAS-20) (Bagby et al., 1994a,b). The TAS-20 is a self-reported measurement and has been used as a reliable, validated, and common metric for measuring alexithymia in a broad variety of studies (Lumley et al., 2007). On the other hand, there is an argument that TAS-20 tends to correlate with negative affect, such as anxiety and depression, and it is sometimes difficult to distinguish the influence of negative emotions from that of alexithymia on the clinical conditions (Subic-Wrana et al., 2005). The Levels of Emotional Awareness Scale (LEAS) is another self-report measurement and has been demonstrated no overlap with measures of negative effect (Lane and Schwartz, 1987; Subic-Wrana et al., 2005). Of note that TAS-20 and LEAS are not correlated well (Subic-Wrana et al., 2005). In addition, some researchers questioned whether self-report measures is appropriate to measure alexithymia and they recommend the use of multiple methods of measurement (Kooiman et al., 2002; Bagby et al., 2006). There has been various instruments developed such as observer-rated measures including the modified Beth Israel Hospital Psychosomatic Questionnaire (BIQ), the Bermond-Vorst Alexithymia Questionnaire (BVAQ) (Morera et al., 2005), and the Toronto Structured Interview for Alexithymia (TSIA) (Caretti et al., 2011). Differences in the evaluation method of Alexithymia are fundamentally problematic in interpreting the influence of alexithymia on clinical conditions. We need a consensus on suitable assessment of alexithymia in accordance with various study designs, including epidemiologic, exploratory, and clinical researches.

Influence of Alexithymia on FGIDs

Alexithymia may contribute to an increased severity of FGID or a poor outcome independent of anxiety and depression from the epidemiological studies listed in **Table 1**. What is the possible mechanism and clinical implication of this association between alexithymia and FGID?

Enhanced perception of visceral stimuli called visceral hypersensitivity is one of the key features of IBS (Drossman and Hasler, 2016). One hypothesis is that alexithymia may enhance the visceral hypersensitivity in IBS. High alexithymia patients often have a tendency to amplify somatic sensations (Porcelli and Todarello, 2007) and sustain the physiological component of emotion response systems (Lumley et al., 2007). The data that support this theory, though, are inconsistent. A somatosensory amplification score (SSAS) was positively correlated with an alexithymia score in patients with somatoform disorder (Tominaga et al., 2014) or those with psychosomatic illness (Nakao et al., 2002), but not in patients with FD (Jones et al., 2004). Healthy subjects with alexithymia showed less sensitivity to a heartbeat detection test (Murphy et al., 2017) and pain from heat exposure (Pollatos et al., 2015), but were hyper sensitive to visceral pain induced by rectal distention (Kano et al., 2003). The insula, which corresponds to the visceral sensory cortex, in patients with alexithymia was strongly activated by visceral pain (Kano et al., 2003, 2015) or from watching pictures of others experiencing pain (Moriguchi et al., 2007). In contrast, the insula was activated less by imagining others' pain (Bird et al., 2010). In the chronic pain conditions, in which a high prevalence of alexithymia has been reported, the association between alexithymia and pain intensity is not always clear (Di Tella and Castelli, 2016). It has been suggested that not only sensory component of pain but also affective component of pain may contribute to the relationship between alexithymia and chronic pain conditions (Di Tella and Castelli, 2016). It is an important issue to be clarified that alexithymia is related to the visceral hypersensitivity. Amplifying visceral or somatic sensation has several aspects: subjective evaluation of physiological sensation such as level of pain or accuracy of heartbeat, subjective believe of their physical condition as measured by questionnaires on the sensory system, and cognitive process such as a mismatch between the actual image of somatic/visceral sensation represented in the brain and the subjective predicted state. The mismatch between actual physiological state and prediction has been hypothesized as one of the pathophysiology of IBS (Mayer, 2011). In addition, the influence of alexithymia on visceral sensation is different between healthy subjects and pathological conditions. It is required to investigate how alexithymia contribute to these aspects over healthy and pathological conditions in a large sample population.

Another possible mechanism may be the influence of alexithymia on physiological stress system including autonomic nervous system (ANS) and hypothalamic-pituitary-adrenal (HPA) axis. These systems are main mediators of brain-gut interaction and alteration of these systems has been reported in FGIDs (Chang, 2011; Drossman, 2016; Kano et al., 2017). Subjects with high alexithymia showed lower skin conductance reactivity at baseline (Gaigg et al., 2016) and during emotional imaginary (Constantinou et al., 2014; Peasley-Miklus et al., 2016) and electrical stimulation (Starita et al., 2016), that indicates physiological hypo-arousal and ANS dysfunction in alexithymia. Cortisol response was increased during anticipation of stress associated with alexithymia (de Timary et al., 2008; Hua et al., 2014). Healthy individual with higher TAS-20 subscale, difficulty of identifying feelings score demonstrated increased adrenocorticotropic hormone response to corolectal distention (Kano et al., 2007). There may be direct association between alexithymia and these stress response system or possibly alteration of visceral sensation is a prerequisite of the change of stress response system.

In conclusion, alexithymia may contribute to an increased severity of FGID or a poor outcome measured by TAS-20. The empirical data may indicate that the association between FGIDs and alexithymia may not be explained simply by "somatosensory amplification," but biased interpretation of

their symptoms not based on appropriate bodily sensation. The physiological component of the emotional or stress response system may be altered; however, the direction of causation between these alterations and the alexithymic cognitive and affective style is not clear. The studies on the association between alexithymia and physiological aspect of FGID has been sparse. Future studies are required to make a consensus of measurement of alexithymia, and elucidate the physiological mechanism of link between alexithymia and FGID.

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Alexithymia and Depression Affect Quality of Life in Patients With Chronic Pain: A Study on 205 Patients With Fibromyalgia

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Pain in fibromyalgia (FM) is accompanied by a heterogeneous series of other symptoms, which strongly affect patients' quality of life and interfere with social and work performance. The present study aimed to evaluate the effects of alexithymia on both the physical and the psychosocial components of the health-related quality of life (HRQoL) of FM patients, controlling for the concomitant effects of depression, anxiety, and pain. In particular, given the strong interconnection between depression and alexithymia, the relationship between alexithymia and HRQoL as mediated by depressive symptoms was further investigated. Data were collected on a consecutive sample of 205 female patients with a main diagnosis of FM. The results showed that about 26% of the patients showed the presence of alexithymia, as assessed by the Toronto Alexithymia Scale (TAS-20). Clinically relevant levels of depressive and anxiety symptoms were present in 61 and 60% of the patients, respectively. The results of the hierarchical multiple regression analyses showed that pain intensity (PI) and depressive symptoms explained the 45% of the variance of the physical component of HRQoL ($p < 0.001$). Regarding the mental component of HRQoL, depressive and anxiety symptoms, alexithymia, and PI significantly explained 61% of the variance ($p < 0.001$). The mediation analyses confirmed that alexithymia had a direct effect on the mental component of HRQoL and showed a statistically significant indirect effect on both the physical and the mental components, through the mediation of depressive symptoms. In conclusion, the results of the present study suggested the presence of both a direct and an indirect effect of alexithymia, in particular of the difficulty identifying feeling, on the HRQoL of patients with FM. Indeed, even though the concomitant presence of depressive symptoms is responsible of an indirect effect, alexithymia *per se* seems to directly contribute to worsen the impact that this chronic pain pathology has on the patients' quality of life, especially regarding the psychosocial functioning.

Keywords: fibromyalgia, alexithymia, depression, quality of life, chronic pain

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INTRODUCTION

Fibromyalgia (FM) is characterized by widespread musculoskeletal pain, with palpation-specific regions of tenderness, associated with other symptoms, such as fatigue, non-restorative sleep, mood disorders, and cognitive impairment (Mease, 2005; Wolfe et al., 2010). This chronic pain syndrome has a complex and multifactorial etiopathogenesis and it affects mainly women (Williams and Gracely, 2007). Its prevalence ranges between 3 and 6% of the world population (World Health Organization (WHO), 2008), even though a recent literature review update showed a significant increase in FM prevalence worldwide (Marques et al., 2017). The heterogeneous series of physical and psychological symptoms experienced by FM patients has a negative impact on patients' functioning and quality of life, strongly interfering with social and work performance (Sturge-Jacobs, 2002; Arnold et al., 2008). Among the psychological ones, depressive and anxiety symptoms have been widely reported, with prevalence ranging between 20 and 80% for depressive and between 13 and 64% for anxiety disorders (Bradley, 2005; Fietta et al., 2007).

Another psychological factor that has recently attracted the attention is alexithymia, a multifaceted personality dimension, largely observed in "psychosomatic" disorders (Taylor, 2000). Alexithymia has been related with several psychiatric and medical disorders, including chronic pain and FM (Lumley et al., 1997, 2002; Taylor et al., 1999; Celikel and Saatcioglu, 2006; van Leeuwen et al., 2012; Di Tella and Castelli, 2016). Alexithymia is characterized by a reduced ability to identify and describe subjective feelings, difficulty in distinguishing between feelings and bodily sensations of emotional arousal, restricted imagination processes, and a stimulus-bound, externally oriented cognitive style (Sifneos, 1973; Taylor et al., 1999). These deficits could interfere with the cognitive processing and regulation of emotions, resulting in increased negative affects (Martínez et al., 2015) and dysregulation of stress-related autonomic arousal, with chronic sympathetic hyperarousal (Lumley et al., 1996; Taylor and Bagby, 2012). In their study, indeed, Martínez et al. (2015) found that the difficulties in identifying their affective states, in interaction with negative pain appraisal (i.e., pain catastrophizing and fear of pain), could lead FM patients to develop emotional distress (in particular anxiety). Moreover, alexithymia can affect health perception, leading alexithymic subjects to misinterpret the bodily expressions of emotions as signs of physical disease and thus worsening the patients' quality of life and enhancing the health care utilization (Lumley et al., 1996, 2007; Tuzer et al., 2011). Even though several studies have identified alexithymia as an important factor in FM syndrome (Sayar et al., 2004; Steinweg et al., 2011; Castelli et al., 2012; Di Tella et al., 2017; Ghiggia et al., 2017), the association between alexithymia and FM patients' quality of life is not clear yet. The few evidences available suggest a possible role of negative affects, particularly depression, in mediating this relationship (Castelli et al., 2012). However, to the best of our knowledge, no study has deeply investigated yet the association between alexithymia and quality of life in FM patients.

The present study aimed thus to evaluate the effects of alexithymia on both the physical and the psychosocial components of the health-related quality of life (HRQoL) of FM patients, controlling for the concomitant effects of depression, anxiety, and pain. In particular, given the strong interconnection between depression and alexithymia, the relationship between alexithymia and HRQoL as mediated by depressive symptoms was further investigated. We hypothesized that the presence of alexithymic trait could negatively influence the impact that FM symptoms had on patients' daily quality of life, both directly and indirectly.

MATERIALS AND METHODS

Study Design

This prospective study was carried out on a consecutive series of FM patients recruited during their first visit at the Fibromyalgia Unit of the "A.O.U. Città della Salute e della Scienza – presidio Molinette" Hospital of Turin. The "A.O.U. Citta della Salute e della Scienza – A.O. Ordine Mauriziano of Turin – A.S.L. TO1 Ethic Committee" approved the study ("Psy-FM-AR Study," procedure number CS/506) and all patients provided their written informed consent.

Subjects and Procedure

At the end of their first visit at the Fibromyalgia Unit, all the female patients with a main diagnosis of FM, made by an expert rheumatologist, and fulfilling the inclusion/exclusion criteria were invited to participate. The main exclusion criteria were: less than 18 years old; low educational level (<5 years) or insufficient knowledge of the Italian language; unstable medical or psychiatric illness or current primary psychiatric diagnosis including severe depression; pain due to traumatic injury or structural/regional rheumatic disease. Out of the 354 consecutive FM patients contacted, 35 refused to participate in the study and 114 were excluded according to the exclusion criteria. A total of 205 patients composed the final sample. Recruited patients arranged an appointment with a trained doctoral clinical psychology student that assessed socio-demographic and clinical characteristics, and administered the pencil-and-paper psychological scales. The appointment lasted approximately 45 min.

Variables and Instruments

Pain Characteristics

The pain intensity (PI) was measured using a Visual Analog Scale (VAS) and the Italian Pain Questionnaire (IPQ). Regarding the VAS, patients were asked to rate the average intensity of pain experienced in the last week on a scale ranging from 0 (No pain) to 10 (Extreme pain). In the IPQ (De Benedittis et al., 1988), a reconstructed Italian version of the McGill Pain Questionnaire, patients had to choose from 42 adjectives those that best described their pain. According to the model of Melzack and Torgerson (1971), the pain descriptors are divided into three main domains: sensory (IPQ-S), that measures modality and temporospatial qualities of pain, e.g., "stabbing," "pulsing"; affective (IPQ-A), that measures tension, fear, and autonomic components of the pain experience, e.g., "nauseating,"

"distressing"; and evaluative (IPQ-E) that measures the subjective intensity of the global pain experiences, e.g., "intolerable," "annoying." The sum scores of each of the dimensions of pain were reported as a portion (0–1) of the maximum possible score of each subscale.

Alexithymia

Alexithymia was assessed using the Italian version of the 20-Item Toronto Alexithymia Scale (TAS-20) (Bressi et al., 1996; Taylor and Bagby, 2004). The TAS-20 is composed by 20 items rated on a five-point Likert scale, from "strongly disagree" to "strongly agree." In addition to the total score, the TAS-20 provides three subscale scores: "Difficulty identifying feelings" (DIF); "Difficulty describing feeling" (DDF); and "Externally oriented thinking scale" (EOT). According to the literature (Taylor et al., 1999), cut-off points were used to divide patients into non-alexithymic (total score ≤ 51), borderline (total score between 51 and 61), and alexithymic (total score ≥ 61).

Psychological Distress

The Italian version of the Hospital Anxiety and Depression Scale (HADS) (Costantini et al., 1999; Bjelland et al., 2002) was used to evaluate the presence of depressive and anxiety symptoms. It consists of 14 items divided into two subscales (range score: from 0 to 21): HADS-D for the depressive and HADS-A for the anxiety symptoms. A score of 8 or more suggests a clinically relevant level of depression/anxiety symptoms (Zigmond and Snaith, 1983).

Health-Related Quality of Life (HRQoL)

The Italian version of the Short-Form 36 Health Survey (SF-36) was used (McHorney et al., 1993; Apolone and Mosconi, 1998). It consists of 36 items divided into 8 subscales, which could be gathered into two main components: the Physical Component (SF-36_PC) composed by the Physical Functioning (PF), Physical Role Functioning (RP), Bodily Pain (BP), and General Health (GH) subscales; and the Mental Component (SF-36_MC) composed by the Vitality (VT), Social Functioning (SF), Emotional Role Functioning (RE), and Mental Health (MH) subscales. The scores range from 0 to 100, with the highest scores corresponding to the better condition.

Statistical Analyses

Normal distribution was assessed following the criteria of absolute skewness (Sk) and kurtosis (K) values lower than 3.0 and 8.0, respectively (Kline, 2005). Based on these criteria, the assumption of normality was met for all the variables. Mean (SD) scores and frequencies were used as descriptive analyses, as appropriate. Pearson's bivariate correlations were used to analyze the relationship between demographic, clinical and psychological variables, and HRQoL.

Two hierarchical multiple regression analyses were used to investigate whether alexithymia was a significant contributing factor for the explanation of the HRQoL in FM patients, using the Physical and Mental Components scores of the SF-36 as outcome variables. Stepwise method was used for variables inclusion of potentially confounding and competing predictors. To avoid unnecessary reductions in statistical power, confounding (age and educational level) and competing (depressive and anxiety symptoms, pain duration, and PI) predictors' variables were included in the regression models only when they were significantly correlated with the outcome variables (p-value < 0.05). Collinearity was assessed using the statistical factors of tolerance and Variance Inflation Factor (VIF).

Lastly, a mediation analysis was conducted to test the mediating effect of depression on the association between alexithymia and patient's HRQoL. As recommended by Preacher and Hayes (2004, 2008), mediation analysis procedures with bootstrap sampling were performed. The bootstrap method estimates indirect effects through one or more mediator variables with bias-corrected bootstrap confidence intervals (CIs) (Preacher and Hayes, 2004, 2008). A total of 1000 bootstrap resamples were used to generate bias-corrected 95% CIs for the indirect effect. Mediation is demonstrated when the indirect effect is significant and the CIs do not contain zero (Preacher and Hayes, 2004, 2008).

All the analyses were performed with the software "Statistical Package for Social Sciences – version 22" (SPSS-22). The mediation analyses were conducted using the PROCESS macro (Hayes, 2013), a computational procedure for SPSS.

RESULTS

Data on the socio-demographic and pain variables are reported in **Table 1**. Patients had a mean (SD) age of 51 (10) years and the majority of them had a secondary school degree at least. On average, the patients had chronic pain from 8 years and the mean PI was higher than 7. The result of the IPQ showed that patients reported the highest scores in the affective pain dimension (IPQ-A).

Data regarding alexithymia and psychological distress are presented in **Table 2**. A total of 26% of the sample reported the presence of alexithymic trait at a clinical level (53 patients) and another 26% showed this trait at a subclinical level (54 patients). More than 60% of the patients reported a clinically relevant level of depressive/anxiety symptoms.

Data regarding the HRQoL are summarized in **Table 2**. Patients reported very low mean values in all the subscales of the SF-36, suggesting the presence of a poor QoL in both its physical and mental components.

Correlational Analyses

In order to verify possible relationships between clinical and psychological variables, and HRQoL, correlation analyses were performed (**Table 3**). Age, educational level, and pain duration were not significantly correlated with the physical and mental components of the SF-36. Pain was negatively and significantly correlated with both the SF-36_PC ($p < 0.001$) and the SF-36_MC ($p < 0.001$): the higher the PI, the lower the HRQoL. Statistically significant negative correlations were found between HADS-D and HADS-A, and both the physical and the mental components of the SF-36 (all $p < 0.001$), showing that higher psychological distress symptoms were correlated with a worse HRQoL. Regarding alexithymia, the DIF and DDF subscales

TABLE 1 | Socio-demographic and clinical variables of the 205 patients.

	N (%)	Mean *(SD)*	Range
Age		51.84 (10.3)	24–74
Educational level (years)		10.78 (3.3)	5–18
Primary School	*14* (*6.9*)		
Secondary School	*83* (*41.1*)		
Higher School	*90* (*44.6*)		
University	*15* (*7.4*)		
Marital status			
Single	*16* (*7.9*)		
Living together	*14* (*6.9*)		
Married	*138* (*68*)		
Divorced	*26* (*12.8*)		
Widowed	*9* (*4.4*)		
Work status			
Student	*1* (*0.5*)		
Employed	*116* (*57.7*)		
Unemployed	*14* (*7*)		
Retired	*32* (*15.9*)		
Housewife	*38* (*18.9*)		
Pain variables			
Pain duration (months)		102.11 (83.9)	4–420
Pain intensity (VAS)		7.24 (2.4)	0–10
IPQ		28.23 (13.4)	2–74
IPQ-S		0.35 (0.15)	0–0.91
IPQ-A		0.39 (0.21)	0–1
IPQ-E		0.31 (0.21)	0–1

IPQ (159 patients): Italian Pain Questionnaire; IPQ-S: Italian Pain Questionnaire-Sensory; IPQ-A: Italian Pain Questionnaire-Affective; IPQ-E: Italian Pain Questionnaire-Evaluative.

TABLE 2 | Alexithymia, psychological distress, and health-related quality of life assessed with the Short-Form 36 Health Survey (SF-36).

	Mean *(SD)*	Range	*N* (%)
TAS-20	52.06 (13.2)		
Non alexithymic (score < 52)			*95* (*47*)
Borderline (score 52–60)			*54* (*26.7*)
Alexithymic (score > 60)			*53* (*26.2*)
DIF	20.45 (7.3)		
DDF	13.71 (4.9)		
EOT	17.9 (4.9)		
HADS	18.47 (8.1)		
HADS-D	9.18 (4.3)		*125* (*61.3*)[#]
HADS-A	9.29 (4.6)		*122* (*59.8*)[#]
SF-36			
Physical Component	**32.4 (15.7)**	**2.5–83.4**	
Physical Functioning	47.8 (21.4)	0–100	
Physical Role Functioning	17.3 (27.1)	0–100	
Bodily Pain	30.4 (16.8)	0–93.3	
General Health	34.3 (18.9)	0–90	
Mental Component	**39.6 (20.4)**	**6–94.3**	
Vitality	29.8 (17.5)	0–85	
Social Functioning	43.1 (22.2)	0–100	
Emotional Role Functioning	35 (39.7)	0–100	
Mental Health	50.6 (20.4)	0–96	

TAS-20: Toronto Alexithymia Scale – total score; DIF: difficulty identifying feelings; DDF: difficulty describing feeling; EOT: externally oriented thinking scale; HADS-D/-A: Hospital Anxiety and Depression Scale-Depression/-Anxiety subscale; SF-36: Short-Form 36 Health Survey. [#]Number (%) of patients with a score above the cut-off (score ≥ 8), suggesting the presence of a clinically relevant level of depressive/anxiety symptoms.

of the TAS-20 were significantly correlated with both the SF-36_PC (DIF: $p < 0.001$; DDF: $p = 0.006$) and the SF-36_MC (both $p < 0.001$), suggesting that higher difficulty identifying and describing feelings were associated with a worse HRQoL. No significant correlations emerged between HRQoL and the EOT subscale of the TAS-20.

Higher alexithymia scores were also significantly correlated with higher scores on the HADS-D (DIF: $p < 0.001$; DDF: $p < 0.001$; EOT: $p = 0.016$) and the HADS-A (DIF: $p < 0.001$; DDF: $p < 0.001$; EOT: $p = 0.021$) scales, suggesting that higher level of alexithymia were associated with a higher psychological distress. Both alexithymia (DIF: $p < 0.001$; DDF: $p = 0.001$) and psychological distress (HADS-D: $p < 0.001$; HADS-A: $p < 0.001$) were significantly correlated with the VAS score: the higher the PI, the higher the alexithymia and psychological distress symptoms.

Regression Analyses

Two hierarchical multiple regression analyses were performed in order to investigate whether alexithymia was a significant predictor of both the physical and the mental components of HRQoL in FM patients. The variables age, educational level, pain duration, and the EOT subscale of the TAS-20 were no longer included in the regression analyses since they showed no significant correlation with the criterions. The DIF and the DDF subscales of the TAS-20 were, therefore, entered in the first regression block and the competing predictors [depression, anxiety, and PI (VAS)] were entered in the second block with the stepwise method.

The regression analysis regarding the Physical Component is reported in **Table 4**. In the first model, when only alexithymia features were entered into the analysis, the difficulty identifying feeling (DIF) subscale of the TAS-20 significantly predicted the criterion [$\beta = -0.36$, $t(196) = -4.31$, $p < 0.001$]. However, alexithymia ceased to be a predictive factor when depression was entered into the analysis, in the third model. The final model (model 3) explained a significant amount (45%) of the variance of the SF-36_PC [$F(4,194) = 41.7$, $p < 0.001$] and PI appeared to be the strongest contributor [$\beta = -0.46$, $t(194) = -8.25$, $p < 0.001$], followed by depression [$\beta = -0.35$, $t(194) = -5.44$, $p < 0.001$].

The regression analysis regarding the Mental Component is reported in **Table 5**. When only alexithymia features were entered into the analysis (model 1), the difficulty identifying feeling (DIF) subscale of the TAS-20 significantly predicted the criterion [$\beta = -0.57$, $t(196) = -8.09$, $p < 0.001$], with a 36% of the variance of the SF-36_MC explained. However, differently from the previous regression, alexithymia continued to be a predictive factor when competing predictors were

TABLE 3 | Pearson's correlations among socio-demographic, clinical, psychological distress, alexithymia, and quality of life assessed with the Short-Form 36 Health Survey (SF-36).

	1	2	3	4	5	6	7	8	9
1 – Age	–								
2 – Educational level	−0.218**	–							
3 – Pain Duration	0.255**	−0.018	–						
4 – VAS	−0.08	0.028	0.077	–					
5 – HADS-D	−0.012	−0.047	0.123	0.328**	–				
6 – HADS-A	−0.059	−0.019	0.137	0.362**	0.678**	–			
7 – TAS-20_DIF	−0.016	0.008	0.054	0.255**	0.526**	0.627**	–		
8 – TAS-20_DDF	0.097	−0.129	0.172*	0.231**	0.401**	0.463**	0.582**	–	
9 – TAS-20_EOT	0.106	−0.318**	0.058	0.051	0.170*	0.162*	0.202**	0.337**	–
10 – SF-36_PC	0.03	0.004	−0.126	−0.575**	−0.505**	−0.420**	−0.341**	−0.194**	−0.012
11 – SF-36_MC	0.058	−0.072	−0.042	−0.483**	−0.652**	−0.697**	−0.600**	−0.390**	−0.084

*VAS: Visual Analog Scale for pain intensity; HADS-D/-A: Hospital Anxiety and Depression Scale-Depression/-Anxiety subscale; TAS-20_DIF/_DDF/_EOT: Toronto Alexithymia Scale_Difficulty identifying feelings/Difficulty describing feeling/Externally oriented thinking subscale; SF-36_PC/_MC: Short-Form 36 Health Survey_Physical Component/Mental Component. *p-value < 0.05; **p-value < 0.01.*

TABLE 4 | Hierarchical multiple regression with Physical Component of Health-related Quality of life (SF-36_PC) as dependent variable (*N* = 199).

	Predictor	R^2	Adj-R^2	*F*	*F*-ΔR^2	*B*	SE *B*	β	*p*
1		0.12	0.11	13.38*	13.38*				
	Constant					47.43	3.48		
	DIF					−0.78	0.18	−0.36	<0.001
	DDF					0.07	0.27	0.02	0.801
2		0.38	0.37	39.96*	82.05*				
	Constant					66.09	3.58		
	DIF					−0.54	0.15	−0.25	0.001
	DDF					0.24	0.23	0.07	0.299
	VAS					−3.29	0.35	−0.53	<0.001
3		0.46	0.45	41.74*	29.54*				
	Constant					66.75	3.35		
	DIF					−0.24	0.16	−0.11	0.129
	DDF					0.36	0.21	0.11	0.095
	VAS					−3.12	0.38	−0.46	<0.001
	HADS-D					−1.30	0.24	−0.35	<0.001

**p-value < 0.001. DIF: difficulty identifying feelings; DDF: difficulty describing feelings; HADS-D: Hospital Anxiety and Depression Scale-Depression; VAS: pain intensity.*

entered into the analysis. The final model (model 4) explained a significant portion (61%) of the variance of the SF-36_MC [$F(5,193) = 62.9$, $p < 0.001$]. Anxiety symptoms [HADS-A: $\beta = -0.30$, $t(193) = -4.39$, $p < 0.001$], depressive symptoms [HADS-D: $\beta = -0.25$, $t(193) = -4.13$, $p < 0.001$] and alexithymia [DIF: $\beta = -0.25$, $t(193) = -3.84$, $p < 0.001$] followed by PI [VAS: $\beta = -0.24$, $t(193) = -4.99$, $p < 0.001$] were the factors that significantly predicted the SF-36_MC score.

Mediation Analysis

To deepen the results of the multiple regression analyses, a mediation analysis was conducted to test the relationship between alexithymia and the patients' HRQoL mediated by depressive symptoms. On the basis of the results of the regression analyses, the DIF subscale was used.

Regarding the Physical component (**Figure 1A**), the standardized regression coefficient between DIF and depressive symptoms was statistically significant ($p < 0.001$), as was the standardized regression coefficient between depressive symptoms and SF-36_PC ($p < 0.001$). The standardized indirect effect was $(0.52)(-0.46) = -0.24$. We tested the significance of this indirect effect using bootstrapping procedures. The bootstrapped unstandardized indirect effect was −0.52, and the 95% CI ranged from −0.73 to −0.35. Thus, the results confirm that, even if DIF did not have a direct effect on the SF-36_PC (standardized regression coefficient = −0.11, $p = 0.13$), it had a significant indirect effect ($\kappa^2 = 0.22$) through depressive symptoms.

Concerning the Mental Component (**Figure 1B**), the standardized regression coefficient between depressive symptoms and SF-36_MC was statistically significant ($p < 0.001$). The standardized indirect effect was $(0.52)(-0.46) = -0.24$. The bootstrapped unstandardized indirect effect was −0.66, and the 95% CI ranged from −0.90 to −0.48. Thus, in addition to confirm the presence of a statistically significant direct effect (standardized regression coefficient = −0.37, $p < 0.001$), the results confirm that the difficulty identifying feeling

TABLE 5 | Hierarchical multiple regression with Mental Component of Quality of life (SF-36_MC) as dependent variable (N = 198).

	Predictor	R^2	Adj-R^2	F	F-ΔR^2	B	SE B	β	p
1		0.37	0.36	56.45*	56.45*				
	Constant					75.22	3.80		<0.001
	DIF					−1.60	0.20	−0.57	<0.001
	DDF					−0.22	0.29	−0.05	0.457
2		0.53	0.52	72.80*	67.31*				
	Constant					76.38	3.29		<0.001
	DIF					−0.80	0.20	−0.29	<0.001
	DDF					0.07	0.26	0.02	0.788
	HADS-A					−2.31	0.28	−0.52	<0.001
3		0.59	0.58	68.74*	27.22*				
	Constant					87.96	3.81		<0.001
	DIF					−0.78	0.19	−0.28	<0.001
	DDF					0.13	0.24	0.03	0.600
	HADS-A					−1.92	0.28	−0.43	<0.001
	VAS					−2.25	0.43	−0.26	<0.001
4		0.62	0.61	62.95*	17.03*				
	Constant					89.62	3.68		<0.001
	DIF					−0.69	0.18	−0.25	<0.001
	DDF					0.18	0.23	0.04	0.444
	HADS-A					−1.32	0.30	−0.30	<0.001
	VAS					−2.08	0.42	−0.24	<0.001
	HADS-D					−1.22	0.30	−0.25	<0.001

p-value < 0.001. DIF: difficulty identifying feelings; DDF: difficulty describing feelings; HADS-D/-A: Hospital Anxiety and Depression Scale-Depression/Anxiety; DT: Distress Thermometer; VAS: pain intensity.

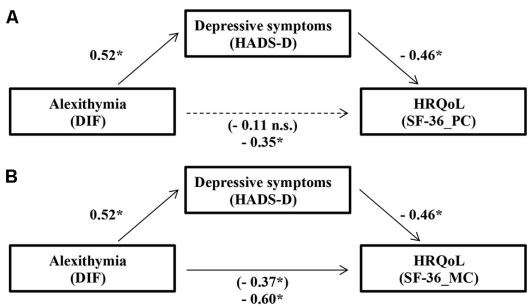

FIGURE 1 | Standardized regression coefficients for the relationship between alexithymia and the Physical **(A)** and Mental **(B)** components of the SF-36 as mediated by depressive symptoms. The standardized regression coefficients between the difficulty identifying feeling (DIF) subscales of the TAS-20 and HRQoL, controlling for depressive symptoms, are in parentheses. *$p < 0.001$.

subcomponent of alexithymia had a significant indirect effect on the Mental Component of the SF-36 ($\kappa^2 = 0.25$) through depressive symptoms.

DISCUSSION

The present study evaluated the effects of alexithymia in a large sample of patients with FM, controlling for the concomitant effects of depression, anxiety, and pain. To deepen the investigation of the specific impact that alexithymia has on both the physical and the psychosocial components of the HRQoL, we also evaluated the mediation role of depressive symptoms. In fact, even though FM does not cause physical injuries or deformed joints, it causes a severe disability in daily living, negatively interfering with the patient's functional, working, and psychosocial capacity (Sturge-Jacobs, 2002; Arnold et al., 2008). Available data underline that the negative impact on the quality of life may be even greater than those experienced in other chronic pain disorders and rheumatic conditions (Martinez et al., 1995; Bergman, 2005; Boonen et al., 2005; Birtane et al., 2007; Ubago Linares Mdel et al., 2008; White et al., 2008; Sicras-Mainar et al., 2009). In the current study, the results confirmed the great impact of the pathology on the patients' quality of life, on both the physical and the mental components, with very low score in all the subscales of the SF-36.

Depressive disorders are the most frequent comorbid psychiatric conditions in FM with a prevalence of 20–80% (Fietta et al., 2007). In a community sample of 44,897 individuals, Kato et al. (2006) showed that 40% of patients with FM had current depressive symptoms without a formal diagnosis of depressive disorder whereas the rate of lifetime major depressive disorder comorbidity ranges from 62 to 86% (Aguglia et al., 2011). In line with these data, in the current study, the mean scores of both the depression and the anxiety subscales of the HADS were above the threshold, suggesting an extensive prevalence of clinically relevant depressive and anxiety symptoms, both present in about 60% of patients.

Up to date, studies evaluating the prevalence and the role of alexithymia in FM patients showed contrasting results (Di Tella and Castelli, 2013). Most studies agree on the higher prevalence of alexithymia in FM compared to healthy controls or to patients with other chronic pain pathologies such as rheumatoid arthritis (Sayar et al., 2004; Huber et al., 2009; Steinweg et al., 2011; Tuzer et al., 2011). The estimated prevalence of alexithymia in non-clinical samples ranges between 7 and 13% (Fukunishi et al., 1999; Mattila et al., 2006; Honkalampi et al., 2009), whereas according to the most recent reviews of the literature, the prevalence of alexithymia in patients with FM ranges from 15 to 20% (Di Tella and Castelli, 2013). Conforming to these data, 26% of the patients with FM recruited in the present study showed the presence of alexithymia and another 26% had a TAS-20 total score in the borderline range, suggesting the presence of a subclinical level of alexithymic traits. Some studies consider the high prevalence of alexithymia in FM as related to the concomitant high prevalence of depressive symptoms (Malt et al., 2002; Evren et al., 2006; Huber et al., 2009). Clinical researches conducted in various clinical settings have indeed shown a high incidence of alexithymia in patients with depression, which varies between 21 and 42% (Saarijärvi et al., 1993; Wise and Mann, 1995; Honkalampi et al., 2000, 2001; Taycan et al., 2017). Since both constructs share many characteristics, such as negative affect, decreased ability to communicate affect to other people, problems with interpersonal communication and less clarity about own feelings, it is reasonable to assume that there is an association between alexithymia and depression (Rude and McCarthy, 2003; Mattila et al., 2008; Picardi et al., 2011). Moreover, some researchers found that the decrease of the level of depression is associated with a TAS-20 scores decrease in patients with major depression, suggesting that alexithymia could be considered as a state-dependent phenomenon in people with depression (Honkalampi et al., 2000, 2001; Saarijärvi et al., 2001). Regarding chronic pain patients, previous studies, which evaluated alexithymia and depression in large heterogeneous chronic pain samples, suggested that depression worked as a full mediator between alexithymia and daily disability in FM (Makino et al., 2013; Saariaho et al., 2013; Shibata et al., 2014). Also the results of our previous exploratory study appeared to support this hypothesis (Castelli et al., 2012). In that study, even if the small sample size cautioned to interpret and generalize the data, the results seem to point out that the relationship between alexithymia and quality of life in FM could be totally mediated by the presence of psychological distress symptoms. In fact, alexithymia ceased to significantly contribute to the explanation of HRQoL when the psychological distress variables (depression for the physical component and anxiety for the mental component of HRQoL) were added as competing predictors (Castelli et al., 2012).

Given the exploratory nature and the small sample size of our previous study (Castelli et al., 2012), we performed a new study on a larger sample. The results of this last study confirmed the previous ones regarding the physical component of HRQoL. As in our previous work, alexithymia, in particular the difficulty identifying feeling subscale, ceased to significantly contribute to the explanation of the SF-36_PC when the depressive symptoms were added as competing predictor. PI and depression were the variables that significantly contributed to explain the variance of the SF-36_PC, with a good final model that explained 45% of the variance. Although PI and pain persistence in FM are independent from a coexisting depression or a concomitant psychological distress (Okifuji et al., 2000; Petzke et al., 2003), our results seem to suggest that these variables have a similar and additive effect in negatively influencing the physical functioning of FM patients, further supporting the multidimensionality nature of this pathology.

Regarding the psychosocial functioning, the results of the present study allowed us to go further with the results of our previous work (Castelli et al., 2012). Indeed, in the hierarchical multiple regression analysis performed on the mental component of HRQoL, alexithymia significantly contributed to the model even when controlling for the presence of psychological distress. Pain, anxiety and depressive symptoms, and the DIF subscale of the TAS-20 were all significant predictors of the SF-36_MC, with a final model explaining a very high percentage of the variance (61%).

This last result suggests that alexithymia has a significant direct effect on the psychosocial functioning of patients with FM. To better evaluate the weight of this effect on the mental component of the SF-36, and the presence of an indirect effect, mediated by depressive symptoms, on both the mental and the physical components, we performed the mediation analyses. The results further supported those of the regression model, confirming the presence of a significant direct effect of alexithymia on the mental component of the SF-36. These data provide methodologically grounded support to the hypothesis that the presence of alexithymia *per se* had a negative impact on FM patients' HRQoL. Furthermore, the results showed that the DIF factor of the TAS-20 had a significant indirect effect on both the components of the HRQoL, mediated by depressive symptoms. The data showed, in fact, that the presence of difficulty identifying feelings had an important negative effect on the presence of depressive symptoms, which in turn negatively affects patients' HRQoL. As showed by the κ^2 value, the effect size of the indirect effect was medium for the physical component and large for the mental one. Taken together, these findings suggest that the patient difficulty identifying emotions may, on one hand, have an indirect effect, increasing symptoms of depression, which in turn may interfere with the individual's ability to deal or cope with pain. On the other hand, the difficulty identifying emotions may also be considered a trait that directly influences illness behavior, as hypothesized by Lumley (Lumley et al., 1996). According to his model, the higher body awareness of individuals with alexithymia makes them focus on benign somatic sensations, thereby increasing sensation magnitude through a positive, autonomic feedback loop. As a result of the inability to identify accurately their own subjective feelings, they attribute these sensations to biological causes rather than psychological ones, thus experiencing these sensations as physical illness instead of the somatic manifestation of their own emotions (Lumley et al., 1996).

Such contrasting results regarding the relationship between alexithymia and depression in chronic pain could partially be

the result of the negligence of the distinction between absolute and relative stability. Indeed, even if alexithymia lacks of absolute stability (i.e., its score may change in the presence of large changes in the severity of depressive symptoms), its relative stability has been demonstrated not only in patients with major depression, but also in patients with functional gastrointestinal disorders (Luminet et al., 2001; Porcelli et al., 2003; Taylor and Bagby, 2004). It can be argued that the lack of absolute stability of alexithymia could lead to attribute the high prevalence of alexithymia in FM only to the concomitant high prevalence of depressive symptoms, masking its direct effect in chronic pain patients, independently from the depressive symptoms.

Some main limitations have to be taken into account while considering the present study. Only female patients were evaluated and we did not include any control groups. Further studies comparing FM to other chronic pain pathologies should therefore be carried out. What is more, while this study contributes with important information regarding how alexithymia and depression may interact in FM, the cross-sectional nature of the study does not allow proving causal relationships. Future researches should address emotional deficits in this chronic pain pathology through longitudinal studies, assessing the variation of these co-occurring symptoms along the disease progression.

CONCLUSION

The results of the present study suggest the presence of both a direct and an indirect effect of alexithymia on the HRQoL in patients with FM. Indeed, even though the concomitant presence of depressive symptoms is responsible of an indirect effect, alexithymia *per se* seems to directly contribute to worsen the impact that this chronic pain pathology has on the patients' quality of life, especially regarding the psychosocial functioning. Taken together these results have an important implication for the treatment of FM patients. As recently reported, indeed, treatment strategies have on average only modest results in FM patients, calling for a more individualized management strategy (Castelnuovo et al., 2016a,b; Häuser et al., 2017). The presence of a direct and an indirect effect of alexithymia in FM, mediated by depressive symptoms, together with the evidence supporting the predictive role of alexithymia on the treatment outcome (Taylor and Bagby, 2004), further support the need for a multidimensional approach that includes its assessment. Even though there is an absence of established efficacious treatments for alexithymia, a recent review provides a strong case for the partial modifiability of alexithymia, but only by means of psychological interventions specifically intended to treat it (Cameron et al., 2014). According to the available research data, indeed, some aspects of alexithymia, as those of other dimensional personality traits, such as neuroticism or extraversion, may be more trait-like and thus enduring, whereas other aspects may be more state-dependent and thus changeable (Cameron et al., 2014). Furthermore, available research data suggest that identifying effective strategies for modifying alexithymia not only improves patients' adaptive emotional processing, but also enhances other aspects of functioning (Cameron et al., 2014). Similar results were found in two very recent studies that evaluated the efficacy of an emotional awareness and expression therapy in chronic pain patients, including FM, which found that the decrease in alexithymia was linked to the improvements in PI and pain interference (Burger et al., 2016; Lumley et al., 2017). These data underline once again the importance to evaluate the presence of alexithymia in FM patients, in order to identify a patient-tailored therapy, aiming at optimizing treatment efficacy, and at minimizing costs and risks due to the use of ineffective therapies.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of 'Comitato Etico Interaziendale A.O.U. Città della Salute e della Scienza di Torino – A.O. Ordine Mauriziano – A.S.L. Città di Torino' with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the 'Comitato Etico Interaziendale A.O.U. Città della Salute e della Scienza di Torino – A.O. Ordine Mauriziano – A.S.L. Città di Torino.'

AUTHOR CONTRIBUTIONS

VT, LC, and GG were responsible for the conception and design of the study. AG, AR, FC, and EF were responsible for data collection and for clinical evaluations. VT and MDT were responsible for data analysis. LC and GG contributed to the interpretation of data. VT and MDT wrote the article, which was critically revised by all the other authors. All authors have approved the final version of the manuscript.

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Explicit and Implicit Components of the Emotional Processing in Non-organic Vision Loss: Behavioral Evidence About the Role of Fear in Functional Blindness

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Non-organic vision loss (NOVL), a functional partial or global vision loss, might be considered a manifestation of conversion disorder. The few previous studies focused on investigating the relationship between cerebral activity and subjective symptoms in NOVL; however, the emotional processing is still neglected. In the present case-controls study, we investigated the capability of two individuals diagnosed with NOVL to recognize implicitly the emotions of fear and anger; this was assessed through a facial emotion recognition task based on the redundant target effect. In addition, the level of alexithymia was measured by asking them to judge explicitly their ability to identify and describe emotions. Both individuals showed selective difficulties in recognizing the emotion of fear when their performance was contrasted with a matched control sample; they also mislabeled other emotional stimuli, judging them as fearful, when they were not. However, they did not report alexithymia when measured using a standard questionnaire. This preliminary investigation reports a mismatch between the implicit (i.e., the behavior in the experimental paradigm) and the explicit (i.e., the subjective evaluation of one's own emotional capability) components of the emotional processing in NOVL. Moreover, fear seems to represent a critical emotion in this condition, as has been reported in other psychiatric disorders. However, possible difficulties in the emotional processing of fear would emerge only when they are inferred from an implicit behavior, instead of a subjective evaluation of one's own emotional processing capability.

Keywords: non-organic visual loss, facial emotion recognition, redundant target effect, fear, alexithymia, visual perception

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INTRODUCTION

Non-organic vision loss (NOVL) is a functional partial or global vision loss in which an organic disease or a pathology in the visual system does not explain a subjective visual disturbance (Beatty, 1999; Stone et al., 2005; Bruce and Newman, 2010). Based on this description, NOVL might be considered a manifestation of a conversion disorder (Stone et al., 2005; World Health Organization, 2007; Bruce and Newman, 2010). Visual complaints without a physical

basis are frequently presented to the clinicians (Beatty, 1999) and the clinical diagnosis is generally formulated according to the results from an extensive neuro-ophthalmic evaluation. To our knowledge, few studies investigating NOVL have been reported in the literature: they focused on the relationship between cerebral activity and subjective symptoms (Werring et al., 2004; Schoenfeld et al., 2011) in affected individuals, while an extensive investigation of the psychological and emotional components has been lacking. In a single case study by Becker et al. (2013), a relationship between the activity of the cerebral occipital lobe and cerebral areas implicated in emotional regulation and moral reasoning was preliminarily sketched out; however, the authors did not investigate extensively the affected individual's behavior upon recognizing emotional stimuli.

In this work, we provide for the first time in the literature, to current knowledge, an investigation of the implicit and explicit components of the emotional processing in two individuals affected by NOVL. To study their capability to implicitly recognize emotions expressed by others, we adopted a facial emotion recognition task based on the "redundant target effect" (Miniussi et al., 1998), according to which people respond faster when two identical targets are presented simultaneously rather than when presented alone. Moreover, the competitive presence of a non- identical stimulus (i.e., the distractor) affects the efficient recognition of the target, with an increase of velocity and a reduction of the level of accuracy. Since this effect occurs in early visual processing rather than in later (decisional or premotor) stages (Miniussi et al., 1998), this method appears suitable for indirectly investigating residual affective recognition in (alleged) blind sight: it preserves participants from making any explicit counterintuitive guesses about unseen events in the blind area (de Gelder et al., 2001). Thus, the individuals' emotional capability is inferred from their behavior in the task. Moreover, following the previous results reported in the literature about aberrant cerebral activity in NOVL (Werring et al., 2004; Schoenfeld et al., 2011), we also studied the individuals' capability to recognize neutral visual stimuli (i.e., geometrical shapes).

On the other hand, the explicit component of the emotional processing was investigated. We focused not only on depressive, anxiety and different psychopathological symptoms and quality of life, but also on the level of alexithymia, using the Toronto Alexithymia Scale 20 (TAS-20) (Bagby et al., 1994; Todarello and Pace, 2010). Focusing on the relationship between somatization and alexithymia, the latter is generally associated with reports of medically unexplained symptoms (Bach and Bach, 1996; Waller and Scheidt, 2006; Mattila et al., 2008; Demartini et al., 2014) and it is frequently observed in various psychiatric disorders especially in the somatoform ones (Demartini et al., 2014; Gulpek et al., 2014). Alexithymia means difficulty in identifying and describing one's own emotions, the tendency to minimize emotional experience and to focus attention externally (Sifneos, 1973). Since this concept refers to the cognitive processing of emotions, instead of subjective intrapsychic conflicts that possibly generate bodily symptoms in psychosomatic disease (Taylor et al., 1991), it is suitable when participants' self-ability to recognize their own emotions is studied independently of the subjective causes of the emotional difficulties, as in the present study.

Embracing the description of NOVL as a somatoform disorder (Stone et al., 2005; World Health Organization, 2007; Bruce and Newman, 2010), we would expect to find that affected individuals have difficulties in emotional processing, with possible dissociation between the explicit and implicit components.

MATERIALS AND METHODS

The present study was approved by the Ethical Committee of the I.R.C.C.S Istituto Auxologico Italiano, Milan, Italy and performed in accordance with the ethical standards of the Declaration of Helsinki. All participants provided a written informed consent.

Neuro-Ophthalmological Evaluation

NOVL is a neuro-ophthalmological diagnosis based on clinical and electrophysiological tests, and neuroimaging exams, which demonstrate the organic integrity of the afferent visual system (Thompson, 1985). The typical diagnostic approach included an in-depth examination to carefully exclude neurological diseases (Stone et al., 2005; Bruce and Newman, 2010), assuming the lack of pathological results is either due to an inexistent pathology or because the adopted measures were not sensitive enough to detect pathology (Schoenfeld et al., 2011). Thus, the disease reported by two participants is judged as functional until proven otherwise. SM and LM (co-authors of the present manuscript) had the specific role of conducting the extensive evaluation of the two cases. When assessing the patients, the indications provided by Bruce and Newman (2010) were followed, collecting detailed patients' medical history: this allowed physicians to appropriately localize potential organic lesions and to guide the neuro-ophthalmological examination. First of all, a complete neuro-ophthalmological examination was performed [best corrected visual acuity; color vision (Ishihara plates); external examination of eyes, orbits and lids, ocular motility, slit lamp examination for intraocular pressure; pupillary reactions; dilated fundus examination]. After, the diagnostic approach required differentiating monocular from binocular visual loss and central visual loss from peripheral visual loss, through the Humphrey test of visual fields with the Swedish Interactive Threshold Algorithm 30-2 (Carl Zeiss Meditec, Dublin, CA, United States). Moreover, the SD-OCT - Spectral Domain Optical Coherence Tomography (SD-OCT) imaging (RTVue-100 Version 5.1, Optovue Inc. Fremont, CA, United States) was used to exclude any structural damage. The functional integrity of the afferent visual system was assessed through electrophysiological exams (visual evoked potentials, pattern electroretinogram, full field electroretinogram and multifocal electroretinogram) and magnetic resonance imaging of the optic nerve. Also, magnetic resonance imaging of the whole brain allowed exclusion of any cerebral lesions. Finally, the absence of any anamnestic reports of neurological disease, tumor or TBI was verified during the collection of the medical history.

SM and LM followed the diagnostic decision tree for unexplained visual field loss with normal visual acuity (**Figure 1**), in order to exclude other possible medical causes for a visual field loss with normal visual acuity, reported in **Table 1**.

More details about the clinical assessment to exclude the presence of a clinically recognizable disease are reported in the following sections. The organic integrity of the afferent visual system was then verified through the objective measurements (clinical and electrophysiological tests, and neuroimaging), leading to the neuro-ophthalmological diagnosis of NOVL.

Psychiatric Evaluation

GC and EM (co-authors of this work) conducted independently a psychiatric evaluation of both patients before the experimental procedure, according to the Italian version of the Structured Clinical Interview for Axis I Disorders (SCID-I) (First et al., 1996). The evaluation led to the same diagnostic conclusion for both patients, that is, a diagnosis of "Conversion disorder with sensory symptom or deficit" [F44.6], according to the nosographical approach (World Health Organization, 2007).

Participants

Case #1 and case #2 were two female individuals admitted to the Neuro-Ophthalmology Service and Electrophysiology Laboratory, Department of Ophthalmology, Scientific Institute Capitanio Hospital, Istituto Auxologico Italiano Milan, Italy for diagnostic evaluation, since they both reported having visual difficulties. However, the two patients had normal bilateral best corrected visual acuity and mild or absolute loss of peripheral vision.

Case #1

The first case was a 37-year-old woman with 13 years of education. She was right handed. She reported a 2-year history of subacute painless vision loss in both eyes, photophobia, and ocular discomfort. The family history was negative for visual impairment. She did not report any history of previous neurological disease, tumor or traumatic brain injury. At the psychiatric evaluation, she denied any concurrent psychological issues. The patient smoked cigarettes. Co-existence of internal-medicine diseases (acute lymphoblastic leukemia treated with bone marrow transplant, systemic arterial hypertension, Hashimoto's thyroiditis and paraparesis: flaccid legs with plausible functional limitations) was independent of visual field loss – because of the evidence of the organic integrity of the afferent visual system. Indeed, regarding her vision functionality, she had moderate myopia in both eyes that was adequately corrected. According to the complete neuro-ophthalmological examination, best corrected visual acuity (BCVA) was 20/20, and her color vision (Ishihara plates) was moderately impaired on the red-green axis. The external examination of eyes, orbits, and lids was normal. Ocular motility was normal without strabismus or nystagmus; ductions, visual pursuit, and saccades were normal. Slit lamp examination revealed a normal anterior segment and normal intraocular pressure. Pupillary reactions were normal without afferent pupillary defect. Dilated fundus examination was normal in both eyes, except for a large choroidal paramacular nevus in the left eye. The Humphrey visual field test (HVF) with the Swedish Interactive Threshold Algorithm 30-2 (Carl Zeiss Meditec, Dublin, CA, United States) revealed absolute concentric loss of peripheral vision in both eyes with the field constricted to 10° centrally (mean deviation score of –22.10 dB for the right eye and of –26.00 dB for the left eye): this result was in line with the literature, according to which, the most common visual field complaint is that related to concentric loss of peripheral vision, like "tunnel vision" (Bruce and Newman, 2010). The spectral Domain Optical Coherence Tomography (SD-OCT) imaging (RTVue-100 Version 5.1, Optovue Inc. Fremont, CA, United States) revealed a normal peripapillary nerve fiber layer, macular ganglion cell complex thickness, and macular volume and structure in both eyes. She underwent pattern visually evoked potentials (p-VEP), pattern electroretinogram (PERG), full field electroretinogram (ffERG), and multifocal electroretinogram (mfERG), which overall showed functional integrity of the afferent visual system. Brain and optic nerve MR imaging was normal, with no evidence of lesions of the anterior and posterior visual pathways. At the follow-up, performed 6 years from the onset of symptoms and during her participation in the present experiments, symptoms and signs remained unchanged, without evidence of organic afferent visual system damage.

Case #2

The second case was a 48-year-old woman with an 8-year education. She was right handed. She reported subacute painless vision loss in her left eye, slow movement of the eyes, and ocular discomfort for 18 months before the neuro-ophthalmological examination. The family history did not indicate any problems; she did not report any history of previous neurological disease, tumor or traumatic brain injury. She was not a smoker. During the psychiatric evaluation, she denied any concurrent psychological issues. Co-existence of internal-medicine diseases (diagnosis of rheumatoid arthritis in 2006 and gastric banding for obesity with significant weight loss in 2014) were independent of visual field loss because of the evidence of the organic integrity of the afferent visual system. Indeed, she had mild bilateral astigmatism, not properly corrected. Her BCVA (20/20) and color vision were normal in both eyes; no afferent pupillary defect was observed in the affected eye. The external examination of orbits, slit lamp evaluation of the anterior segment, and intraocular pressure were normal in both eyes. Pupillary reactions and ocular motility were normal. Dilated fundus examination did not reveal any pathological changes in either eye. HVF revealed loss of peripheral vision in the right eye and mild and absolute loss of peripheral vision in the left eye (Cloverleaf visual field: mean deviation score of –10.95 dB for right eye and of −21.53 dB for left eye); this result is in line with the most common visual field complaints related to a concentric loss of peripheral vision, like "tunnel vision" (Bruce and Newman, 2010). SD-OCT did not show any changes in optic nerve or macular parameters. P-VEP, PERG, and ffERG revealed normal retinal function and optic nerve conduction. Brain neuroimaging showed only a few non-specific areas of altered signal in the frontal subcortical white matter. MRI

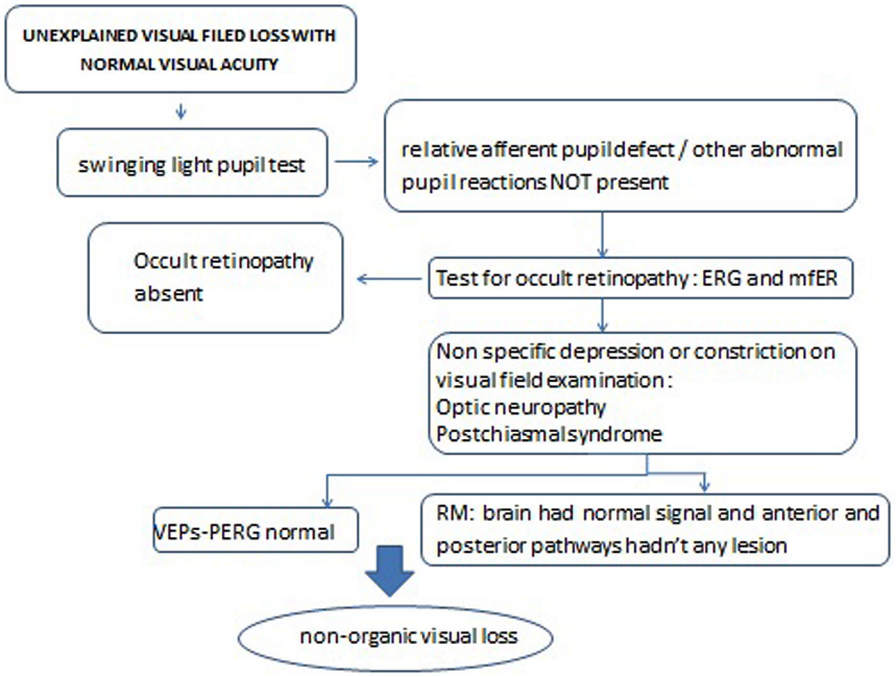

FIGURE 1 | Decision tree in the case of "unexplained visual field loss with normal visual acuity."

TABLE 1 | About the diagnostic process, other causes and test to exclude them are reported.

Cause of visual field loss with normal visual acuity	Clinical evidences	Instrumental evidences	Conclusion
Retinopathy	Manifest	– No ophthalmoscopy lesion – Macula normal on OCT.	Manifest retinopathy absent
	Occult	– Normal ERG – Normal mfERG	Occult retinopathy absent
	No clinical evidence	*No instrumental evidence*	
Optic neuropathy	– Normal optic nerve ophthalmoscopic appearance	– Normal Neuroimaging – Normal VEP	Optic neuropathy absent
	– Normal peripapillary retinal nerve fiber layer thickness values by three-dimensional OCT	– Normal PERG	
	No clinical evidence	*No instrumental evidence*	
Retrochiasmal lesion	–Normal optic nerve at the ophthalmoscopic appearance	– Normal Neuroimaging – Normal VEP	Retrochiasmal lesion absent
	– Normal peripapillary nerve fiber layer macular complex ganglion cell thickness on OCT	– Normal PERG	
	No clinical evidence	*No instrumental evidence*	

did not show pathological changes in the orbits or optic nerves.

Experimental Procedure

The procedure was conducted by FS, co-author of the work.

Control Group

Twenty-five right-handed healthy volunteers (16 women, *Age M* = 42 years; *SD* = 14; range: 23–61, *Education M* = 15; *SD* = 2; range: 8–18) participated in this study. They all reported normal or corrected-to-normal visual acuity and no history of neurological or psychiatric illness.

Psychological Assessment

After the experimental task, the participants completed self-report questionnaires. The Beck Depression Inventory (BDI) (Beck et al., 1961; Ghisi et al., 2006) was used to measure the presence of depressive symptoms. The State-Trait Anxiety

Inventory (STAI) was used to measure state- and trait- anxiety (Spielberger et al., 1983; Macor et al., 1990). The Symptom Checklist 90-R (SCL-90) (Derogatis and Savitz, 2000) was used to assess the presence of psychopathological symptoms, while the Toronto Alexithymia Scale 20 (TAS-20) (Bagby et al., 1994; Todarello and Pace, 2010) was adopted to measure the level of alexithymia. No participant reported difficulties or required assistance in reading.

The Experimental Task

The experiment consisted of two tasks, the first was a recognition *go-no go* task of neutral visual stimuli, while the second involved a recognition of emotional visual stimuli. For both tasks, the participants were seated at a distance of ∼60 cm from a computer screen of which the vertical midline lay on the sagittal midplane of their trunk and head. They had to press the spacebar of a keyboard with their dominant hand to answer the questions according to the instructions. All participants completed the experimental test without any complaints about difficulties in their ability to look at the screen.

Non-emotional Task

The stimuli were presented in black against a white background. A target (an empty square/an empty triangle) was presented in the upper or lower visual field in the following conditions: (1) in the *unilateral condition*, the target was presented on the right OR left of a fixation cross; (2) in the *bilateral condition*, the target was presented simultaneously on the right AND left of the fixation cross; (3) in the *incongruent condition*, the target was presented on the right OR left of the fixation cross while a distractor (an empty circle) was presented concurrently on the opposite side of the visual display. Moreover, catch trials (representing the *no-go* condition) in which a distractor (an empty circle) was presented unilaterally, bilaterally, or together with another distractor, were implemented in the experiment. An answer in these conditions represents a false alarm, since participants should not have provided any answer. The square and the triangle (the target) were shown independently in different blocks. Participants were required to respond as soon as possible after they noticed the target. The stimuli stayed until the participants answered or for duration of 1500 ms. The inter-stimulus interval varied randomly between 650 and 950 ms (**Figure 2A**). For each condition (unilateral, bilateral, incongruent), 32 valid trials and 16 catch trials were presented in 4 blocks (ABBA: square, triangle, triangle, square). Overall, 576 trials were administered. There was a 2- to 3-min break between blocks. *Accuracy* (% hits - % false alarms) and *Reaction Time* (*RT*) from stimuli onset were recorded for valid trials.

Emotional Task

Photographs of male and female faces (Ekman and Friesen, 1976) with either an angry, a fearful, or a neutral expression, were presented in four different conditions: (1) in the *unilateral condition*, the target (anger/fear) was presented on the right OR left of a fixation cross; (2) in the *bilateral condition*, the target was presented simultaneously on the right AND left of the fixation cross; (3) in the *neutral incongruent condition,* the emotion target was presented on the right OR left of the fixation cross along with a neutral expression; (4) in the *emotional incongruent condition*, the target was presented on the right OR left of the fixation cross along with a different emotion. Moreover, in the catch trials, a distractor (represented in half the trials by neutral stimuli and in the other half by a contrasting emotion) was presented unilaterally, bilaterally, or in opposition to a neutral and another emotion stimuli. The emotions of fear and anger were studied independently in different blocks. Participants were required to respond as soon as they noticed the target. The stimuli stayed until the participants responded or for a duration of 1500 ms. The inter-stimulus interval varied randomly between 650 and 950 ms (**Figure 2B**). For each condition (*unilateral, bilateral, neutral incongruent; emotional incongruent*), 32 valid trials and 16 catch trials were presented in 4 blocks (ABBA: anger, fear, fear, anger). Overall, 768 trials were administered. There was a 2- to 3-min break between blocks. *Accuracy* (% hits – % false alarms) was measured. The negative scores on accuracy indicated a higher number of false alarms, meaning that the subject mislabeled an emotion stimulus as the target. Moreover, *Reaction Time* (*RT*) from stimuli onset was recorded relative to valid trials.

Analysis

The analysis was conducted by FS (author of the present manuscript). The scores of each psychological questionnaire were computed according to the seminal articles (Macor et al., 1990; Derogatis and Savitz, 2000; Ghisi et al., 2006; Todarello and Pace, 2010). For the non-emotional task, the data were collapsed together for the upper and the lower visual fields as well as for those relative to the square and the triangle. Regarding the control group's RT, 1.2% of valid trials were eliminated due to omissions; in other words, when individuals did not erroneously provided any answer and then no information about accuracy or RT was available for the successive analyses. In terms of the emotional task, the emotions of anger and fear were studied independently. Concerning the control group's RT, 12.62% of valid trials for anger and 7.7% of valid trials for fear were eliminated due to omissions. The two patients' scores for each psychological subscale as well as for the experimental data were compared to the means and the SDs of the control group using Crawford's *t*-test for single cases (Crawford and Howell, 1998; Crawford et al., 2010).

RESULTS

Case #1

Psychological Assessment

Patient 1 reported a significantly higher number of symptoms in the sub-scale relative to *somatization* (SCL-90) [$t = 4.668$; $p < 0.001$; 95% CI = 4.760 (3.36–6.14)] compared to the control group (**Table 2**). No other difference emerged [$p > 0.05$].

Non-emotional Task

Patient 1 showed a significantly lower level *of Accuracy* in the unilateral- [$t = 4.94$; $p < 0.001$; 95% CI = −4.175 (−5.4 to −2.93)],

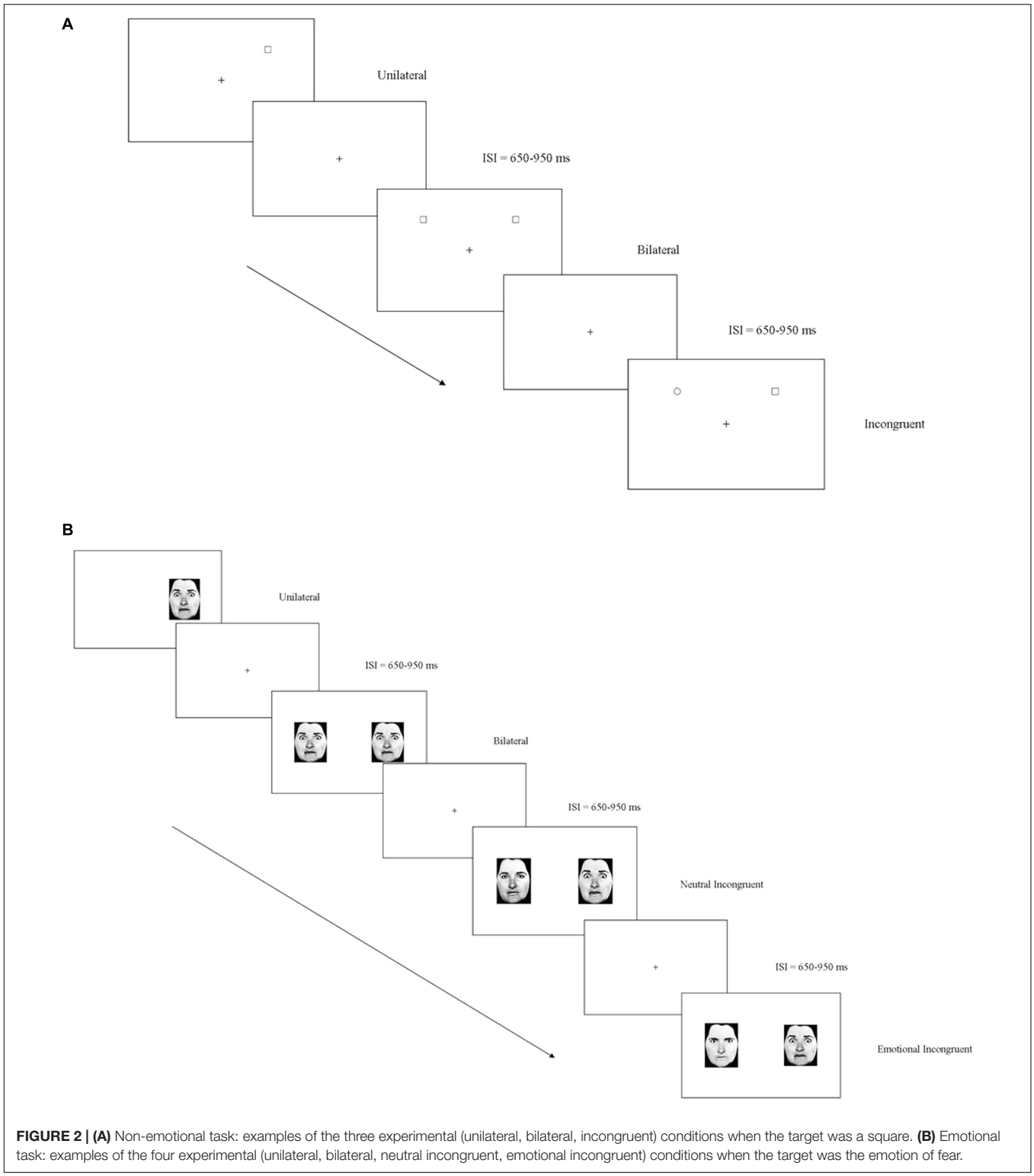

FIGURE 2 | (A) Non-emotional task: examples of the three experimental (unilateral, bilateral, incongruent) conditions when the target was a square. **(B)** Emotional task: examples of the four experimental (unilateral, bilateral, neutral incongruent, emotional incongruent) conditions when the target was the emotion of fear.

bilateral- [$t = 9.1$; $p < 0.001$; 95% CI = −9.29 (−11.92 to −6.64)], and incongruent conditions [$t = 5.67$; $p < 0.001$; 95% CI = 5.78 (−7.45 to −4.1)] compared to the control group. The participant did not differ significantly from the control group in *RT* [$p \geq 0.2$] (**Figure 3A**).

Emotional Task

Regarding the experimental conditions in which the target was the emotion of anger, the participant showed a similar level of *Accuracy* [$p \geq 0.8$] and *RT* [$p \geq 0.29$] to the control group (**Figure 3B**).

The participant had a significantly lower level of *Accuracy* in the emotion of fear compared to the control group in all the experimental conditions [unilateral $t = 7.53$; $p < 0.001$; 95% CI = −7.72 (−9.92 to −5.51); bilateral $t = 6.7$; $p < 0.001$ 95% CI = −6.9 (−8.81 to −4.92); neutral incongruent $t = 3.59$; $p < 0.001$; 95% CI = −3.66 (−4.76 to −2.55); and emotional incongruent $t = 3.63$; $p < 0.001$; 95% CI = −3.7 (−4.81 to −2.58)] (**Figure 3C**). Notably, the accuracy was negative across all the experimental conditions: the participant showed a higher number of false alarms and labeled the stimuli erroneously as fearful, specifically when they were presented unilaterally or bilaterally. When the stimulus was contrasted with a neutral expression or with another emotion, the errors decreased. No difference emerged with respect to the control group's performance [$p \geq 0.09$] in *RT*.

Case #2

Psychological Assessment

Patient 2 reported a significantly higher number of symptoms on the *somatization* scale (SCL-90) [$t = 9.884$; $p < 0.001$, 95% CI = 10.08 (7.21–12.93)] compared to the control group. No other difference emerged [$p > 0.05$] (refer to **Table 2**).

Non-emotional Task

Patient 2 had a significantly lower level *of Accuracy* only in the incongruent condition [$t = 3.03$; $p < 0.002$, 95% CI = 3.36 (−4.38 to −2.33)] when contrasted with the control group, as shown in **Figure 4**. Moreover, no difference emerged in *RT* between the participant's and the control group's performance [$p \geq 0.47$] (**Figure 4A**).

Emotional Task

Regarding the experimental conditions in which the target was the emotion of anger, the participant showed a lower level of *Accuracy* in the unilateral [$t = 2.48$; $p = 0.02$ 95%, CI = −2.53 (−3.34 to −1.71)], bilateral [$t = 2.13$; $p = 0.04$, 95% CI = −2.18 (−2.92 to −1.44), and emotionally incongruent [$t = 2.07$; $p = 0.04$, 95% CI = −2.11 (−2.81 to −1.39)] conditions but not in the neutral incongruent [$p = 0.08$] condition. Specifically, when the anger stimuli were showed unilaterally and bilaterally, the participant mislabeled the emotion, as suggested by the negative scores. The patient was faster in *RT* compared to the control group only in the neutral incongruent condition [$t = 2.47$; $p = 0.02$; 95% CI = −2.47 (−3.26 to −1.67] (**Figure 4B**).

Regarding the emotion of fear, the participant showed a lower level of *Accuracy* compared to the control group in all experimental conditions [unilateral $t = 4.01$; $p < 0.001$; 95% CI = −4.09 (−5.3 to −2.87); bilateral $t = 4.1$; $p < 0.001$; 95% CI = −4.18 (−5.42 to −2.94); neutral incongruent $t = 7.5$; $p < 0.001$; 95% CI = −7.65 (−9.83 to −5.46); and emotionally incongruent $t = 7.33$; $p < 0.001$; 95% CI = −7.48 (−9.61 to −5.34)]. Again, the accuracy was negative across the experimental conditions. No difference emerged in terms of the control group's performance [$p \geq 0.26$] in *RT* (**Figure 4C**).

DISCUSSION

In this case-controls study, we investigated the ability of two individuals with NOVL to recognize the emotions of fear and anger expressed by others. Our results clearly showed that both individuals showed a certain difficulty in efficiently recognizing the emotion of fear. They also mislabeled other emotional stimuli,

TABLE 2 | For each psychological subscale of the administered psychological questionnaires, case #1's and case #2's scores are reported and contrasted with the control group's means and standard deviations.

Psychological questionnaires	Max score	Control group M (*SD*)	Case #1 score	Case #2 score
Beck Depression Inventory	63	6.04 (4.8)	1	0
State-Trait Anxiety Inventory				
State	80	34.32 (8)	32	23
Trait	80	36.36 (9.37)	27	25
Symptom Checklist 90-R				
Somatization	4	0.31 (0.25)	1.5**	2.83**
Obsessive-compulsive	4	0.61 (0.56)	0.5	0.8
Interpersonal sensitivity	4	0.51 (0.58)	1.2	0
Depression	4	0.53 (0.51)	0.23	0.31
Anxiety	4	0.39 (0.34)	0.6	0.60
Hostility	4	0.44 (0.55)	0.3	0.17
Phobic Anxiety	4	0.11 (0.21)	0	0
Psychotic Paranoid Ideation	4	0.33 (0.53)	0.6	0.1
Paranoid Ideation	4	0.72 (0.74)	1.5	0.17
Toronto Alexithymia Scale 20				
Difficulty identifying feelings	28	11.52 (4.83)	7	15
Difficulty describing feelings	16	9.12 (3.46)	14	4
Externally oriented thinking	16	9.52 (3.37)	15	8

*$p < 0.05$; **$p < 0.001$; *M, mean; SD, standard deviation. For more details, refer to the section of the "Results."*

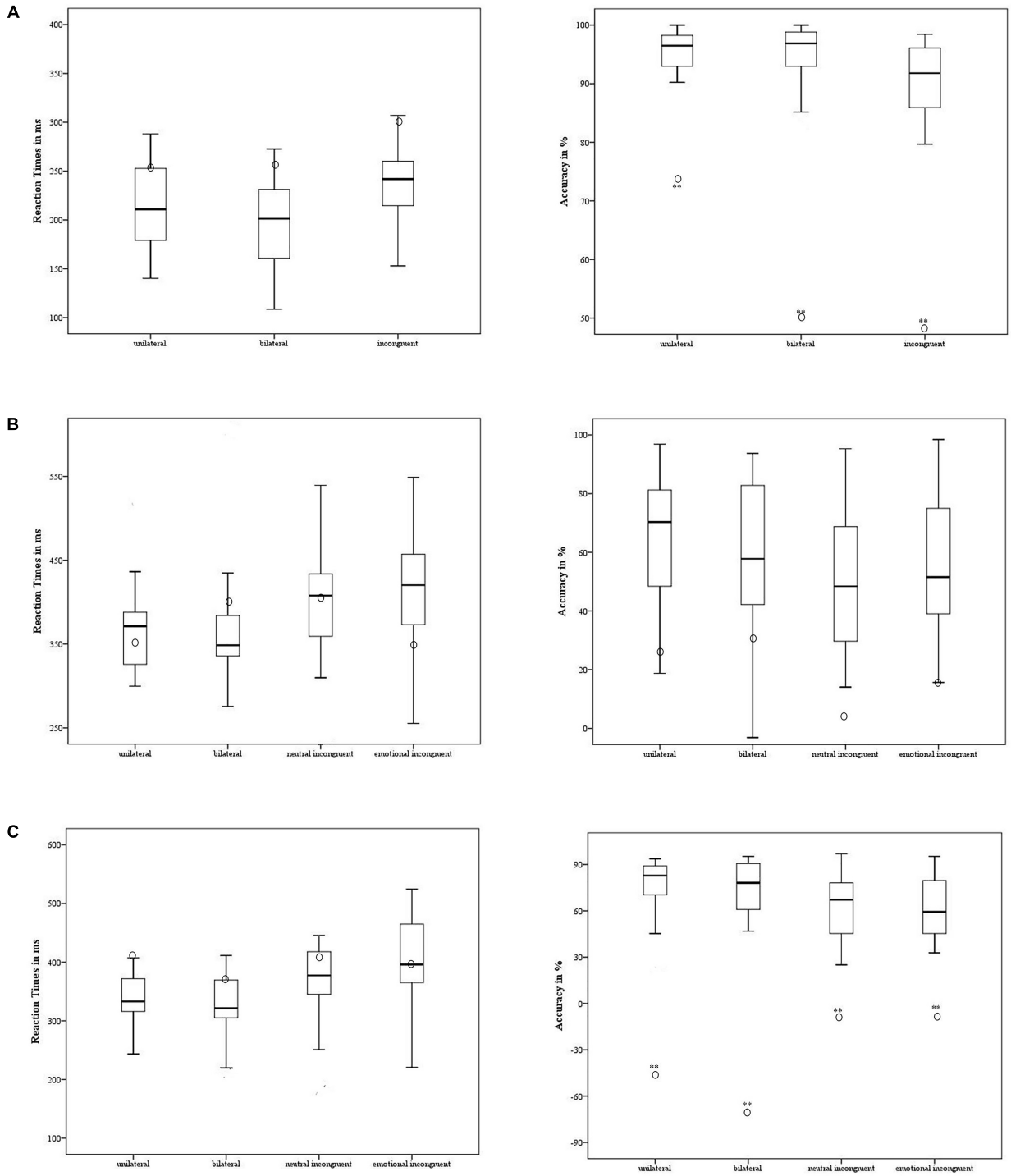

FIGURE 3 | Case #1's behavioral performance in the non-emotional task **(A)**, emotional task – anger **(B)**, and emotional task – fear **(C)** was contrasted with the control group. The means of accuracy (right side) and RT (left side) are reported for case #1 (in circle) and the control group (the minimum, the lower quartile, the median, the upper quartile, and the maximum are shown). *$p < 0.05$; **$p < 0.001$.

judging them as fearful. On the other hand, they described themselves as completely proficient in their emotional capability: no sign of alexithymia was reported in the TAS – 20 (Todarello and Pace, 2010).

The first result we discuss is the difficulties of the two participants to efficiently recognize the emotion of fear. Why would fear be erroneously processed in NOVL? To answer this question, we might take in account two facts. Firstly,

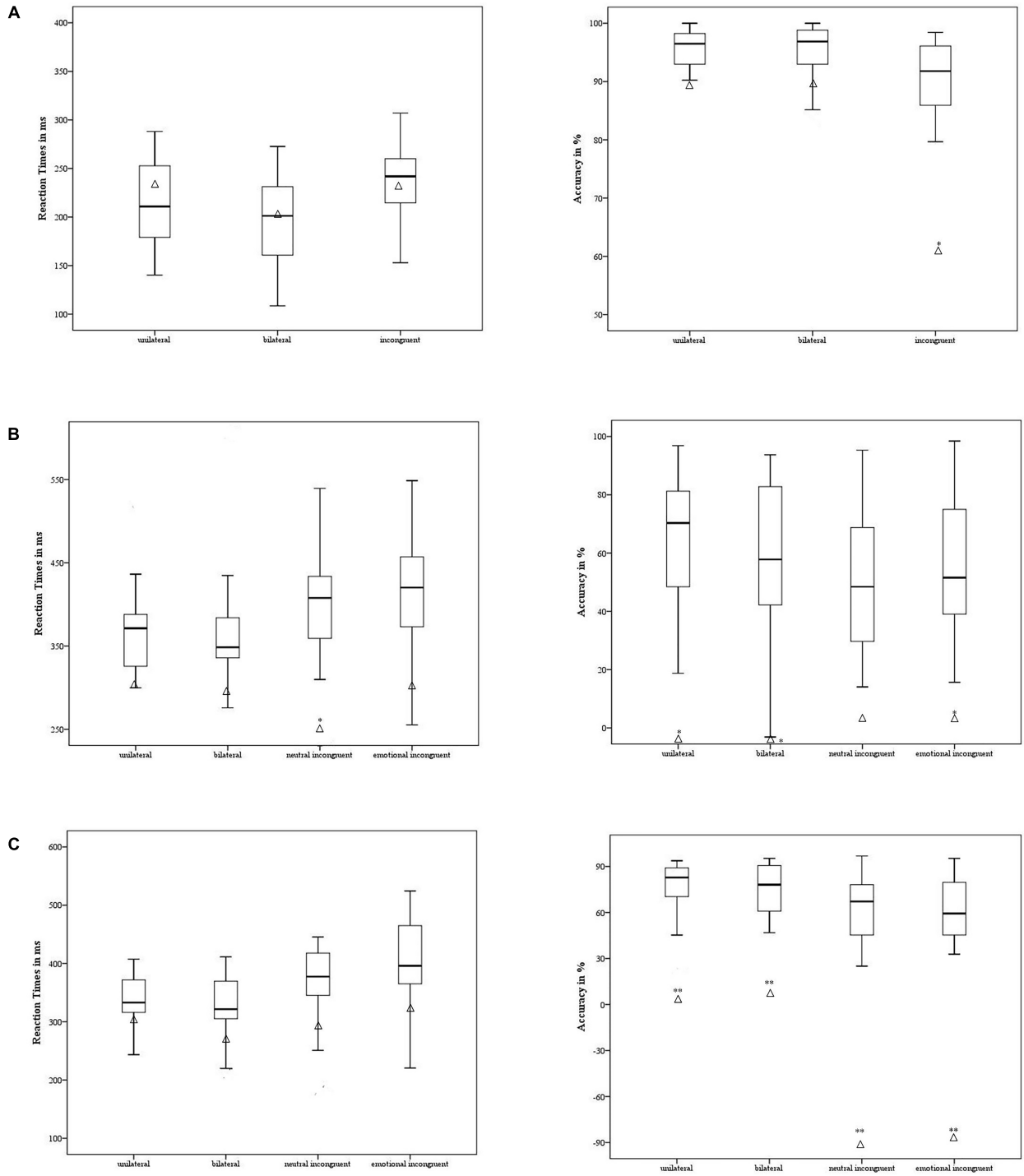

FIGURE 4 | Case #2's behavioral performance in the non-emotional task **(A)**, emotional task – anger **(B)**, and emotional task – fear **(C)** was contrasted with the control group. The means of accuracy (right side) and RT (left side) are reported for case #2 (in triangle) and the control group (the minimum, the lower quartile, the median, the upper quartile, and the maximum are shown). $*p < 0.05$; $**p < 0.001$.

the conversion symptom is described as a defensive reaction to upsetting, traumatic, and potentially frightening situations. Secondly, fear is an emotion evoked rapidly by situations that are subjectively perceived (even though not consciously) as dangerous (Adolphs, 2008). However, just as the detection of fearful stimuli from the environment is crucial for surviving, so is the extinction of this emotion when the threating stimuli disappear (Barad et al., 2006). Indeed, considering the

environment as an excessive threat would cause a constant neurophysiological fear-related activation with very high levels of stress (van der Kolk, 1997). One survival mechanism to overcome this impasse might be to turn off the sensitivity to read the emotion of fear in others' faces as the main vehicle of alert (Adolphs, 2008) or to read one's own arousing, bodily panic-related sensations as symptoms of mental illness (Demartini et al., 2014), because of alexithymia. Thus, in NOVL, individuals might have a specific difficulty in recognizing the emotion of fear as a *defensive mechanism*. This mechanism was already hypothesized for other forms of psychopathology (Maren et al., 2013). Among these disorders, the most representative is the post-traumatic stress disorder: affected individuals generally show a reduced accuracy or a decreased sensitivity to fearful expressions (Rougemont-Bucking et al., 2011; Poljac et al., 2011) in emotion recognition tasks. This impairment might be due to a dysfunction in that cerebral network (hippocampus, amygdala and medial prefrontal cortex) involved in the generation of a context-dependent behavior based on previous experiences (van der Kolk, 1997; Maren et al., 2013). Indeed, a reduced medial prefrontal cortex activity (Bremner et al., 1999) associated with an exaggerated amygdala response to general negative stimuli in post-traumatic stress disorder (Bremner et al., 1999; Rauch et al., 2000; Bryant et al., 2008) was observed in neuroimaging studies; moreover, a similar cerebral mechanism in terms of greater arousal activity (Seignourel et al., 2007; Bakvis et al., 2009a,b) as well as abnormalities in the amygdala and its interactions with other cerebral areas (Voon et al., 2010; Aybek et al., 2015) has also been reported in conversion disorder, motor variant. Considering that both individuals affected by NOVL showed a certain difficulty in recognizing efficiently the emotion of fear, a similar mechanism for this psychopathological condition might be hypothesized, requiring further investigation in which the behavioral results are linked to the cerebral functional activity. We might suggest focusing on the role of the amygdala, instead of occipital (visual) areas, as previously done by Werring et al. (2004) and Schoenfeld et al. (2011).

According to the behavioral results, the two individuals affected by NOVL not only showed a selective difficulty in recognizing efficiently the emotion of fear, but they also mislabeled other emotional stimuli, judging them as fearful. This behavior might be explained according to two different lines of results. The first involves the phenomenon of *negative bias* toward emotional stimuli, generally reported in several psychopathological conditions, such as depression (Mandal and Bhattacharya, 1985; Gur et al., 1992), eating disorders (Harrison et al., 2010), as well as schizophrenia (Kohler et al., 2003) and borderline personality disorder (Dyck et al., 2009): individuals erroneously misidentify neutral or positive stimuli as negatively valenced; this misattribution may in part underline global difficulties and inappropriate behavior in social interactions (Kohler et al., 2003). The performance of the two individuals with NOVL in the emotional task might be the expression of this negative bias.

Secondly, the mislabeling of emotion stimuli as fearful might also be related to the neuroanatomical fear-related network (the direct subcortical inputs from the thalamus to the amygdala, bypassing the slower conscious analysis in the ventral visual) (Vuilleumier et al., 2003). This network quickly primes the perception of fear-related stimuli to allow for a fast response (Butler et al., 2009; Norton et al., 2009; West et al., 2010). This faster processing of the fearful stimulus is reflected in the experimental behavior: responses to negative stimuli tend to be quicker than responses to positive stimuli (Ohman et al., 2001; Leppanen et al., 2003; Hugenberg, 2005) when participants must simply perceive stimuli without making any cognitive judgments about them. However, if the fear-related processing is impaired, it may cause an early mislabel of a neutral expression as fearful, in other words before it is can be completely processed in the primary visual areas. This mechanism, which has been preliminarily suggested in schizophrenia (Premkumar et al., 2008; Habel et al., 2010; Bedwell et al., 2013), might explain the performance of the two individuals with NOVL in the emotional task. Future research using neuroimaging and neurophysiological techniques might support this hypothesis.

Despite the behavioral results, both individuals affected by NOVL judged themselves as proficient in the emotional processing: in fact, no sign of alexithymia was reported in the Toronto Alexithymia Scale 20 (TAS-20) (Bagby et al., 1994; Todarello and Pace, 2010). Moreover, the two participants did not report abnormal levels of anxiety (of which fear represents the core) in the State-Trait Anxiety Inventory (STAI) (Spielberger et al., 1983; Macor et al., 1990). Thus, a discrepancy emerged between the behavioral results, showing an aberrant facial emotion recognition of fear, and the conscious self-judgment of emotion recognition capability. Even though the relation between these two components remains to be explored, as well as the emotional processing of other primary emotions, we might suggest a failure of self-reported scales to discern alexithymia when applied in this clinical population. Indeed, the self-reports measure emotional processing and internal feelings by asking individuals to quantify and describe their emotions and feelings explicitly. However, the assumption is that they might show an inability to recognize and verbally describe their emotions, an impaired capacity for empathy and self-insight, or an inability to discriminate between emotional states and bodily sensations (Frawley and Smith, 2001). Rather, when individuals are expected to be alexithymic, indirect measures of emotional processing might be more suitable to avoid false negative cases.

In the non-emotional task, in which participants were asked to recognize geometrical shapes, different results between the two patients were observed. The case #1 showed lower level of accuracy in all experimental conditions respect to the control group; instead the case #2 only in the incongruent one, in which an unattended stimulus competed with the target (de Gelder et al., 2001). Heterogeneous, but limited results are reported in literature about dysfunctional primary sensory process in NOVL: Schoenfeld et al. (2011) and Becker et al. (2013) reported unaltered visual cortex responses in presence of a visual target; however, altered amplitude of the visual evoked potential N1, which reflects the operation of the discrimination process within the focus of attention (Vogel and Luck, 2000), was observed (Schoenfeld et al., 2011). Thus, our results cannot be a supporting or a contrasting evidence about preserved

perceptual ability in NOVL, specifically if we take in account the reduced number of participants assessed and the absence of any neurophysiological or neuroimaging measure of cerebral activity during the task. Of course, future investigation is necessary to clarify the functionality of visual primary areas in NOVL, with the aim to recognize possible broader neural and cognitive difficulty (and then not completely limited to the emotional processing), as yet suggested for conversion disorder, motor variant in which alteration in the activity of the primary motor and sensory cortex, in addition to that of the limbic circuit, was observed (Boeckle et al., 2016 for a review).

CONCLUSION

This preliminary investigation reports, for the first time in the literature, an interesting mismatch between the explicit (i.e., the subjective evaluation of their own emotional capability) and the implicit (i.e., the behavior in experimental paradigm) components of the emotional processing in participants with NOVL. Of course, future investigation with an enlarge numbers of participants and with more strictly inclusive and exclusive criteria, specifically in relation to the clinical history and the psychiatrist evaluation, is necessary. However, this report might represent a starting point for more detailed research to investigate how visual problems, when not directly related to physical damage, may (or may not) be related to psychological factors as well as alexithymia, and might be conceptualized as a maladaptive reaction construct in unelaborated traumatic experiences (Franzoni et al., 2013), as already reported in functional motor symptoms (Demartini et al., 2014).

AUTHOR CONTRIBUTIONS

FS: conceived the study, conducted the experimental part and the statistical analyses, and wrote the paper. LM: enrolled and evaluated the patients with NOVL and reported their description in the manuscript. GC: conceived and conducted the psychological evaluation and revised the manuscript. AM: supervised the experimental part and the neurological assessment of the patients. SBM: supervised the evaluation of the patients with NOVL and revised the manuscript. EM: conceived the study, supervised the study, and revised the manuscript.

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MINI REVIEW
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Headache and Alexithymia in Children and Adolescents: What Is the Connection?

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Background: Headache is one of the most common complaints in children and adolescents and comorbidity rates are very high and the major associated diseases are depression, anxiety, atopic disorders, sleep, and behavioral disorders. In recent years, it has been highlighted that difficulties regulating emotions such as alexithymia have also been associated with diagnosis of somatization.

Methods: We carried out a mini review analyzing the relation between alexithymia and primary headache (e.g., migraine and tension type headache) in children and adolescents by synthesizing the relevant studies in the literature on PubMed, PsycINFO, and Google Scholar. Search terms were "alexithymia" combined with the "primary headache," "migraine," "tension type headache," "children," and "adolescents."

Results: All analyzed studies found higher levels of alexithymia in children and adolescents with headache than control groups but there are different opinions about the relationship between headache and alexithymia. For example, some studies suggest that the association between headache and alexithymia in children may be due to an incomplete development of emotive competency or a general immature cognitive development, instead other studies found a correlation between headache symptoms, insecure attachment, and alexithymia. There seems to be also differences between children with migraine compared to those with tension type headache (TTH).

Conclusion: There are some studies on adults suffering from headache or migraine and alexithymia, but there is only a moderate amount of research on pediatric age with different opinions and theories about this relationship. Further studies on children and adolescents are necessary to effectively understand this relationship and to help children to reduce headache and improve emotional consciousness.

Keywords: headache, migraine, tension type headache, alexithymia, children, adolescents

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INTRODUCTION ON PRIMARY HEADACHE

Primary headaches are the most frequent complaints among the pediatric population with migraine and tension type headache (TTH) being the most common type. This disorder causes individual suffering and impairments in quality of life, daily activities (Dyb et al., 2015), school attendance (Rousseau-Salvador et al., 2014) and a variety of serious family issues (Wöber-Bingöl, 2013). Moreover, primary headache can be associated with several comorbid conditions which

may worsen headache symptomatology, prognosis, therapeutic selection and post- therapeutic outcomes (Mark, 2015). In the pediatric population, tension type headache, and migraine are commonly associated with various diseases. For instance, psychiatric and neurological comorbidity, in particular sleep disorders, anxiety and depression, epilepsy and ADHD (Bellini et al., 2013). It has also been shown an association with medical disorders such as atopy, cardiovascular disease, especially ischemic stroke and Patent Foramen Ovale (PFO) (Bellini et al., 2013). In some studies, it has been shown that children with migraine had significantly higher levels of internalizing and somatic symptoms, as well as social and family problems relative to those without headache and had higher levels of somatic symptoms than children with tension-type headache (Anttila et al., 2004; Arruda and Bigal, 2012). In recent years, alexithymia has been studied among the emotional disturbances associated with somatic symptoms including primary headache, and there are some different opinions about this relationship.

ALEXITHYMIA CONSTRUCT

Alexithymia has also been recognized to be associated with several somatic illnesses and mental disorders. The term alexithymia was coined by Sifneos in 1973 (Sifneos, 1973) (from the Greek; a=lack, lexis=word, thymos emotion), concerning a cognitive-affective disturbance that affects the way individuals experience and express their emotions, internal states and feelings (Taylor, 1984). There is a reduced ability to identify and describe feelings, a limited imagination, and a concrete, externally- oriented way of thinking. Recently, it has been proposed a two-dimensional alexithymia. The affective dimension refers to the level of subjective emotional experience and comprises of a reduced ability to experience emotional feelings (emotionalizing factor), and diminished imaginative capabilities (fantasizing factor) (Vorst and Bermond, 2001; Koelen et al., 2015). The cognitive dimension refers to the more verbal-explicit aspects, such as the inability to verbalize emotions and to differentiate between emotions, as well as between emotions and somatic sensations and the presence of an "externally oriented thinking" style (Bermond et al., 2010; Goerlich-Dobre et al., 2014). Many studies have highlighted the association between alexithymic traits and psychiatric diseases. Most of them have found a positive association with internalizing disorders such as depression and anxiety traits (Leweke et al., 2012; Scimeca et al., 2014; Li et al., 2015). Additionally, alexithymia is co-present with eating (Lulé et al., 2014), behavioral disorders (e.g., severe disruptive behavior) (Manninen et al., 2011) and personality disorders such as borderline personality (Loas et al., 2012). Other studies focused on the association between alexithymia and mother's little or lack of education and broken family, disadvantageous living conditions in childhood (Joukamaa et al., 2007) and insecure attachment strategies (Besharat and Khajavi, 2013; Koelen et al., 2015). Finally, some studies have noticed that children with recurrent pain disorders (i.e., migraine, tension type headache, skeletal muscle pain, abdominal pain) compared to healthy controls, show higher level of alexithymic features (Allen et al., 2011; Cerutti et al., 2016). For example, in one study conducted by Burba et al. (2006), adolescents with somatoform disorder had higher levels of alexithymia and anxiety than healthy adolescent control subjects.

RELATIONSHIP BETWEEN ALEXITHYMIA AND PRIMARY HEADACHE IN CHILDREN AND ADOLESCENTS: WHAT WE KNOW AND WHAT WE CAN HYPOTHESIZE?

There are a few studies devoted to the investigation of the possible link between headache and alexithymia in adults (De Andrade et al., 2013), and even fewer on children and adolescent populations. For example, it has been observed that adults with migraine or TTH had a higher alexithymia level, compared to healthy controls (Wise et al., 1994). Furthermore, there would seem to be no difference between the severity of alexithymia among the cases of experiencing episodic vs. chronic TTH (Yücel et al., 2002). The association between alexithymia and primary headache in children and adolescence is not well-known yet. Some authors have tried to study the phenomenon and provide some hypotheses. In a pilot study conducted by Gatta et al. (2011), the aim was to analyse alexithymic features in children with primary headache (both TTH and migraine). They found a significant association between TTH and alexithymia in the experimental group. Children with TTH had major alexithymic problems compared to children with migraine and the control group. Two dimensions were particularly compromised in children with headache: recognizing their own feelings and tendency for operatory thought. On account of these results, the Authors supposed alexithymia to create a condition in which feelings or emotions (emotive or somatic), when not distinguished, may undergo a process of reinforcement and become a symptom of disease. Moreover, there were some children with high level of alexithymia in their control group and the authors suggested that they may still be in a developmental phase also regarding emotional recognition and awareness, in accordance with the Lane and Schwartz (Lane and Schwartz, 1987) cognitive-developmental model of emotions. In a more recent study, Gatta et al. (2015) investigated alexithymic features in children and adolescents with primary headache (both migraine and tension type headache) and in their mothers, in order to examine the possibility of a relationship between headache and emotional regulation, in particular alexithymia. They have confirmed their prior results: a significant relation between TTH and alexithymia was found, but not between Migraine and alexithymia. They assumed that the differences between TTH and migraine may be due to different pathogenesis of the two disorders. Genetic factors may underline the etiology of migraine more than TTH, while TTH has a more complex multifactorial pathogenesis, influenced also by the familial and social environment. In fact, primary headache is more common in families with a history of psychological disorders (Galli et al., 2009). Lastly, their results partially support the hypothesis that alexithymia in a child may correspond to a similar kind of emotional dysregulation in the mother, emphasizing a connection between these two factors (Jørgensen et al., 2007). Even if they have

not found significant alexithymic differences between mothers of the three groups (Migraine, TTH and control), they believed that emotional difficulties may lie in other aspects of emotional regulation implied in mood and anxiety disorders, which have a high prevalence in parents of children with headache (Feldman et al., 2010). In line with this study, Cerutti et al. (2016) examined the association between migraine and alexithymia, exploring the hypothesis of alexithymia predicting psychopathological symptoms in adolescents and mothers with migraines. Furthermore, determining any differences between adolescents and their mothers suffering from migraine vs. adolescents and mothers in the control groups (and the relation with both mother and child with migraine). In contrast with Gatta's results, they discovered that adolescents and their mothers with migraine had higher rates of alexithymia. Additionally, they demonstrated that both adolescents and mothers, both suffering from migraine, also appear to experience greater psychological distress than the adolescents and mothers in the control groups. In light of these results, they supposed a possible intergenerational transmission of alexithymia and a child's alexithymia may reflect the mother's deficit in regulating emotions and expressing feelings (Yürümez et al., 2014). At this point, it is fundamental to analyse the relationship between headache, attachment style and alexithymia. It has been observed a connection between migraine features (high attack frequency and severe pain intensity) and attachment style, especially the ambivalent one (Tarantino et al., 2017). Moreover, children with migraine and with ambivalent attachment style report higher symptoms of anxiety, depression, and somatization. Also, Williams et al (Williams et al., 2017) showed that the somatic condition of migraine acted as a stressor, reducing children's perception of the security of their parental attachments. It seems that children with migraine exhibit a significantly higher prevalence of avoidant attachment and a lower prevalence of secure attachment (Esposito et al., 2013). From these evidence, a potential influence of attachment style on emotional expression and primary headache may be taken into consideration. Some genetic studies have attempted to understand whether alexithymia is a transmissible construct. For example, Baughman et al., have found different results in two separate studies. In the first one (Baughman et al., 2011), the phenotypic correlations between alexithymia and emotional intelligence traits seemed to be attributable to correlated genetic and correlated non-shared environmental factors. In the second one (Baughman et al., 2013), they found that, in addition to the antecedent factors, there was also an influence by shared-environment. The genetic component observed supports previous suggestions that biological base may contribute to the development of alexithymia (Larsen et al., 2003). However, Picardi et al. (2011) suggested that emotional distress may confound the estimation of the heritability of alexithymia, corroborating the notion that alexithymia is substantially heritable and enhancing the role of unshared environmental factors.

Cerebral anomalies may be underlying both alexithymia and migraine, but there is still no certainty and accuracy about this correlation. In a research conducted by Liu et al. (2013) gray matter and white matter changes have been compared in a group of the early clinical stage of migraine patients without aura for 1 year. When they re-examined the patients, a year following the first observation, gray matter reduction was observed in the dorsolateral and medial part of the superior frontal gyrus, orbitofrontal cortex, hippocampus, precuneus, and primary and secondary somatosensory cortices. However, no differences in white matter changes were found. Thus, a possible connection between migraine and alexithymia may be due to changes in specific cerebral areas. In fact, altered gray matter volume (Kano and Fukudo, 2013; Grabe et al., 2014) and a reduced activation in the posterior cingulate cortex (Mantani et al., 2005) seem to be related to lower alexithymia levels.

CONCLUSIONS

Mechanisms through which psychological mechanisms influence a physical disorder are complex and difficult to detect with the available tools (Kano and Fukudo, 2013). Studies on children and adolescents are often not simple and with *bias*. Indeed, the majority of studies involve children and adolescents together (aged between 8 and 15 years), and since childhood and adolescence are ages of change and the psychological characteristics are constantly developing, some children might find it difficult to verbally express themselves. This might depend on their incomplete emotional development and immature brain areas (i.e., 28). Moreover, some bias can influence the assessment of alexithymia. Alexithymia Questionnaire for Children is the only tool for measuring the alexithymic construct at a developmental age, but it has some critical issues (Rosenberg et al., 2016). The major problem is the validity of self- report measures of alexithymia. Especially in childhood there are several problems with self-report measurement due to problems in understanding questions, reading difficulties, social desirability, and last but not least, the lack of a general understanding of their internal states. Expressing emotions, feelings and using imagination is moresimple for an adult in respect to a child, on account of their experience and acquired competences (both verbal and emotional) (Lumley et al., 2005). The concept that the headache and alexithymia in children are connected is supported by the literature, however, this is rather limited. Further studies on children and adolescents and more accurate instruments are necessary to better understand this relationship and to help children in reducing headache and improve emotional consciousness. Research psychologists and physicians have to work together to improve the existent questionnaire and knowledge about the origins of both alexithymia and primary headache in order to reduce severity of headache and psychological suffering of children and adolescents.

AUTHOR CONTRIBUTIONS

GN, NF, and VG conceived and designed the study. DC, RC, PV, and VG were responsible for critical revision of this manuscript. All authors approved the final version of this manuscript.

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Alexithymia and Autism Spectrum Disorder: A Complex Relationship

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Alexithymia is a personality construct characterized by altered emotional awareness which has been gaining diagnostic prevalence in a range of neuropsychiatric disorders, with notably high rates of overlap with autism spectrum disorder (ASD). However, the nature of its role in ASD symptomatology remains elusive. Here, we distill research at the intersection of alexithymia and ASD. After a brief synopsis of the studies that played a pioneering role in the identification of the overlapping fields between alexithymia and ASD, we comb the literature for evidence of its overlap with ASD in terms of prevalence, etiology, and behaviors. Through a formalized framework of the process of emotional interpretation and expression, we explore evidence for where and how deficits arise in this complex network of events. We portray how these relate to the dynamic interplay between alexithymic and autistic traits and find emerging evidence that alexithymia is both a cause and consequence of autistic behaviors. We end with a strategic proposal for future research and interventions to dampen the impacts of alexithymia in ASD.

Keywords: alexithymia, autism spectrum disorders, autism, ASD etiology, personality

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INTRODUCTION

Over the last two decades the relationship between alexithymia and autism spectrum disorder (ASD) has gained significant attention – there has been a surge in the number of studies aimed at investigating the relationship between these conditions, including from a conceptual and etiological point of view, as well as with regards to the implications of this relationship for clinical and therapeutic practices. Alexithymia is highly prevalent and plays an important and complex role in ASD, with approximately half of individuals with ASD estimated as having alexithymia, but the nature of its role remains elusive. Empirical evidence of the biological basis of alexithymia in ASD is suggestive of its role as a root cause, while empirical evidence of alexithymia as a byproduct of core ASD deficits is suggestive, conversely, of its role as consequence of ASD. It may also play a role as both cause and consequence of ASD in a feedforward cycle between alexithymia and ASD symptomatology.

Here, we review existing literature on alexithymia and its relationship to ASD. Our first aim is to provide a brief synopsis of the research on the relationship between ASD and alexithymia, including clarifying when and how they originate. Next, we will illustrate the prevalence of alexithymia in ASD as well as their overlap in terms of etiology and features, propose both empirically and theoretically driven causal and consequential roles for alexithymia in ASD, and suggest clinically useful constructs and interventions as well as specific areas for beneficial future investigation.

AUTISM SPECTRUM DISORDER

Autism spectrum disorder has long been well-known and has a stable definition in psychiatric nosography. Initially, the typical characteristics of this disease were identified by Eugen Bleuler as early symptoms of schizophrenia, or by Melanie Klein of psychosis (Wing, 1997; Wolff, 2004). The current meaning of the term 'autism' was developed by and can be attributed to Asperger (1938, 1944), while the lemma 'infantile autism' was introduced by Kanner (1943). Asperger and Kanner used the term to indicate a disorder of organic origin with severe behavioral, affective, communication and social skills impairment, characterized by little interest in others, speech disorder, attention deficit and compulsive and repetitive behavior. Since the early 1980s – and especially after the publication of the DSM-III (American Psychiatric Association [APA], 1980) – it has been recognized as an autonomous pathological condition definitively differentiated from schizophrenia. Eventually, descriptions of the condition were slightly modified and accurate criteria for its assessment were provided in 1987 by the DSM-III-R (American Psychiatric Association [APA], 1987). The publication of the DSM-IV (American Psychiatric Association [APA], 1994) placed autism in the wider category of pervasive developmental disorders, a complex of syndromes that affect social interaction, communication and the capacity to develop varied interests. In this new conceptualization, a milder form of autism, Asperger's syndrome, was distinguished, in which mental retardation and linguistic impairment are less severe. With the publication of the DSM-IV and later of the DSM-V (American Psychiatric Association [APA], 2013), a view of autism was gradually developed based on the idea of a spectrum: autism is no longer seen as a categorical condition, but is understood instead in terms of continuous traits, hence the adoption of the term ASD. In this view, the condition is characterized by the co-occurrence of various psychological disorders due to underlying neuropsychological and functional impairments. Historically, many hypotheses have been put forth on the origin of autism. Though some of them – mainly in the realm of psychoanalytic research – have suggested both a relational and environmental origin, it is now clear that genetic factors play a predominant role in its etiology (Colvert et al., 2015).

ALEXITHYMIA

Unlike ASD, alexithymia does not have a steady classification in the psychiatric nosography. Alexithymia was first introduced into the lexicon of psychiatry by Peter E. Sifneos in the early 1970s (Sifneos, 1973) to characterize a number of patients with psychosomatic complaints who were being treated by various psychoanalysis research groups across Europe and North America (Sifneos, 2000). Literally, it indicates the lack of terms to express emotions and moods (a: lack; lexis: word; thymos: mood or emotion, see Lesser, 1981). In fact, a common trait in these patients was their inability to verbalize their emotions, either due to their unawareness of the feelings that corresponded to these emotions or due to their confusion of emotional and bodily feelings. Indeed, they would typically describe their emotional experience in terms of the somatic sensations they incurred, reflecting the so called "operatory thinking" which had already been described by Marty and de M'Uzan (1963) and Marty et al. (1963). Their incapacity to speak of their emotions was further accompanied by an impoverished narrative style, especially in the use of figures of speech and metaphors, and by a characteristic aprosodia, as if the emotional experience were uninteresting and extraneous to them.

Sifneos originally hypothesized that the patients exhibiting these symptoms suffered from a particular form of linguistic impairment due to an "emotional agnosia" (Sifneos, 1967); later he suggested that these symptoms should be rather interpreted in terms of a "feeling aphasia" (Sifneos, 1996). While Sifneos was originally open to the possibility of considering alexithymia as a pathological personality trait causally related to psychosomatic illness (Sifneos, 1974), later research challenged the idea of alexithymia as a single diagnostic category since characteristic aspects of alexithymia were seen among non-psychosomatic clinical populations as well. Further research actually showed that alexithymic traits could be observed in people suffering from very different clinical conditions such as neurodegenerative diseases (Sturm and Levenson, 2011; Ricciardi et al., 2015), psychiatric conditions such as depression and suicidality (Honkalakampi et al., 2000; Hintikka et al., 2004) – though the interplay between affective and cognitive impairments in the etiology of depression is still a point of interesting contention (Gonda et al., 2015), schizophrenia (Fogeley et al., 2014), eating disorders (Nowakowski et al., 2013), and ASD (Bird and Cook, 2013). Moreover, 10% of the non-clinical population exhibits some alexithymic traits (Salminen et al., 1999).

Today alexithymia is considered a "sub-clinical phenomenon" (Silani et al., 2008), not identifying a personality disorder *per se*, but a personality trait with a dimensional nature (Taylor et al., 1991; Taylor, 1994). This is characterized by an impairment in the awareness of emotions due to a deficit in processing of affective information (Vermeulen et al., 2006). The main characteristics of alexithymia include (1) difficulty identifying feelings and distinguishing between feelings and bodily sensations of emotional arousal, (2) difficulty describing feelings to other people, (3) reduced capacity to fantasize and to imagine, (4) stimulus-bound, externally oriented cognitive style (Nemiah et al., 1976; Krystal, 1988; Taylor et al., 1997; Timoney and Holder, 2013), and, more recently, (5) low perspective-taking as well as difficulty understanding and describing the emotions of others (Saymur et al., 2013).

The lack of emotional awareness has a negative impact on subjective emotion regulation (Connelly and Deney, 2007) and compromises the understanding of others' emotions, giving rise to problems in social interaction. In particular, because of their difficulty identifying and classifying feelings, people suffering from alexithymia cannot interpret or recognize emotional stimuli (e.g., facial expression or tone of voice), both verbal and nonverbal (Spitzer et al., 2005; Vanheule et al., 2007; Megank et al., 2009). As a consequence, they have difficulty establishing social relationships characterized by intimacy and proximity, understanding the intentions and attitudes of others, and

making morally relevant decisions that take into account others' points of view. These aspects of alexithymia together with the communication and social skills deficits are among the most relevant overlapping elements between alexithymia and ASD.

The idea of a relationship between alexithymia and ASD was recently developed, starting from the observation that both types of patients exhibit similar social difficulties. This phenomenon established itself in the context of psychological research as a result of the development of the construct of emotional intelligence by Salovey and Mayer (1990) and Goleman (1996), which focuses on the links between emotion and cognition, critical to the development of emotional competence (Saarni, 1999). Emotional intelligence and emotional competence are similar constructs that are used to investigate the capacity to detect, comprehend and logically organize emotional information concerning oneself and others, together with the capacity to manage and regulate behavior in social interactions. It is in this line of study that alexithymia and ASD began to be considered as conditions characterized by widely overlapping traits related to social difficulties and deficits in emotional competence.

THE INTERSECTION BETWEEN ALEXITHYMIA AND ASD

The idea that alexithymia and ASD are somehow related was first considered in the mid-1990s. At the time, several clinical studies were performed on groups of people suffering from eating disorders (especially anorexia nervosa). On one hand, they highlighted the co-occurrence of these disorders with impairments in social competence, while on the other hand, they stressed the co-occurrence of an impairment of social competence with some traits that were considered typical of ASD, such as empathy disorders (cf. Gillberg, 1992), as well as others that were considered typical of alexithymia, such as the difficulty expressing emotions verbally, identifying feelings and distinguishing emotions from somatic sensations (cf. i.a. Gillberg et al., 1995; Rastam et al., 1997; De la Rubia and Rojas, 2001; Soya and Tenaglia, 2001). In a short time, the relationship between alexithymia and ASD started to be investigated more widely, including with respect to aspects not related to compromised social competence. Other areas of intersection were identified, such as disorders of cognitive functioning, impaired self-awareness and mentalization, poor linguistic mastery and difficulty with behavior control (Corcos, 2003; Fitzgerald and Bellgrove, 2006; Hill and Berthoz, 2006). This has led to greater attention on the incidence of alexithymic traits in clinical populations suffering from ASD and on the assessment that about half of people suffering from ASD exhibit some relevant alexithymic traits (Hill et al., 2004; Berthoz and Hill, 2005; Bird and Cook, 2013).

The cognitive, linguistic and behavioral issues of people with ASD have long been known (cf. i.a. Hermelin and O'Connor, 1970; Baron-Cohen et al., 1985; Denckla, 1986; Frith, 1991; Rogers and Pennington, 1991; Tager-Flusberg, 1992; Yirmiya et al., 1992; Rapin and Dunn, 1997). However, in this context, research has focused more specifically on the co-occurrence of these issues with specific characteristics typical of alexithymia such as the difficulty identifying and attributing emotions (Hill et al., 2004; Moriguchi et al., 2006; Silani et al., 2008; Cook et al., 2013), an excessively pragmatic and utilitarian thinking style (Patil et al., 2016), poor emotional lexicon (Lartseva et al., 2015), difficulties understanding metaphorical language (Wotschak and Klann-Delius, 2013), issues with the interpretation of nonverbal clues (Bird et al., 2011), aprosody (Heaton et al., 2012), difficulties with emotion regulation and emotional expression (Weiss et al., 2014; Costa et al., 2017), and difficulty discriminating bodily sensations due to an altered somatic sensibility (Liss et al., 2008; Shah et al., 2016; Gaigg et al., 2018).

In spite of the high volume of research devoted to the relationship between alexithymia and ASD, no one unequivocal answer has been provided to the question surrounding their precise relationship. In fact, it is still not clear whether this should be interpreted in causal terms (and in which direction), whether one of them is a secondary phenomenon due to the occurrence of dysfunctions caused by the onset of the other (i.e., whether there is a comorbidity or an epiphenomenal relationship), or whether it is a mere, yet unspecified, co-occurrence. This situation of etiological uncertainty is partly due to our incomplete understanding of the cognitive, physiological, and neurophysiological mechanisms underlying the onset of both conditions. It is thus of particular importance to assess our current knowledge of their relationship and to continue to analyze the literature for new clues in this direction.

EVIDENCE OF DIAGNOSTIC, ETIOLOGICAL, AND PHENOTYPIC OVERLAP BETWEEN ALEXITHYMIA AND ASD

Alexithymia is common in ASD, both low and high-functioning (Hill et al., 2004; Fitzgerald and Bellgrove, 2006; Paula-Pérez et al., 2010; Griffin et al., 2016). It is also more prevalent in relatives of individuals with ASD, potentially constituting an element of the broader autism phenotype found in such relatives (Szatmari et al., 2008). Etiologically, research on ASD and alexithymia suggest both broad genetic and neurobiological overlap, including oxytonergic and serotonergic system activation and amygdala, cingulate, and prefrontal cortex functioning (Elagoz Yuksel et al., 2016; Muller et al., 2016; Donovan and Basson, 2017). Most importantly however, there is also much trait overlap between alexithymia and ASD. Individuals with alexithymia have difficulty in both the verbal and the nonverbal identification of emotions: they are unable to describe their feelings, use emotion terms, or recognize emotions in facial expressions and other nonverbal emotional stimuli such as tones of voice or situations with strong emotional connotations. They often confuse emotions with somatic sensations. In parallel, individuals with ASD have difficulty with the cognitive processing of their emotions, identifying, and describing feelings (Hill et al., 2004; Shah et al., 2016).

More specifically, they have difficulty with general emotional competence, including emotion perception, recognition and regulation, particularly facial emotion recognition, but also recognition of emotional tones of speech and prosody, verbal content, and body movement, including the coordination or integration thereof (Serafini et al., 2017; Gaigg et al., 2018). It is important to note here that these deficits may, however, be linked to the deficits generally seen in speech and language competence in individuals with ASD (South and Rodgers, 2017) and as they relate to emotions in alexithymia (Allen et al., 2013). Similar and consequent, but not identical to the above, another area of overlap is social, in individuals' relationship and response to others, including cognitive and emotional states, notably in the form of cognitive and affective empathy. Individuals with ASD and alexithymia display reduced levels of enjoyment of prosocial interactions (Gebauer et al., 2014). Evidence is also substantial that individuals with ASD and alexithymia display decreased levels of empathy (Luminet et al., 2006; Lartseva et al., 2015), possibly linked to neurobiological deficits in limbic and paralimbic neural activity responses to emotionally salient stimuli (Moriguchi and Komaki, 2013). Connected to empathy, a concrete, utilitarian thinking style, not dissimilar to "operative thinking," is common in alexithymia (Suslow and Junghanns, 2002) and ASD, though the roles of this type of thinking on moral judgment has been suggested to be different in alexithymia as compared to ASD (Lemche et al., 2004). Clearly, alexithymia and ASD share many overlapping features in emotional, social, cognitive – verbal and nonverbal – realms, with varying degrees of convergent consequences on their individual and social behavior and lives. This lays the foundation for investigating the nature of their complex relationship in the context of emotional processing.

MECHANISTIC LINKS IN EMOTIONAL PROCESSING BETWEEN ALEXITHYMIA AND ASD

To better hone in on where the deficits arise in alexithymia and ASD, we break down the phenomenon of emotional processing and, at each level, we review evidence of a deficit and how this may shed light on the role of alexithymia in ASD. Briefly, the steps we define are (1) interpreting one's emotions – through interoception, affective and cognitive manifestations, (2) responding to and regulating one's emotions – verbally and nonverbally, and (3) appropriately interpreting and responding to others' emotions.

Interpreting Emotion in the Self – General Emotional Awareness, Recognition of Sensory Manifestations of Emotion, and Cognitive Appraisal Thereof

A factor that plays a relevant role in our emotion perception and thus in emotion understanding is interoceptive awareness: through it, we become capable of identifying, distinguishing, and assessing the physiological activations related to our emotions. Several studies show that the mechanism responsible for our emotion awareness have significant overlaps with the neural systems that support our interoceptive awareness (Damasio et al., 2000; Critchley et al., 2004; Pollatos et al., 2007). The general notion of interoceptive awareness has been further specified by distinguishing two underlying different, and partially independent, capacities that are included in it: the so-called interoceptive accuracy and interoceptive sensibility (Garfinkel and Critchley, 2013; Garfinkel et al., 2015). The notion of interoceptive accuracy describes our capacity to identify internal body sensations, while the notion of interoceptive sensibility refers to our capacity to focus on our internal sensations and to take them into consideration, including from a cognitive point of view.

This distinction is relevant in order to understand the relationship between alexithymia and ASD since the difficulty in recognizing and distinguishing physiological activations is a trait typical of alexithymia while atypical forms of sensory perception are characteristic of people suffering from ASD. Some studies show that alexithymics exhibit an excessive activation with respect to the physiological component of emotional arousal (Kano and Fukudo, 2013) and an atypical interoceptive awareness (Herbert et al., 2011; Ernst et al., 2014) which can be interpreted as the result of an increased interoceptive accuracy which is not accompanied by an adequate interoceptive sensibility. Atypical forms of interoceptive awareness were observed in people suffering from both alexithymia and ASD (Brewer et al., 2016): since interoceptive accuracy is mainly related to difficulties discriminating among interoceptive signals typical of alexithymia, it was suggested that alexithymia might be responsible for the atypical interoception manifested in people suffering from ASD, and that this might reflect itself in their difficulties understanding their bodily states as well as their and others' emotions (Lombardo et al., 2007; Cook et al., 2013). Interestingly, this interoceptive deficit may be linked to weak theory of mind, a common feature of ASD, since an inability to understand one's own complex inner states may extend to and manifest itself as an inability to understand those of others. This said, results are controversial and some studies found that difficulties in emotional awareness were related neither to impairments in self-reflection nor mentalizing (Silani et al., 2008; Bird and Viding, 2014), while others have shown only partial correlation between theory of mind, emotion perception and the cognitive understanding of the emotion of others, i.e., perspective taking (Moriguchi et al., 2006; Oakley et al., 2016).

Altered interoceptive sensitivity observed in alexithymia could have implications at a cognitive level (interoceptive sensibility), as well as at a metacognitive level (general interoceptive awareness), inducing difficulties in making sense of one's sensory experiences, either due to a core sensory processing deficit or to sensory overload as a consequence of inadequate filtering. The presence of alexithymia in people with ASD may in fact involve a disruption in how physiological arousal modulates the subjective experience of feelings (Gaigg et al., 2018). Other studies have outlined how alexithymia in people with ASD may be interpreted as a consequence of the extreme sensory processing patterns of ASD (Serafini et al., 2017), and, more specifically, of the atypical

sensory function and associated intolerance of uncertainty, possibly due to a deficit in limbic-, insula-, and medial prefrontal cortex-based network integration (South and Rodgers, 2017). This said, since significant data points to deficits in the synthetic interpretation of physiological responses to emotion, and implied processing of large-scale information flow, it may be of particular interest to explore the link with ASD theories of weak central coherence and executive dysfunction.

Responding to and Regulating Emotion in the Self – Expression and Action, Verbal, and Nonverbal

We have seen that deficits in alexithymia can arise at the level of emotional understanding, but many difficulties may be linked to emotional expression or externalization. Whether an emotion has been consciously recognized or not, alexithymia and its linked disturbances in ASD may reflect a mismatch between the affective and expressive – including linguistic, visual artistic, musical – systems.

An example of emotional reactivity in alexithymia, emotional responsiveness to music and speech prosody provides a powerful lens – arguably representative of responses to other emotionally salient stimuli – into the emotional processing disruptions seen in alexithymia and ASD. Alexithymia, not lack of emotional responsiveness to music, may be the cause of reduced verbal responsiveness to music in ASD – indeed, though results are controversial in alexithymia, and some studies measuring autonomic reactions to emotionally salient stimuli showed evidence of both hyper-arousal, as per blunted sympathetic activation in response to anger recall (Neumann et al., 2004), and hypo-arousal, as per heightened blood pressure responses to anger provocation (Waldstein et al., 2002), overall physiological responsiveness to the emotionally salient stimuli of music among ASD individuals is intact (Allen et al., 2013), as is recognition of emotion in music (Quintin et al., 2011; Gebauer et al., 2014), suggesting the difficulty comes from the disjunction, and associated complications, between emotional understanding and expression. This is consistent with solid evidence and discussion over the last few decades on the hypothesis that alexithymia is generated by a decoupling between physiological, cognitive, and sometime expressive responses to emotionally salient stimuli, i.e., broadly between physiological arousal and subjective experience (Stone and Nielson, 2001; Eastabrook et al., 2013). Indeed, consistent with the above, the emotional impairments in ASD gravitate around the emotional language processing system (Lartseva et al., 2015), again highlighting alexithymia, or the lack of words to express emotions, as a causative factor of ASD. More specifically, while individuals with ASD are able to correctly classify emotional language stimuli as emotionally positive or negative, they are unable to explain their choices in further depth and display atypical patterns of attention and memory performance, as well as abnormal physiological and neural activity – they show deficits in recalling emotional material and in semantically processing emotional content (Luminet et al., 2006) and are less primed by emotional contexts to process emotional words more easily (Suslow and Junghanns, 2002). More broadly, they have deficits in general emotional and internal state vocabulary (Lemche et al., 2004) and the fact that they have difficulty perceiving and processing speech prosody or melody of speech that has emotional content (Goerlich-Dobre et al., 2014) confirms their difficulty with general emotional language, as it relates to themselves and others. This may be due to the increased cognitive load required to process emotionality in music, as evidence by increased neural activity in emotional music-reactive brain regions (Gebauer et al., 2014). While differences remain inconsistent (Swart et al., 2009; Bhatara et al., 2010), it seems clear that broad brushstrokes of emotional verbalization are conserved while subtleties are not, and the core deficit in alexithymia seems to be at the level of detailed symbolization – largely through verbal conceptualization – of emotional experience. This supports its role as causative factor of ASD symptomatology.

Though less common, emotions may naturally also be expressed in the form of nonverbal expression, of particular relevance in the context of ASD, which is replete with differences in sensory and cognitive perception and expression, of the self and the external world (Markram and Markram, 2010). Differences in nonverbal emotional expression at the level of body posture and facial expression are seen in ASD, with evidence of abnormalities in emotional facial expression which may be explained by co-occurring alexithymia (Trevisan et al., 2016). Art allows individuals with alexithymia to express themselves and potentially access the verbal expression system which they need to process and vent their emotions (Meijer-Degen and Lansen, 2006); interestingly, individuals with ASD have high rates of synesthesia and often use colors to express their emotions (Neckar and Bob, 2017). Dance, or rhythmic movement therapy, is another effective outlet for symptoms of alexithymia (Malkina-Pykh, 2013) and may be intricately linked to emotional competence (Bojner Horwitz et al., 2015). As mentioned above, music is another alternate vehicle for understanding, processing, and communicating emotions (Allen and Heaton, 2010; Zangwill, 2013). Individuals with ASD have intact or superior musical pitch processing and are able to properly identify the positive or negative emotional valence of music stimuli. As seen above, their responsiveness to emotionality in music is complex, however, and reflected in a network of both intact and altered brain circuit responses to emotional processing of music (Caria et al., 2011). This evidence of nonverbal emotional expression as an outlet for individuals with alexithymia and ASD further suggests that alexithymia may be a causative factor for some of the emotional symptoms of ASD, but can be compensated for through alternate means of emotional interoception and expression. Indeed, an important part of responding to emotion is at the level of action planning, or strategizing a response plan (usually subconsciously) to difficult emotions (Samson et al., 2015b), and when provided with such a strategy, individuals with ASD respond well, highlighting the tremendous potential, through training, to help individuals with ASD understand and deal with their emotions in a healthy way.

The above responses to one's emotions represent a crucial step to emotional regulation – expression of emotional conflicts may be a first avenue toward their subsequent recognition and regulation. In addition, an important component of emotional

processing is being able to regulate emotions within and to adapt to various contexts. This is particularly important in the context of ASD, since a frequent feature of ASD is behaviors reflecting a lack of sound emotional regulation, with many individuals with ASD displaying uncontrollable tantrums and outburst and self-harm behaviors (Samson et al., 2014). Interestingly, behavioral suppression strategies that focus on inhibiting emotion-expressing behavior has been shown to be the strategy used by individuals with ASD, who naturally favor emotional expressive suppression over cognitive reappraisal (Samson et al., 2012, 2015a,b). This is highly similar to alexithymia, in which individuals rely more on suppressing than reappraising their emotions (Swart et al., 2009). Though contentious, as per scarce previous studies which may have failed to analyze the effect of alexithymia as a whole rather than through its subdimensions (Samson et al., 2012), this may point to further support for the alexithymia hypothesis whereby alexithymic features may be at the core of the similarly manifested emotional regulation difficulties seen in ASD. While still important, regardless of the nature of the interaction between alexithymia and ASD in the context of emotional regulation, it is important to note, and incorporate into treatment plans, that strategies that focus on situational reappraisal, by creative a narrative that down-regulates the impact of negative emotions, are a significantly more adaptive long-term strategy (Gross, 2015).

Interpreting and Responding to Emotion in Others – Expression and Action, Immediate, and Subsequent

A final important step, or aspect, of emotional processing, is in understanding of the self and others, and appropriate response to the valuable information about the human and non-human external world that emotions provide. These challenges generalize beyond the self to the emotions of others, with repercussions on how individuals behave socially. Not surprisingly, individuals with alexithymia have difficulties interpreting and describing the emotional and cognitive states of others. These difficulties manifest themselves as deficits in emotional mentalizing (Moriguchi et al., 2006; Swart et al., 2009), poorer recognition of emotional expression in faces (Grynberg et al., 2012; Cook et al., 2013), deficits in the recognition of vocal affect (Heaton et al., 2012), and alexithymia-induced deficits in eye fixation, a rich source of information regarding emotional state (Bird et al., 2011; Lee and Anderson, 2017). In addition, levels of alexithymia correlate negatively with models-of-self but also models-of-others, and alexithymics show decreased emotional contagion (i.e., mentalization of affects reflected in autonomic muscular activity) in response to others' facial responses (i.e., somatic affects), as seen as deficits in facial muscle emotional processing as measured by somato-motor electromyographic activity (Sonnby-Borgström, 2009; Scarpazza et al., 2018). Consistently, stronger alexithymia and lower capacity for self-memory are predictive of larger mentalizing impairments and autism quotient scores (Lombardo et al., 2007), which may provide an interesting link to the cognitive deficits in theory of mind and cognitive and affective aspects of differences in empathy seen in ASD.

Interestingly, moral decision-making, which generally incorporates rational and emotional insights, is less subject to emotional biases in individuals with ASD due to the presence of alexithymia (Brewer et al., 2015). This was corroborated by a study which found no differences in moral decision-making in individuals with both ASD and alexithymia – while ASD reduced utilitarian bias due to elevated distress in social situation, alexithymia increased utilitarian bias due to reduced empathic concern (Patil et al., 2016). This may be consistent with the fact that alexithymia decreases altruism in real social decisions (Feldmanhall et al., 2013). Finally, other consequences of alexithymia on social interaction include compromised social assertiveness (Roelofs et al., 2015) and reduced interest in people and shared interests – consistently, empathic brain activity in the anterior insula was predicted by alexithymia, not ASD (Bird et al., 2010), and the degree of anterior insula activity has been correlated to individuals' self-reported degree of alexithymia and empathy (Silani et al., 2008).

As such, alexithymia may break down a rung in the ladder of internal and external emotional reaction in individuals with ASD, impinging on their ability to appropriately respond to emotion. Our balanced synopsis seems to support the 'alexithymia hypothesis' (Bird and Cook, 2013) that posits that alexithymia, not ASD, is a leading cause of the emotional deficits inherent to ASD symptomatology.

SYNTHETIC PERSPECTIVE

To best inform therapeutic strategies, it will be critical to better structure our understanding of the etiologies of and relationship between alexithymia and ASD. Emerging overlapping etiologies between alexithymia and ASD will be of particular interest, including the potential association of certain subtypes of alexithymia with ASD. In addition, it will be important to keep in mind the peripheral, and more indirect, links between alexithymia and ASD. Alexithymia in itself may cause anxiety and related sleep issues (Tani et al., 2004), and the inability to healthily express and externalize emotions could lead to a variety of psychosomatic manifestations which may be manifested as immune, gastrointestinal, and circadian disruptions, all frequently seen in ASD.

Undoubtedly, alexithymia is a heuristically useful concept for clinicians and non-clinicians alike. Alexithymia is a negative prognostic factor for health and psychotherapy outcomes (Kojima, 2012), and emotion processing difficulties have been linked to depression in ASD (Hill et al., 2004), making it important to recognize and treat alexithymic traits as soon and as best as possible. Central to the concept of neurodiversity, it will be important to let this recognition of alexithymia guide clinical and non-clinical care – since there is potential for training individuals with alexithymia to better recognize emotional expressions in faces (Cook et al., 2013) and have better recollection of emotional memories (Luminet et al., 2006), there is tremendous potential for providing the tools for effectively coping with, strategizing

with, and coherently expressing emotions that may not be obvious to individuals with alexithymia or ASD (Costa et al., 2017), including compensatory intellectual strategies, nonverbal reasoning skills and re-learning the rules of socio-moral norms (Patil et al., 2016). Cognitive reappraisal of emotionally salient situations, a response which is not natural, but easily learned in individuals with alexithymia and ASD, is a further example of a concrete, actionable intervention with positive health outcomes (Gross, 2015). Further examples of effective therapy will thus include cognitive behavioral therapy (Spek et al., 2008), but also mindfulness-based therapies that encourage heightened interoceptive sensitivity and accuracy (Gaigg et al., 2018) as well as more non-traditional forms of therapy tailored to individual modes of perception and communication, including verbal, artistic, musical, and kinesthetic expression. Since evidence is only growing of the benefits of alternate, nonverbal, forms of expression in alleviating alexithymia-linked challenges (Heiman et al., 1994), it is most important to first recognize alexithymia to be able to then invest in developing and implementing creative therapies and original systems of communication that are tailored to an individual's mode of perception and experience. Adopting such changes will hopefully provide an extra step toward the full adoption and embracement of inclusive neurodiversity, during which our thinking about alexithymia, including as it relates to ASD, must keep being increasingly creative and multidimensional as we develop unique individualized strategies.

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Alexithymia in Young Adults With Substance Use Disorders: Critical Issues About Specificity and Treatment Predictivity

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Several studies have reported high rates of alexithymia in drug-dependent individuals, but supporting evidence attests association between alexithymia and a variety of psychiatric disorders, raising doubts about its specificity. Moreover, controversies are emerging about alexithymia assessment: self-report measures present shortcomings with respect to discriminant validity and reliability. As regards treatment for substance use disorders (SUDs), alexithymia has been linked to poorer outcomes, but the results are inconsistent. The aim of the present study is to investigate alexithymia in substance-dependent young adults by examining: (a) the specificity of alexithymia in drug-dependent inpatients, compared to healthy individuals and patients with psychiatric disorders (behavioral and emotional disorders) and (b) the predictivity of alexithymia in determining treatment outcomes in terms of relapses, drop-outs from treatment and the rate of relapse per month of treatment. Two studies were conducted to fulfill these aims: Study 1 and Study 2. Study 1 involved 90 late adolescents, aged 17–21. To fulfill the first aim, 30 inpatients diagnosed with SUD were compared with 30 healthy controls and 30 individuals referred to an outpatient neuropsychiatric unit (a). The participants completed the Toronto Alexithymia Scale—20 (TAS-20) and the Symptom Checklist-90-Revised (SCL-90-R). The results indicated that both clinical groups reported higher TAS-20 scores than the non-clinical subjects, but they did not differ from each other (a); moreover, a large correlation was detected between alexithymia and depressive symptoms, as assessed by the SCL-90-R. Study 2 involved 55 inpatients with SUD recruited in a therapeutic community. The participants completed the TAS-20, and clinicians filled out the Observer Alexithymia Scale (OAS). No association was found between self-report and observational measures. Neither self-reported nor observed alexithymia predicted the number of relapses, drop-out from treatment, or the rate of relapses per month of treatment (b). When the interaction with gender was explored, the global score of alexithymia and the "Distant" OAS subscale predicted the number rate relapses only in males. The TAS-20 did not discriminate between the clinical groups. The limited ability of both observed and self-reported measures in predicting treatment outcome raises questions on the specificity of alexithymia among the substance-dependent inpatient population.

Keywords: alexithymia, substance use disorder, young adulthood, treatment outcome, 20 Item -Toronto Alexithymia Scale

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THEORETICAL BACKGROUND

Alexithymia refers to the psychological dysfunctional trait of having no words to express emotions or feelings (Sifneos, 1973). It is a multidimensional construct comprising emotional and cognitive components: difficulties in identifying and describing feelings as well as in differentiating somatic sensations and feelings, lack of fantasy, and imagination and an externally oriented cognitive style (Nemiah and Sifneos, 1970; Nemiah et al., 1976; Taylor et al., 1997). Interestingly, the relevance of alexithymia has grown exponentially in the last decades; it is currently considered a relevant concept for a range of psychological and physical disorders (Taylor et al., 1997; Taylor and Bagby, 2004), and attention is paid to its relationships with other constructs, such as emotional intelligence, negative affect, and its role in predicting treatment outcomes (Morie et al., 2016).

Alexithymic Traits in Drug-Dependent Individuals

Vast research has suggested that alexithymia is quite common in patients with substance use disorders (SUDs) (Handelsman et al., 2000; Speranza et al., 2004; Cleland et al., 2005; De Rick and Vanheule, 2006; Oyefeso et al., 2008; Lindsay and Ciarrochi, 2009; Thorberg et al., 2009; Torrado et al., 2013; Nehra et al., 2014). When considering alexithymia as a categorical variable, while rates in the general adult population range between 6 and 17% (Hintikka et al., 2001; Kokkonen et al., 2001; Franz et al., 2008), adults with SUDs—both abstinent and undergoing treatment—show higher percentages. Despite a first overestimation of 78% (Rybakowski et al., 1988), the prevalence is typically estimated in the range of 43.5 to 67% (Taylor et al., 1990; Haviland et al., 1994; Farges et al., 2004; Speranza et al., 2004; Oyefeso et al., 2008; Lindsay and Ciarrochi, 2009; Thorberg et al., 2009), even though a recent review asserts that it is about 30–49% (Cruise, 2017). Differences in alexithymia rates can be explained by looking at the assessment methods applied and sample characteristics, including the severity of the disorder, the type of treatment (outpatient or inpatient), and the substance being abused (alcohol, opioids, etc.,). Also, when alexithymia is measured as a continuous variable, individuals with SUDs show higher alexithymia traits (Handelsman et al., 2000; Cleland et al., 2005; Ghalehban and Besharat, 2011; Lyvers et al., 2012; Torrado et al., 2013; Nehra et al., 2014). Difficulties in identifying and expressing emotions are also related to increased drug use among adolescents (Trinidad and Johnson, 2002), and using cut-off scores, alexithymia prevalence among young substance abusers (aged 14–25) is noteworthy, ranging from 35 to 43% (Troisi et al., 1998; Farges et al., 2004; Dorard et al., 2008a,b, 2017; Parolin et al., 2017). Studies have used the self-report TAS-20 and almost exclusively address outpatient youth with cannabis use disorders (including both abuse and dependence), with only two exceptions. The study by Farges et al. (2004) did not specify the substance, and in the study by Parolin et al. (2017), a majority of the inpatient participants were opioid dependent. Despite rates among young substance users seeming higher than that among the general population of youth (Säkkinen et al., 2007), when young substance users and controls were compared, the difference in prevalence did not reach statistical significance (Dorard et al., 2008b).

The relationship between alexithymia and addiction is supported by a significant positive association between alexithymic traits and craving, the severity of the disorders and related difficulties (Cleland et al., 2005; Thorberg et al., 2010, 2011a,b). It has been hypothesized that alexithymia may be a vulnerability factor that predates SUDs (Taylor et al., 1997; De Rick and Vanheule, 2006; de Timary et al., 2008). As suggested by Taylor et al. (1997), the role of alexithymia as risk factor for SUDs may be explained by taking into account inherent aspects of the construct (such as immature self-awareness and scarce cognitive regulation of one's emotions). Alternatively, it can be the result of interactions with other risk factors, such as drug expectations, negative affectivity, insecure attachment, executive function, and personality disorders (Pinard et al., 1996; Lumley, 2000; Thorberg et al., 2009; Lyvers et al., 2012; De Carli et al., 2016). Despite some data on clinical (Cecero and Holmstrom, 1997; Uzun, 2003) and non-clinical populations (Kauhanen et al., 1992; Bruce et al., 2012) confirming the theoretical assumption suggesting that alexithymia is a risk factor in the genesis of SUDs, questions remain, and empirical evidence is scarce and non-univocal, as reported by Thorberg et al. (2009) in a review study. Moreover, alexithymia may be a predisposition factor for psychiatric disorders others than drug addiction (Taylor et al., 1997), thus calling the specificity of the association with SUDs into question. Thus, the relationship between alexithymia and drug dependence remains quite unclear (Teixeira, 2017); alexithymia might be a consequence or correlate of the drug disorder (Thorberg et al., 2009).

In alexithymia research, the TAS-20 is the most widely used and studied measure (Taylor et al., 2003; Meganck et al., 2008). Several studies have adopted the TAS-20 to investigate alexithymia in patients with SUDs (Haviland et al., 1988c, 1994; Taylor et al., 1990; Haviland, 1996), reporting rates of 42–50%, thus higher than non-clinical (4–18%) and psychiatric groups (12–33%) (Handelsman et al., 2000; Taylor, 2000). The TAS-20 can discriminate well between psychiatric young patients and non-clinical youth (Kooiman et al., 2002; Marchesi et al., 2014).

Despite its worldwide use in research and clinical practice, the TAS-20 has been criticized for some shortcomings: a critical review of the literature revealed the insufficient reliability of its third subscale ("Externally oriented thinking"), showed the presence of different factor structures in various patient samples and underlined a lack of studies on its criterion validity (Kooiman et al., 2002). As a matter of fact, there are significant relationships between alexithymia, as measured by the TAS-20, and negative affects, depression, and anxiety in both non-clinical (Honkalampi et al., 2010; Deno et al., 2011) and clinical samples (Marchesi et al., 2000; Gatta et al., 2016), including patients with SUDs (Haviland et al., 1988a,b, 1991, 1994; Taylor et al., 1990; Farges et al., 2004; de Haan et al., 2011, 2012a; Morie et al., 2015). In order to examine if the TAS-20 measures the broader construct of negative affects rather than identifying alexithymia itself in clinical groups, Marchesi et al. (2014) compared patients with different diagnoses (major depression, panic disorder, eating disorder, and SUD) to controls. The results indicated that all

clinical groups showed higher TAS-20 scores than the controls but not when controlling for anxiety and depression, suggesting that alexithymia as measured by the TAS-20 may have an issue with discriminant validity.

This leads to a more general limitation concerning the assessment of alexithymia with self-report measures, which can be called into question, since they require respondents to report on their psychological states, yet alexithymic individuals lack this capacity by definition (Lane et al., 1997; Lumley, 2000; Waller and Scheidt, 2004). In the specific case of SUDs, substance abusers self-reported higher alexithymia on the TAS-20 than controls and patients with other psychiatric disorders, but their actual performance on a task that required them to identify and describe feelings was not significantly different (Lindsay and Ciarrochi, 2009). As the authors of the instrument acknowledged (Taylor et al., 1997), a multi-method approach is recommended to assess alexithymia: the TAS-20 could be used in combination with other-report instruments (Kooiman et al., 2002). Unfortunately, to date, few studies have compared different measures, especially in the field of addiction. The Observer Alexithymia Scale (OAS; Haviland et al., 2000) represents an alternative assessment measure. The OAS has been used in studies on substance abusers, both adults and adolescents, together with the TAS-20 (Dorard et al., 2008a; Thorberg et al., 2010, 2013; Parolin et al., 2017). It demonstrated adequate psychometric properties and rather low correlations with the TAS-20 total scores and subscales, indicating a lack of correspondence between the two measures (Dorard et al., 2008a).

Alexithymia as Predictor of Treatment Outcomes

Since alexithymia is a well-recognized and clinically relevant concept, studies have examined whether alexithymic traits may have implications for how drug-dependent patients respond to treatment, but the empirical evidence is non-univocal. Alexithymia (encompassing low self-awareness and interest in introspective activities, scarce empathy and emotion regulation, high negative affectivity and impulsivity and non-optimal coping strategies) may impede treatment and facilitate the use of substances in case of heightened distress (Bagby et al., 1993; Parker et al., 1998; Oyefeso et al., 2008; Shishido et al., 2013). Some evidence has attested that alexithymia may interfere with treatment success. As regards relapse, a cross-sectional investigation on outpatients with alcohol use disorder (Ziółkowski et al., 1995) found significant differences in total scores and alexithymia rates between long abstainers ($>$ 1 year) (33% of alexithymics) and short abstainers ($<$ 1 year) (63% of alexithymics); stepwise multiple linear regression analysis indicated that the overall TAS-20 score accounted for 20% of the variation in abstinence. Similarly, in a cohort of outpatients with alcohol use disorders, Loas et al. (1997) found significantly higher levels of alexithymia at treatment intake among outpatients who relapsed at 15-month follow-up, even after controlling for depression. The TAS-20 factor accounted for 17% of the variance in abstinence, indicating that alexithymia can predict higher risk of relapse. Alexithymia may also predict treatment engagement, in terms of session attendance and working alliance (drug-dependent outpatients who were higher in alexithymia attended fewer sessions and formed weaker alliances) (Cleland et al., 2005). In studies on inpatients with alcohol use disorder (de Haan et al., 2012b), baseline alexithymia showed no relation to abstinence, time in treatment or changes in disorder severity at 1-year follow-up. Similarly, as concerns SUDs (de Haan et al., 2011), alexithymia (measured as both a continuous and a categorical variable) was not related to abstinence, and high-scoring alexithymics did not differ from low-scoring alexithymics in mean time in treatment or dropout rates (50 vs. 43%). A prospective study on alcoholics (Junghanns et al., 2005) found that alexithymia scores were not associated with the risk of relapse at 6-week follow-up. A recent study confirmed that alexithymia was not strongly associated with treatment adherence or retention in an 8-week randomized clinical trial (Morie et al., 2015). Thus, empirical evidence on the relationship between alexithymia and treatment outcome in SUDs is limited and non-univocal. Substance use treatment is hindered by high rates of relapse (60–70%) (Bradizza et al., 2006) and premature termination, to the extent that it is more common for a patient to drop out of addiction treatment than to complete the treatment (Stark, 1992; Brorson et al., 2013). On the contrary, completion of addiction treatment is one of the most consistent factors associated with a favorable treatment outcome (Hser et al., 2004). This implies the importance of identifying predictors of treatment retention and adherence.

Alexithymia has been recognized as being associated with several psychiatric disorders, including chronic pain. The mediation of pain intensity by prescription painkiller use suggests a process in which more intense pain leads to more frequent use of stronger (prescription) painkillers, which increases the risk of dependence (Elander et al., 2014). The self-medicating hypothesis proposes that individuals use substances to cope with negative affects (Ghalehban and Besharat, 2011). Because of their cognitive inability to identify their emotions, alexithymic individuals may use drugs to regulate their emotions and alleviate stress (Shorin, 1998). Thus, it is difficult to determine whether alexithymia is a specific characteristic of SUDs. These doubts increase in light of the controversy over how to assess the construct to discriminate between primary and secondary alexithymia and related outcomes. Since some evidence has raised concerns on the TAS-20's discriminant validity, a multimethod assessment could spread light on this debate. In addition, little research has addressed this issue in adolescents. Finally, it is not clear whether alexithymia can be considered a risk factor for negative treatment outcomes.

Objectives

The aim of the present study is to investigate alexithymia in substance-dependent young adults, focusing on some methodological issues. In particular, we are interested in examining whether the available and commonly used assessment measures (self-report and observational) are suitable for evaluating alexithymia in SUD populations. We examine this issue by investigating two objectives: (a) the specificity of alexithymia in drug-dependent inpatients, compared to healthy

individuals and patients with psychiatric disorders, and (b) the predictivity of alexithymia in determining treatment outcomes in terms of relapses, drop-outs from treatment and rates of relapse per month of treatment. To fulfill these aims, two studies were conducted, referred to as Study 1 (a) and Study 2 (b).

Study 1 investigates whether young adults diagnosed with SUDs differ from referred psychiatric outpatients and controls in terms of alexithymia levels, as measured by the TAS-20. Based on previous literature, we hypothesized that drug-dependent and referred youths would show higher levels of alexithymia than controls.

Study 2 focuses on a group of inpatients with SUDs and addresses two questions. First, we investigated whether self-report and observational measures differ in their evaluation of alexithymia. According to previous studies, our hypothesis proposes a lack of correspondence between self-report and observational measures, in light of the doubts regarding the validity of self-report tools in assessing alexithymia in clinical samples. Second, Study 2 investigated the ability of alexithymia to predict treatment outcomes. Based on the relevance ascribed to alexithymia in clinical practice and recognizing the lack of consensus on the association between alexithymia and SUD treatment outcomes, we were interested in the predictive role of observed and self-reported alexithymia (at the baseline) for treatment response 1 year after admission, in terms of relapses, dropouts from treatment and rates of relapse per month of treatment. We hypothesized that alexithymia (implying poor introspective capacity, high negative affectivity and non-optimal coping) can predict higher risk of relapse and dropout from treatment. A negative relationship with treatment success would support the need to specifically address alexithymia and adjust treatment protocols.

STUDY 1

Materials and Methods

Participants

Study 1 involved 90 late adolescents, aged 17–21, who comprised two clinical groups and a comparison group **Table 1**. The clinical groups included 30 inpatients diagnosed with SUDs and admitted to a residential treatment facility (SUD group) and 30 late adolescents referred to an outpatient neuropsychiatric unit (clinically referred group).

The SUD group included 30 young inpatients admitted to a therapeutic community for SUDs (Villa Renata, Comunità di Venezia, Venice, Italy) and met the following inclusion criteria: (a) diagnosed with SUD according to DSM-5 (APA, 2013) criteria; (b) referred and admitted to the residential treatment community for less than 3 months; and (c) age ranging from 17 to 21 years.

A cohort of 30 patients referred to the Mental Health Public Service (SCIAF ULSS 6, Padua, Italy) for psychopathological problems was recruited. The inclusion criteria were: age between 17 and 21 years, a diagnosis classification of "behavioral and emotional disorders with onset usually occurring in childhood and adolescence" (F90-F98) or "affective [mood] disorders" (F30-F39) (according to ICD-10; World Health Organization, 2016), and no mental delay (QI $>$ 70, according to Wechsler, 2003).

The comparison group included 30 healthy young adults, recruited in high schools near Venice, Italy. The main selection criteria used in the data collection were: (a) the absence of psychiatric disorder diagnosis; (b) absence of current drug use; and (c) age between 17 and 21 years.

Procedure and Instruments

This first study was carried out in accordance with the recommendations of the Code of Ethics approved by the General Assembly of the Italian Association as well as the Ethical Committee of University of Padua (protocol reference number: 2038). All of the subjects provided written informed consent (parental, in the case of minors) to participate to the study.

All of the participants completed the TAS-20 and the SCL-90-R; for the two clinical groups, administration occurred at treatment intake, as part of an assessment protocol.

- *The 20-item Toronto Alexithymia Scale* (TAS-20; Bressi et al., 1996). Developed by Bagby et al. (1994a,b), the TAS-20 is a self-report scale made of 20 items that must be rated from 1 (*strongly disagree*) to 5 (*strongly agree*); the sum of the items generates a total score and scores for three subscales. The scale has a three-interrelated-factor solution: difficulty identifying feelings (F1), difficulty describing feelings (F2), and externally oriented thinking (F3). Although predominantly used as a dimensional construct, the total score can be compared to cut-off scores that categorize respondents into alexithymic ($\geq$ 60), borderline/intermediate ($\leq$ 51 and $\geq$ 60) and non-alexithymic. The scale was evaluated as a reliable and valid measure in non-clinical and clinical samples (Parker et al., 1993, 2003; Bagby et al., 1994a,b; Bressi et al., 1996; Taylor et al., 2003), even though the TAS-20 has shown some psychometric shortcomings (Kooiman et al., 2002). The reliability and factor solution of the TAS-20 in samples of substance abusers have been tested and shown sufficiently good results, with the only exception being the Externally Oriented Thinking subscale (Haviland et al., 1988c; Cleland et al., 2005). Moreover, an Italian study conducted on adolescents (La Ferlita et al., 2007) only partially replicated the original factor structure of the TAS-20 and showed higher levels of alexithymic traits in comparison to adults.
- *The Symptom Checklist-90-Revised* (SCL-90-R; Derogatis, 1994). The SCL-90-R is a self-report measure assessing 90 clinical symptoms on a 5-point Likert scale, ranging from 0 (*not at all*) to 4 (*extremely*). The symptoms are factored into nine psychiatric dimensions (depression, anxiety, somatization, obsessive-compulsive behavior, interpersonal sensitivity, hostility, phobic anxiety, psychoticism, and paranoid ideation) plus altered appetite and disturbed sleep. The instrument provides three global scores: the global stress index (GSI), the positive symptom total (PST) and the positive symptom distress index (PSDI). Both the original version and the Italian translation (Sarno et al., 2011) show adequate psychometric properties (Derogatis, 2011). The present study

TABLE 1 | Descriptive characteristics of each group.

	Sud group		Clinical groups		Healty group	
	M	***SD***	***M***	***SD***	***M***	***SD***
Age	19.40	1.25	17.93	1.44	18.70	1.24
	***N* (%)**		***N* (%)**		***N* (%)**	
Male	16 (53)		16 (47)		12 (40)	
Female	14 (46)		14 (53)		18 (60)	
Poli-abusers	(90)					
Heroin as primary drug of abuse	(63)					

is based on the SCL-90-R, since it can distinguish between clinical and non-clinical individuals via the cut-off score of the GSI.

Plan of Analysis

First, the TAS-20 scale scores were compared between the substance-dependent, referred clinical sample, and non-clinical control groups. One ANOVA model was computed for each TAS-20 subscale, controlling for participants' gender and age. Then, partial correlations between alexithymia and depressive symptomatology were computed, controlling for gender and age.

Results

Figure 1 shows the differences in TAS-20 scores between the groups. Controlling for age and gender, the effect of group was significant for Difficulty in Describing Feelings [$F_{(2,85)} = 3.19$, $p = 0.046$, $\eta_p^2 = 0.08$], Difficulty Identifying Feelings [$F_{(2,85)} = 5.17$, $p = 0.008$, $\eta_p^2 = .11$], and Global Scale [$F_{(2,85)} = 5.14$, $p = 0.008$, $\eta_p^2 = 0.11$] but not for Externally Oriented Thinking [$F_{(2,85)} = 2.84$, $p = 0.06$, $\eta_p^2 = 0.05$]. Two out of three significant results remained unaltered after Bonferroni correction for multiple comparisons (significance threshold, $p < 0.013$). The Difficulty in Describing Feelings scale did not survive the correction for multiple comparison. Post hoc comparison (Tukey contrasts) showed that the substance-dependent and non-clinical control groups differed on the Difficulty Describing Feelings scale ($b = 4.13$, 95% CI [0.58; 7.69], $p = 0.02$), but there was no difference between the substance-dependent and referred patient groups ($b = -0.63$, 95% CI [−4.19; 2.92], $p = 0.91$) as well as between non clinical controls and referred patients ($b = 3.50$, 95% CI [−0.06; 7.06], $p = 0.06$). For Difficulty Identifying Feeling, only the referred patient group

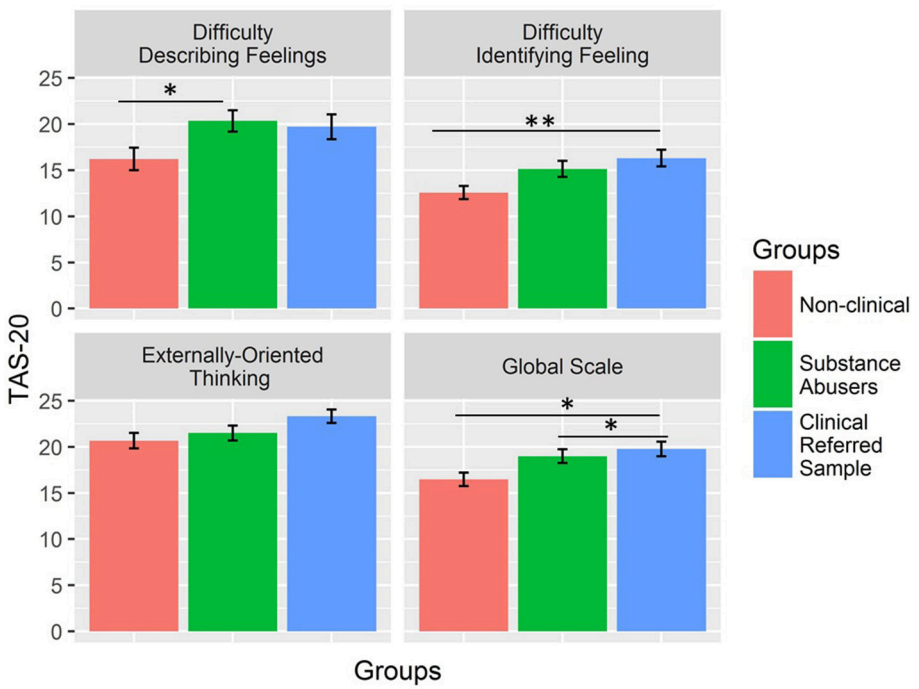

FIGURE 1 | TAS-20 differences between groups.*$p < 0.05$; **$p < 0.01$.

differed from the control group ($b = 3.73$, 95% CI [1.06; 6.41], $p = 0.004$) because there was no difference between the substance-dependent group and both the control ($b = 2.57$, 95% CI [−0.11; 5.24], $p = 0.06$) and referred patient groups ($b = 1.17$, 95% CI [−1.51; 3.84], $p = 0.55$). Finally, for the Global Scale, we found significant differences when comparing the substance-dependent ($b = 2.51$, 95% CI 0.21; 4.81], $p = 0.03$) and referred patient groups ($b = 3.29$, 95% CI 0.99; 5.59], $p = 0.003$) with the control groups, but no differences between them ($b = 0.78$, 95% CI [−1.52; 3.08], $p = 0.70$).

In the global sample, the partial correlation between alexithymia and depression, as measured by the SCL-90-R and controlling for gender and age, was $r_{(88)} = 0.45$, $p < 0.001$. The correlation was essentially the same in the substance abusers group, $r_{(28)} = 0.44$, $p = 0.01$.

STUDY 2

Materials and Methods

Participants

A total of 55 inpatients with SUD were involved in Study 2; in addition to those who participated to Study 1 ($N = 30$), 25 additional participants were included.

Inpatients were recruited from a therapeutic community (Villa Renata, Comunità di Venezia, Venice, Italy). The therapeutic community treatment model (De Leon et al., 2015), is based on a long-term residential and intensive approach that combines therapeutic and educational activities. Inpatients attend daily occupational, house-service, and recreational activities together with staff members, who offer monitoring and support to foster self-help learning. Weekly individual and group psychotherapy is provided, with the primary goal of changing the negative patterns of behavior, thinking, and feeling that predispose the individual to drug use as well as developing interpersonal skills and psychological wellbeing.

The participants (described in **Table 2**) fulfilled the following inclusion criteria: (a) met the DSM-5 (APA, 2013) criteria for SUD; (b) referred and admitted to the residential treatment community for less than 3 months; and (c) age ranging from 17 to 24 years. At recruitment, the participants had been abstinent for 2.83 months on average. Additionally, 46% overdosed from one to three times in the past, and 21% had a drug-related illness (hepatitis C). In relation to treatment, 40% of participants had previously attended an inpatient treatment but had not concluded it. At 1 year after admission, 49% of the participants dropped out from treatment, while 59% relapsed during the 12 months of treatment. These data are in line with previous studies, reporting dropout rates of 17–57% for residential treatment (Brorson et al., 2013) and relapse rates of 40–60% (McLellan et al., 2000).

Procedure and Instruments

This second study was carried out in accordance with the recommendations of the Code of Ethics approved by the General Assembly of the Italian Association as well as the Ethical Committee of University of Padua (protocol reference number: 2038). All patients provided written informed consent (parental, in the case of minors) to participate to the study.

The participants of Study 2 completed the TAS-20 at admission, and their individual treating psychologists completed the OAS after 8 to 12 weeks of treatment. After 1 year of residential treatment, or after dropout, the number of relapses was reported from the community registers.

- *The Observer Alexithymia Scale* (OAS; Haviland et al., 2000). The OAS is a 33-item observational scale to be completed by a subject's relative or acquaintance. The instrument was developed by asking clinicians to describe the prototypical characteristics of an alexithymic person. Items are rated on a 4-point scale and cover five alexithymic features: distant (being unskilled in intrapersonal and interpersonal issues), uninsightful, somatizing, humorless, and rigid. The reliability and validity of the OAS have been tested in both non-clinical (Haviland et al., 2000) and clinical samples (Haviland et al.,

TABLE 2 | Descriptive characteristics of SUD group.

INPATIENTS SUD GROUP			
Age	**Age**	***M***	***SD***
		21.10	2.15
		***N* (%)**	
Gender	Male	30 (54%)	
	Female	25 (45%)	
SES	Not attained an upper secondary educational qualification	33 (60%)	
	Unemployed	35 (63%)	
Past history	Had one or both parents presenting a past or current Substance Use Disorder	24 (43%)	
	Experienced maltreatment, sexual or physical abuse during childhood	34 (61%)	
Comorbidities	Psychiatric illness	16 (29%)	
Poly-drug use	Poly-drug use	47 (86%)	
Primary substance of abuse	Different synthetic drugs	46 (83%)	
	Cocaine	10 (18%)	
	Heroin	38 (69%)	
	Use of non-prescribed drugs	29 (53 %)	

2001; Thorberg et al., 2010). Adequate internal consistency, test-retest reliability and factorial validity emerged; moreover, total OAS scores differed significantly between the clinical and non-clinical groups (Haviland et al., 2001). Despite these results and its clinical utility, the OAS presents some limitations: some researchers (Meganck et al., 2010) have questioned its validity because of insufficient interrater reliability and problematic criterion validity (it seems that the OAS is based on a broader definition of alexithymia than the original one, including some characteristics that are correlates of alexithymia rather than constitutive dimensions).

Plan of Analysis

In different regression models controlling for gender and age, both self-report and observational measures of alexithymia were used as predictors for the number of relapses, number of dropouts from treatment, and the rates of relapse per month of treatment. We used the ratio between the number of relapses to months of treatment due to the high incidence of dropouts, which made the absolute number of relapses a potentially biased effect depending on the length of the hospitalization. Next, gender was added as a possible moderator of the association between alexithymia and outcome measures.

Results

Table 3 shows the partial correlations between observed and self-reported alexithymia after controlling for gender and age. **Table 4** presents all of the linear and logistic regression models used to test the role of alexithymia (both self-reported and observed) in predicting relapses and dropouts. For each model, the interaction effect gender*alexithymia is also provided. Since the interactions between gender and two scales of the OAS were significant in predicting the rate of dropouts per months of treatment, we computed simple slope analyses to explore these results, which are plotted in **Figure 2**. The effects of the OAS total score scale were positive and significant for males [$b = 0.01$, SE $= 0.005$, $t_{(44)} = 2.15$, $p = 0.04$] but not significant for females [$b = -0.006$, SE $= 0.003$, $t_{(44)} = -1.73$, $p = 0.09$]. Indeed, the same effect was found for the Distant scale, which was significant and positive for males [$b = 0.03$, SE $= 0.01$, $t_{(44)} = 2.60$, $p = 0.01$] but not significant for females [$b = -0.01$, SE $= 0.01$, $t_{(44)} = -1.04$, $p = 0.30$].

DISCUSSION

The present study contributes to the current debate on alexithymia, specifically concerning two controversial aspects: its associations with SUDs (i.e., in terms of prevalence and treatment predictivity) and some assessment issues, since the TAS-20 has received criticism, despite its worldwide use and validity.

Specificity of Alexithymia in Drug-Dependent Young Adults

The aim of Study 1 was to investigate whether late adolescents diagnosed with SUDs differ from late adolescent referred psychiatric outpatients and controls in levels of alexithymia, as measured by the TAS-20. On the basis of previous literature attesting that the TAS-20 can discriminate well between psychiatric patients and non-clinical youths (Kooiman et al., 2002; Marchesi et al., 2014), we hypothesized that drug-dependent and referred youth would show higher levels of alexithymia than controls. The results indicated that patients in both clinical groups, regardless of their specific disorder, presented higher TAS-20 scores than non-clinical subjects, but the clinical groups did not differ from each other. In considering the lack of difference between the two clinical groups, it is important to acknowledge that SUD populations show high rates of comorbidity and that our study only relied on the SCL-90-R. Our data resemble those of Marchesi et al. (2014), who compared different groups of adult patients (with major depression, panic disorder, eating disorder, and SUDs) and controls. Thus, despite numerous studies suggesting the presence of a specific link between alexithymia and addiction (i.e., as a risk factor), alexithymia might be non-univocally related to SUD nor to other distinct disorders. Instead, it could be associated with the broader concept of psychological distress, regardless of the symptomatological phenomenology. Consistent with this idea, Study 1 highlighted a large correlation between alexithymia and depressive symptoms. A vast body of literature shows that alexithymia is positively related to psychological distress in general and depressive and anxiety symptomatology (Haviland et al., 1991), and this association has also been detected when adopting the TAS-20 in non-clinical (Honkalampi et al., 2010; Deno et al., 2011), clinical (Marchesi et al., 2000) and SUD groups (Haviland et al., 1988a, 1991, 1994; Taylor et al., 1990; de Haan et al., 2011, 2012a; Morie et al., 2015). Recently, empirical support has been given to the notion that alexithymia, as measured by the TAS-20, may represent an issue with discriminant validity (Marchesi et al., 2014) and that the TAS-20 assesses a general psychological distress factor rather than identifying alexithymia itself (Leising et al., 2009).

Predictivity of Self-Report and Observed Alexithymia

Study 2 focused on a group of young adults diagnosed with SUD. First, it examined whether self-report and observational measures differ in the evaluation of alexithymia. Despite a wide consensus on the need to use a multi-method approach to assess alexithymia, such an approach is rarely achieved (Kooiman et al., 2002). In the present sample, clinician-rated alexithymia (by the OAS) was not correlated with self-report alexithymia (by TAS-20); our results are consistent with those of a previous study on adolescent substance-abusers that compared OAS and TAS-20 scores and indicated a lack of correspondence between the scores of the two assessment tools (Dorard et al., 2008a). As a whole, the adequacy of the TAS-20 in assessing alexithymia, as with other self-reports, appears to be questionable. This might particularly be the case for clinical groups characterized by low levels of self-reflective capacity, including such individuals with SUDs.

Contrary to expectations, neither self-reported nor observed alexithymia predicted the number of relapses, retention or dropout from treatment. Our results are in line with those

TABLE 3 | Partial correlations between self-reported and observed alexithymia measures controlling for gender and age.

	1	2	3	4	5	6	7	8	9	10
Difficulty identifying feelings (F1)										
Difficulty describing feelings (F2)	0.58***									
Externally Oriented Thinking (F3)	0.30*	0.38***								
TAS 20 Total	0.86***	0.83***	0.64***							
Distant	−0.05	−0.09	0.14	−0.02						
Uninsightful	0.24†	0.07	−0.01	0.15	0.37**					
Somatiazing	−0.01	−0.15	−0.07	−0.09	0.14	0.18				
Humorless	−0.01	0.13	0.26†	0.13	0.31*	0.43***	0.19			
Rigid	−0.33*	−0.11	−0.15	−0.27*	0.24†	0.26*	0.17	0.32*		
OAS Total	−0.01	−0.06	0.04	−0.02	0.72***	0.75***	0.5***	0.61***	0.57***	

$^{***}p < 0.001$; $^{**}p < 0.01$; $^{*}p < 0.05$; $^{\dagger}p < 0.1$.

of other empirical works indicating the lack of an association between alexithymia and abstinence, time in treatment and treatment adherence (Junghanns et al., 2005; de Haan et al., 2011, 2012b; Morie et al., 2015).

Different possible explanations can be given for these results. One explanation looks at alexithymia, its stability and its role as a vulnerability factor. As noted by de Haan and colleagues (de Haan et al., 2012a, 2014), alexithymia can be a vulnerability factor for substance use (and thus be reasonably addressed in treatment) only if it is a stable personality trait, but research results are conflicting regarding the stability of alexithymia. Studies support the idea that alexithymia is (at least partially) a state-related phenomenon (de Haan et al., 2012a, 2014). It has been conceived of as a secondary and situational response to negative affectivity, anxiety and depression (Haviland et al., 1988a; Pinard et al., 1996; Taylor et al., 1997; Honkalampi et al., 2000; de Timary et al., 2008; De Carli et al., 2017). Moreover, studies supporting the view of alexithymia as a structural trait in substance-dependent patients consider quite limited periods of time (Keller et al., 1995; Pinard et al., 1996; Rosenblum et al., 2005) or demonstrate its relative but not its absolute stability (de Timary et al., 2008; Thorberg et al., 2016). The state-dependent nature of alexithymia in drug-dependent individuals could explain why alexithymia measured at treatment intake is unrelated to events occurring later (by up to 1 year).

Second, in accordance to other authors (Cleland et al., 2005; Junghanns et al., 2005), the limited predictive capacity of alexithymia may depend on the fact that alexithymia may influence treatment outcomes only when interacting with other factors, such as negative affectivity, anxiety or depressive symptoms. Maybe the availability of more detailed measures of time (including when relapses and treatment dropouts occur), concurrent levels of alexithymia and negative affectivity could help to clarify the relation between alexithymia and treatment indexes.

Third, the lack of association can be explained by the fact that dropout and relapse might depend on different and/or multiple factors, rather than single variables. To date, there is a general lack of consistency in these predictors across studies. A number of factors have shown no or minimal predictivity for treatment retention, including demographic variables (gender, socioeconomic status, employment, and education). The most consistent risk factors for dropout include cognitive deficits, weak treatment alliance, personality disorders, younger age (Brorson et al., 2013), and client motivation (Ball et al., 2006; Palmer et al., 2009). Regarding relapses, investigators have identified some risk factors, like severity of SUD and its sequelae, psychiatric comorbidity, family history of SUDs, stressors, and coping. Importantly, the most reliable predictive models of relapses and dropout take into account a multitude of predictors and their interactions (Bradizza et al., 2006; Moos and Moos, 2006; Brorson et al., 2013; Brecht and Herbeck, 2014).

Finally, methodological issues regarding the assessment measures, sample characteristics, and type of treatment have been pointed to the lack of a strong association between alexithymia and outcomes (Cleland et al., 2005). Regarding treatment, alexithymia may exert a different degree of influence on treatment success by treatment approach (de Haan et al., 2012b; Morie et al., 2015). However, the available results are highly preliminary and limited; thus, conclusions on the relationship between alexithymia and treatment type cannot be drawn.

At an exploratory level, we tested the moderating role of gender on the association between alexithymia and treatment outcomes. The interaction effects between gender and two of the subscales for observed alexithymia were significant. Specifically, the global score and the Distant factor predicted the number of relapses in males but not in females. The effect of the global score seems to be driven by the Distant subscale. This factor describes an avoidant style toward relationships and inner states, and probably toward the treatment alliance too. Due to the explorative nature of the investigation, interpretations should be made extremely carefully. However, future studies could focus on the relevance of avoidant behaviors between males but not females in the quality of treatment outcomes. It is possible that the presence of avoidant strategies is more risky for men than for women, probably because it could be more closely related to impulsive behaviors. Such a finding, even if presented for the first time, has similar results in previous literature, such as a moderating effect of gender in

TABLE 4 | Regression models to test alexithymia predictive ability.

	Linear regressions				Logistic regressions				Linear regressions			
	Relapses		Relapses		Drop-out		Drop-out		Relapses/Months		Relapses/Months	
	b	*t*	*b*	*t*	*b*	z val	*b*	z val	*b*	*t*	*b*	*t*
OAS: Distant	0.02	0.60	0.10	1.83†	−0.04	−0.50	0.07	0.70	0.01	1.05	0.02	2.54**
Gender	0.11	0.33	0.08	0.24	−0.43	−0.74	−0.49	−0.82	−0.01	−0.19	−0.02	−0.33
Age	0.10	1.36	0.11	1.48	0.06	0.42	0.07	0.50	0.02	1.34	0.02	1.51
Distant *Gender			−0.16	−2.05*			−0.25	−1.57			−0.03	−2.56**
R^2	0.05		0.13						0.07		0.19*	
Model Confrontation	$F_{(1, 50)} = 4.21, p < 0.05$				$\chi^2_{(1)} = 2.69, p > 0.05$				$F_{(1, 50)} = 6.57, p < 0.01$			
OAS: Unisightful	−0.01	−0.36	0.06	0.91	−0.05	−0.67	−0.06	−0.56	0.00	−0.30	0.01	1.17
Gender	0.10	0.30	0.14	0.43	−0.37	−0.64	−0.38	−0.66	−0.02	−0.26	−0.01	−0.12
Age	0.11	1.39	0.12	1.61	0.05	0.37	0.05	0.34	0.02	1.38	0.02	1.66†
Unisightful *Gender			−0.12	−1.48			0.03	0.18			−0.03	−1.77†
R^2	0.05		0.09						0.04		0.11	
Model Confrontation	$F_{(1, 50)} = 2.18, p > 0.05$				$\chi^2_{(1)} = 0.03, p > 0.05$				$F_{(1,50)} = 3.14, p = 0.08$			
OAS: Somatizing	−0.02	−0.33	0.17	1.54	−0.01	−0.05	0.00	−0.02	−0.01	−0.65	0.02	0.86
Gender	0.15	0.39	−0.01	−0.02	−0.39	−0.60	−0.39	−0.59	0.00	0.04	−0.02	−0.26
Age	0.11	1.39	0.10	1.32	0.05	0.38	0.05	0.38	0.02	1.38	0.02	1.31
SOM*Gender			−0.27	−2.03*			0.00	−0.01			−0.03	−1.42
R^2	0.05		0.13						0.05		0.09	
Model Confrontation	$F_{(1, 50)} = 4.11, p < 0.05$				$\chi^2_{(1)} = 0.01, p > 0.05$				$F_{(1, 50)} = 2.03, p > 0.05$			
OAS: Humorless	0.04	0.37	0.19	1.51	0.02	0.13	0.18	0.78	0.00	0.15	0.02	1.04
Gender	0.08	0.24	0.14	0.42	−0.41	−0.70	−0.36	−0.62	−0.02	−0.30	−0.01	−0.17
Age	0.11	1.43	0.13	1.76†	0.05	0.40	0.08	0.56	0.02	1.39	0.02	1.63
Humorless *Gender			−0.43	−2.05*			−0.46	−1.15			−0.06	−1.57
R^2	0.05		0.13						0.04		0.09	
Model Confrontation	$F_{(1, 50)} = 4.22, p < 0.05$				$\chi^2_{(1)} = 1.38, p > 0.05$				$F_{(1, 50)} = 2.48, p > 0.05$			
OAS: Rigid	−0.09	−1.43	−0.05	−0.65	−0.15	−1.23	0.00	0.03	−0.01	−1.08	0.00	−0.27
Gender	0.05	0.15	0.04	0.12	−0.49	−0.83	−0.60	−0.96	−0.02	−0.39	−0.02	−0.42
Age	0.14	1.75†	0.14	1.80†	0.10	0.71	0.14	0.94	0.02	1.63	0.02	1.72†
RIG*Gender			−0.07	−0.60			−0.37	−1.47			−0.02	−0.79
R^2	0.08		0.09						0.07		0.08	
Model Confrontation	$F_{(1, 50)} = 0.36, p > 0.05$				$\chi^2_{(1)} = 2.41, p > 0.05$				$F_{(1, 50)} = 0.62, p > 0.05$			

(Continued)

TABLE 4 | Continued

	Linear regressions				Logistic regressions				Linear regressions			
	Relapses		Relapses		Drop-out		Drop-out		Relapses/Months		Relapses/Months	
	b	*t*	*b*	*t*	*b*	z val	*b*	z val	*b*	*t*	*b*	*t*
OAS: Total	0.00	−0.30	0.04	1.77†	−0.02	−0.79	0.01	0.30	0.01	−0.14	0.01	2.08*
Gender	0.10	0.31	0.10	0.33	−0.35	−0.60	−0.36	−0.60	−0.02	−0.27	−0.02	−0.29
Age	0.11	1.41	0.13	1.74†	0.06	0.44	0.07	0.54	0.02	1.39	0.02	1.77†
OAS_tot*Gender			−0.08	−2.52*			−0.06	−1.02			−0.02	−2.78**
R^2	0.04		0.17†						0.04		0.19†	
Model Confrontation	$F_{(1, 50)} = 6.37, p > 0.05$				$\chi^2_{(1)} = 1.05, p > 0.05$				$F_{(1, 50)} = 7.75, p > 0.05$			
TAS: Difficulty identifying feelings	−0.02	−0.75	−0.04	−1.07	−0.02	−0.38	−0.07	−0.99	0.00	−0.47	−0.01	−0.87
Gender	0.14	0.42	0.11	0.33	−0.36	−0.61	−0.44	−0.73	−0.01	−0.19	−0.02	−0.27
Age	0.10	1.31	0.11	1.44	0.05	0.34	0.08	0.57	0.02	1.33	0.02	1.46
TAS*Gender			0.04	0.77			0.10	1.02			0.01	0.76
R^2	0.05		0.07						0.05		0.06	
Model Confrontation	$F_{(1, 50)} = 0.59, p > 0.05$				$\chi^2_{(1)} = 1.08, p > 0.05$				$F_{(1, 50)} = 0.58, p > 0.05$			
TAS: Difficulty communicating feelings	−0.03	−0.84	−0.04	−0.83	−0.03	−0.57	−0.08	−0.89	−0.01	−1.99*	−0.02	−2.31*
Gender	0.19	0.54	0.17	0.49	−0.29	−0.47	−0.35	−0.56	0.02	0.38	0.01	0.23
Age	0.1	1.32	0.1	1.34	0.05	0.33	0.06	0.43	0.02	1.26	0.02	1.41
F2_tot*Gender			0.02	0.32			0.09	0.07			0.01	1.22
R^2	0.06		0.06						0.12		0.15	
Model Confrontation	$F_{(1, 50)} = 0.1, p > 0.05$				$\chi^2_{(1)} = 0.50, p > 0.05$				$F_{(1, 50)} = 1.50, p > 0.05$			
TAS: Externally oriented thinking	−0.03	−0.78	−0.04	−0.68	0.03	0.50	0.00	0.02	−0.01	−1.01	−0.01	−1.36
Gender	0.08	0.26	0.08	0.25	−0.40	−0.69	−0.40	−0.69	−0.02	−0.32	−0.02	−0.32
Age	0.09	1.12	0.09	1.12	0.07	0.51	0.08	0.58	0.01	1.05	0.02	1.16
TAS*Gender			0.01	0.15			0.07	0.54			0.01	0.91
R^2	0.06		0.06						0.06		0.08	
Model Confrontation	$F_{(1, 50)} = 0.02, p > 0.05$				$\chi^2_{(1)} = 0.30, p > 0.05$				$F_{(1, 50)} = 0.82, p > 0.05$			
TAS: Total	−0.01	−1.00	−0.03	−1.24	−0.25	0.80	−0.04	−0.95	0.00	−1.37	−0.01	−2.06
Gender	0.17	0.50	0.15	0.45	−0.62	0.53	−0.42	−0.70	0.00	0.03	0.00	−0.06
Age	0.09	1.19	0.10	1.30	0.33	0.74	0.07	0.51	0.01	1.12	0.02	1.38
TAS*Gender			0.02	0.78			0.05	1.05			0.01	1.52
R2	0.06		0.08						0.08		0.13	
Model Confrontation	$F_{(1, 50)} = 0.61, p > 0.05$				$\chi^2_{(1)} = 1.05, p > 0.05$				$F_{(1, 50)} = 2.30, p > 0.05$			

***$p < 0.001$; ** $p < 0.01$; *$p < 0.05$; †$p < 0.1$.

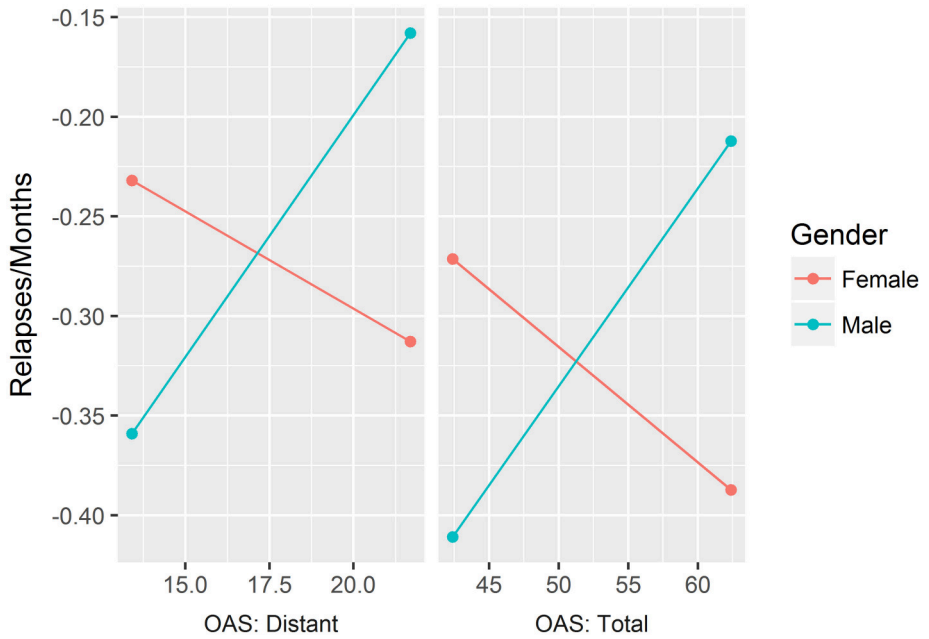

FIGURE 2 | Simple slope analyses of the effects of 2 OAS scales (i.e, Distant and Total) on the rate of relapses per month.

the association between hostility and treatment termination (Petry and Bickel, 2000). The study of moderators of risk factors for treatment dropout is extremely relevant to foster tailored interventions (Brorson et al., 2013) and deserves future attention.

In conclusion, the present study suggests that alexithymia, as measured by the TAS-20, does not distinguish young inpatients with SUDs from referred patients and controls—it only differentiates between clinical and non-clinical groups. As recent empirical studies have proposed, alexithymia might be more associated with negative affectivity or psychological distress, rather than characterizing distinct disorders. These results, together with the lack of correspondence between the TAS-20 and the OAS observational scale, raise doubts on the validity of alexithymia being measured by self-reports. Finally, the limited ability of both observed and self-reported measures in predicting treatment dropout and relapses highlights the need for more complex predictive models in treatment research.

Despite some strengths, such as the multi-method assessment of alexithymia, addressing substance abuse at a specific age (young adulthood) and adopting a wide window of time (1 year), the research shows some limitations. First of all, the relatively small samples involved suggest caution in interpreting the results, particularly the lack of effects of alexithymia in predicting treatment outcomes. In addition, the prediction of outcomes was limited to 1 year of treatment, meaning that no inferences can be made on long-term results of the intervention. In addition, no assessment of symptom severity was available. Furthermore, the lack of systematic biochemical analyses to confirm abstinence/relapses must be acknowledged. Also, with regard to the comparison group of referred patients in Study 1, the participants were not affected by a specific psychiatric disorder but presented heterogeneous diagnoses. Another difference with the SUD group was the condition of being outpatients, instead of inpatients, which is likely to be associated with diminished illness severity. In addition, observed alexithymia was not assessed in the nonclinical or referred samples, since it was not possible to identify observers who were comparable to the therapists for the SUD group. Finally, as already mentioned, the predictivity of alexithymia was analyzed by taking single factors into consideration, rather than multiple variables.

Future studies should try to extend the observational measure of alexithymia to other disorders to explore whether the lack of correlation with the TAS-20 is specific to SUDs. In addition, future perspectives could try to replicate the moderating effect of gender on the association between alexithymia and treatment outcome. Also, not only can observers' ratings of alexithymia improve our understanding of the concept, but so can integration with other fields of study, such as family functioning (Gatta et al., 2017), endocrine functioning (Riem et al., 2017), and brain activity (De Carli et al., 2018).

AUTHOR CONTRIBUTIONS

MP, MM, PD, PC, MG, and AS have given a substantial contribution to the conception and implementation of the work, taking part to data acquisition, analysis and discussion, drafting, and revising the manuscript. All authors revised and reached an agreement on the final version of the work.

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Alexithymia Components Are Differentially Related to Explicit Negative Affect But Not Associated with Explicit Positive Affect or Implicit Affectivity

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Alexithymia represents a multifaceted personality construct defined by difficulties in recognizing and verbalizing emotions and externally oriented thinking. According to clinical observations, experience of negative affects is exacerbated and experience of positive affects is decreased in alexithymia. Findings from research based on self-report indicate that all alexithymia facets are negatively associated with the experience of positive affects, whereas difficulties identifying and describing feelings are related to heightened negative affect. Implicit affectivity, which can be measured using indirect assessment methods, relates to processes of the impulsive system. The aim of the present study was to examine, for the first time, the relations between alexithymia components and *implicit* and *explicit* positive and negative affectivity in healthy adults. The 20-item Toronto Alexithymia Scale, the Implicit Positive and Negative Affect Test and the Positive and Negative Affect Schedule (PANAS) were administered to two hundred and forty-one healthy individuals along with measures of depression and trait anxiety. Difficulties identifying feelings were correlated with explicit negative trait affect, depressive mood and trait anxiety. Difficulties describing feelings showed smaller but also significant correlations with depressive mood and trait anxiety but were not correlated with explicit state or trait affect as assessed by the PANAS. Externally oriented thinking was not significantly correlated with any of the implicit and explicit affect measures. According to our findings, an externally oriented, concrete way of thinking appears to be generally unrelated to dispositions to develop positive or negative affects. Difficulties identifying feelings seem to be associated with increased conscious negative affects but not with a heightened disposition to develop negative affects at an automatic response level.

Keywords: alexithymia, 20-Item Toronto-Alexithymia Scale, explicit affect, implicit affect, Implicit Positive and Negative Affect Test

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INTRODUCTION

Alexithymia is a cognitive-affective disturbance that is characterized by impairments in the experience, regulation and communication of emotions (Nemiah and Sifneos, 1970; Taylor and Bagby, 2000). The alexithymia construct emerged following attempts of clinicians to specify the emotional deficits of psychosomatic patients (Ruesch, 1948; Sifneos, 1973). These patients showed an unawareness of feelings or an incapacity to put into words what they were experiencing. Their associations were characterized by an absence of fantasy and a detailed recounting of circumstances and events in their environment (Nemiah and Sifneos, 1970). Alexithymia is best conceptualized as a dimensional personality trait and not as a categorical all-or-none phenomenon (Parker et al., 2008). Currently, the predominant measure of alexithymia is a self-report instrument, the 20-Item Toronto Alexithymia Scale (TAS-20, Bagby et al., 1994a), a questionnaire with satisfactory psychometric properties (Parker et al., 2003). The TAS-20 does not assess all facets of alexithymia but is focused on three main features of alexithymia: difficulties in recognizing and verbalizing emotions and an externally oriented thinking style (Taylor and Bagby, 2004). Patients with mental disorders such as panic disorder (De Berardis et al., 2007), somatoform disorders (Waller and Scheidt, 2004) or autistic disorders (Berthoz and Hill, 2005) show frequently high degrees of alexithymia.

It is an important question whether individuals who have problems in identifying and describing emotions experience less or more emotions in their everyday lives or show no apparent deviations in the frequency of experiencing emotions compared to individuals without these difficulties. It is possible, for example, that individuals who develop less frequently and weaker reactions of happiness in everyday life may tend to talk less about their positive feelings and describe more situational details or their concrete actions which are more salient to them compared to individuals with frequent and strong positive emotions. Early in alexithymia research, based on clinical observations it was hypothesized that alexithymic individuals manifest tendencies to experience more negative affects and less positive affects so that they were also described as anhedonic (Sifneos, 1987; Bagby and Taylor, 1997).

Typically, state (actual) and trait (habitual) affects are measured by means of self-report questionnaires. The Positive and Negative Affect Schedule (PANAS; Watson et al., 1988) assessing the intensity or frequency of experience of positively and negatively valenced affects has been repeatedly administered to assess state and trait affectivity as a function of alexithymia. As expected, in a sample of university students alexithymic individuals were found to endorse more negative trait affects and less positive trait affects than non-alexithymic individuals (Parker and Taylor, 1997). In a correlational study based on a community sample ($n = 137$), the total score of the TAS-20 showed positive correlations of small to medium sizes with trait measures of negative affect and negative correlations of medium to large effect sizes with trait measures of positive affect (Lundh and Simonsson-Sarnecki, 2001). In a large sample ($n = 377$) of patients presenting to primary care physicians with physical symptoms (de Gucht et al., 2004), all TAS-20 scales showed negative correlations of (small to) medium size with positive state affect. Moreover, difficulties identifying ($r = 0.51$) and describing feelings ($r = 0.20$) (but not externally oriented thinking) were associated with negative state affect. In a sample of university students ($n = 175$), difficulties identifying and describing feelings, and externally oriented thinking showed negative correlations of medium size with positive state affect and only difficulties identifying feelings ($r = 0.21$) and the TAS total score ($r = 0.18$) correlated significantly (positively) with negative state affect (Swinkels and Giuliano, 1995, study 3). However, Palmer et al. (2002) found in a general community sample ($n = 107$) only small and non-significant negative correlations between TAS-20 scales and positive affect and only a significant correlation of difficulties identifying feelings with negative affect ($r = 0.46$) (PANAS: reference period of the affect rating was the last month). In a rather large mixed sample of older adults from the general population and university students ($n = 248$), Henry et al. (2006) observed a negative correlation with positive affect only for difficulties identifying feelings ($r = -0.21$) whereas difficulties identifying feelings and difficulties describing feelings were positively correlated with negative affect ($r = 0.25$ and 0.37). In the latter study, externally oriented thinking showed a small but significant negative correlation with negative affect ($r = -0.15$) (PANAS: reference period of the affect rating here was the last week). Overall, there is evidence that the alexithymia components difficulties identifying and describing feelings and externally oriented thinking are negatively related to experiences of positive affect and that primarily difficulties identifying feelings and secondarily difficulties describing feelings are associated with experiences of negative affect. Considering that in healthy subjects positive affects are experienced far more frequently and intensely than negative affects (Zelenski and Larsen, 2000; Myrtek et al., 2005) reduced feeling of positive affects should be given more weight when examining the affective deviations in alexithymia.

Previous research on emotions in alexithymia has focused primarily on negative emotional conditions. There is ample evidence across patient and general population samples for medium relationships between difficulties identifying and describing feelings with depressive mood. In contrast, the alexithymia component externally oriented thinking shows no or only small correlations with depressive symptoms (see Li et al., 2015, for a meta-analysis). Moreover, there are findings indicating large correlations between difficulties identifying and difficulties communicating feelings and trait anxiety but no correlations between externally oriented thinking and trait anxiety (Hendryx et al., 1991; Berthoz et al., 1999). The above-mentioned results based mainly on self-report or direct measures of emotions suggest a differential association between alexithymia components and negative affect.

When direct assessment procedures such as the PANAS are administered conscious affective experiences are reported which has been termed *explicit affect*. Explicit affect is assumed to build on propositionally organized memory that is subject to conscious reflections (Quirin et al., 2009a). Instead, *implicit affect* relates to processes of the impulsive system and represents

automatic activations of cognitive representations of affective experiences. The impulsive system is thought to elicit behavior through associative links and motivational orientations (Strack and Deutsch, 2004). The Implicit Positive and Negative Affect Test (IPANAT) has been constructed to assess implicit affectivity (Quirin et al., 2009a). In this indirect test, the extent of fit between mood adjectives and nonsense words has to be rated. The IPANAT is a reliable instrument for the measurement of implicit affect and captures much variance from a stable psychological disposition (Quirin and Bode, 2014). Differential patterns of correlations with concurrently administered explicit and implicit tests suggest strong convergent and discriminant validity of the IPANAT (Quirin et al., 2009a; study 3). The IPANAT has been translated now into more than 10 languages and has found wide distribution (Quirin et al., 2016).

The IPANAT predicts spontaneous psycho-physiological reactions, above and beyond self-reported affectivity. Implicit positive affect predicted low cortisol levels in everyday life (Mossink et al., 2015). Furthermore, low implicit positive affect was found to be associated with circadian cortisol release and high implicit negative affectivity was found to be related to cortisol response to acute stressors (Quirin et al., 2009b). Recently, implicit affectivity measured by the IPANAT was associated with cardiovascular activity during and after stressful tasks (van der Ploeg et al., 2016). Finally, implicit negative affect predicted neural activation in response to threat, in brain areas responsible for fear and flight behavior (Suslow et al., 2015). Thus, it seems that the IPANAT is useful in gathering information on dispositions to affective reactions in the absence of conscious self-reflection. Against this background, it is quite possible that explicit affect scores are less informative about spontaneous affective responsivity and experiences than implicit affect scores.

The aim of our study was to examine, for the first time, implicit and explicit positive and negative affectivity as a function of alexithymia in healthy adults. For this purpose, we administered the IPANAT and state and trait versions of the PANAS as well as measures of depressed mood and trait anxiety. Based on previous research with the PANAS, it was hypothesized that all alexithymia components would be negatively correlated with measures of positive affect. Moreover, it was expected that the alexithymia features difficulties identifying feelings and difficulties describing feelings would be positively correlated with measures of negative affect. In the light of the foregoing considerations, it could be derived that the alexithymia facet externally oriented thinking is not related to negative affect but negatively associated to positive affect. That is, individuals high on externally oriented thinking might be characterized by a decreased disposition to develop positive emotions. In contrast, especially the alexithymia component difficulties identifying feelings appears to come along with an increased disposition to develop negative emotions. We expected that the healthy individuals in our study would report more positive state and trait affect than negative state and trait affect. Moreover, it was hypothesized that our subjects would manifest more implicit positive affect than implicit negative affect. We controlled verbal intelligence of participants because it has been found to be associated with alexithymia (e.g., Lamberty and Holt, 1995; Montebarocci et al., 2011).

MATERIALS AND METHODS

Participants

Two hundred and forty-one volunteers (192 women) with a mean age of 24.76 years (*SD*: 3.85) and a mean school education of 12.37 years (*SD*: 0.75) participated in the present study. All participants were native German speakers. They were free of any lifetime history of psychiatric or neurological disorders. According to self-report all participants did not use psychotropic medication. Participants were recruited via public notices. Notices with a short description of the study, the exclusion criteria and a contact telephone number were posted in several locations on the campus of the University (e.g., libraries and canteens). More than 92% of participants were university students from various disciplines.

Men did not differ from women on any of the variables examined in our study (i.e., alexithymia components, affect scores (IPANAT, PANAS, BDI-II and STAI), verbal intelligence, and education), except age. Men (mean age: 26.53; *SD*: 3.70) were about 2 years older than women (mean age: 24.31; *SD*: 3.77) [$t(239) = 3.70$, $p < 0.001$].

The present study was carried out according to the Declaration of Helsinki (World Medical Association, 2013). Written informed consent was obtained from all study participants prior to data collection. The study was approved by the competent ethics committee of the Medical Faculty at the University of Leipzig.

Psychometric Instruments

Alexithymia was measured by the 20-Item Toronto-Alexithymia Scale (TAS-20; German version: Bach et al., 1996). The TAS-20 consists of three subscales: Difficulties identifying feelings (DIF; consisting of 7 items), Difficulties describing feelings (DDF; consisting of 5 items), and Externally oriented thinking (EOT; consisting of 8 items). Items are rated on a 5-point Likert scale (from 1 = "strongly disagree" to 5 = "strongly agree"). Validation studies have revealed adequate convergent and discriminant validity, internal consistency, and reliability for the TAS-20 (Bagby et al., 1994a,b; Parker et al., 2003). In the present sample, mean scores for Difficulties identifying feelings, Difficulties describing feelings, Externally oriented thinking, and the total scale were 14.32 ($SD = 4.67$), 11.48 ($SD = 3.84$), 15.62 ($SD = 4.00$), and 41.42 ($SD = 9.03$), whereas Cronbach's alphas for the scales were 0.79, 0.75, 0.62, and 0.79 (which were very similar to the coefficients reported by Bagby et al. (1994a) for a sample of university students: 0.79, 0.75, 0.66, and 0.80).

The *Implicit Positive and Negative Affect Test* (IPANAT, Quirin et al., 2009a) was applied to assess implicit positive and negative affectivity. The IPANAT measures affect indirectly by asking to evaluate to what extent artificial words express certain moods. Six artificial words (e.g., TALEP and VIKES) are presented along with three positive (happy, cheerful, and energetic) and three negative mood words (inhibited, helpless, and tense). Assessments are made on a 4-point scale [from 1 (*doesn't fit at all*) to 4 (*fits very well*)]. Factor analysis has yielded two orthogonal factors that can be interpreted as positive affect and negative affect (Quirin et al., 2009a, 2016). For each scale, Cronbach's alphas were found to be

above.80, whereas 1-year test-retest reliability was about 0.60. The latter finding suggests that the IPANAT captures much variance from a stable affective disposition. In our study, the mean item score for the IPANAT-PA was 2.33 (*SD*: 0.33) and that for the IPANAT-NA was 1.88 (*SD*: 0.46). These IPANAT scores were very similar to those reported previously for German university students (Quirin et al., 2009a). In the present study, Cronbach's alpha was 0.79 for implicit PA and 0.76 for implicit NA.

The Positive and Negative Affect Schedule (PANAS; German version: Krohne et al., 1996) was administered to measure state and trait positive affect (PA) and negative affect (NA). The PANAS consists of 10 negative and 10 positive mood questions, rated on a five-point scale (1 = not at all, 5 = extremely). The mean PANAS-PA trait score was 36.67 (*SD*: 5.35) and the mean PANAS-NA trait was 16.29 (*SD*: 5.01) in our sample. Moreover, the mean PANAS-PA state was 33.84 (*SD*: 5.91) and the mean PANAS-NA state was 13.21 (*SD*: 3.96). In our study, Cronbach's alpha was 0.74 for the PANAS-PA S (state) and 0.79 for the PANAS-NA S. Moreover, Cronbach's alpha was 0.81 for the PANAS-P T (trait) and 0.85 for the PANAS-NA T.

Depressed mood and trait anxiety were measured by administering the Beck-Depression Inventory (BDI-II; German version: Hautzinger et al., 2009) and the State-Trait-Anxiety Inventory trait version (STAI; German version: Laux et al., 1981). In our sample, the mean BDI-II score was 7.08 ($SD = 4.99$) and the mean STAI-Trait score was 38.06 ($SD = 9.00$). Cronbach's alpha was 0.79 for the BDI-II and 0.88 for the STAI in our sample.

Verbal intelligence was assessed by means of the Mehrfachwahl-Wortschatz-Intelligenztest (MWT-B), a multiple-choice test using artificial and existent vocabulary of the German language (Lehrl, 2005). The MWT-B consists of 37 items and has no time restrictions. In our sample, the mean MWT-B IQ-score was 113.49 ($SD = 11.31$).

Statistical Analyses

If not otherwise stated, statistical data analyses were conducted by means of the Statistical Package for the Social Sciences (SPSS), version 24.0. Paired samples *t*-tests were conducted to determine differences between positive and negative affect as assessed by implicit (IPANAT) and explicit affectivity measures (PANAS state and PANAS trait). In these *t*-tests a Bonferroni-corrected statistical significance threshold of $p < .017$ was applied ($\alpha = 0.05/3$). Product-moment correlation analyses were performed to investigate the relationships between implicit and explicit affectivity and the associations of alexithymia with implicit and explicit affectivity, verbal intelligence, education, and age. Since the correlations of alexithymia scores (Difficulties identifying feelings, Difficulties describing feelings, Externally oriented thinking and TAS-20 total score) with implicit and explicit (positive and negative) affectivity (IPANAT-PA, IPANAT-NA, PANAS-S PA, PANAS-S NA, PANAS-T PA and PANAS-T NA), depression (BDI-II), trait anxiety (STAI), verbal intelligence (MWT-B), education and age were central in the present paper and included in total 44 calculations we administered a Bonferroni-corrected statistical significance threshold of $p < 0.001$ in the correlational analyses [$\alpha = 0.05/(4 \times 11) = 0.0011$]. Steiger's Z-test was used to compare (significant) correlation coefficients (applying formulas as implemented in Lee and Preacher (2013)). Partial correlation analysis was conducted to illustrate the correlation between an alexithymia component and an affect score when other relevant alexithymia components were controlled.

General Procedure

At the beginning of the study, demographic data were registered and participants were given the TAS-20, MWT-B, IPANAT, PANAS-S, BDI-II, STAI, and PANAS-T in a fixed order. Participants were tested individually and received a financial compensation for taking part in the study.

RESULTS

Relationships between Implicit and Explicit Affectivity

In our sample, implicit negative affect did not correlate with explicit positive and negative affectivity (trait or state) as assessed by the PANAS, depressive mood (BDI-II), or trait anxiety (STAI-T). Implicit positive affect was only found to be correlated with explicit positive trait affect ($r = 0.22$; $p \leq 0.001$).

Comparison between Positive and Negative Affect As Assessed by IPANAT and PANAS State and Trait

According to the results of dependent *t*-tests, study participants had higher implicit positive than implicit negative affect scores [$t(240) = 12.97$, $p < 0.001$]. Moreover, participants reported more explicit positive state affect than explicit negative state affect [$t(240) = 44.94$, $p < 0.001$] and more explicit positive trait affect than explicit negative trait affect [$t(240) = 41.85$, $p < 0.001$].

Relationships between Alexithymia Scores

As could be expected, the total score of the TAS-20 showed significant correlations with all TAS-20 subscales (Difficulties identifying feelings: $r = 0.74$, $p < 0.001$; Difficulties describing feelings: $r = 0.82$, $p < 0.001$; Externally oriented thinking: $r = 0.61$; $p < 0.001$). The alexithymia component Difficulties identifying feelings was significantly correlated with Difficulties describing feelings ($r = 0.47$; $p < 0.05$) but not with Externally oriented thinking: $r = 0.05$; $p = 0.46$). Finally, Difficulties describing feelings was significantly correlated with Externally oriented thinking: $r = 0.33$; $p < 0.001$).

Relationships of Alexithymia Scores with Implicit and Explicit Affectivity

Product-moment correlation analysis showed significant positive correlations of Difficulties identifying feelings with explicit negative trait affect (PANAS), depressive mood (BDI-II) and trait anxiety (STAI) (see **Table 1**). The alexithymia component Difficulties describing feelings was significantly positively

correlated with depressive mood (BDI-II) and trait anxiety (STAI).

According to Steiger's *Z*-tests the correlation coefficient of Difficulties identifying feelings and depression was significantly higher than that of Difficulties describing feelings and depression ($Z = 3.08$, $p < 0.01$). Moreover, the correlation between Difficulties identifying feelings and trait anxiety was significantly higher than that between Difficulties describing feelings and trait anxiety ($Z = 4.44$, $p < 0.001$). The correlations of Difficulties identifying feelings with depression and trait anxiety remained significant when adjusting for Difficulties describing feelings ($r_p = 0.36$ and $r_p = 0.44$; $ps < 0.001$). However, the correlations of Difficulties describing feelings with depression and trait anxiety became non-significant when controlling for Difficulties identifying feelings ($r_p = 0.03$ and $r_p = -0.02$).

Externally oriented thinking was not significantly correlated with any of the implicit and explicit affect measures. All correlations coefficients of Externally oriented thinking with implicit and explicit affect were negative (but non-significant) (see **Table 1** for details). The total score of the TAS-20 was found to be significantly positively correlated with explicit negative trait affect, depressive mood and trait anxiety.

Relationships of Alexithymia Scores with Intelligence, Age and Education

Product-moment correlation analysis showed no significant correlations between Difficulties identifying feelings, Difficulties describing feelings, Externally oriented thinking and the total TAS-20 score on the one hand and verbal intelligence on the other hand. There were also no significant correlations of alexithymia scores with age and years of school education (see **Table 1** for details).

TABLE 1 | Product moment correlations between alexithymia components (20-Item Toronto Alexithymia Scale) and implicit and explicit affectivity measures, intelligence, education and age (N = 241).

Variable	DIF	DDF	EOT	TS
IPANAT-PA	−0.02	−0.03	−0.02	−0.03
IPANAT-NA	0.03	0.00	−0.02	0.01
PANAS-S PA	0.00	−0.03	−0.12	−0.07
PANAS-S NA	0.19	0.07	−0.08	0.09
PANAS-T PA	−0.08	−0.06	−0.06	−0.10
PANAS-T NA	0.38***	0.11	−0.03	0.23*
Depression (BDI-II)	0.41***	0.22*	−0.10	0.26**
Trait anxiety (STAI trait)	0.48***	0.23*	−0.09	0.29***
Intelligence (MWT-B IQ)	−0.18	−0.14	−0.07	−0.18
Education	−0.03	0.00	−0.04	−0.03
Age	−0.19	−0.13	0.00	−0.15

*$p \leq 0.001$ (two-tailed), **$p \leq 0.0001$ (two-tailed), ***$p \leq .00001$ (two-tailed). DIF, Difficulties Identifying Feelings scale; DDF, Difficulties Describing Feelings scale; EOT, Externally Oriented Thinking scale; TS, Total score of the 20-Item Toronto-Alexithymia Scale; IPANAT-PA, Positive affect scale – Implicit Positive and Negative Affect Test; IPANAT-NA, Negative affect scale – Implicit Positive and Negative Affect Test; PANAS-S PA, Positive affect scale of the Positive and Negative Affect Schedule state version; PANAS-S NA, Negative affect scale of the Positive and Negative Affect Schedule state version; PANAS-T PA, Positive affect scale of the Positive and Negative Affect Schedule trait version; PANAS-T NA, Negative affect scale of the Positive and Negative Affect Schedule trait version; BDI-II, Beck-Depression Inventory; STAI-trait, State-Trait Anxiety Inventory, trait version; MWT-B IQ, intelligence quotient as assessed by the Mehrfach-Wahl-Intelligenztest version B.*

DISCUSSION

The primary aim of the present study was to investigate the relationship of the personality trait alexithymia with implicit and explicit positive and negative affectivity in healthy adults. We applied an indirect (IPANAT) and direct tests (PANAS, BDI-II and STAI) to assess implicit and explicit affectivity in a sample of young adults and conducted correlation analyses for all alexithymia components of the TAS-20. As hypothesized, the participants of our study reported much more positive state and trait affect than negative state and trait affect. This is not surprising but confirms the observation that there is a clear preponderance of positive affect in healthy people (Diener and Diener, 1996; Zelenski and Larsen, 2000). Importantly, a prevalence of positive affect was also observed at an implicit affect level: our study participants were characterized by higher implicit positive than implicit negative affect scores. As could be expected, implicit positive affect showed a small to medium correlation with explicit positive trait affect in our sample.

Contrary to our hypothesis, none of the alexithymia components was negatively correlated with positive affect. We found no correlations between the different facets of alexithymia and implicit or explicit (state and trait) positive affect. Thus, our findings contrast with those of previous research based on a student sample (Swinkels and Giuliano, 1995, study 3) or an outpatient sample (de Gucht et al., 2004) but are similar to those of other studies based primarily on samples of the general population suggesting no (Palmer et al., 2002) or only a negative correlation of difficulties identifying feelings and positive affect (Henry et al., 2006). The small correlation between externally oriented thinking and explicit positive state affect ($r = -0.12$) was the highest observed in the present sample between alexithymia components and positive affect scales. According to our findings, there is no substantial relationship between the facets of alexithymia as assessed by the TAS-20 and the actual or habitual experience of positive affect. It is possible that individuals with clinically relevant degrees of alexithymia might manifest tendencies to experience less positive affects and might thus appear anhedonic. However, our null findings challenge the idea that alexithymic features go along with a reduced experience of positive affect, at least in healthy and educated young adults.

The present results confirm our hypothesis that the alexithymia components difficulties identifying feelings and difficulties describing feelings are positively associated with negative affect. We observed significant positive correlations of difficulties identifying feelings with explicit negative trait affect (PANAS), depressive mood and trait anxiety. The alexithymia component difficulties describing feelings was not found to be significantly correlated with explicit negative state and trait affect as assessed by the PANAS but correlated positively with

depressive mood and trait anxiety. However, when controlling for difficulties identifying feelings difficulties describing feelings was not any more significantly related to depressive mood and trait anxiety. According to our findings, the alexithymia component difficulties identifying feelings is more strongly associated with negative affect than difficulties describing feelings which is consistent with results from other studies administering the PANAS (Swinkels and Giuliano, 1995; Palmer et al., 2002; de Gucht et al., 2004). Our data are also in line with previous findings (Berthoz et al., 1999) indicating stronger relations of difficulties identifying feelings with depression and trait anxiety compared to those of difficulties describing feelings. In clear contrast to difficulties identifying feelings, externally oriented thinking was not related to any of the negative affectivity measures administered in our study which is consistent with the results of previous research (Hendryx et al., 1991; Swinkels and Giuliano, 1995; Berthoz et al., 1999; Palmer et al., 2002; de Gucht et al., 2004).

An important focus of the present investigation was to examine for the first time implicit affectivity as a function of alexithymia. According to our data, none of the alexithymia components of the TAS-20 was related to implicit positive or implicit negative affect. Thus, administering an indirect measure of affectivity we found no evidence for correlations between alexithymia facets and implicit affect. Implicit affect is thought to be related to processes of the impulsive system (Quirin et al., 2009a). It has been found to predict endocrine stress reactions in everyday life as well as cardiovascular and endocrine responses to acute stressors (Quirin et al., 2009b; Mossink et al., 2015; van der Ploeg et al., 2016) as well as brain activation to subtle threat stimuli (Suslow et al., 2015). It should be noted that for externally oriented thinking and difficulties describing feelings non-correlations with positive and negative affectivity could be observed for the indirect (IPANAT) as well as the direct measure (PANAS). Based on our data it can be concluded that in healthy and educated adults the alexithymia facet externally oriented thinking is independent from dispositions to develop positive or negative affects.

Difficulties identifying feelings was also not correlated with implicit or explicit positive affect in our sample but it showed substantial correlations with explicit negative trait affect (and depression and trait anxiety) but not with implicit negative affect. Thus, it can be concluded that difficulties identifying feelings seem to be associated with an increased conscious experience of negative affects but not with a heightened disposition to develop negative affects at an automatic response level. Lumley (2000) proposed an explanation for the overlap of difficulties identifying feelings and depression suggesting that negative affect could promote critical perceptions of the self thereby increasing the probability that individuals report that they are poor at detecting their emotions. As has been pointed out above, implicit affectivity has been found to predict psychophysiological response to stressors and threat (Quirin et al., 2009b; Mossink et al., 2015; Suslow et al., 2015). It is interesting to note in this context that research on the psychophysiological responsivity to stressors or aversive stimuli in alexithymia has not produced clear results. Previous research has found hyper-responsivity (e.g., Martin and Pihl, 1986; Infrasca, 1997), hyporesponsivity (e.g., Linden et al., 1996; Pollatos et al., 2008) or non-significant changes (e.g., Friedlander et al., 1997) in physiological parameters in response to stressors in alexithymic compared to non-alexithymic individuals. Thus, all in all there appears not to exist a robust (positive) relationship between alexithymia and spontaneous physiological reactivity to stressors or aversive stimuli.

The constellation of high explicit negative affect and normal implicit negative affect in individuals with difficulties identifying feelings could alternately be explained by deficits in down-regulating negative affective experiences. This means, even though these individuals are characterized by a normal (not heightened) disposition to develop negative affects at an automatic response level they could have problems in controlling negative affects and therefore consciously experience and report these affects for a longer time. According to Lumley (2000), in persons with difficulties in identifying feelings because of their limited ability to regulate and resolve negative affects negative affectivity remains unmodulated yielding a chronic, undifferentiated dysphoria (see also Taylor et al., 2016).

The exclusive use of a self-report measure to assess alexithymia could be criticized as a limitation of our study. Concerns have been raised that individuals with impaired affect awareness can accurately rate themselves on this lack of awareness on a self-report scale (e.g., Lane et al., 2015). However, it is conceivable that high alexithymic individuals get negative feedback from the social environment about their deficits in perceiving, feeling and communicating emotions, and their superficial ways of thinking and talking. For example, the TAS-20 item "*People tell me to describe my feelings more*" which assesses difficulties describing feelings refers to a critical comment or request of others (Bagby et al., 1994a). Against this background, alexithymic individuals might become aware of and be able to report on their own inabilities due to the integration of interpersonal feedback into their self-concept (Günther et al., 2016). Interestingly, findings from recent studies on deficits in affect perception in alexithymia in which self-report and objective measures were administered indicate that self-reported alexithymia (i.e., TAS-20) could be a better predictor of affect recognition performance than observer-rated alexithymia (Ihme et al., 2014; Brandt et al., 2015).

To sum up, the data of the present investigation suggest that when examining the relationship between alexithymia and affectivity one should not focus on total or summary scores but should take into consideration the different facets of alexithymia and administer direct as well as indirect measures of affectivity. Alexithymic characteristics and experience of affects appear to be largely independent of each other. In our study, alexithymia components were found to be differentially related to explicit negative affect but not associated with explicit positive affect or implicit affectivity. Based on our findings, it can be concluded that in healthy young adults an externally oriented, concrete way of thinking is unrelated to dispositions for positive or negative affects. Instead, difficulties identifying feelings appear to be associated with an increased conscious experience of negative

affects but not with a heightened disposition for negative affects at an automatic response level. Clearly, the generalizability of our findings is limited, as we recruited primarily female university students as participants. Therefore, it is necessary that future research on this topic includes also samples of men, elderly people and individuals with less education. It appears promising to administer the IPANAT in psycho-physiological research on affective responsivity in alexithymia along with direct measures of affectivity. Longitudinal experiments examining the recovery from (implicit and explicit) negative affects over time as a function of alexithymia components could give more detailed insights into the emotion regulation deficits associated with difficulties identifying feelings.

AUTHOR CONTRIBUTIONS

TS and U-SD contributed equally to the conception and design of the study as well as to the analysis and interpretation of data. TS organized collection of data. TS wrote the first draft of the manuscript and U-SD made critical revisions. Both authors approved the final version of the manuscript for publication.

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Type D Personality and Alexithymia: Common Characteristics of Two Different Constructs. Implications for Research and Clinical Practice

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In the last few decades, particular attention has been paid to the role of personality specific traits that can affect the loss of health, i.e., Type D personality and Alexithymia. They have been conceptualized in a different period, this means that they are different both for their theoretical positions and their empirical studies. Some authors have speculated that there is a potential conceptual overlap between Type D personality and alexithymia constructs but there is a shortcoming in the literature. The aim of the study was to examine the potential overlap between the constructs of type D personality and alexithymia, replicating previous two studies, to extend these findings to Italian population. The participants were 247 Italian adults (males = 43%), recruited in primary health care practices of Palermo. All participants did not have chronic diseases during tests administration. They ranged in age from 35 to 69 years old (M = 52.34 years, SD = 9.76). Participants were administered Type D Personality Scale (DS-14) and Toronto Alexithymia Scale (TAS-20). A series of confirmatory factor analyses was performed to evaluate the factorial structure underlying the TAS-20 and DS-14 items. Globally results showed that alexithymia and type D personality are distinct constructs, but they are also strictly positively related with each other. Negative affectivity (NA) was highly correlated with Difficulties in identifying feelings and Difficulties in describing feelings, while Social inhibition (SI) was highly correlated with Difficulties in describing feelings. These results are consistent with those of other studies conducted in this area. Future research should consider evaluating the relationship between a deficit of affect regulation and type D personality to improve the effectiveness of interventions of health cure.

Keywords: alexithymia, type-D personality, psychosocial risk factors, TAS-20, DS-14

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INTRODUCTION

Research has extensively supported the role of psychological risk factors both in the pathogenesis and outcomes of physical diseases among different patient populations (Lumley et al., 1997, 2007; Taylor et al., 1997; Kudielka et al., 2004; Porcelli, 2009; Basinska and Wozniewicz, 2013; Solano, 2013). These studies have shown associations between individual's personality dimensions and a self-management of physical disease. In the last few decades, a particular attention has been paid

to the role of personality specific traits (i.e., Type D personality and Alexithymia) which can affect the loss of health. They have been conceptualized in a different period, this means that they are different both for their theoretical positions and their empirical studies. By the contrast, it seems to be a potential conceptual overlap between the constructs.

In 1995, Denollet and colleagues introduced the construct of Type-D personality. It is defined such as the subject's general tendency to psychological distress, characterized by negative affectivity (NA) and social inhibition (SI) (Denollet et al., 1995). NA is concerned with tendencies to experience negative emotions such as dysphoria, depressive mood, anxiety, hostility, anger, and irritability, whereas SI is expressed in a tendency to avoid the expression of these negative emotions as well as the behaviors associated with these dysfunctional emotions (Denollet and Conraads, 2011; Gremigni and Casu, 2013). Inhibition occurs mostly in social situations, and the individual is aware of being inhibited. The risk factor would be the synergy between these two dimensions (NA and SI) and not by single factors. It is worth noting that this personality construct emphasizes the normal characteristics of personality more than psychopathological aspects. However, individuals with high levels on both traits (NA and SI) are more likely to experience chronic distress (Mols and Denollet, 2010).

Interestingly, the first ideas about the Type D personality were not derived from a theoretical model, but rather emerged from empirical analyses which aimed to demonstrate the negative effect of repressive coping (Denollet et al., 1995; Grande et al., 2013). For example, Denollet linked emotional distress to stable personality traits but a comprehensive theoretical model of the pathogenic mechanisms that operate through the interaction of NA and SI has not been developed (Grande et al., 2013).

Type D personality was originally developed to understand the role of specific psychological factors in the outcomes among cardiovascular patients' population (Pedersen and Denollet, 2003). Recently it has been increased an interest in the construct and its value is confirmed in several patient's population (Mols and Denollet, 2010). Recent meta-analytic results showed that Type D is associated with poor mental and physical health status both in clinical and non-clinical populations (Mols and Denollet, 2010). This type of personality ranges from 13 to 32.5% in the general population and from 26 to 35% in patients affected by cardiovascular disease. Type D personality it is considered one of the psychopathological conditions that affect health and longevity, therefore, it entails psychological and medical treatment (Kheradmand et al., 2016). Moreover, people with type D personality are at the continuous risks of psychiatric and physical disorders (Ogrodniczuk et al., 2012; Basinska and Wozniewicz, 2013; van Middendorp et al., 2016).

In 2005 Denollet constructed the Type-D Scale (DS-14), a scale that contains two sub-scales, namely Negative Affective and Social Inhibition which are scored in a Likert scale. It is the instrument largely employed to measure the Type D personality. Several cross-cultural studies carried out in Europe both in cardiovascular patient populations and in general population confirm the validity and reliability of DS-14 scale (Pedersen and Denollet, 2003; Denollet, 2005). The DS-14 not only can be evaluated in cardiovascular population but also in other clinical and general populations (Emons et al., 2007; Spindler et al., 2009; Grande et al., 2010; Howard and Hughes, 2012; Kupper et al., 2013), as well as chronic pain (Barnett et al., 2009). Gremigni and Sommaruga (2005) highlighted the good psychometric properties of the Italian version of DS-14, and they recommend its use in psychological screening for rehabilitation and clinical research.

The Alexithymia is a personality construct which refers to one's inability to successfully deal with emotional regulation (Taylor and Bagby, 2000). This construct consists of the following components: difficulty in identifying and describing feelings, an impoverished fantasy life, and externally-oriented thinking (Taylor et al., 1991).

Alexithymia is usually defined such as a deficit in the mental processing of feelings and emotional experiences (affect regulation), that produced a bounded ability to express feelings and a widely developing about the emotional experience. Indeed, the individuals affected by alexithymia find complication distinguishing specific emotions, identifying feelings from body sensations and possess an externally orientated way of thinking (Sifneos et al., 1977). They are often assailed by a widespread negative affection, social evasion and poor emotionally relationships with other people.

In the early 1970's Nemiah and Sifneos (1970) introduced the construct (Sifneos, 1973; Nemiah et al., 1976). Originally, their study was based on several clinical observations about the cognitive and affective style of patients with classic psychosomatic disease but Alexithymia has been found to be associated with poor health outcomes in a variety of populations (Kauhanen et al., 1994, 1996; Valkamoa et al., 2001; Taylor and Bagby, 2004; Henry et al., 2006; Lumley et al., 2007).

Over 40 years after the original definition, a great deal of evidence supports the connection between difficulties with affect regulation and poor physical and mental health. Alexithymia it is now widely recognized as a trans-nosographic construct, that is as a non-specific risk factor for many physical diseases such as neoplastic diseases as breast cancer, chronic pain syndrome, essential hypertension, chronic urticaria (Taylor et al., 1997; Epifanio et al., 2005a,b, 2013; Maniaci et al., 2006; Porcelli, 2009), functional gastrointestinal disorders, and for many mental disease such as depression, eating disorders, addiction disorder, dissociative disorders, Post-traumatic Stress Disorder, panic attacks (Caretti and La Barbera, 2005; Taylor and Bagby, 2013; Epifanio et al., 2014).

The TAS-20 (Bagby et al., 1994) is the instrument largely employed to its measure. TAS-20 assesses the presence of alexithymic characteristics by three factors: difficulty in distinguishing between feelings and emotions, difficulty in identifying and describing feelings, externally-oriented thinking. Thanks to good psychometric characteristics, TAS-20 is a measure widely used. This has allowed both the comparison as well as the generalizing the results of adults subjects mostly.

Several studies underlined common characteristics between Type-D and Alexithymia constructs: both dimensions of Type D (i.e., NA and SI) and Alexithymia were positively correlated

with neuroticism and negatively correlated with extroversion in general population (De Fruyt and Denollet, 2002; Yekta et al., 2011) and they were associated with anxiety and depression (Kudielka et al., 2004; Schiffer et al., 2008; Tselebis et al., 2010; Korkoliakou et al., 2014; Nekouei et al., 2014). Both in type D and alexithymic individuals there is a predominance of an insecure attachment style which is, for its part, associated with a deficit of affective regulation (Huis in't Veld et al., 2011). Both constructs are only some of the crucial risk factors for cardiovascular diseases that encourage unhealthy lifestyles; they can also be defined as non-specific risk factors (Mols and Denollet, 2010; Epifanio et al., 2014). However, they can be found in other clinical and general populations.

According to these studies, some authors have speculated a potential conceptual overlap between Type D personality and alexithymia constructs but there is still a dearth of research on this topic. Only two previous studies have examined the link between Type D personality and Alexithymia simultaneously in a Scottish students' sample (Williams et al., 2011) and in Iranian students' sample (Kheradmand et al., 2016).

Williams et al. (2011) highlighted that the Type D personality and Alexithymia are conceptually and theoretically overlapping constructs but at the same time they show some distinct factor structures. A series of confirmatory factor analyses was performed and results showed that alexithymia and type D personality are distinct constructs, but they are also strongly related to each other. This study should be considered as preliminary within this line of research, but it is limited since the sample was composed predominantly by female university students. The authors underlined the need to conduct further research on clinical and non-clinical samples to better understand the relationship which occurs among these two constructs.

Kheradmand et al. (2016) investigated the "simultaneous" factor structure of Alexithymia and type D personality, reproducing the same research method used by Williams et al. (2011) in a sample of Iranians students. The results confirmed previous data and conclusion: alexithymia and Type-D personality are overlapping but they also are distinct constructs.

THE PRESENT STUDY

The aim of the study was to examine the potential overlap between the constructs of type D personality and alexithymia, replicating the studies by Williams et al. (2011) and Kheradmand et al. (2016). The hypothesized model of the relations between the constructs appears in **Figure 1**. Moreover, the current study was also aimed at extending these findings to a different sample. Our sample was composed by Italian adults who were older than Scottish and Iranian university students' sample and with different socio-cultural characteristics. We believe that this is necessary in order to extend the knowledge and to increase the understanding of these constructs which are used both in clinical activities and in the treatment of patients with physical illnesses.

MATERIALS AND METHODS

Participants

This research was part of a larger research program designed to explore the relationship between Alexithymia, Type-D personality and cardiovascular risk in the non-clinical population. For the purpose of the current study, 277 consecutive Italian adults routinely attending medical check-ups from their physician, were recruited in primary health care practices in the province of Palermo. Information on clinical characteristics was obtained from the patients' medical records and included diabetes, hypertension, hypercholesterolemia, angina, left ventricular ejection fraction (LVEF), ischemic heart disease (IHD), or congestive heart failure (CHF). Thirty participants were excluded from participation in the study because they had a diagnosis of these diseases. The 247 remaining participants were individuals belonging to a non-clinical population. All participants received written information about the study and written informed consent was obtained from them.

The 247 participants (males = 43%) ranged in age from 35 to 69 years old ($M = 52.34$ years, $SD = 9.76$). Thirteen percentage of the participants were unmarried, 80% were married, 5% were separated or divorced, and 2% were widow/widower. With regard to their educational status, 20% were university graduated, 39% had obtained a certificate of secondary education, and 41% had eight or less years of education. With regard to their occupational status, 55% were workers, 26% were housewives, 12% were retired, and 6% were unoccupied.

Measures

Alexithymia

Participants were administered the Toronto Alexithymia Scale (TAS-20; Taylor et al., 1992; Italian adaptation by Bressi et al., 1996). It consists of 20 items articulated in three subscales: Difficulty identifying feelings (DIF), which evaluates the difficulty in recognizing, feelings and distinguish emotions from feelings (5 items, e.g., "I am often confused about what emotion I am feeling"); Difficulty describing feelings to others (DDF), which evaluates the difficulty in verbalizing feelings to others (5 items, e.g., " It is difficult for me to find the right words for my feelings"); Externally oriented thinking (EOT), which evaluates the tendency of individuals to focus their attention externally and to use concrete way of thinking (8 items, e.g., "Looking for hidden meaning in movies or plays distracts from their enjoyment"). Items were scored on a 5-point Likert scale ranging from 1 (*strongly disagree*) to 5 (*completely agree*). A total score higher than 60 characterizes individuals with Alexithymia. In the present study, the scale had adequate internal consistency: Cronbach's alpha coefficients were 0.88, 0.82, and 0.78 for DIF, DDF, and EOT, respectively.

Type D Personlality

Participants were administered the Type-D Scale 14 (DS14; Denollet, 2005; Italian adaptation by Gremigni and Sommaruga, 2005). It consists of 14 items articulated in two subscales: NA, which evaluates dysphoria, anxiety and irritability (7 items, e.g.,

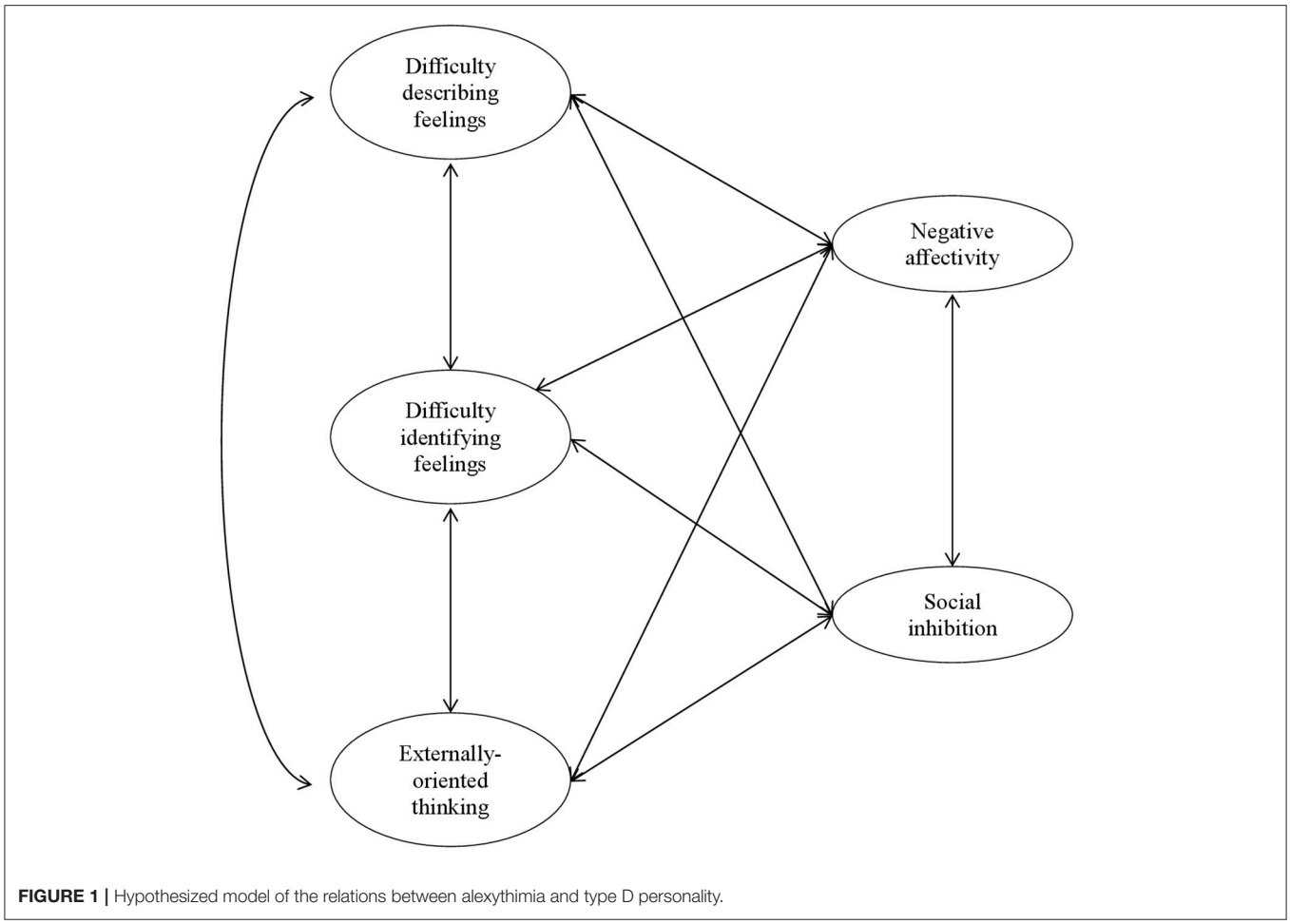

FIGURE 1 | Hypothesized model of the relations between alexythimia and type D personality.

"I am often down in the dumps"); SI, which evaluates social discomfort, reticence and lack of social poise (7 items, e.g., "I often feel inhibited in social interactions"). Items were scored on a 5-point Likert scale ranging from 0 (*false*) to 4 (*true*). A score higher than 10 in both subscales characterizes individuals with a type D personality. In the present study, the scale had adequate internal consistency: Cronbach's alpha coefficients were 0.86 for NA and 0.83 for SI.

Procedure

The Institutional Review Boards (IRB) of the University of [blinded for the review process] approved this study. It was conducted in conformity with the guidelines provided by the Italian Association of Psychology (Associazione Italiana di Psicologia, 2014) for the ethical treatment of the participants. All participants voluntarily agreed to take part in this investigation without receiving compensation. A prior permission was obtained from each of them. Participants were consecutively recruited at health primary care service of Palermo from 2015 to 2016. Several trained psychologists administered DS-14 and TAS-20 in doctor's waiting rooms. All participants received written information about the study and the scales administration did not take more than 20 min to complete.

Data Analysis Approach

A series of Confirmatory Factor Analyses (CFA) was performed to evaluate the associations between type D personality and alexithymia. The hypothesized model appears in **Figure 1**. The CFA was based on examining the covariance matrix using Mplus 7 software (Muthén and Muthén, 1998-2012). In order to establish the measurement scale of each factor, their variance was fixed to 1. Since the items exhibited a multivariate non-normal distribution (the normalized Mardia's coefficient was 8.18, $p < 0.001$), the robust maximum likelihood (MLR) estimation method was used. It adjusts standard errors of parameter estimates and chi-square statistics ($SB\chi^2$) to account for non-normality (Satorra and Bentler, 1994). The goodness of fit of the model was assessed using a range of goodness-of-fit statistics and evaluation of the appropriateness of the model parameters. The χ^2 statistic assessed the sample and implied covariance matrix with a good-fit model being indicated by a non-significant result. However, the χ^2 statistic is strongly associated with sample size, and as such, good models tend to be excessively rejected. Therefore, Tanaka (1987) suggested that a model should not be rejected simply on the basis of a significant χ^2 result. Therefore, model fit was judged to be good if Comparative Fit Index (CFI; Bentler, 1990) and Tucker–Lewis Index (TLI;

Tucker and Lewis, 1973; Bentler and Bonett, 1980) ≥0.95, if Root Mean Square Error of Approximation (RMSEA; Steiger, 1990) <0.05, and Standardized Root Mean Squared Residuals (SRMR; Jöreskog and Sörbom, 1993; Hu and Bentler, 1999) <0.5.

Given the small size of the sample with respect to the number of observed variables, the number of indicators of the factorial model was reduced by using item parceling (Bandalos and Finney, 2001). Three item parcels were built for each latent dimension, thus ending with 15 parcels (each parcel contained 2–3 items). Following Hattie (1985) to test the unidimensionality of each parcel (Bandalos and Finney, 2001), we examined the SRMR associated to a one-factor solution derived from a ML Exploratory Factor Analysis. SRMRs of the 15 parcels ranged from 0.00 to 0.06 ($M = 0.032$, $SD = 0.015$). Thus, we considered unidimensionality achieved for all parcels.

RESULTS

Preliminary Analyses

In order to explore how some personal characteristics may influence the levels of alexithymia and the presence of Type-D personality, a series of chi square analyses was performed. Results revealed the existence of differences related with educational level for both alexithymia [$\chi^2_{(2)} = 31.50$, $p < 0.001$] and Type D personality [$\chi^2_{(1)} = 11.76$, $p = 0.001$]; more specifically, 70% of participants with a low educational level tended to be classified as alexithymic and 66% of them tended to be classified with a Type D personality. Results revealed no significant associations of alexithymia and Type-D personality with gender [$\chi^2_{(2)} = 2.79$ ns, for alexithymia, $\chi^2_{(1)} = 0.51$ ns, for Type-D personality], and marital status [$\chi^2_{(2)} = 0.12$ ns, for alexithymia, $\chi^2_{(1)} = 2.89$ ns, for Type-D personality].

Descriptive Statistics and Correlations

Mean, standard deviation, skewness, kurtosis, and Pearson's correlation coefficients of the parcels for study variables are given in **Table 1**. The data had a normal univariate distribution, skewness, and kurtosis values being approximately in the range −1 and +1 (Muthén and Kaplan, 1985) (**Table 1**).

Confirmatory Factor Analyses

A series of CFA was performed to evaluate the interrelations between type D personality and alexithymia dimensions as measured by DS14 and TAS20, respectively. Goodness-of-fit indices for alternative models being run are shown in **Table 2**. Firstly, a one-dimensional model was tested. It did not fit the data very well. The best fitting model was a five-correlated factors model: 3 factors were related to the TAS-20 subscales (DIF, DDF, and EOT), and 2 factors were related with the DS-14 subscales (NA and SI). The standardized solution is shown in **Figure 2**. Results showed that NA was highly correlated with DIF, while SI was highly correlated with DDF.

TABLE 2 | Goodness-of-fit indexes for alternative CFA models.

	$SB\chi^2$	df	*p*	CFI	RMSEA	RMSEA 90% C.I.
One-factor model	338.48	90	<0.001	0.774	0.106	0.094–0.118
Five-factors model	107.60	80	0.02	0.975	0.037	0.015–0.054

TABLE 1 | Means and standard deviations of study variables.

	NA1	NA2	NA3	SI1	SI2	SI3	DDF1	DDF2	DDF3	DIF1	DIF2	DIF3	EOT1	EOT2	EOT3
NA1	–														
NA2	0.627	–													
NA3	0.564	0.510	–												
SI1	0.248	0.373	0.312	–											
SI2	0.310	0.395	0.333	0.466	–										
SI3	0.324	0.423	0.489	0.462	0.558	–									
DDF1	0.240	0.150	0.268	0.331	0.281	0.315	–								
DDF2	0.157	0.175	0.271	0.168	0.234	0.311	0.315	–							
DDF3	0.177	0.146	0.192	0.173	0.205	0.286	0.177	0.293	–						
DIF1	0.496	0.397	0.547	0.247	0.265	0.378	0.380	0.339	0.178	–					
DIF2	0.457	0.329	0.505	0.180	0.213	0.304	0.329	0.366	0.249	0.638	–				
DIF3	0.407	0.367	0.458	0.182	0.263	0.250	0.364	0.320	0.241	0.546	0.655	–			
EOT1	0.095	0.122	0.161	0.226	0.147	0.174	0.385	0.139	0.125	0.152	0.129	0.113	–		
EOT2	0.158	0.196	0.200	0.230	0.200	0.329	0.259	0.138	0.221	0.186	0.159	0.199	0.305	–	
EOT3	0.119	0.126	0.072	0.164	0.168	0.243	0.271	0.091	0.164	0.074	0.101	0.117	0.258	0.338	–
M	1.82	1.22	2.10	1.55	1.00	1.11	2.51	2.50	3.02	2.41	2.06	2.24	2.42	2.99	2.50
SD	1.11	1.08	1.12	0.98	1.17	1.03	1.15	1.15	1.54	1.09	1.13	1.29	1.03	0.97	1.01

NA, negative affectivity; SI, social inhibition; DDF, difficulty in describing feelings; DIF, difficulty in identifying feelings; EOT, externally-oriented thinking. Coefficients higher, in absolute value, than 0.15 were significant at $p < 0.05$.

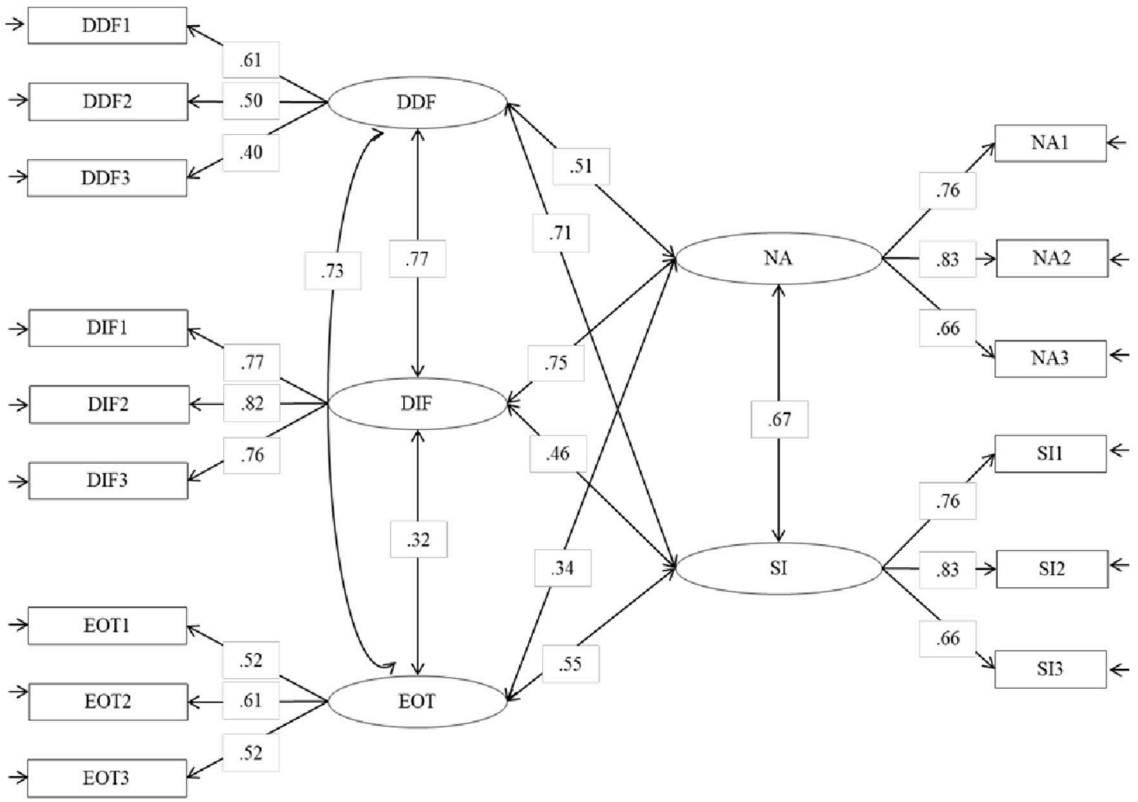

FIGURE 2 | Statistical model of the relations between alexythimia and type D personality. Standardized solution, all parameters are significant with $p < 0.05$.

DISCUSSION

The aim of the study was to examine the potential overlap between the constructs of type D personality and Alexithymia, replicating the studies performed by Williams et al. (2011) and Kheradmand et al. (2016) with Scottish and Iranian university students, respectively. Authors found that alexithymia and type D personality are distinct constructs, but they are also strictly related to each other. Our study was also aimed at extending these findings to a different sample, composed by Italian adults recruited in primary health care practices but all participants did not have chronic diseases. They were adults, with an average age of fifty-two and the most of them were married.

The results of the present study confirmed previous findings showing that alexithymia and type D personality are generally distinct constructs. The dimensions DDF, DIF and EOT underlying TAS20 (the scale more largely used to assess alexithymia) were clearly differentiated from the dimensions NA and SI underlying DS14 (the scale more largely used to assess type D personality). Notwithstanding, some dimensions of alexithymia were highly correlated with some dimensions of type D personality. More specifically, NA was highly correlated with DIF and DDF, while SI was highly correlated with DDF. The deficit in the mental processing of feelings and emotional experiences (DIF and DDF) can produce a prevalence of NA such as dysphoria, depression, anxiety, anger, hostility, a tendency to refer mostly somatic symptoms and difficulties in the interpersonal relationship (SI). For example, individuals with a high level of alexithymia can have sudden outbursts of anger and/or tears but they do not know why. That is because the individual with alexithymic functioning has an emotional activation but he or she does not recognize the feeling associated because of a deficit in emotional processing. We believe that the NA could be considered such as an excessive level of express emotion, an affect dysregulation "upward." Furthermore, individuals with a high level of alexithymia have also difficulties in the interpersonal relationship because they cannot put into words what they are experiencing, they are not able to communicate their feeling to others, and they are not able to establish an empathic relationship. The difficulties in emotional processing bring the individual with high levels of alexithymia to avoid interpersonal relationship. So, SI could be an expression of these difficulties.

Ogrodniczuk et al. (2012) examined the association between type D personality and alexithymia in a psychiatric outpatient sample. They found that patients with Type D Personality also presented high levels of alexithymia (more than individuals with Type non-D personality), large difficulty in describing emotions and thinking oriented to the outside. The authors explained the association between NA and DIF as that: "…type D persons may be aware of their negative emotions,

their awareness may be more a vague perception of distress rather than a clear appreciation of the precise nature of the distressing emotions. Furthermore, SI associated with Difficulty Describing Feelings can suggest that the socially avoidant behavior of type D persons might be related to a difficulty in articulating their emotional experiences to others" (Ogrodniczuk et al., 2012, p. 129). If so, the Type D would be a stable tendency to cope emotions at the base of which there is the affective dis-regulation. Alexithymia could explicate the Type D personality structure. This suggest that is necessary to conduct further researches aimed at understanding the relationship between a deficit of affect regulation and type D personality. If that is the case, then it has important clinical implications: elevated levels of alexithymia may influence outcomes of both psychodynamic psychotherapy (Ogrodniczuk et al., 2011) and treatments of functional somatic disorders (Porcelli et al., 2003, 2007). It is widely acknowledged that assessment of alexithymia can inform treatment strategies and prognosis of various somatic disorders (Lumley et al., 2007; Taylor and Bagby, 2012). Therefore, only measuring the type D personality cannot be sufficient to promote the effectiveness of interventions of health care. Furthermore, when Type-D is linked to alexithymia, in this specific case, it is necessary to promote psychological intervention helping individuals to recognize, to verbalize and to become aware of feelings and only after this process the individual's emotional response can be modulate.

The use of both scales can increase our ability to spot some of the special condition that are strictly connected with the development or the exacerbation of somatic disease. Although there is evidence that some personality traits can trigger the onset of the somatic disease or interfere with the care, they may be also influenced by a disease which can be chronic or incurable. Hence, the previous cross-sectional studies with individuals who have already had the disease show some limits. For example, they were unable to establish specific relations between personality traits and chronic diseases. In some studies, the presence of type D personality varies over time in dialysis patients (Loosman et al., 2017) and in fibromyalgia patients (van Middendorp et al., 2016). Therefore, type D personality is possibly more a state instead of a trait phenomenon, such as the study carried on the fibromyalgia presumes.

Finally, our preliminary analyses showed a significant association of alexithymia and Type D personality with educational level; more specifically, we found that participants with low educational levels tended to report higher levels of alexithymia and Type D personality.

This finding is consistent with the few studies on Alexithymia and Type D personality conducted in general population to date (Mattila et al., 2010; Beutel et al., 2012). However, the link among these psychological constructs and some socio-demographic characteristics is still unclear, given the cross-sectional nature of previous research. One possible explanation of this result could be associated to the adoption of self-report scales and to individual's difficulty of understanding the text of the items that require a good educational level. Thus, further research is needed to examine this educational bias in a wide sample.

There are some limitations of the current study which should to be noted. First, the sample size is tiny, but it is focused on Italian adults who have different sociodemographic characteristics than samples in previous studies. Second, this study is also limited by the use of self-report measures. The self-report measures have some limitations, such as poor self-insight, dissemblance, and various style responses (Keefer et al., 2015). Particularly, the exclusive use of a self-report measure to assess alexithymia could be criticized because individuals with impaired affect awareness can accurately rate themselves on this lack of awareness on a self-report scale. For these reasons, it may be useful to examine the overlap of alexithymia and Type D using other measures, in addition to the TAS-20, i.e., the Toronto Structured Interview for Alexithymia (TSIA, Bagby et al., 2006). TSIA allowed bypassing the limitations associated with the self-report method for measuring Alexithymia (Keefer et al., 2017). This suggest that is necessary to conduct further researches for understanding the process of emotion regulation associated with type D to improve the effectiveness of interventions of health cure.

AUTHOR CONTRIBUTIONS

MSE, SI, PA, GL, and SL contributed equally to the conception and design of the study as well as to the analysis and interpretation of data. MSE wrote the first draft of the manuscript and SI, GL, and SL made critical revisions. All authors approved the final version of the manuscript for publication.

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The Role of Difficulty in Identifying and Describing Feelings in Non-Suicidal Self-Injury Behavior (NSSI): Associations With Perceived Attachment Quality, Stressful Life Events, and Suicidal Ideation

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Objective: Core alexithymic features, such as the difficulty in identifying and describing feelings, are associated with poor attachment styles and emotional trauma, which influence the capacity to regulate affect. Additionally, emotional regulation has been found to be the most commonly identified function associated with non-suicidal self-injury behavior (NSSI) in adolescents as they attempt to modulate strong emotions. However, few studies have examined the link between difficulty in identifying and describing feelings (core components of alexithymia), NSSI behaviors, quality of attachment, life stressors and suicidal ideation in healthy early adolescents. Consequently, this study aims to investigate these constructs and the relationship among them in a large non-clinical sample of adolescents.

Methods: Seven hundred and nine middle school students (50.4% males), aged 10–15 years (M = 12.6; SD = 1.06) were involved in this study. In order to investigate the variables considered in the study, the following measures were administered: the Deliberate Self-Harm Inventory exploring non-suicidal self-injurious behaviors; the Alexithymia Questionnaire for Children examining difficulty in identifying and describing feelings; the Inventory of Parent and Peer Attachment assessing the quality of parental and peer attachment; the Life Stressor Checklist-Revised outlining stressful/traumatic events and the Children's Depression Inventory evaluating suicidal ideation.

Results: We found significantly positive relationships among difficulty in identifying and describing feelings, NSSI behaviors, stressful events, and suicidal ideation. Data indicated a significant negative association of difficulty in identifying and describing feelings with quality of attachment to parents and peers. Further findings highlighted that difficulty in identifying and describing feelings significantly mediated the effect of quality of attachment (parent and peer) on NSSI and suicidal ideation.

Conclusion: The ability to identify and describing feelings is important to managing emotional expression and understanding the feelings of others, both crucial in attaining successful interpersonal relationships. Our data revealed that, while controlling for stressful life events, low levels of attachment may increase adolescents' difficulty in identifying and describing their own feelings, which in turn may increase the risk of both NSSI and suicidal ideation.

Keywords: alexithymic features, NSSI, attachment, stressful life events, adolescents

INTRODUCTION

In recent years, there has been growing interest in research on alexithymia, as documented by a series of major systematic reviews in the international literature. Although the literature is not always unanimous about the definition of "alexithymia," research suggests that alexithymia is a multi-dimensional deficit in affect recognition and regulation (Timoney and Holder, 2013). For some authors, it refers to a personality construct normally distributed in the population (Parker et al., 2008) whilst others use the term to denote a limited ability to identify, describe and communicate one's feelings, which in turn reflects difficulties in affective self-regulation (Taylor et al., 1997). Thus a reduced ability to connect emotions with words (or "absence of words for emotions" as attested by its etymology from the Greek alpha = absence, lexis = language, thymos = emotions) has been used to define the construct of alexithymia (Taylor et al., 1997; Taylor, 2010). In general, the following clinical features have been considered as dimensions of alexithymia: difficulty in identifying and describing emotions, difficulty in distinguishing between subjective emotional states and the somatic components of emotional activation, poverty of imaginative processes, and cognitive style oriented toward external reality.

In line with previous investigation of healthy adults (Paivio and McCulloch, 2004), difficulties in identifying and describing inner feelings have been conceptualized as core components of alexithymia which may be associated with problems in building and maintaining close relationships with others and using social support to protect themselves against the potentially pathological influences of stressful events (Kojima et al., 2003). The difficulty in "identifying and describing ones' own inner feelings" may make people reluctant to participate in social activities (Kojima, 2012).

It has been suggested that alexithymia is broadly associated with various mental and physical health problems (Cerutti et al., 2016, 2017; Gatta et al., 2016). Individuals with alexithymia are more likely to have a limited ability to adaptively cope with stressful conditions and tend to encompass unhealthy behaviors such as alcohol and drug use (Lumley et al., 2007). Some studies have indicated that self-injuries are associated with a higher level of alexithymia than non-self-injuries among high school students and adolescent inpatient populations (Garisch and Wilson, 2010; Cerutti et al., 2014). Other studies have highlighted that adolescents inpatients with non-suicidal self-injury (NSSI) are more likely to have a pervasive and comprehensive Theory of Mind impairment (Laghi et al., 2016).

Non-suicidal self-injury is defined as the intentional injuring of one's body without apparent suicidal intent and for reasons not socially acceptable within one's culture (Muehlenkamp et al., 2012). Similar to other risky behaviors (e.g., alcohol and substance abuse), it typically begins between the age of 13 and 15 years (Favazza and Rosenthal, 1993; Hilt et al., 2008; Cerutti et al., 2011; Muehlenkamp et al., 2012). The transition to adolescence seems to mark a developmental period distinguished by its increased rates of NSSI behaviors (Peterson et al., 2008; Cerutti et al., 2014; Manca et al., 2014). International studies have revealed a wide variability in prevalence rates, with percentages ranging from 12 to 56% in non-clinical populations of adolescents (Cerutti et al., 2011; Muehlenkamp et al., 2012) and from 20 to 80% in clinical populations (Hilt et al., 2008; Ferrara et al., 2012; Cerutti et al., 2014; Kara et al., 2015).

During the last two decades, NSSI has attracted the attention of researchers among clinical and non-clinical settings (Klonsky and Muehlenkamp, 2007; Nixon et al., 2008; Nixon and Heath, 2009; Muehlenkamp et al., 2012; International Society for the Study of Self-Injury, 2015; Zetterqvist, 2017) since this phenomenon is widespread across the Western world. It represents a serious public health problem (Klonsky et al., 2013; Cerutti et al., 2014; Serafini et al., 2017) owing to the greater risk for later suicidal behavior especially among individuals who engaging NSSI repeatedly (Joiner, 2005; Joiner et al., 2012; Grandclerc et al., 2016).

There is evidence that NSSI is generally used to cope with distressing negative affective states, especially anger and depression, and mixed emotional states. However, to date, there is a paucity of studies exploring how individuals who engage in self-injury may experience difficulty expressing and verbalizing emotions in early adolescence and adolescence (Cerutti et al., 2014). Research is needed to examine a broader range of stressful childhood experiences, as few studies have examined the relationship between negative experiences or stressful life events, alexithymia and NSSI among young people. In a previous study, Paivio and McCulloch (2004) found that alexithymia partially mediated the relationship between traumatic experience and self-injurious behaviors among female undergraduate students.

Furthermore, it has been suggested that stressful and traumatic life events (e.g., abuse) in childhood may be related to self-injurious behavior in adulthood (Ross and McKay, 1979; Terr, 1991; van der Kolk et al., 1991). Studies have also highlighted that not all individuals with a history of abuse later engage in NSSI, and not all individuals who self-injure have been abused (Klonsky and Muehlenkamp, 2007). The stress exposure

model of psychopathology indicate that experiencing higher rates of life stressors or negative life events contribute to a higher risk for negative mental health outcomes (Liu et al., 2014). Nock (2010) suggested that stressful life events have the similarly prominent role as proximal risk factors for NSSI behavior, since in presence of stressful life events specific physiological responses are experienced by some individuals, who further may be at risk for engaging in NSSI as a coping strategy. This is more evident in individuals with difficulties in emotional regulation (Tang et al., 2016). Additionally, negative life events ranging from traumatic stressors to major life changes are consistently associated with suicidal ideation (Liu et al., 2014). It is well known that environmental influences have a particular impact on children's psychological development, especially the 'emotional climate' provided by the parents (Taylor, 2010). Studies have highlighted that early attachment difficulties may contribute to later self-injurious behaviors (van der Kolk et al., 1996; Conterio and Lader, 1998; Walsh, 2006). Specifically, Gratz et al. (2002) examined the role of the parent–child relationship as a risk factor for NSSI revealing that emotional neglect and the quality of the parent–child relationship were associated with risk of developing NSSI later. In view of new forms of sociality, adolescents make an important transition from family to peer group through gradual autonomy from primary attachment figures. The interest toward the peer group, with whom adolescents can share experiences and affection, becomes a determining factor to promote the growth and construction of personal identity.

Although research supports the relation between stressful life events and NSSI behaviors, to date there are few studies that have been undertaken on the degree to which stressful life events lead to NSSI among adolescents, except for research focusing on childhood abuse and other severe early life adversities (Tang et al., 2016). Only a small number of empirical studies have investigated the relationship between NSSI and core alexithymic features (i.e., difficulty in identifying and describing feelings) in different populations while no systematic review of the literature has been conducted to date. Moreover, the overall relationships among the difficulty in identifying and describing feelings, quality of parental and peer attachment, NSSI, suicidal ideation, and of stressful life events among young adolescents have not been sufficiently investigated.

The Present Study

In light of the above considerations, this study aimed to investigate the plausibility of a theoretical model in which low quality of attachment toward both peers and parents could represent emotional risk factors that may predispose adolescents to have increased difficulties in identifying and describing their own feelings which, in turn, may heighten the likelihood of developing both NSSI and suicidal ideation. Specifically, we hypothesized NSSI and suicidal ideation to be positively correlated with adolescents' difficulty in identifying and describing feelings. NSSI, suicidal ideation and difficulty in identifying and describing feelings, instead, were hypothesized to be negatively related to the quality of attachment toward both parents and peers. Lastly, in line with previous arguments (Klonsky and Muehlenkamp, 2007; Cerutti et al., 2011; Laukkanen et al., 2013) highlighting the positive relationship of stressful life events to NSSI, suicidal ideation, and difficulty in identifying and describing feelings, we also included in our model the number of stressful life events as a control variable.

MATERIALS AND METHODS

Participants

Seven hundred and nine Italian early adolescents (50.4% male), aged 10–15 years were involved in the present study. Participants were recruited in two middle schools in Rome. Exclusion criteria for participation included the presence of a diagnosed psychiatric illness and/or history of psychiatric treatment, history of significant neurological illness or brain injury, history of chronic pains and recurrent somatic symptoms. The vast majority (92.5%) of the participants were Caucasian.

Procedure

The participants and their parents/caregivers gave their written informed consent before inclusion in the present study. The administration of the self-reported questionnaires took place during school time in the classrooms. Anonymity of participants was ensured. Questionnaires took approximately 30–45 min to complete. All participants completed the questionnaire battery.

This study was approved by the Ethics Committee of the Department of Dynamic and Clinical Psychology, Sapienza University of Rome.

Measures

Deliberate Self-Harm Inventory

The Deliberate Self-Harm Inventory (DSHI; Gratz, 2001) was used to assess non-suicidal self-injury behavior (NSSI). The DSHI is a 17-item self-report measure that assesses lifetime history of NSSI (defined as the deliberate, direct destruction of body tissue without suicidal intent), including frequency, duration, and type of NSSI behavior. The DSHI was recently validated in the Italian context by Cerutti et al. (2012) and was found to have adequate internal consistency, and good convergent and discriminant validity. An overall score of NSSI was created by summing participants' scores on the 10 items (Gratz, 2006). In the present study, good reliability ($\alpha = 0.62$) was found.

Suicidal Ideation

Suicidal ideation was assessed by using one item from the Children's Depression Inventory-2 (CDI-2; Kovacs, 2015; Italian adaptation by Camuffo and Cerutti, in press) The item has three response options that score 0 (*absence of suicidal ideation*), 1 (*mild suicidal ideation*), or 2 (*severe suicidal ideation*). For our purposes, we recoded this item by merging the last two response-choices into one. The new dichotomous variable ranged from 0 (absence of suicidal ideation) and 1 (presence of suicidal ideation).

Difficulty in Identifying and Describing Feelings

For this study, we assessed the difficulty in identifying feelings (DIF) and describing feelings (DDF) by using the difficulty in

identifying feelings subscale (DIF-S) and difficulty in describing feelings subscale (DDS) of the Alexithymia Questionnaire for Children (AQC; Rieffe et al., 2006; Di Trani et al., 2009). The DIF-S is composed by seven items (e.g., "I am often confused about the way I am feeling inside"; $\alpha = 0.77$) whereas the DDF-s by five items (e.g., "I find it difficult to say how I feel inside; $\alpha = 0.64$). Both subscales are scored on a three-point rating scale (from 0 = not true to 2 = often true) and assessed the degree to which children feel unable to recognize and describe their own feelings. Both subscales showed positive correlations with somatic problems and several negative moods like anger, sadness, and fear (Rieffe et al., 2006).[1]

The Inventory of Parent and Peer Attachment

The Inventory of Parent and Peer Attachment (IPPA; Armsden and Greenberg, 1987) was used to measure the quality of parent (IPPA-PA) and peer (IPPA-PE) attachment in adolescence. The good psychometric properties of the IPPA have been already confirmed in several studies with Italian samples (Laghi et al., 2009; Pace et al., 2011). The Parent Attachment Scale consists of 28 items whereas the Peer Attachment Scale consists of 25 items. The items of both instruments were scored on a five-point scale (from 1 = "not true at all" to 5 = "completely true") and assessed three dimensions of attachment, respectively: "Trust," "Communication," and "Alienation." The Trust scale measures the extent to which adolescents trust their parents ($\alpha = 0.82$) and peers ($\alpha = 0.88$) to respect and accept their feelings (e.g., "My parents/peer respect my feelings"). The Communication scale measures the extent adolescents experience having a high quality of communication (e.g., "When my parents/friends know that something is bothering me, they ask me about it") with their parents ($\alpha = 0.78$) and peers ($\alpha = 0.85$). The Alienation scale measures the degree to which adolescents experience negative feelings (e.g., "I don't get much attention from my parents/friends") toward parents ($\alpha = 0.80$) and peers ($\alpha = 0.71$). For our purposes, the individual's mean score on the three scales was considered as the indicator of parent and peer attachment. Furthermore, these aggregated scores were highly reliable: alphas for the global attachment scale toward parent and peers were, respectively, 0.84 and 0.77.[2]

Life Stressor Checklist-Revised

A reduced 13-item version of the *Life Stressor Checklist-Revised* (Wolfe et al., 1996; Giannantonio, 2005) was used to assess the presence and impact of a variety of stressful or traumatic events that may have occurred in the participant's life. Specifically, participants are asked to indicate whether or not they experienced each event, as well as their level of distress in response to the events they endorsed. For the present study, the dichotomous responses (yes vs. no) to all of the items were summed to create an overall measure of the number of stressful life events experienced.

[1] Although we also assessed the subdimension of externally oriented thinking, we did not include it because it showed very low reliability (for similar findings and considerations, see also Rieffe et al., 2006).

[2] Before computing the reliability the Alienation scale was recoded.

Data Analytical Approach

As a preliminary step, we computed the correlations among the variables of interest. Then, we examined the hypothesized model (**Figure 1**) in a structural equation modeling (SEM) framework using M*plus*8 (Muthén and Muthén, 1998–2017). A general latent factor measuring participants' difficulty in identifying and describing their feelings was modeled by using the two subscales DIF-S and DDS-S. The composite mean scores of IPPA-PA and IPPA-PE scales were used as the indicators to model parental and peer attachment. These variables were posited as single indicator latent variables by estimating the error terms from their reliabilities (Kline, 2010). As suicidal ideation was coded as a dichotomous variable, parameter estimates were based on the Weighted Least Squares Mean-Variance adjusted (WLSMV) estimator. This method is particularly suited for dealing with categorical data. Specifically, M*plus* 8 computed probit regression coefficients (Muthén and Muthén, 1998–2017) to assess the impact of our predictors on the dichotomous outcome variable suicidal ideation (Muthén and Muthén, 1998–2017). Non-significant χ^2 likelihood ratio statistic, comparative fit index (CFI) and Tucker-Lewis index (TLI) greater than 0.95, and root mean square error of approximation (RMSEA) values lesser than 0.05 (Kline, 2010) were considered as indicators of a good model fit. According to the principle of *parsimony* (i.e., reducing the model's complexity by increasing the number of degrees of freedom without worsening the fit), we tested a series of increasingly liberal mediational models, in which direct paths from independent variables to our outcome variables (i.e., suicidal ideation and self-harm) were sequentially freely estimated. In detail, we estimated a full mediational model (i.e., without direct effects from our focal predictors parent and peer attachment to our distal outcomes suicidal ideation and self-harm). Next, we added the direct effects to evaluate if a partial mediational model significantly fit the data. According to MacKinnon (2008), paths were retained only if they resulted in a significant increment of model fit (we compared these nested models by using the DIFFTEST function in M*plus*8; Muthén and Muthén, 1998–2017). In line with recent recommendations (Hayes and Scharkow, 2013), we computed the 95% bias-corrected confidence intervals (CI) to formally test the significance of our hypothesized mediational effects (ab). If the lower and upper limits of the 95% CI did not include zero, we concluded that the mediated effect was statistically different from zero. Finally, both participants' sex and life events were used as control variables in order to partial out their effects.

RESULTS

Sample Characteristics

The participants mean age was 12.6, with a standard deviation of 1.06. Among adolescents 83% reported at least one brother or sister. Socio-demographic characteristics of parents are described in **Table 1**.

According to Gratz inventory (Gratz, 2001), results indicated that 204 adolescents (28.8%) endorsed at least one lifetime

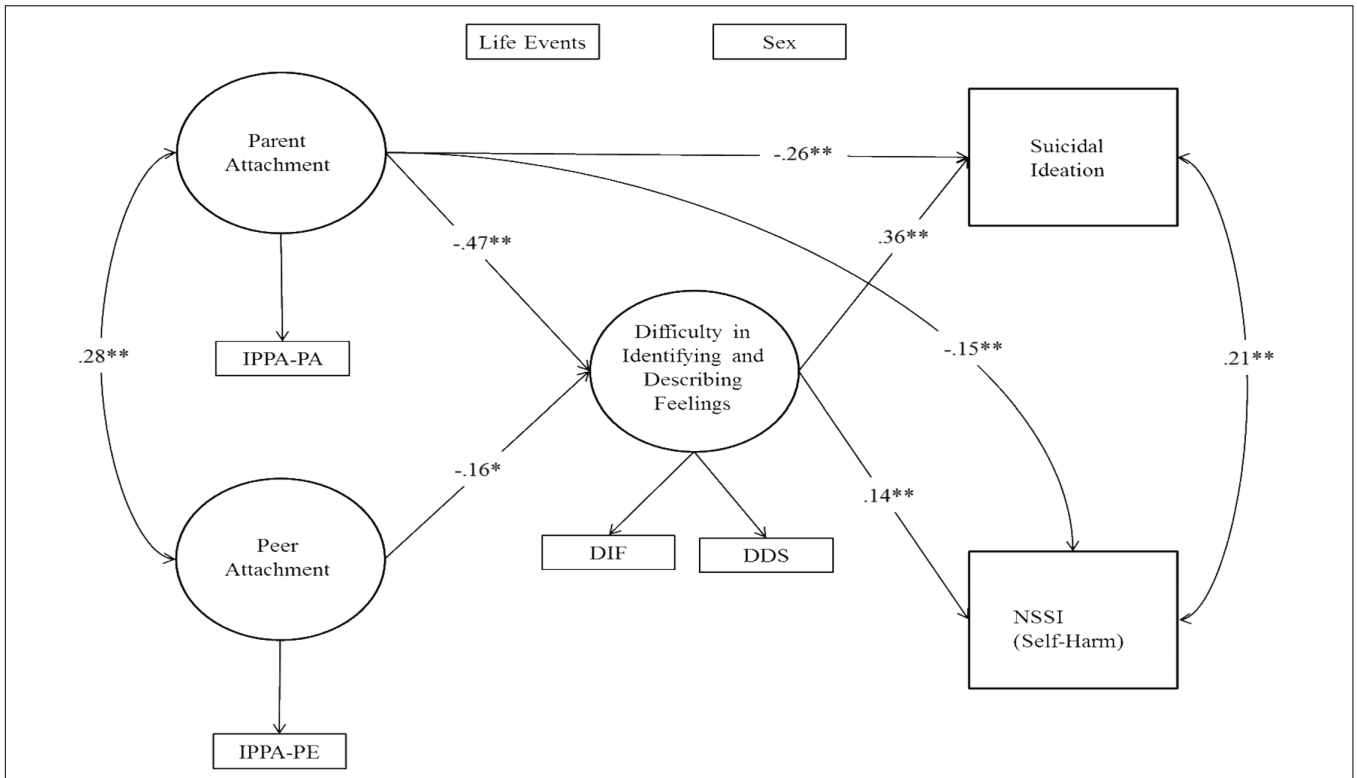

FIGURE 1 | Mediational model. Variance explained (R^2). Difficulty in identifying and describing feelings (R^2 = 0.434); suicidal ideation (R^2 = 0.328); NSSI (R^2 = 0.156). The effects of sex and stressful events were estimated but not depicted for the sake of simplicity.

episode of NSSI and 97 of them (13.7%) reported more than one episode with at least two different methods while only1.4% reported engaging in repetitive NSSI (≥5 episodes) during the last year. Detailed results are reported in **Table 1**. No statistical differences between boys and girls emerged regarding the presence or absence of NSSI behavior.

Correlation Analysis

Correlations were mostly as expected (**Table 2**). Suicidal ideation, NSSI, difficulty in identifying and describing feelings were (a) positively correlated with stressful life events and (b) negatively correlated with both parental and peer attachment. Girls were more likely to report higher difficulties in identifying their feelings than boys.

TABLE 1 | Sample description.

		Total (*N* = 790)%	Boys (*n* = 357)%	Girls (*n* = 352)%
Educational level	Primary	20		
	Secondary	42		
	University	33		
	Missing	5		
Civil status	Single	0.7		
	Married/cohabiting	77.2		
	Separated/divorced	12.4		
	Widowed	2.3		
	Missing	7.4		
NSSI behavior	Presence	28.8	16.1	12.7
	Absence	71.2	34.3	36.9

Mediational Models

The full mediational model showed a marginal fit $\chi^2(9) = 25.82$, $p < 0.001$, CFI = 0.98, TLI = 0.94, RMSEA = 0.05 [90% CI: 0.03, 0.08]. Thus, we proceeded by testing two partial mediational models. First, we added the direct paths from peer attachment to both suicidal ideation and NSSI. This partial mediational model showed a marginal fit $\chi^2(7) = 26.01$, $p < 0.001$, CFI = 0.98, TLI = 0.92, RMSEA = 0.06 [90% CI: 0.04, 0.09] and was not statistically different from the full mediational model $\Delta\chi^2(2) = 2.22$, $p = 0.33$. Then, we estimated a second partial mediational model in which we added the direct paths from parental attachment to both suicidal ideation and NSSI. This partial mediational model showed a perfect fit to the data and $\chi^2(7) = 10.01$, $p = 0.19$, CFI = 1.00, TLI = 0.99, RMSEA = 0.03 [90% CI: 0.00, 0.06] and was statistically different from the full model $\Delta\chi^2(2) = 13.91$, $p = 0.001$, thereby providing evidence for freely estimating the direct effects of parental attachment.

Once selected the second partial mediational model as the best fitting one, we computed the 95% CI for our hypothesized mediational effects. Results indicated that higher levels of parental attachment (ab = −0.27, [95% CI: −0.44, −0.15]) and peer attachment (ab = −0.10, [95% CI: −0.21, −0.03])

TABLE 2 | Correlation matrix.

	NSSI	Sui-Id	DIF	DDF	IPPA-PA	ATTP	Str. events	Sex
NSSI	–	0.320***	0.261***	0.212***	−0.276***	−0.131***	0.314***	−0.064
Sui-Id		–	0.357***	0.232***	−0.331***	−0.154***	0.227***	0.010
DIF			–	0.603***	−0.451***	−0.164***	0.351***	0.096*
DDF				–	−0.391***	−0.219***	0.284***	0.060
IPPA-PA					–	0.232***	−0.316***	0.008**
IPPA-PE						–	−0.129***	0.243***
Str. events							–	−0.037
Sex								–

*NSSI, non-suicidal self-injury; Sui-Id, suicidal ideation (0 = absence of suicidal ideation, 1 = presence of suicidal ideation); DIF, difficulty in identifying feelings; DDF, difficulty in describing feelings; IPPA-PA, parent attachment; IPPA-PE, peer attachment; sex (0 = boys, 1 = girls). *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.*

were related to a lack of suicidal ideation via the mediational role of difficulty in identifying and describing feelings (the 95% asymmetric lower and upper CI limits did not include zero). Similarly, the difficulty in identifying and describing feelings significantly mediated the effect of parental attachment (ab = −0.18, [95% CI: −0.23, −0.02]) and peer attachment (ab = −0.04, [95% CI: −0.10, −0.01]) on NSSI.

Alternative Mediational Model

We also investigated the fit of three alternative models representing plausible alternative explanations of the covariance structure. First, we tested an alternative model in which we posited NSSI and suicidal ideation as independent variables and parental and peer attachment as distal outcomes (the difficulty in identifying and describing feelings was the mediator). This alternative model showed a good fit, $\chi^2(7) = 12.31$, $p = 0.09$, CFI = 0.99, TLI = 0.98, RMSEA = 0.03 [90% CI: 0.00, 0.06] similar to the hypothesized mediational model, suggesting that both models could be equally appropriate to explain our data. The second alternative model, in which we posited the difficulty in identifying and describing feelings as the primary predictor, parent and peer attachment as the mediators, and NSSI and suicidal ideation as outcomes, showed a lower fit $\chi^2(7) = 30.61$, $p < 0.001$, CFI = 0.97, TLI = 0.90, RMSEA = 0.07 [90% CI: 0.05, 0.10] compared to the hypothesized model. Finally, the third alternative model, in which we considered parent and peer attachment as primary predictors, NSSI and suicidal ideation as mediators, and the difficulty in identifying and describing feelings as distal outcome, showed an unacceptable fit $\chi^2(7) = 73.74$, $p < 0.001$, CFI = 0.92, TLI = 0.70, RMSEA = 0.12 [90% CI: 0.09, 0.14] compared to the hypothesized model.

DISCUSSION

The primary aim of this study was to investigate the difficulties in identifying and describing feelings, two core facets of alexithymia, and NSSI behavior among a sample of Italian students. Our findings highlighted that self-harmers have higher difficulties in identifying and describing their own feelings, confirming the fact that they are perplexed about their emotions and find it difficult to distinguish between them (Taylor et al., 1997; Hamza et al., 2015). This result moves us in the direction of supporting an affect regulation function of NSSI in which adolescents with difficulties in identifying and describing their feelings may use NSSI as a way of regulating their emotions (Klonsky and Muehlenkamp, 2007), and is consistent with a previous study using a community sample of high school students (Laukkanen et al., 2013).

Importantly, we also tested a theoretical mediational model in which the difficulty in identifying and describing feelings was the mediator of the associations between NSSI and quality of attachment toward both parents and peers. Results supported the hypothesized mediation model: low levels of quality of attachment may enhance the risk of both NSSI and suicidal ideation by compromising adolescents' abilities to identify their own feelings. This result is in line with findings showing the importance of quality attachment in emotion regulation. Specifically, a negative environment (i.e., neglectful environments) influences the nature and quality of the relationships in which parents and children engage and it may interrupt the development of healthy emotion regulation skills in children and adolescents (Trickett et al., 2011; Peh et al., 2017; Williams et al., 2017). There is evidence that a lack of attachment security in early life affects the development of processes involved in emotion regulation (Schore, 2001; Taylor, 2010). In other words, the child who in absence of a secure attachment to parents fails to develop adequate self-regulatory capacities (Taylor, 2010). Similarly, our results also support the importance in extending the investigation on attachment beyond early childhood through to adolescence, and particularly in investigating the perceptions adolescents have of the quality of their actual attachment relationships. Specifically during adolescence age, the interactions with peers assume an increasingly higher priority, attachment behavior is also often oriented toward non-parental figures (Kerns et al., 2006) because peers are perceived as primary sources of consolation and support.

Accordingly, it seems that poor emotional bonds with both parents and peers may act as distal risk factors for developing later psychopathology. Our findings confirm that NSSI behaviors can be considered as a dysfunctional emotion-regulation strategy in presence of a inability to identifying feelings, consistent with recent results of Peh et al. (2017) that suggested how NSSI may be viewed as maladaptive attempts to cope with negative effects.

However, our model also suggests that these negative effects might be counteracted by helping adolescents understand and recognize their own feelings. In a systematic review of the literature exploring the link between alexithymic features and NSSI, Norman and Borrill (2015) showed that individuals, who are able to understand and communicate their feelings, are likely to engage in NSSI behaviors in order to regulate their emotions. Furthermore, identifying and labeling an emotional experience in itself reduces emotional intensity that, in turn, may help to prevent the perceived need to engage in NSSI (Sleuwaegen et al., 2017).

This result can have high clinical relevance if we consider that, to date, only a few studies have investigated the mediational role played by core alexithymic facets in association with NSSI behaviors and other risk factors during early adolescence and adolescence. For instance, Garisch and Wilson (2010) found that alexithymia mediated the association between bullying and self-harm in high school students. This is in line with the findings of the present study supporting the hypotheses that the inability to regulate and communicate emotions in a normally adaptive way plays an important role in NSSI behaviors. The role of alexithymia in maladaptive behavior was also explored by Swannell et al. (2012) who reported that alexithymia (i.e., difficulty in describing feelings) partially mediated the effect of childhood abuse on self-harm in females but not in males.

Consistent with other studies, our findings indicated that NSSI is moderately prevalent among a non-clinical adolescent population (Hilt et al., 2008). Specifically, 28.8% reported one or more lifetime histories of NSSI behaviors (<5) while 1.4% reported engaging in repetitive NSSI (five or more episodes during the last year) using different methods.

Moreover, adolescents who engaged in NSSI showed a poor perception of quality of attachment with both parents and peers. This is consistent with literature indicating that early attachment relationships have important implications for mental health later in life (Arbuthnott and Lewis, 2015) and in line with study Hallab and Covic's (2010), which measured attachment by the same tool adopted in this paper and showed that those who self-injured had the worst perceived quality of attachment to parents compared with those who did not intentionally hurt themselves.

With regards to suicidal ideation, findings revealed that suicidal ideation is negatively related to quality of attachment to parents and peers and positively correlated with DIF. Suicidal thought is also positively correlated with the number of stressful events.

Parcel and part of our analysis, we also confirmed that a greater number of life events (as reported by adolescents) were an additional risk factor for NSSI episodes. While a positive perception of the quality of attachment to parents and to peers was related to a smaller number of NSSI behaviors.

However, while a history of childhood trauma has been reported as a common risk factor for NSSI, the role of family, peer relationships and attachment has not been thoroughly explored. Given the limited studies investigating these interrelations, the current study is an important contribution to the extant literature. With regard to the relationship between stressful life events and NSSI, a previous cited study by Paivio and McCulloch (2004) restricted its focus exclusivity on child maltreatment as predictor variable in their mediational model, and did not consider other types of traumatic or stressful life events.

Conversely, consistent with recent research findings (Cerutti et al., 2011; Liu et al., 2014), the present study extend the focus on other important adverse experiences not only maltreatment. In fact, our results provide evidence that an increased frequency of NSSI is associated with a greater number of stressful life events as experience of sexual harassment, being victim of bullying, witnessing potentially traumatic events, etc.

Limitation

Our study has several limitations that should be addressed. First, our data were correlational in nature and, therefore, no relationships of cause-effect could be established. Second, although we tested for possible alternative models, we recognize that longitudinal data are superior for analyzing mediational hypotheses. In particular, future longitudinal studies should test the possible reciprocal influences among attachment, NSSI, and suicidal ideation as suggested by the good model fit reported by the first alternative model. Third, the value of retrospective histories of stressful or traumatic experiences might be questionable, given the possibility of under-reporting, over-reporting or false memory. Lastly, social desirability response bias may also have affected the results.

Clinical Implication

Despite these limitations, the present study highlights the risk factors having a significant impact upon NSSI among early adolescents who reported engaging in self-injury behavior when compared to their non-injuring counterparts. These findings add further information to the scant existing literature about possible links between core alexithymic facets (i.e., difficulty in identifying and describing feelings) and NSSI and their relationships with perceived attachment quality, stressful life events and suicidal ideation. Specifically, when the quality of attachment with both peers and parents is compromised, helping children understand their own emotions may reduce the risk of higher NSSI and suicidal thoughts.

However, more research is needed to further explore the variables considered in this study. There is, therefore, a need for more data to better understand this association in order to provide useful information for the planning of preventive interventions in younger populations.

AUTHOR CONTRIBUTIONS

All of the authors have substantially and equally contributed to the development and preparation of the manuscript. Furthermore, all the authors have approved the final version of the manuscript. Finally, all authors have agreed to be accountable for all aspects of the manuscript in ensuring that questions related to the accuracy or integrity of any part of it are appropriately investigated and resolved.

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SYSTEMATIC REVIEW
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The Relationship Between Alexithymia and Emotional Awareness: A Meta-Analytic Review of the Correlation Between TAS-20 and LEAS

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Background: Alexithymia and emotional awareness may be considered overlapping constructs and both have been shown to be related to psychological and emotional well-being. However, it is not clear how the constructs relate to each other empirically or if they may overlap more or less in different populations. The aim of this review was therefore to conduct a meta-analysis of correlations between the most commonly used measures of alexithymia (i.e., the self-report instrument Toronto Alexithymia Scale; TAS-20) and emotional awareness (i.e., the observer-rated instrument Level of Emotional Awareness Scale; LEAS) and to explore potential moderators of their relationship.

Methods: Electronic databases were searched for studies published until the end of February 2018. Study samples were coded as medical conditions, psychiatric disorders and/or healthy controls and sample mean age and gender distribution were extracted. Correlations between the TAS-20 and the LEAS were subjected to a random effect of meta-analysis and moderators were explored in subgroup analyses and meta-regressions. Publication bias was considered.

Results: 21 studies reporting on 28 independent samples on correlation analysis were included, encompassing a total of 2857 subjects (57% women). The aggregated correlation between TAS-20 and LEAS was $r = -0.122$ (95% CI [−0.180, −0.064]; $Z = -4.092$; $p < 0.001$), indicating a significant, but weak, negative relationship between the measures. Heterogeneity was moderate, but we found no indication of significant differences between patients with medical conditions, psychiatric disorders or healthy controls, nor that mean age or percentage of female subjects moderated the relationship. The overall estimate became somewhat weaker after adjusting for possible publication bias.

Conclusions: Our results indicate that TAS-20 and LEAS measure different aspects of emotional functioning. The small overlap suggests that alexithymia and emotional awareness are distinct constructs of emotional well-being. Clinicians need to assess both aspects when considering treatment options for individual patients. Moreover, from the

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clinical standpoint, an easy reliable and valid way of measuring emotional awareness is still needed. More research should be focus on the differences between alexithymia and emotional awareness in specific conditions, but also how to integrate self-report instrument and observed based measures in a clinical situation.

Keywords: alexithymia, level of emotional awareness, LEAS, toronto alexithymia scale, TAS-20, meta-analysis

INTRODUCTION

Alexithymia, which literally means "lack of words for emotion," is conceptualized as a general impairment in the capacity for processing emotional information, relating to both verbal and non-verbal stimuli (Lane et al., 1996). Individuals who are high in alexithymia have difficulties identifying their own or others' feelings (Lane and Schwartz, 1987) and show an externally-oriented thinking style and a scarcity of fantasy life (Taylor et al., 1997). An externally-oriented thinking style refers to a person's tendency to be concrete, stimulus-bound and oriented to practical aspects of a situation.

Several concepts partly overlap with alexithymia, such as emotion suppression, isolation, denial, and repression. However, while these concepts refer to active, defensive processes that reduce the experience or expression of emotion, alexithymia is generally considered to be a deficit rather than a defense (Lumley et al., 2010). The question of what type of deficit constitutes alexithymia, have not been settled. According to Lane et al. (2015a), an important question is whether the difficulty in putting emotions into words is observed because alexithymic individuals know what they feel but have difficulty describing it, or that simply are unaware of what they feel.

Another construct closely related to alexithymia is emotional awareness (Lane and Schwartz, 1987). Both concepts encompass potential difficulties in identifying one's own and others' feelings and having difficulties putting emotions into words. Emotional awareness can be said to be a facet of alexithymia, but is narrower in scope since its definition does not entail limited imaginal ability and externally-oriented thinking (Lumley et al., 2010).

Several self-report instruments to capture alexithymia are available (see for example the Bermond-Vorst Alexithymia Questionnaire, the Schalling-Sifneos Personality Scale and the MMPI alexithymia scale), but since its revision, the Toronto Alexithymia Scale-20 (TAS-20) has more or less become a standard in the field (Lumley et al., 2010). The TAS-20 is a 20 item self-report questionnaire measuring alexithymic traits using a five-point Likert scale (Bagby R. M. et al., 1994). The instrument includes three subscales: (1) Difficulty Identifying Feelings (DIF), (2) Difficulty Describing Feelings (DDF) and (3) Externally Oriented Thinking (EOT). The TAS-20 has been translated into 18 different languages and has shown rather robust reliability data (Taylor et al., 2003; albeit see also Kooiman et al., 2002). Studies have supported the construct validity by showing that high scores on TAS-20 are correlated with lower levels of psychological mindedness, need-for-cognition and openness to feelings and fantasy (Bagby M. et al., 1994) as well as affective orientation and emotional intelligence (Taylor et al., 2016), providing support that the TAS-20 captures an impairment in experiencing and describing emotions and is a valid measure of the alexithymia construct (Taylor et al., 2016).

Despite TAS-20 being in common use, it has been argued that what can be reported in self-report instruments such as the TAS-20 is actually a respondent's belief about her or his own ability to be emotionally aware and not actual emotional awareness capacity (Lundh et al., 2002). Observer-rated instruments may address this caveat and have been recommended to be used simultaneously with self-report instruments (Waller and Scheidt, 2006). Such instruments may include performance tests, where emotional capacity is directly assessed, or observer-based ratings, where emotional awareness capacity is judged by an external observer. A few performance tests (see for example the Level of Emotional Awareness Scale, the Rorschach Inkblot Test and the Scored Archetypal Test) and several observer ratings (see for example the Affect Consciousness Interview, the Beth Israel Hospital Questionnaire, the 24-item Toronto Structured Interview for Alexithymia and the 33-item Observer Alexithymia Scale) exist.

Since its conception, the Level of Emotional Awareness Scale (LEAS; Lane et al., 1990), with its straightforward administration and interpretive procedure, has become an increasingly used observer-rated test to capture facets of alexithymia and emotional awareness. The test consists of 20 vignettes that describe emotion-provoking interactions between two persons. Scores from 0 to 5 are assigned for the categories "self," "other," and "total," with lower scores reflecting a lower level of emotional awareness. The inter-rater reliability of LEAS is typically high, with several studies having a Cronbach alpha of 0.90 and over. The LEAS has also met certain demands for criterion validity since it correlates with for example empathy and psychological maturity (Lane et al., 1990; Bydlowski et al., 2002; Igarashi et al., 2011). The instrument has been found to predict emotion-related criteria, such as the ability to identify emotions and physiological brain activation in response to emotional stimuli (Lane et al., 1995, 1996).

Research using both measures of alexithymia (TAS-20) and emotional awareness (LEAS) is still not that common. Studies although exist for different populations, including psychiatric, medical and healthy participants. Regarding psychiatric populations, somatoform/functional disorders and eating disorders have been more prominent studied. Correlations between TAS-20 and LEAS have consistently been negative, albeit not significant (Simson et al., 2002; Bydlowski et al., 2005; Subic-Wrana et al., 2005; Parling et al., 2010; Baker et al., 2014; Lane et al., 2015a). For healthy participants (including healthy controls) the results have been mixed, with a few studies

showing positive correlations (Lundh et al., 2002; Waller and Scheidt, 2004; Bydlowski et al., 2005) although most studies show a negative association (Lane et al., 1998b; Subic-Wrana et al., 2001; Lumley et al., 2005; Parling et al., 2010; Igarashi et al., 2011; Baeza-Velasco et al., 2012; Baker et al., 2014; Lichev et al., 2014; Maroti et al., 2017). In the few studies including medical conditions (or medical controls), the results have also been mixed, with some studies showing positive associations (Baeza-Velasco et al., 2012; Maroti et al., 2017), while others do not (Consoli et al., 2009; Lane et al., 2015a; Burger et al., 2016; Neumann et al., 2017).

Despite the fact that the concepts of alexithymia and emotional awareness overlap theoretically, and that instruments such as the TAS-20 and LEAS have co-existed for more than 20 years, it is not quite clear how the constructs relate to each other empirically. Further, we do not know if alexithymia and emotional awareness may be more or less closely related in different patient populations. Therefore, the primary aim of this study was to perform a meta-analysis on the correlations between TAS-20 and LEAS. Given the construction of TAS and LEAS, a significant negative correlation was a primary hypothesis (i.e., higher self-reports of alexithymia would correlate with a lower level of emotional awareness). We further aim to explore potential moderators (age, gender, medical conditions) of the relationship. Since the relationship between these commonly used measures has not been investigated thoroughly before, our findings may yield important implications for theory, as well as for the measurement of alexithymia and emotional awareness in research and clinical practice.

METHODS

Information Sources and Literature Search

The International Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009) were used during the systematic search procedure. Searched databases included Pubmed, PsychInfo, MedLine, Web of Science, Cochrane, and ScienceDirect. We also searched through Karolinska Institutet's own search database called reSearch, an alternative to Scopus database, as well as an Internet search through Google Scholar. Each database was searched from its inception until the end of February 2018. The following terms were applied for the search strategy: "TAS-20 and LEAS" and "Toronto Alexithymia Scale and Level of Emotional Awareness," excluding for Google Scholar. For Google Scholar the search term "TAS-20 and Level of emotional awareness" resulted into 198 items, which was more relevant to handle as compare to several thousands of hits when applying the terms "Toronto alexithymia scale" and "LEAS." Furthermore, Google Scholar interpreted the "LEAS" as "Less."

Usually the first combination ("TAS-20 and LEAS") resulted in a larger number of articles than comparing with the other one ("Toronto Alexithymia Scale and Level of Emotional Awareness"). For calculation of the total amount of records in **Figure 1**, the results only of one combination (the large one) were included. This yielded 260 potentially relevant articles.

Eligibility Criteria

Eligible articles included only original research studies published in peer-reviewed journals. We screened articles written in English, Germany, French, Italian, Spanish, Turkish and Persian if they have had English-written abstract and readable report data on TAS-20 and LEAS in the result section. In some articles, the correlations were mentioned as non-significant but not presented in detail. Therefore, we contacted 19 authors of those articles and asked for correlation data. In six cases, further data was obtained and included into the analysis. A total of 21 studies could finally be included in the meta-analysis.

Review articles, dissertations, books, publications related to scientific meetings, case reports and those articles having—for the authors of this article—unreadable languages in the abstract and/or result section (Turkish and Persian) were excluded. We also excluded 3 studies publishing data from the same cohort. Additionally, 121 articles were excluded because of inclusion/exclusions criteria and/or using the same cohort (3 articles). Almost all of the included studies were cross-sectional. In a few studies interventions were made and in that case the initial data of TAS-20 and LEAS was used.

Selection of Articles and Data Extraction

Two authors (D.M. and I.B-L.) completed data extraction from the databases, according to the search terminology and eligibility criteria. They also read the abstracts and result section in order to identify the scales used for measurements. If necessary, they contacted corresponding authors for further details. Finally, if articles met the inclusion criteria, the full-text articles were extracted from databases or by ordering them from Karolinska Institutet's Library. All authors reached a consensus regarding eligibility criteria and inclusion of the article into the meta-analysis.

The following data was extracted for analysis: the size and characteristics of sub- and total groups, the main pathology studied, the values of TAS-20 and LEAS presented in mean and standard deviation, the coefficients and p-values of correlations between total TAS-20 and total LEAS.

Meta-Analytic Procedures

The correlations between TAS-20 and LEAS and their corresponding sample sizes were entered into the software program Comprehensive Meta-Analysis (CMA; version 2.2.064; Biostat, Englewood, NJ, USA). Procedures within CMA were then used to calculate study weights and the aggregated mean correlation, including its 95% confidence interval. The random-effects model (REM) was applied since we a priori assumed that the true correlation would differ between samples considering the broad inclusion criteria in terms of study populations (Borenstein et al., 2009).

When interpreting the aggregated mean correlation, we followed established conventions in the field and considered a correlation of $\geq$0.10 as weak, $\geq$0.30 as moderate, and $\geq$0.50 as strong (Cohen, 1992). We inspected forest plots for potential outliers and performed sensitivity analyses (using the "one study removed" and "cumulative analysis" features in CMA) to inspect the impact of single studies or samples.

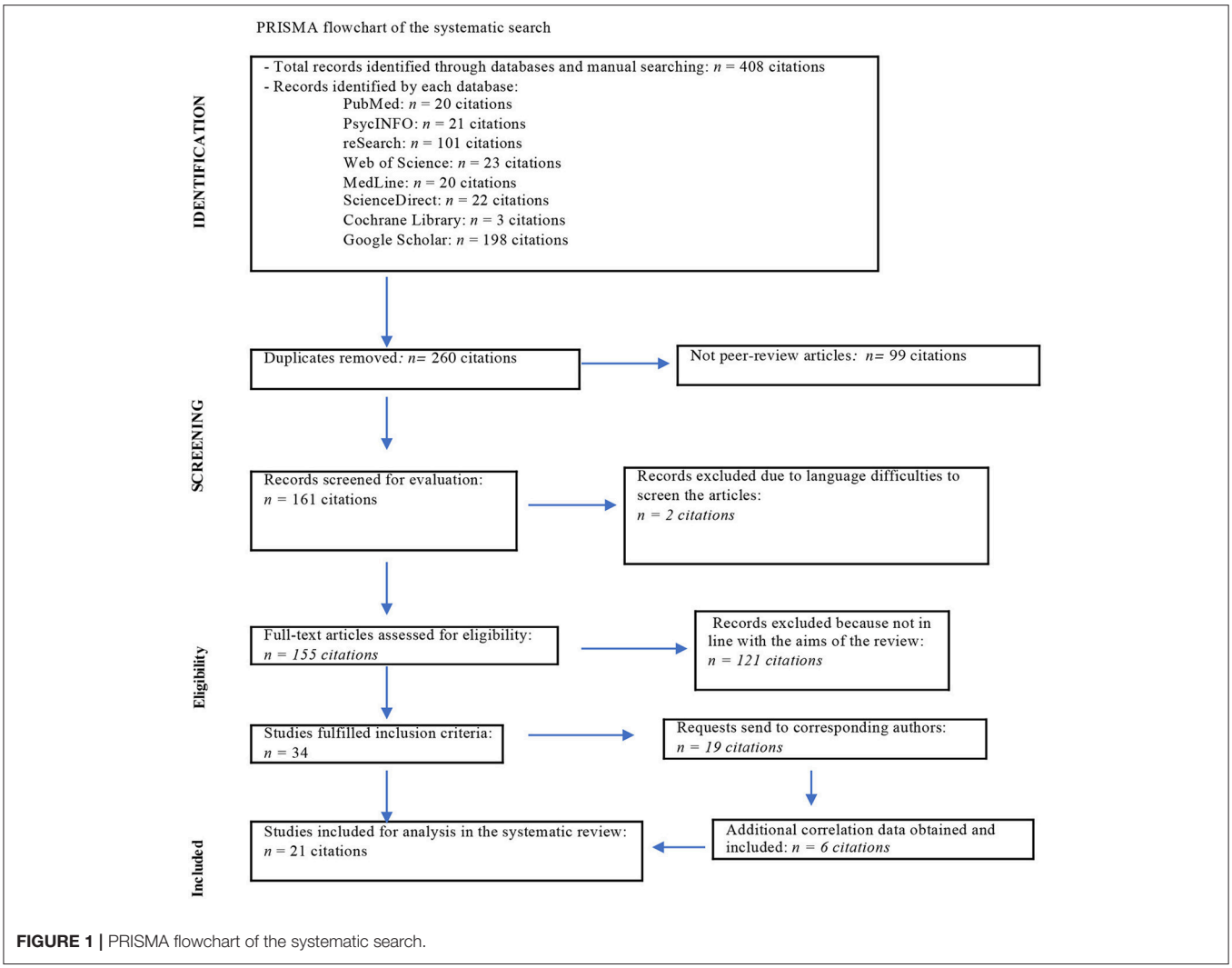


FIGURE 1 | PRISMA flowchart of the systematic search.

We calculated the Q statistic to test for between-sample heterogeneity and we also estimated the I^2 statistic, which expresses the degree of heterogeneity in terms of percentages: an I^2 value of 0% indicates no heterogeneity, ≥25% low, ≥50% moderate, and ≥75% indicates substantial heterogeneity (Higgins et al., 2003). A higher I^2 value suggests a greater potential for explaining any observed heterogeneity by exploring subgroups and covariates.

Moderators

Subgroup analyses within CMA were used to test if the association between TAS-20 and LEAS differed in different samples. Due to the low number of studies for specific conditions, we decided to group the study samples in three main categories: "Healthy Controls" (e.g., university students, stratified community samples), "Psychiatric Conditions" (e.g., eating disorders, substance disorders, mixed psychiatric disorders, somatoform disorders) or "Medical Conditions" (e.g., hypertension, traumatic brain injury, rheumatoid arthritis, fibromyalgia, chronic fatigue syndrome). Two studies were excluded from subgroup analyses since the samples could not be coded; Suslow et al. (2000) used a mixed sample of psychiatric patients and healthy controls and Pietri and Bonett (2016) studied women with or without a history of domestic violence with no data on diagnoses. The mixed effects method for subgroup analysis was used and since there were few studies in each group we pooled the estimate of Tau-Square across the subgroups as recommended by Borenstein et al. (2009).

Further, we also extracted continuous sample data for mean age and the percentage of females and applied random effects (method of moments) meta-regression models (Borenstein et al., 2009) in order to test for these as possible covariates of the main effect. Two studies (Lane et al., 1998b; Subic-Wrana et al., 2001) did not include data for sample mean age and were thus excluded from that specific analysis.

Publication Bias

Lastly, we examined the possible presence of publication bias by inspecting funnel plots and applying (Duval and Tweedie, 2000) a trim-and-fill procedure (as implemented in Comprehensive

Meta-Analysis version 2.2.064 package). The random effects model was applied in this procedure as well.

RESULTS

Study Characteristics

Study characteristics are presented in **Table 1** (Lane et al., 1998b, 2015a; Suslow et al., 2000; Lundh et al., 2002; Simson et al., 2002; Waller and Scheidt, 2004; Bydlowski et al., 2005; Lumley et al., 2005; Consoli et al., 2009; Parling et al., 2010; Subic-Wrana et al., 2010; Igarashi et al., 2011; Baeza-Velasco et al., 2012; Lichev et al., 2014; Maroti et al., 2017; Neumann et al., 2017). In summary, the 21 studies included a total of 2,857 subjects and were conducted in six different countries (France, $k = 5$; Germany, $k = 6$; Japan, $k = 1$; Sweden, $k = 3$; USA, $k = 5$ and Australia, $k = 1$). The 21 studies investigated TAS-20 and LEAS in a total of 28 independent samples: twelve samples of healthy controls (total $n = 1561$), six samples of patients with medical conditions ($n = 328$), eight samples of patients with psychiatric conditions ($n = 820$) and two studies with a mixed sample of psychiatric patients and healthy controls ($n = 148$). The mean age across all samples was 37 year and on average 57% of sample subjects were female.

Meta-Analytic Results

The aggregated mean correlation across all 28 samples was $r = -0.122$ (95% CI [−0.180, −0.064]; $Z = -4.092$; $p < 0.001$), suggesting a significant, but small, correspondence between the measures. We found no indication of outliers in sensitivity analyses and confidence intervals largely overlapped across samples (see forest plot in **Table 2**). Still, heterogeneity was significant ($Q = 52.32$; $p = 0.002$) and low to moderate ($I^2 = 48.39$), indicating that the aggregated mean correlation may differ among subgroups of samples and/or may be moderated by covariates.

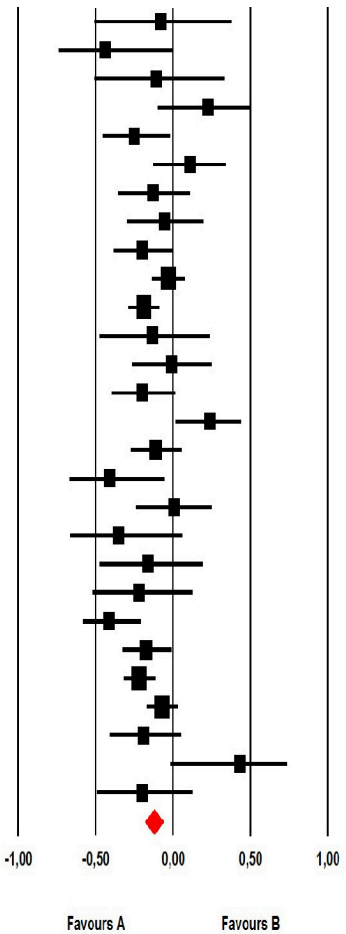
TABLE 1 | Study characteristics and descriptive statistics.

Study	Country	Sample	Coded as	*n*	% female	Mean age	TAS-20 total (SD)	LEAS-20 total (SD)
*Baker et al., 2014	Australia	Functional voice disorder HC	Psychiatric	20 20	100	39	X	76.2 (9.8) 80.8 (7.7)
*Baeza-Velasco et al., 2012	France	Musculoskeletal disorders HC	Medical	39 22	100	53	48.7 (11.5) 39.7 (12.7)	53.4 (7.1) 54.8 (6.2)
Burger et al., 2016+	USA	Chronic musculoskeletal pain	Medical	72	79	49	50.8 (12.3)	31.3 (5.2)
Bydlowski et al., 2005	France	Eating disorders HC	Psychiatric	70 70	100	19	75.9 (11.3) 66.9 (10.9)	61.0 (8.8) 66.4 (6.0)
*Carton et al., 2010	France	Substance disorders	Psychiatric	64	22	38	56.2 (11.7)	50.0 (8.33)
Consoli et al., 2009	France	Essential hypertension secondary hypertension	Medical	73 25	55 48	53 52	52.4 (11.6) 48.4 (12.1)	46.2 (11.5) 52.8 (8.4)
Igarashi et al., 2011	Japan	University students	Healthy	344	65	20	44.1 (9.4)	50.0 (9.38)
Lane et al., 1998b	USA	Healthy participants	Healthy	380	52	X	X	X
*Lane et al., 2015a+	USA	Somatic symptom disorders Mixed medical conditions	Psychiatric Medical	59 30	85 67	43 45	51.81 (13.1) 44.45 (12.7)	32.8 (4.28) 32.3 (4.85)
Lichev et al., 2014+	Germany	Healthy participants	Healthy	84	46	24	46.7 (10.1)	36.1 (5.1)
Lundh et al., 2002	Sweden	Healthy participants	Healthy	78	83	28	42.0 (9.1)	68.3 (8.9)
Lumley et al., 2005	USA	Healthy participants	Healthy	140	75	20	44.10 (10.3)	62.70 (8.43)
Maroti et al., 2017+	Sweden	Chronic fatigue HC	Medical	65 30	81	43	45.5 (11.4) 33.5 (6.4)	29.5 (5.4) 34.7 (6.9)
*Neumann et al., 2017+	USA	Traumatic brain injury	Medical	24	24	46	61.54 (7.26)	36.9 (7.9)
Parling et al., 2010	Sweden	Anorexia Nervosa HC	Psychiatric	35 35	100	22	55.8 (12.2) 43.3 (10.1)	62.8 (6.3) 62.4 (8.1)
*Pietri and Bonett, 2016	France	Mixed (Victims of domestic violence+HC)	Not included in sub-group analysis	80	100	35	X	X
Simson et al., 2002+	Germany	Mixed psychiatric	Psychiatric	146	73	31	55.2 (10.5)	24.4 (5.2)
Subic-Wrana et al., 2001+	Germany	University students	Healthy	338	52	X	X	30.4 (6.0)
Subic-Wrana et al., 2005+	Germany	Mixed psychiatric	Psychiatric	386	72	41	X	X
Suslow et al., 2000	Germany	Mixed (Psychiatric+HC)	Not included in sub-group analysis	68	56	28	45.9 (13.6)	62.2 (10.4)
Waller and Scheidt, 2004++	Germany	Somatoform disorder HC	Psychiatric	40 20	50	43	46.6 (8.9) 35.6 (8.9)	2.7 (0.5) 2.7 (0.4)

*+, Used LEAS-10 (instead of LEAS-20). ++ In this study the authors seem to have divided the total score of LEAS-10 with 10. X, missing data. *indicates articles those corresponding authors send additional data for correlations analysis.*

TABLE 2 | Forest plot of correlations between the TAS-20 and the LEAS of included studies.

Study name	Subgroup within study	Statistics for each study				Correlation and 95% CI
		Correlation	Lower limit	Upper limit	*p*-value	
Baker et al., 2014	Healthy	−0.080	−0.505	0.376	0.741	
Baker et al., 2014	Psychiatric	−0.440	−0.739	0.003	0.052	
Baeza-Velasco et al., 2012	Healthy	−0.108	−0.507	0.329	0.636	
Baeza-Velasco et al., 2012	Medical	0.224	−0.098	0.504	0.172	
Burger et al., 2016	Medical	−0.249	−0.454	−0.018	0.035	
Bydlowski et al., 2005	Healthy	0.110	−0.128	0.336	0.366	
Bydlowski et al., 2005	Psychiatric	−0.130	−0.354	0.108	0.285	
Carton et al., 2010	Psychiatric	−0.055	−0.297	0.193	0.667	
Consoli et al., 2009	Medical	−0.200	−0.383	−0.002	0.048	
Igarashi et al., 2011	Healthy	−0.030	−0.135	0.076	0.579	
Lane et al., 1998b	Healthy	−0.190	−0.285	−0.091	0.000	
Lane et al., 2015a	Medical	−0.136	−0.473	0.236	0.477	
Lane et al., 2015a	Psychiatric	−0.009	−0.264	0.248	0.946	
Lichev et al., 2014	Healthy	−0.200	−0.397	0.015	0.068	
Lundh et al., 2002	Healthy	0.240	0.018	0.439	0.034	
Lumley et al., 2005	Healthy	−0.110	−0.271	0.057	0.196	
Maroti et al., 2017	Healthy	−0.409	−0.670	−0.057	0.024	
Maroti et al., 2017	Medical	0.006	−0.238	0.250	0.962	
Neumann et al., 2017	Medical	−0.353	−0.662	0.059	0.091	
Parling et al., 2010	Healthy	−0.160	−0.473	0.188	0.369	
Parling et al., 2010	Psychiatric	−0.220	−0.515	0.122	0.206	
Pietri and Bonett, 2016	Mixed	−0.410	−0.578	−0.209	0.000	
Simson et al., 2002	Psychiatric	−0.173	−0.326	−0.011	0.037	
Subic-Wrana et al., 2001	Healthy	−0.220	−0.319	−0.116	0.000	
Subic-Wrana et al., 2005	Psychiatric	−0.072	−0.171	0.028	0.158	
Suslow et al., 2000	Mixed	−0.190	−0.410	0.051	0.121	
Waller and Scheidt, 2004	Healthy	0.430	−0.015	0.733	0.058	
Waller and Scheidt, 2004	Psychiatric	−0.200	−0.488	0.128	0.230	
Total		−0.122	−0.180	−0.064	0.000	



Moderators

In our moderator analyses, we found no significant difference (total between $Q = 0.595$; $p = 0.743$) between samples of Healthy Controls ($r = -0.087$, 95% CI [−0.173, 0.000], $Z = -1.951$; $p = 0.051$; $k = 12$), Psychiatric Conditions ($r = -0.130$, 95% CI [−0.237, 0.019], $Z = -2.303$; $p = 0.021$; $k = 8$) or Medical Conditions ($r = -0.120$, 95% CI [−0.257, 0.021], $Z = -1.668$; $p = 0.095$; $k = 6$), suggesting that the small, negative correlation between TAS and LEAS is quite robust across our coded subgroups. Further, in our meta-regression analyses, we found no indication that the correlation varied as a function of sample mean age (intercept = −0.063; $\beta < 0.001$; $p = 0.648$), nor the percentage of female subjects in the sample (intercept = −0.230; $\beta = 0.002$; $p = 0.145$), suggesting stability across age and gender.

Publication Bias

Duval and Tweedie (2000) trim-and-fill procedure suggested possible presence of some publication bias and trimmed four studies to the right of the main aggregated effect, adjusting the overall estimate to $r = -0.092$.

DISCUSSION

In this study, we performed a meta-analysis of the correlation between two commonly used measures of alexithymia and emotional awareness, i.e. the TAS-20 and the LEAS. Through our search strategy, we were able to include 21 studies, reporting on the correlation in 28 different samples. In line with our expectations, we found a significant negative correlation between the instruments; however, the relationship was weak ($r = -0.122$). Moderator analyses indicated that this small overlap was robust across subgroups of healthy subjects and patients with psychiatric or medical conditions and was unaffected by sample age or gender. The weak overall correlation suggests that TAS-20 and LEAS captures distinct facets of alexithymia and/or measure different constructs. The instruments should therefore be regarded as complimentary and be used according to specific research or clinical questions targeted.

Given that alexithymia and emotional awareness are closely related conceptually, the negligible overlap between TAS-20

and LEAS may seem puzzling. One explanation can simply be that although the instruments are related conceptually they are not related empirically. Studies have found that different areas and activations of brain networks might be involved in alexithymia and emotional awareness (Lane et al., 2015b). For example, functional neuroimaging studies have reported decreased activation of the dorsomedial prefrontal cortex when negative emotional stimuli were being processed for subjects reporting high alexithymia in TAS-20 (van der Velde et al., 2013). In contrast, increased activation of the dorsal anterior cingulate cortex has been associated with processing of emotions in subjects with a high emotional awareness capacity (Lane et al., 1998a; McRae et al., 2008).

Albeit puzzling from a conceptual standpoint, the small correlation between TAS-20 and LEAS is not unexpected from an empirical point of view. Several studies have shown that associations of self-report and observed based measures usually are low, whereas different self-reports and observed based measurement tend to correlate higher with each other (Lumley et al., 2005). For example, in a study evaluating the reliability and validity of the Dutch version of the OAS, the OAS correlation with TAS-20 was low, while a strong correlation was found for Toronto Structured Interview for Alexithymia and OAS (Meganck et al., 2010).

Another possible interpretation of the negligible overlap between the instruments is that it simply may be difficult to infer one's own emotional awareness capacity using a self-report measure like TAS-20, otherwise a stronger negative correlation would be expected. This idea parallels research into subjective memory and objective memory where only a negligible or small correlation is typically found (Burmester et al., 2016).

In line with this, Lundh et al. (2002) found that almost 20% of the individuals reported low levels of alexithymia but performed worse than others on the LEAS. In addition, 15% of patients with high levels of alexithymia performed better than others on the LEAS. Thus, the relationship between alexithymia and emotional awareness may be non-linear, which could also explain the low aggregated correlation found in this review. If not non-linear, at least different depending on patient characteristic studied. In Lundh et al.'s (2002) study, TAS-20 was found to correlate highly with perfectionism. This result can be said to corroborated by a study in which raters, who were blind to patient TAS-20 scores, coded videotaped interviews for the number of emotions expressed by psychiatric patients. Those patients who rated themselves as having more difficulty describing their emotions were actually better able to express their emotions than others, not worse (Leising et al., 2009). Future research should therefore investigate if perfectionistic tendencies contributes to the correlation between TAS-20 and LEAS. Moreover, given that almost 20% of the individuals reported low levels of alexithymia but performed worse than others on the LEAS in Lundh et al.'s (2002) study, the contribution of somatization may be important in future research. One hallmark of somatization is the tendency to report few emotional problems (i.e., pensée opératoire) but actually have internal emotional conflicts (Taylor et al., 1997).

The weak relationship between alexithymia and emotional awareness also seem to contradict theories of emotion that suggest that a persons ability to use words and concepts to label emotional experience is related to their ability to experience and differentiate emotions (e.g., Barrett, 2006; Kashdan et al., 2015). Our results indicate that some people who report a lack of words for emotions on the TAS-20 are clearly quite able to use emotional words when describing motions in an observer-rated procedure such as LEAS. Conversely, some people with low alexithymia may show limited emotional awareness on the LEAS. While, again, this may indicate that it is difficult to infer one's own emotional awareness capacity using self-report measures, it could also indicate that the ability to perceive and experience emotions is not simply a matter of conceptual capacity but other mechanisms may also be involved.

Our results may also have clinical implications since an overestimation or underestimation of patients' particular emotional capacities could affect the outcome of therapeutic interventions. Clinicians may need to consider both alexithymia and emotional awareness and adjust therapeutic interventions to address the patients' particular beliefs and deficits. For example, having lower emotional awareness capacity, as measured with the LEAS, has been shown to moderate treatment effectiveness in both cognitive behavioral therapy (CBT) and psychodynamic psychotherapy (PDT) for patients with a comorbid psychiatric diagnosis (Beutel et al., 2013). Reporting higher levels of alexithymia on TAS-20 has also been found to be a negative prognostic indicator for psychodynamic-oriented treatments (McCallum et al., 2003; Leweke et al., 2009; Ogrodniczuk et al., 2011). Alexithymia may not affect more structured cognitive-behavioral treatments, and certain results do indicate that alexithymia may even be associated with better outcomes of such treatments (Rufer et al., 2004; Spek et al., 2008; de Haan et al., 2011). In other words, and as stated above, TAS-20 and LEAS should not be used interchangeably, but could be informative when used simultaneously in order to find the most suitable treatment options for a particular patient. In somatic diseases, alexithymia also predicted or moderated treatment outcomes (Porcelli et al., 2003). Thus, reducing alexithymia contribute to ameliorate symptoms in patients with functional gastrointestinal disorders (Porcelli et al., 2017) and cancer-related pain (Porcelli et al., 2007). Recent study on antidepressants indicates that pharmacological treatment per see with known side effects such as emotional blunting contributes to at least of some aspects of alexithymia (DIF) (Kajanoja et al., 2018).

On a clinical note, using both the instrument TAS-20 and LEAS to capture alexithymia and emotional awareness is time consuming. For example, it can take patients up to 1.5 h to complete even the 10-vignettes version of LEAS (Maroti et al., 2017) and even a skilled rater needs at least 15–20 min to score the answers. Although computerized versions of rating LEAS have been developed (Barchard et al., 2010) an easy, reliable and valid way of measuring emotional awareness is still needed. If judgements from the clinician are involved, the clinicians own emotional awareness capacity needs to be taken into account, since the clinician's capacity sets the limit of the level of emotional awareness that reasonably can be detected.

Emotional awareness might be influenced by several factors and circumstances, which might be difficult to capture in research

situation. Nevertheless, our results increase knowledge and awareness how to interpret the scales in research practice and point out the necessity to develop less time consuming clinically adapted scales or tests.

LIMITATIONS

Through our search strategy, we identified 34 studies that were eligible but could include 21 due to missing, incomplete or unclear data. We tried to address this by emailing the first authors. Most of the excluded studies were published in a language other than English (i.e., French); hence, our results may have been systematically skewed due to the selective inclusion of studies. However, an ad hoc subgroup test of the difference between countries proved insignificant (between $Q = 0.073$; $p = 0.787$). Also, given that adjustment for publication bias lowered the overall estimate even further, it seems unlikely that additional studies would change our overall result.

This study is focused on the correlation between the total scores of TAS-20 and LEAS. It could be that the instruments overlap more when looking at particular subscales. However, because of reliability issues, using subscales of TAS-20 has not been recommended (Kooiman et al., 2002). Additionally, since the subscales of the instruments focus on quite different aspects (e.g., "difficulty describing feelings" in TAS-20 and "other" in LEAS), we suspect that it will be difficult to interpret the meaning of a possible overlap or a lack thereof. Since the total scores of the instruments aim at assessing each respective "phenomenon" (i.e., alexithymia or emotional awareness), it was determined to be the most suitable level of analysis for this review.

Another limitation of this study was that distress/negative affect (such as anxiety and depression) was not used as a covariate. Typically, TAS-20 but not LEAS (Lane et al., 2015b) have been found to correlate with negative affect. Moreover, several studies have shown that associations between LEAS and the population studied were not altered by removing variance due to negative affect (Bydlowski et al., 2005; Subic-Wrana et al., 2005; Consoli et al., 2009). On the other hand, control for negative affect made associations with the TAS-20 non-significant. Taken together, this implies that negative affects influence the instrument in this study in a different way and might impact the low correlation found between TAS-20 and LEAS.

INTERIM CONCLUSION

In this review, we tried to answer the question of whether TAS-20 and LEAS correlate in healthy populations and medical and psychiatric conditions. The results indicate that the correlation is small to negligible in all studied groups. These particular instruments should therefore not be used interchangeably and instead be used in order to answer specific research questions.

AUTHOR CONTRIBUTIONS

DM and IB-L performed and compiled the main bibliography work. PL performed the statistical analysis. IB-L coordinated and supervised the process of manuscript writing. All authors wrote the paper and approved the final version for submission.

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Alexithymia Is Related to the Need for More Emotional Intensity to Identify Static Fearful Facial Expressions

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Individuals with high levels of alexithymia, a personality trait marked by difficulties in identifying and describing feelings and an externally oriented style of thinking, appear to require more time to accurately recognize intense emotional facial expressions (EFEs). However, in everyday life, EFEs are displayed at different levels of intensity and individuals with high alexithymia may also need more emotional intensity to identify EFEs. Nevertheless, the impact of alexithymia on the identification of EFEs, which vary in emotional intensity, has largely been neglected. To address this, two experiments were conducted in which participants with low (LA) and high (HA) levels of alexithymia were assessed in their ability to identify static (Experiment 1) and dynamic (Experiment 2) morphed faces ranging from neutral to intense EFEs. Results showed that HA needed more emotional intensity than LA to identify static fearful – but not happy or disgusted – faces. On the contrary, no evidence was found that alexithymia affected the identification of dynamic EFEs. These results extend current literature suggesting that alexithymia is related to the need for more perceptual information to identify static fearful EFEs.

Keywords: alexithymia, emotional facial expressions, morphing, dynamic facial expressions, fear

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INTRODUCTION

The identification of emotional facial expressions (EFEs) is fundamental for social interaction and survival of the individual (Adolphs, 2002). For example, being able to correctly recognize a fearful or a happy facial expression is a crucial adaptive mechanism to infer others' intentions and anticipate their behavior. Research has shown that this ability is affected not only by clinical conditions such as depression and anxiety (Demenescu et al., 2010) or schizophrenia (Kohler et al., 2009) but also by subclinical differences in the ability to process emotional stimuli, such as alexithymia (Grynberg et al., 2012).

Alexithymia is a personality trait characterized by difficulties in identifying and describing feelings and discriminating between feelings and bodily sensations of emotional arousal, which accompany them (Sifneos, 1973; Taylor et al., 1991). Previous research found alexithymia to be related to worse performance in EFE recognition (Lane et al., 1996; Jessimer and Markham, 1997). Specifically, previous literature mainly manipulated stimulus presentation time, showing that the difficulty in EFE identification was evident when stimuli were presented under temporal constraints but not when stimulus exposure time was extended (for a review see Grynberg et al., 2012). For example, when EFEs were presented for 66 or 100 ms, level of alexithymia was negatively

correlated with labeling sensitivity of angry EFEs and marginally negatively correlated with labeling sensitivity of fearful and happy EFEs (Ihme et al., 2014a). On the contrary, no such correlations were found when the same EFEs were presented for 1 or 3 s (Pandey and Mandal, 1997; Ihme et al., 2014b). The implications of these results appear twofold. Firstly, alexithymia may be associated to the need for more time to accurately recognize EFEs. Secondly, the difficulties of alexithymic individuals in EFEs identification appear evident only under certain experimental conditions.

Despite growing evidence on the impact of alexithymia in the identification of EFEs, previous research has focused on the response to intense static EFEs. Nevertheless, these are rarely encountered in everyday life and individuals are faced with the challenge of identifying dynamic changes in emotional expression often displayed at varying degrees of intensity (Sarkheil et al., 2013). In fact, alexithymia may be hypothesized to be related not only to the need for more time but also for more perceptual information to identify EFEs, as previously hypothesized in Grynberg et al. (2012). Therefore, manipulating the intensity of EFEs using both static and dynamic stimuli would enable the extension of current literature on the impact of alexithymia on EFE identification by testing whether or not individuals with alexithymia need more emotional intensity to identify EFEs. Indeed, in the broader literature of emotion processing, the manipulation of emotional intensity can be crucial to uncover impairments in EFE recognition, which are not evident when using intense EFEs (e.g., Willis et al., 2014), making emotion recognition tasks more sensitive to subtle differences in identification (Calder et al., 1996; Wells et al., 2016).

Regarding the issue of intensity in static EFEs, two studies exist that used morphed faces to understand the impact of alexithymia in the identification of static EFEs varying in emotional intensity. Nevertheless, they have the limitations of focusing mainly on alexithymia within the autistic population, reporting contrasting results. Specifically, the first study found alexithymia to be related to less precision, expressed as higher attribution threshold, in the identification of EFEs both in the autistic and control group (Cook et al., 2013). On the contrary, the second study found high levels of alexithymia to be related to reduced accuracy in identifying EFEs at low emotional intensity in the autistic but not in the control group (Ketelaars et al., 2016) raising the possibility that autism *per se* may represent a confounding factor contributing to the results. Given the inconsistency of results, it appears that further research is needed in order to understand the role of emotional intensity in the relationship between alexithymia and EFE identification. In addition, no study has investigated the impact of alexithymia in the identification of dynamic EFEs varying in emotional intensity. Nevertheless, static and dynamic faces appear to convey partially different types of information. Besides being more ecologically valid, dynamic stimuli convey additional temporal information regarding the change of emotional intensity over time (Kamachi et al., 2001), which is not available in static stimuli. This seems to contribute to enhanced perceived intensity of dynamic EFEs (Yoshikawa and Sato, 2008) and has been suggested to facilitate their identification (Sarkheil et al., 2013). In fact, neuroimaging studies have shown that recognizing dynamic as opposed to static morphed EFEs appears not only to enhance the activation of areas involved in affective processing, including the amygdala and fusiform gyrus (LaBar et al., 2003; Trautmann et al., 2009), but also to activate additional brain areas involved in motion processing, including pre- and post-central gyrus, known for sensory-motor integration of motion-related information (Sarkheil et al., 2013).

Given the current literature, the aim of the present study was to investigate the impact of emotional intensity in the relationship between alexithymia and EFE identification when presenting both static and dynamic EFEs. To this end, two experiments were conducted in which participants with low (LA) and high (HA) levels of alexithymia were tested in their ability to identify static (Experiment 1) or dynamic (Experiment 2) morphed EFEs, which ranged from neutral to intense emotional expression.

In both experiments presentation of happy, fearful and disgusted EFEs was chosen for several theoretical reasons. Firstly, both positively and negatively valenced emotions were included to understand if the effect of alexithymia may be valence or emotion related. Secondly, with regards to fear and disgust, these were included because neuroimaging and lesion studies indicate that identification of fearful and disgusted EFEs is related to functional and structural integrity of a circumscribed set of brain areas (Adolphs, 2002). Specifically, the amygdala appears a crucial structure in recognition of fearful EFEs (Adolphs, 2002; Fusar-Poli et al., 2009) and lesion of this structure impairs their recognition (Adolphs et al., 1994, 1999), while the insula appears crucially involved in the recognition of disgusted EFEs (Adolphs, 2002; Fusar-Poli et al., 2009). Regarding alexithymia, aberrant activation of amygdala (e.g., Kugel et al., 2008; Pouga et al., 2010; Wingbermühle et al., 2012; Moriguchi and Komaki, 2013; Jongen et al., 2014) and insula (e.g., Karlsson et al., 2008; Heinzel et al., 2010; Reker et al., 2010) have been found among the neural correlates underlying this condition (for a meta-analysis see van der Velde et al., 2013).

In Experiment 1, compared to LA, HA were hypothesized to need more emotional intensity to identify the emotion expressed by EFEs. On the contrary, in Experiment 2, the additional information inherent to dynamic – as opposed to static – EFEs might facilitate the task, enabling HA to overcome their difficulties. Therefore, in Experiment 2, differences in the emotional intensity needed by HA and LA to identify EFEs may or may not be evident.

EXPERIMENT 1

Participants were presented with pictures of static happy, disgusted and fearful EFEs. The emotion in each EFE could be expressed at 6 levels of emotional intensity: 0, 20, 40, 60, 80, and 100% (**Figure 1**). Participants were required to identify the emotion expressed by the EFE, by making a forced choice button press. In order to test differences between LA and HA, for each participant, expression identification rate for each EFE was calculated at each intensity level. Then, expression identification rates were fit to a psychometric function to calculate the percentage of emotional intensity at which participants had

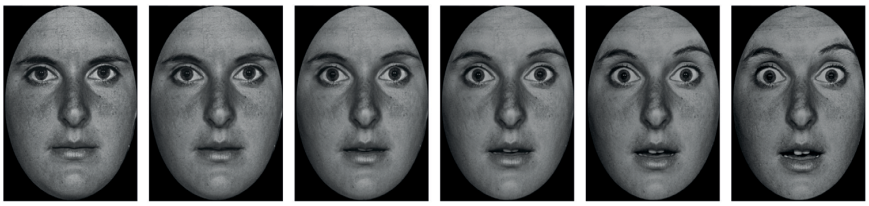

FIGURE 1 | Example of morphed pictures of fearful facial expressions used as EFEs ranging from 0 to 100% emotional intensity.

equal probability to identify the facial expression as neutral or emotional, i.e., point of subjective equality (PSE). Compared to LA, HA were hypothesized to need more emotional intensity to identify the presence of the emotional expression in the face, hence showing higher PSE.

Methods

Participants

The study was designed and conducted in accordance with the ethical principles of the World Medical Association Declaration of Helsinki and the institutional guidelines of the University of Bologna and was approved by the Ethics Committee of the Department of Psychology. All participants gave informed written consent to participation after being informed about the procedure of the study.

Three-hundred university students completed the 20-item Toronto Alexithymia Scale (TAS-20; Taylor et al., 2003). Depending on the score, students were classified as LA (TAS-20 $\leq$ 36) or HA (TAS-20 $\geq$ 61) (Franz et al., 2004) and were then randomly contacted to participate in the study. Once in the laboratory, the alexithymia module of the structured interview for the Diagnostic Criteria for Psychosomatic Research (DCPR; Mangelli et al., 2006) was administered to increase reliability of screening and confirm TAS-20 classification. Participants with discordant classification on the two measures did not complete the task (n = 1). Due to the high co-occurrence of alexithymia and depression (Li et al., 2015), participants completed the Beck Depression Inventory (Beck et al., 1961) and did not complete the experimental task if their score was higher than the cut-off for severe depression (i.e., 28, n = 1). All participants had equivalent educational backgrounds and were students at the University of Bologna.

Forty volunteers with no history of major medical, neurological or psychiatric disorders completed the study: 20 LA (6 males; TAS-20 M = 30.25, SD = 4.12; age M = 24.55, SD = 2.98 years); 20 HA (6 males; TAS-20 M = 63.37, SD = 2.25; age M = 23.03, SD = 2.32 years). *A priori* targets for sample size and data collection stopping rule were based on sample and effect sizes reported in the literature on alexithymia and EFE identification (sample size of an average of 38 participants in total as indicated in a recent review (Grynberg et al., 2012)).

Independent Measure

Stimuli consisted of black and white photographs of 20 actors (10 males) with each actor depicting 3 EFEs, respectively of happiness, disgust and fear. Half of the pictures were taken from the Karolinska Directed Emotional Faces database (Lundqvist et al., 1998) and half from the Pictures of Facial Affect database (Ekman and Friesen, 1976). Pictures were trimmed to fit an ellipse in order to uniform them and remove distracting features from the face, such as hair or ears and non-facial contours. Each emotional facial expression was then morphed with the neutral facial expression of the corresponding identity using (Abrosoft FantaMorph, 2009) in order to create stimuli of 20% increments of emotional intensity ranging from 0 to 100% emotional intensity. This resulted in a total of 360 stimuli (20 cm $\times$ 13 cm size), i.e., 20 actors expressing 3 emotions with 6 degrees of intensity (0, 20, 40, 60, 80, and 100%; **Figure 1**).

Procedure

The experiment took place in a sound attenuated room with dimmed light. Participants sat in a relaxed position on a comfortable chair in front of a computer monitor (17″, 60 Hz refresh rate) used for stimuli presentation at 57 cm distance. Each trial started with the presentation of a fixation cross (500 ms) in the center of the screen followed by the stimulus (100 ms) and subsequently a black screen (3000 ms) during which participants could provide the answer by pressing a key. The experiment consisted of 360 randomized trials divided in two blocks of 180 trials so that participants could rest if desired. Stimulus presentation time was chosen based on previous literature on EFEs recognition, indicating 100 ms as a sufficiently long presentation time to identify EFEs reliably above chance level and without incurring in ceiling effects (Calvo and Lundqvist, 2008; Calvo and Marrero, 2009).

Participants were instructed that at each trial a face would briefly appear on the screen and their task would be to identify the emotion expressed by the face by pressing one of four keys with their index and middle finger of either hand. These were labeled "N" for neutral (i.e., Italian = "neutro"), "F" for happiness (i.e., Italian = "felicità"), "P" for fear (i.e., Italian = "paura") and "D" for disgust (i.e., Italian = "disgusto"). Before beginning the task, participants familiarized with the position of keys by having the experimenter calling out loud in random order the keys and participants pressing them until they felt confident they could press them correctly while fixating the screen. The order of keys was counterbalanced among participants.

Dependent Measure

Correct responses for each emotional facial expression were used to calculate the mean expression identification rate at each intensity level. Then, for each subject, expression identification rates for each emotional facial expression were fit to a psychometric function using a generalized linear model with a binomial distribution in MATLAB software (MathWorks, Natick, MA, United States) (Nakajima et al., 2017). The point of subjective equality (PSE) was then calculated and used for statistical analysis. This represented the percentage of emotional intensity at which subjects had equal probability to identify the facial expression as neutral or emotional (**Figure 2**).

Results and Discussion

A 3×2 repeated measures analysis of variance (RM ANOVA; emotion: happiness, disgust, fear; group: LA, HA) on PSE scores showed a significant main effect of group [$F(1,38) = 5.38$, $p = 0.026$, $\eta_p^2 = 0.12$] and emotion [$F(2,76) = 35.75$, $p < 0.001$, $\eta_p^2 = 0.48$]. More importantly, there was a group by emotion interaction [$F(2,76) = 4.69$, $p = 0.012$, $\eta_p^2 = 0.11$]. Newman-Keuls *post hoc* test shows that HA had higher PSE compared to LA only for the fearful emotional facial expression (fear: $p < 0.001$, $M_{HA} = 54.05$, $M_{LA} = 43.71$; disgust: $p = 0.832$, $M_{HA} = 38.36$, $M_{LA} = 37.78$; happiness: $p = 0.415$, $M_{HA} = 36.32$, $M_{LA} = 34.08$). Therefore, HA need more emotional intensity to identify fearful facial expressions compared to LA (**Figure 3**).

In summary, results showed that HA required more emotional intensity to identify the presence of fear expression in the face compared to LA. Crucially, while previous studies showed that HA need more time to identify EFEs as efficiently as LA (Grynberg et al., 2012), the present study extends the current literature suggesting that HA also need more perceptual information, specifically to identify fearful EFEs.

EXPERIMENT 2

Participants were presented with videos of dynamic happy, disgusted and fearful EFEs, which started at 0% emotional intensity and terminated at 100% emotional intensity (**Figure 4**). Participants were required to identify the emotion expressed by the EFE, by making a forced choice button press, which would also terminate video presentation. Participants responded as soon as they recognized the emotion, without necessarily waiting for termination of the video. In order to test differences between LA and HA, accuracy and reaction times (RTs) for accurate responses were calculated. Here, RTs also represented the percentage of emotional intensity at which participants identified the emotion displayed by the face. Therefore, differences in RTs indicated differences in the percentage of emotional intensity needed to identify the emotion expressed by the EFE. Contrary to Experiment 1, here, differences in the emotional intensity needed by HA and LA to identify EFEs may or may not be evident, given that dynamic EFEs may be easier to be identified than static ones.

Methods

Participants

Recruitment of participants followed the same procedure as Experiment 1. Two participants did not take part to the experimental task because their TAS-20 classification was not

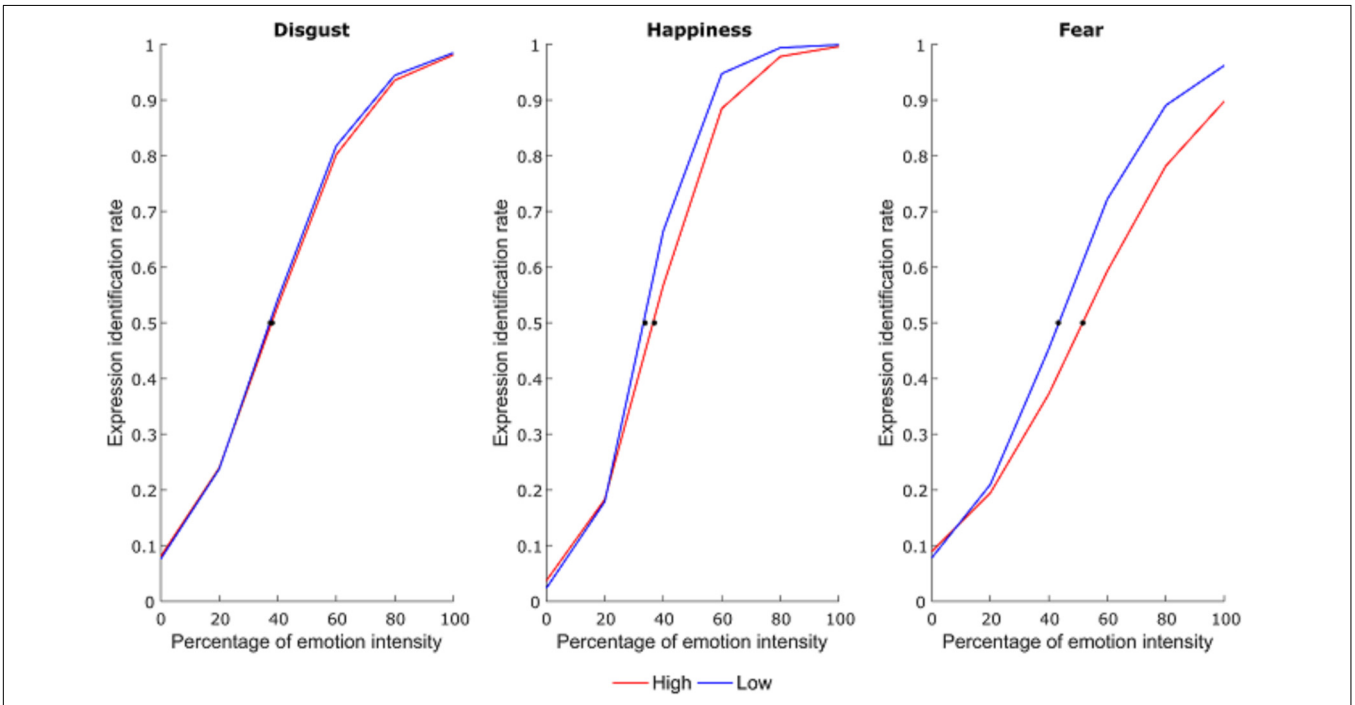

FIGURE 2 | Average psychometric function for each emotional expression as a function of group. The dots represent the point of subjective equivalence (PSE).

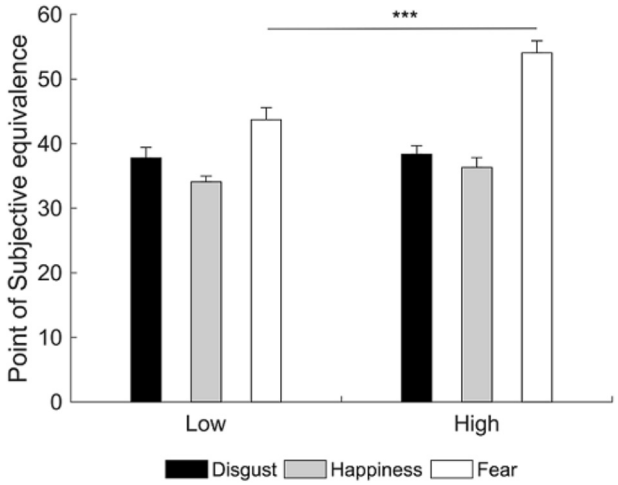

FIGURE 3 | Mean point of subjective equivalence (PSE) for each emotional facial expression as a function of group. Participants with high alexithymia have higher PSE than those with low alexithymia for the fearful facial expression, indicating they need more emotional intensity to identify fearful facial expressions. Error bars represent standard errors. Significant differences are indicated as follows: $***p < 0.001$.

confirmed by their DCPR score. No participant reported a severe level of depression on the BDI.

Forty volunteers with no history of major medical, neurological or psychiatric disorders completed the study: 20 LA participants (8 males; TAS-20 M = 31.29, SD = 3.23; age M = 22.89 years, SD = 2.00 years) and 20 HA participants (8 males; TAS-20 M = 64.84, SD = 4.14; age M = 22.84 years, SD = 1.93 years).

Independent Measure

Stimuli consisted of black and white photographs of 10 actors (5 men) with each actor depicting 3 EFEs, respectively of happiness, disgust and fear. Pictures were chosen from the Pictures of Facial Affect database (Ekman and Friesen, 1976) and trimmed to fit an ellipse in order to uniform stimuli and remove distracting features from the face such as hair or ears and non-facial contours. Each emotional facial expression was then morphed with the neutral facial expression of the corresponding identity using (Abrosoft FantaMorph, 2009) in order to create videos of 1% increments of emotional intensity ranging from 0 to 100% of emotional intensity. Each increment lasted 1 s, resulting in a video with a total duration of 100 s (**Figure 4**). This resulted in a total of 30 stimuli (20 cm × 13 cm size), i.e., 10 actors expressing 3 emotions.

Procedure

The experiment took place in a sound attenuated room with dimmed light. Participants sat in a relaxed position on a comfortable chair in front of a computer monitor (17″, 60 Hz refresh rate) used for stimuli presentation at a distance of 57 cm. The experiment consisted of 30 randomized trials, each showing a dynamic facial expression changing from neutral to fear, happiness or disgust. Each trial started with the presentation of a fixation cross (3000 ms) in the center of the screen followed by the presentation of the dynamic stimulus with the duration of 100 s.

Participants were instructed that at each trial a video of a face ranging from neutral to emotional would appear on the screen and their task would be to press one of three keys (D, J, or K) as soon as they recognized the emotion expressed by the face, without having to wait for termination of the video. The keys were labeled "F" for happiness (i.e., Italian = "felicità"), "D" for disgust (i.e., Italian = "disgusto") and "P" for fear (i.e., Italian = "paura"). Participants used the index and middle fingers of the right hand and the index finger of the left hand to press the keys. The order of keys was counterbalanced between participants. Key press terminated video presentation allowing the task to proceed to the next trial.

Dependent Measure

Accuracy (i.e., percentage of correct response) and RTs for accurate responses were calculated. It should be noted that RTs

FIGURE 4 | Example of morphed pictures of fearful facial expressions used to create the dynamic EFEs ranging from 0 to 100% emotional intensity.

also represented the percentage of emotional intensity at which participants identified the emotion displayed by the face. For example, an average RT of 3000 ms indicated that, on average, a participant correctly identified the emotion displayed by the face when this was expressed at 30% emotional intensity. Therefore, differences in RTs indicated differences in the percentage of emotional intensity needed to identify the emotion expressed by the EFE.

Results and Discussion

The 3×2 RM ANOVA (emotion: happiness, disgust, fear; group: LA, HA) on accuracy revealed a significant main effect of emotion [$F(2,76) = 13.83$; $p < 0.001$; $\eta_p^2 = 0.27$]. Newman-Keuls *post hoc* test showed that participants were most accurate in identifying happiness ($M = 96.05\%$) than fear ($p = 0.003$; $M = 90.75\%$) and disgust ($p < 0.001$; $M = 86.84\%$) and were more accurate in identifying fear than disgust ($p = 0.029$). Results showed no significant main effect or interaction with the factor group (all p-values ≥ 0.669) indicating that the two groups exhibited comparable accuracy in identifying the emotion expressed by dynamic faces.

Similarly the 3×2 RM ANOVA (emotion: happiness, disgust, fear; group: LA, HA) on RTs revealed a significant main effect of emotion [$F(2,76) = 78.22$; $p < 0.001$; $\eta_p^2 = 0.67$]. Newman-Keuls *post hoc* test showed that participants were fastest in identifying happiness ($M = 24770$ ms) than fear ($p < 0.001$; $M = 32623$ ms) and disgust ($p < 0.001$; $M = 36549$ ms) and were more accurate in identifying fear than disgust ($p < 0.001$). Results showed no significant main effect or interaction with the factor group (all p-values ≥ 0.142) indicating that the two groups required comparable time to identify the emotion expressed by dynamic faces. Because RTs also represent the percentage at which participants recognize the emotion, these results also show that the groups required comparable amount of emotional intensity to identify the emotion expressed by the face.

Contrary to Experiment 1, results of Experiment 2 show no significant difference between LA and HA in accuracy and RTs when identifying the emotion expressed by dynamic morphed faces.

GENERAL DISCUSSION

The aim of the present study was to investigate the role of alexithymia in identifying the emotional expression of static and dynamic EFEs ranging from neutral to intense emotional expression, in order to test whether or not HA need more emotional intensity to identify EFEs. In fact, previous studies have focused on manipulating presentation time of intense static EFEs, revealing that HA need more time to identify EFEs, compared to LA (Grynberg et al., 2012). Here, instead, we manipulated emotional intensity of static and dynamic EFEs. Under these conditions we showed that HA need more emotional intensity to identify static fearful EFEs, compared to LA. Nevertheless, when the groups were faced by dynamic EFEs, no significant difference was found in performance, with groups requiring comparable amount of emotional intensity to identify the EFEs.

In Experiment 1, the difficulty in processing fearful EFEs is in line with previous literature, which found a difficulty of alexithymic individuals in fear processing not only limited to EFEs labeling (Jessimer and Markham, 1997; Lane et al., 2000; Montebarocci et al., 2010) but also across a broad range of stimuli, tasks and dependent measures. For example, compared to LA, HA rate the expression of fearful but not other EFEs as less intense (Prkachin et al., 2009). In addition, HA show impairment in embodied aspects of fearful stimuli processing. This is evidenced by reduced rapid facial mimicry in response to static fearful faces (Sonnby-Borgstrom, 2009; Scarpazza et al., 2018), failure to show enhanced perception of tactile stimuli delivered to their face while observing a fearful – as opposed to happy or neutral – face being simultaneously touched (Scarpazza et al., 2014, 2015) and reduced skin conductance response when viewing a conditioned stimulus predictive of a shock during classical fear conditioning (Starita et al., 2016). Finally, HA show impairments in processing fearful stimuli also when examining their electrophysiological responses. Compared to LA, HA fail to show enhanced amplitude of the N190 event related potential, during visual encoding of fearful – as opposed to happy or neutral – body postures (Borhani et al., 2016). This general difficulty in fear processing has been interpreted in light of the decreased activation of the amygdala observed in alexithymia in response to the presentation of EFEs (Kugel et al., 2008; Jongen et al., 2014), in particular fearful ones (Pouga et al., 2010), and negative emotional stimuli (Wingbermühle et al., 2012; van der Velde et al., 2013), such as observing a painful stimulation being delivered to someone's hand (Moriguchi and Komaki, 2013). Although involved in processing EFEs in general (Fusar-Poli et al., 2009), the amygdala appears a crucial structure in processing fearful EFEs (Adolphs et al., 1994, 1999). Therefore, it is possible that a reduced response in the amygdala in HA may underlie the present results, though future studies using neuroimaging techniques should be conducted to test this hypothesis.

In contrast to the difference found in response to fearful EFEs, no difference between the groups was found when identifying happy or disgusted facial expressions. In this regard, previous behavioral studies on EFEs processing have reported mixed results. For example, in Prkachin et al. (2009), though HA showed reduced sensitivity for matching sad, angry and fearful faces to the corresponding target EFE, they showed no significant difference from LA when matching happy, disgusted or surprised EFEs; in addition, they were able to recognize all EFEs during a non-speeded task and rated the intensity of happy and disgusted EFEs similarly to LA. On the contrary, other labeling studies found that alexithymia was related to a global deficit to recognize EFEs, including happiness and disgust (Jessimer and Markham, 1997; Lane et al., 2000; Montebarocci et al., 2010). Given the contrasting results, alexithymia may affect processing of happy and disgusted EFEs depending on the experimental conditions. Specifically, here results seem to suggest that while HA require more emotional intensity to identify static fearful EFEs, they may

not have such need in the identification of happy and disgusted EFEs.

Contrary to Experiment 1, when dynamic morphed faces were presented in Experiment 2, no difference was found between the two groups in EFE recognition. This result may be related to the type of information conveyed by dynamic as opposed to static stimuli. Indeed, the intensification of emotional expression over time provides additional structural and configurational information, which is not available in static stimuli (Kamachi et al., 2001) and which seems to contribute to differential processing of the two types of stimuli. For example, dynamic EFEs are perceived as more intense than static ones even when the stimulus emotional intensity is the same (Yoshikawa and Sato, 2008; Rymarczyk et al., 2011; Rymarczyk et al., 2016a,b). In addition, dynamic EFEs trigger stronger facial mimicry compared to static faces (Sato et al., 2008; Rymarczyk et al., 2011, 2016a,b). Finally, recognizing dynamic as opposed to static morphed EFEs activates an extended neural network comprising not only areas involved in affective processing (LaBar et al., 2003; Sato et al., 2004), but also motion processing (Sarkheil et al., 2013). It is possible that the involvement of such additional mechanisms during the identification of dynamic EFEs might have facilitated the task and led to the absence of significant differences in performance between HA and LA. Future studies should investigate this hypothesis and in particular test whether reduced facial mimicry found in HA in response to static fearful EFEs (Sonnby-Borgstrom, 2009; Scarpazza et al., 2018) may be restored by the presentation of dynamic EFEs and be related to improvement in dynamic EFE identification. Additionally, the comparable performance in dynamic EFEs identification between HA and LA highlights the subclinical nature of alexithymia, further supporting the notion that difficulties in EFE identification of HA become evident only under specific task conditions (Grynberg et al., 2012) and may not necessarily be evident in their everyday life.

To conclude, the present study shows that high – as opposed to low - levels of alexithymia are related to the need for more emotional intensity to perceive fear in static EFEs. On the contrary, no significant difference in performance was found when individuals with high and low levels of alexithymia were faced by dynamic EFEs, possibly due to the additional structural and configurational information regarding the change of emotional intensity over time (Kamachi et al., 2001), which may have facilitated emotion identification. Given that partially different brain networks are involved in processing the two types of stimuli, future studies should use neuroimaging techniques to elucidate the neural mechanisms underlying the current behavioral results.

AVAILABILITY OF DATA

The raw data supporting the conclusions of this manuscript will be made available by the authors, without undue reservation, to any qualified researcher.

AUTHOR CONTRIBUTIONS

FS, KB, CB, and CS conceived and designed the study and critically revised the manuscript for important intellectual content. FS, KB, and CB acquired and analyzed the data and drafted the manuscript.

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ORIGINAL RESEARCH
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Inter-individual Differences in Heart Rate Variability Are Associated with Inter-individual Differences in Empathy and Alexithymia

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In the present study, we investigated whether inter-individual differences in vagally mediated heart rate variability (vmHRV) would be associated with inter-individual differences in empathy and alexithymia. To this end, we determined resting state HF-HRV in 90 individuals that also completed questionnaires assessing inter-individual differences in empathy and alexithymia. Our categorical and dimensional analyses revealed that inter-individual differences in HF-HRV were differently associated with inter-individual differences in empathy and alexithymia. We found that individuals with high HF-HRV reported more empathy and less alexithymia than individuals with low HF-HRV. Moreover, we even found that an increase in HF-HRV was associated with an increase in empathy and a decrease in alexithymia across all participants. Taken together, these findings indicate that individuals with high HF-HRV are more empathetic and less alexithymic than individuals with low HF-HRV. These differences in empathy and alexithymia may explain why individuals with high HF-HRV are more successful in sharing and understanding the mental and emotional states of others than individuals with low HF-HRV.

Keywords: social cognition, social interaction, empathy, alexithymia, vagus nerve, high-frequency heart rate variability

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INTRODUCTION

Social relationships have always been of utmost importance for humans. Although the number and type of relationships may have changed over the course of evolution, the challenges and opportunities associated with social relationships may have remained the same (Dunbar, 1998). Evolutionary pressures may, thus, have selected a suite of skills that may have helped us to initiate or maintain positive relationships and to avoid or terminate negative relationships (De Waal, 2008). Of these skills, the ability to share and understand others' emotional and mental states, which entails a simulation of these states while making a self-other distinction, appears to be of particular relevance (Preston and De Waal, 2002). Infants are already capable of sharing others' emotional and mental states, but a full understanding of these states on basis of a self-other distinction emerges during late childhood (Frith and Frith, 2003), implying that the ability to share and understand

emotional and mental states comprise various processes that become more and more complex throughout our development. It is important to note that these processes involve a simulation of others' emotional and mental states on the neural and autonomic level, an interpretation of the simulated states on basis of the corresponding neural and autonomic changes, and a distinction between the simulated and observed states (Preston and De Waal, 2002; De Waal, 2008). These processes have been linked to inter-individual differences in empathy, a personality trait describing an individual's awareness of *other's* emotional and mental states (Deutsch and Madle, 1975), and alexithymia, a personality trait describing an individual's awareness of *one's own* emotional and mental states (Nemiah et al., 1976). Individuals with low levels of empathy and/or high levels of alexithymia are severely impaired in their ability to share and understand emotional and mental states of others and the self (e.g., Baron-Cohen et al., 1999; Parker et al., 2001; Dolan and Fullam, 2004; Moriguchi et al., 2007; Silani et al., 2008; Decety et al., 2013), which may explain why these individuals frequently have difficulties to establish and maintain positive relationships (e.g., Rilling et al., 2007; Chiu et al., 2008; Mokros et al., 2008; Feldmanhall et al., 2013). It is, thus, not surprising that the interest for biomarkers indicating such impairments has steadily been growing over the last decade. It should be noted, however, that the search for these biomarkers is more complex than initially thought (Kapur et al., 2012; Davis et al., 2015).

Vagally mediated heart rate variability (vmHRV), an index of parasympathetically induced changes in consecutive heart beats (Berntson et al., 1997), has been suggested to be a promising biomarker for inter-individual differences in social behavior and social cognition (Porges, 2007; Thayer and Lane, 2009). Inter-individual differences in vmHRV reflect inter-individual differences regarding the engagement of prefrontal and (para-)limbic brain regions during the regulation of emotional and cognitive processes (Porges, 2007; Thayer and Lane, 2009; Thayer et al., 2012), indicating that inter-individual differences in vmHRV may work as biomarker for inter-individual differences in the social domain. Individuals with high vmHRV are more efficient in establishing and maintaining positive relationships than individuals with low vmHRV (e.g., Kogan et al., 2014; Beffara et al., 2016; Lischke et al., 2018), implying that the relationships of individuals with high vmHRV are more characterized by mutual understanding than the relationships of individuals with low vmHRV (Kok and Fredrickson, 2010). Inter-individual differences regarding the ability to share and understand emotional and mental states may explain why individuals with high vmHRV are more likely to achieve a mutual understanding in social relationships than individuals with low vmHRV. Individuals with high vmHRV may be more efficient in regulating emotional and cognitive processes during the simulation of the respective states (e.g., Geisler et al., 2010, 2013; Williams et al., 2015) and may be more efficient in regulating cognitive processes that are necessary for the interpretation of the respective states (e.g., Hansen et al., 2003; Segerstrom and Nes, 2007; Luft et al., 2009) than individuals with low vmHRV, which may result in a more efficient sharing and understanding of the respective states in individuals with high as compared to low vmHRV (e.g., Cote et al., 2011; Quintana et al., 2012a; Lischke et al., 2017). However, individuals with high and low vmHRV do not only differ from one another with respect to processes that are relevant for the sharing and understanding of emotional and mental states, but also with respect to personality traits that are relevant for the sharing and understanding of these states. Empathy related personality traits, like, for example, compassion for other's emotional and mental states, are more pronounced in individuals with high than low vmHRV (e.g., Oveis et al., 2009; Kogan et al., 2014; Stellar et al., 2015), whereas alexithymia related personality traits, like, for example, difficulties in identifying or describing one's own emotional and mental states, appear to be more pronounced in individuals with low than high vmHRV (e.g., Fukunishi et al., 1999; Panayiotou and Constantinou, 2017). It should be noted, however, that the association between inter-individualdifferences in vmHRV and inter-individual differences in alexithymia related personality traits is less clear than the association between inter-individual differences in vmHRV and inter-individual differences in empathy related personality traits (e.g., Virtanen et al., 2003; Zohar et al., 2013), indicating a need for further studies investigating this association. Similarly, there is a need to further study the association between inter-individual differences in vmHRV and inter-individual differences in empathy related personality traits because this association has only been investigated in a few studies (e.g., Oveis et al., 2009; Kogan et al., 2014; Stellar et al., 2015).

In the present study, we addressed these issues in a relatively large and homogenous sample of healthy participants by measuring inter-individual differences in vmHRV as well as inter-individual differences in empathy and alexithymia related personality traits. On basis of previous studies (e.g., Fukunishi et al., 1999; Oveis et al., 2009; Kogan et al., 2014; Stellar et al., 2015; Panayiotou and Constantinou, 2017), we expected participants with high vmHRV to report more empathy and less alexithymia than participants with low vmHRV. We also expected inter-individual differences in vmHRV to be differently associated with inter-individual differences in empathy and alexithymia across all participants.

MATERIALS AND METHODS

Participants

According to an *a priori* power analysis with G*Power3 (Faul et al., 2007), we had to recruit 90 participants to be able to detect medium effect sizes in our categorical ($f = 0.30$, $1\text{-}\beta = 80$, $\alpha = 0.05$) and dimensional ($f^2 = 0.15$, $1\text{-}\beta = 80$, $\alpha = 0.05$) analyses regarding the association between inter-individual differences in vmHRV and inter-individual differences in empathy or alexithymia. In order to be considered for recruitment, participants had to pass a screening concerning the presence of current mental disorders and the use of current psychotropic medication. Female participants were not considered for recruitment to control sex-differences in empathy (Christov-Moore et al., 2014), alexithymia (Levant et al., 2009) and vmHRV (Koenig and Thayer, 2016). We, thus, recruited 90 male participants at the Institute of Sport

TABLE 1 | Participant characteristics.

	M	*SEM*
Age (years)	26.20	0.43
Body mass index (kg/m^2)	24.05	0.27
Physical activity (h/w)	7.05	3.70
Respiratory activity (Log-pHF-HRV, Hz)	−0.72	0.01
Heart rate variability (Log HF-HRV, ms^2)	2.69	0.05
Empathy (EQ-15)[a]	16.42	0.01
Alexithymia (TAS-20)[b]	44.13	1.15

Log-pHF-HRV = log-transformed peak of high frequency heart rate variability, Log-HF-HRV = log-transformed high frequency heart rate variability, EQ-15 = Empathy Quotient 15 (Allison et al., 2011), TAS-20 = Toronto Alexithymia Scale 20 (Bagby et al., 1994a,b).
[a]*Data was available for 79 participants.*
[b]*Data was available for 89 participants.*

Science of the University of Rostock (see **Table 1**). All participants provided written-informed consent to the study protocol that was approved by the ethics committee of the University of Rostock and carried out in accordance with the Declaration of Helsinki.

Procedure

After arriving at the laboratory, participants were asked to use the bathroom to control for the effects of bladder filling and gastric distension on vmHRV (Quintana and Heathers, 2014). Participants were then seated in a comfortable chair and prepared for a 5 min heart rate (HR) recording. As recently recommended (Quintana et al., 2016), participants were instructed to breathe spontaneously and to keep their eyes open during the recording. After the recording, participants completed questionnaires assessing inter-individual differences in empathy (Allison et al., 2011) and alexithymia (Bagby et al., 1994a,b).

Heart Rate Variability

HR was recorded continuously with a chest belt system, the RS800 HR monitor (Polar Electro Oy, Kempele, Finland), providing a sampling rate of 1000 Hz. HR monitors like the RS800 have been shown to record changes in consecutive heart beats as accurate as conventional electrocardiograms (Weippert et al., 2010; Quintana et al., 2012b), indicating that the recorded data were valid and reliable measures of instantaneous HR. Device specific software (Polar ProTrainer 5; Polar Electro Oy, Kempele, Finland) was used to transfer the recorded data to a computer for further data processing with Kubios HRV 2.2 (Tarvainen et al., 2014). Following established guidelines (Task Force of the European Society of Cardiology, 1996), the recorded data was visually inspected, detrended (smoothn priors: $\lambda = 500$) and, whenever necessary, corrected using adaptive filtering. Thereafter, the recorded data was subjected to a spectral analysis to determine HF-HRV, a measure of vagally mediated cardiac activity (Berntson et al., 1997), and the peak of HF-HRV (pHF-HRV), a measure of respiratory activity (Berntson et al., 1997). Besides these measures, no further measures were determined to avoid interpretational issues arising from the use of measures that do not clearly reflect vagally mediated cardiac activity (Berntson et al., 1997).

Questionnaires

The Empathy Quotient (EQ-15; Allison et al., 2011) is a 15 item self-report questionnaire for the assessment of empathy. The EQ-15 comprises a main scale for the assessment of global empathy and several subscales for the assessment of specific aspects of empathy (e.g., emotional reactivity or social skills). However, the subscales are highly inter-correlated with one another (Muncer and Ling, 2006; Allison et al., 2011), implying that the EQ-15 measures empathy as an unidimensional rather than multidimensional construct. Following previous recommendations (Muncer and Ling, 2006; Allison et al., 2011), we only considered the main scale in our analyses. The main scale had good psychometric properties [$\alpha = 0.75$], which were comparable to those that have previously been reported (Muncer and Ling, 2006; Allison et al., 2011)

The Toronto Alexithymia Scale 20 (TAS-20; Bagby et al., 1994a,b) is a 20 item self-report questionnaire for the assessment of alexithymia. The TAS-20 consists of a main scale assessing global differences in alexithymia and of several subscales assessing specific differences in alexithymia (e.g., difficulties in identifying or describing feelings). However, the high correlations between the different subscales and the low reliabilities of some subscales complicate the interpretation of the respective subscales (Kooiman et al., 2002; Muller et al., 2003). Accordingly, it has been suggested that the TAS-20 may be better suited to measure alexithymia as an unidimensional rather than multidimensional construct (Vorst and Bermond, 2001). We, therefore, considered the main scale but not the subscales in our analyses. The main scale had excellent psychometric properties [$\alpha = 0.86$], which were similar to those that have previously been reported (Bagby et al., 1994a,b).

Statistical Analysis

All statistical analyses were conducted with SPSS 22 (SPSS Inc., Chicago, IL, United States). To investigate whether inter-individual differences in vmHRV would be associated with inter-individual differences in empathy and alexithymia, dimensional and categorical analyses were performed. In all analyses, pre-cautions were taken to control for inter-individual differences in age (years), body mass index (BMI, kg/m^2), physical activity (h/w) and respiratory activity (pHF-HRV, Hz) that may contribute to inter-individual differences in vmHRV (Quintana et al., 2016). Inter-individual differences in physical and respiratory activity were of particular concern because participants were recruited at a Sport Science facility, where the prevalence of athletes that differ from non-athletes in vmHRV due to inter-individual differences in physical and respiratory activity is higher than in the general population (Aubert et al., 2003). For the categorical analyses, analyses of covariance (ANCOVAs) were computed to determine whether participants with high and low HF-HRV would show inter-individual differences in empathy and alexithymia. Assignment of participants to the high and low HF-HRV group was based on a median split. For the dimensional analyses, multiple hierarchical

regression analyses were computed to determine whether inter-individual differences in HF-HRV would be differentially associated with inter-individual differences in empathy and alexithymia across all participants. Prior to all analyses, HF-HRV and pHF-HRV were log transformed (log 10) to account for deviations from normality distribution. The significance level for the analyses was set at $p \leq 0.05$ (two-tailed). In addition to the significance level (p), effect sizes (η_p^2 and R^2) were determined to facilitate the interpretation of significant findings (Cohen, 1988).

RESULTS

Inter-individual Differences in Heart Rate Variability and Inter-individual Differences in Empathy

A one-way ANCOVA showed that participants with high HF-HRV reported more empathy than participants with low HF-HRV [$F(1,73) = 6.51$, $p = 0.013$, $\eta_p^2 = 0.08$; see **Figure 1**], independent of inter-individual differences in age, BMI, physical or respiratory activity. Across all participants, inter-individual differences in HF-HRV were positively associated with inter-individual differences in empathy as indicated by a multiple regression analysis [$t(73) = 2.17$, $p = 0.033$; see **Table 2**]. The multiple regression analysis also indicated that there was no association of inter-individual differences in age, BMI, physical or respiratory activity with inter-individual differences in empathy [all $p > 0.339$; see **Table 2**]. Most of the variance regarding inter-individual differences in empathy was, thus, explained by inter-individual differences in HF-HRV [$F(1,73) = 4.71$, $p = 0.033$; see **Table 2**], not by inter-individual differences in age, BMI, physical or respiratory activity [$F(4,74) = 0.19$, $p = 0.944$; see **Table 2**]. More precisely, inter-individual differences in HF-HRV explained 6% of variance regarding inter-individual differences in empathy in addition to the 2% of variance that tended to be explained by inter-individual differences in age, BMI, physical or respiratory activity.

TABLE 2 | Association between inter-individual differences in heart rate variability and inter-individual differences in empathy across all participants.

	Empathy (EQ-15[a])		
Predictors	R^2	ΔR^2	β
Step 1	0.01	0.01	
Age (years)			−0.08
Body mass index (kg/m^2)			0.67
Physical activity (h/w)			0.00
Respiratory activity (Log-pHF-HRV, Hz)			0.01
Step 2	0.07	0.06*	
Age (years)			−0.09
Body mass index (kg/m^2)			0.11
Physical activity (h/w)			−0.06
Respiratory activity (Log-pHF-HRV, Hz)			−0.05
Heart rate variability (Log-HF-HRV, ms^2)			0.26*

Log-pHF-HRV = log-transformed peak of high frequency heart rate variability, Log-HF-HRV = log transformed high frequency heart rate variability, EQ-15 = Empathy Quotient 15 (Allison et al., 2011).
[a]*Data was available for 79 participants.*
*$p \leq 0.05$.

Inter-individual Differences in Heart Rate Variability and Inter-individual Differences in Alexithymia

A one-way ANCOVA revealed that participants with high HF-HRV reported less alexithymia than participants with low HF-HRV [$F(1,83) = 3.99$, $p = 0.049$, $\eta_p^2 = 0.05$, see **Figure 2**], irrespective of inter-individual differences in age, BMI, physical or respiratory activity. Across all participants, inter-individual differences in HF-HRV were negatively associated

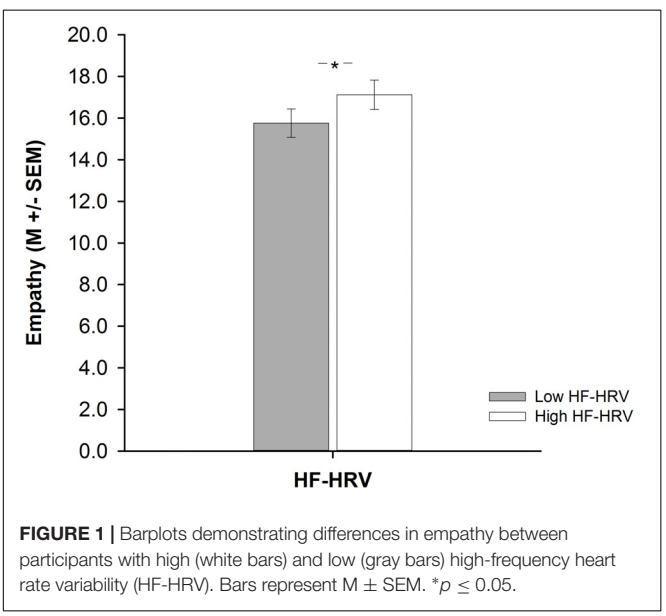

FIGURE 1 | Barplots demonstrating differences in empathy between participants with high (white bars) and low (gray bars) high-frequency heart rate variability (HF-HRV). Bars represent M ± SEM. *$p \leq 0.05$.

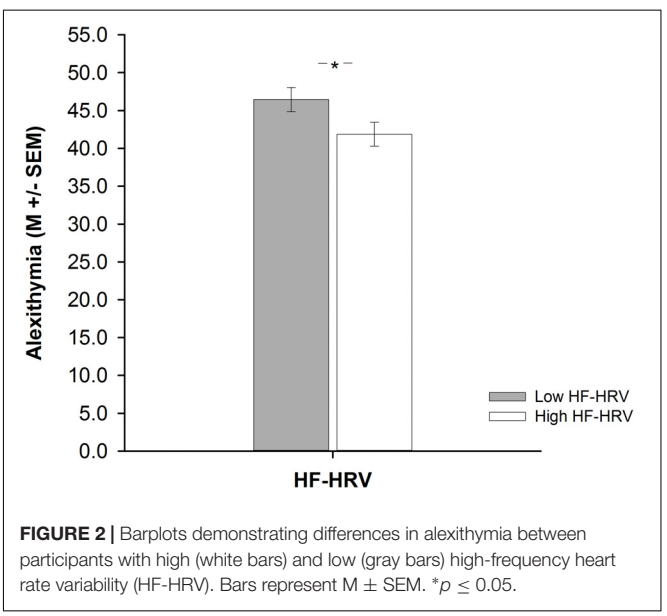

FIGURE 2 | Barplots demonstrating differences in alexithymia between participants with high (white bars) and low (gray bars) high-frequency heart rate variability (HF-HRV). Bars represent M ± SEM. *$p \leq 0.05$.

with inter-individual differences in alexithymia as indicated by a multiple regression analysis [$t(83) = -2.02$, $p = 0.047$; see **Table 3**]. The multiple regression analysis further indicated that inter-individual differences in age were also negatively associated with inter-individual differences in alexithymia [$t(83) = -2.81$, $p = 0.006$; see **Table 3**] and that inter-individual differences in BMI, physical or respiratory activity were not associated with inter-individual differences in alexithymia [all $p > 0.416$; see **Table 3**]. However, inter-individual differences in alexithymia were more relevant for explaining inter-individual differences in HF-HRV [$F(1,83) = 4.07$, $p = 0.047$; see **Table 3**] than inter-individual differences in age, BMI, physical or respiratory activity [$F(4,84) = 1.98$, $p = 0.106$; see **Table 3**]. Inter-individual differences in HF-HRV explained 4% of variance regarding inter-individual differences in alexithymia in addition to the 9% of variance that tended to be explained by inter-individual differences in age, BMI, physical or respiratory activity.

DISCUSSION

In the present study, we investigated the association of inter-individual differences in vmHRV with inter-individual differences in empathy and alexithymia related personality traits. Inter-individual differences in vmHRV were determined on basis of inter-individual differences in resting state HF-HRV and inter-individual differences in empathy and alexithymia were determined on basis of inter-individual differences in questionnaire scores. In line with our expectations, we found a positive association between inter-individual differences in vmHRV and inter-individual differences in empathy. Our categorical analyses revealed that participants with high vmHRV were more empathetic than participants with low vmHRV and our dimensional analyses indicated that an increase in vmHRV was associated with an increase in empathy across all participants. Also as expected, we found a negative association between inter-individual differences in vmHRV and inter-individual differences in alexithymia. Our categorical analyses showed that participants with high vmHRV were less alexithymic than participants with low vmHRV and our dimensional analyses indicated that an increase in vmHRV was associated with a decrease in alexithymia across all participants.

Previous studies revealed a similar association of inter-individual differences in vmHRV with inter-individual differences in empathy and alexithymia related personality traits (e.g., Fukunishi et al., 1999; Oveis et al., 2009; Kogan et al., 2014; Stellar et al., 2015; Panayiotou and Constantinou, 2017). With respect to empathy it is noteworthy that individuals with high vmHRV show more agreeableness with others and more compassion for others' emotional or mental states than individuals with low vmHRV (e.g., Oveis et al., 2009; Kogan et al., 2014; Stellar et al., 2015). Agreeableness is a personality trait that is closely related to compassion and compassion is a personality trait that is closely related to empathetic concern (Goetz et al., 2010), a distinct dimension of empathy that has been regarded as an important precursor of prosocial behavior (Batson and Shaw, 1991). Inter-individual differences in vmHRV may, thus, be differentially associated with distinct empathy dimensions, implying the possibility of positive associations with empathy dimensions that facilitate prosocial behavior, such as empathetic concern (e.g., Toi and Batson, 1982; Batson et al., 1983), and negative associations with empathy dimensions that impair prosocial behavior, such as empathetic distress (e.g., Toi and Batson, 1982; Batson et al., 1983). In the present study, we were unable to test this possibility because the psychometric properties of our empathy questionnaire argued against the use of the questionnaire's subscales in the respective analyses. Future studies should, thus, employ empathy questionnaires with psychometrically sound subscales to further elucidate the association between inter-individual differences in vmHRV and inter-individual differences in empathy. With respect to alexithymia it is noteworthy that individuals with high vmHRV report fewer difficulties in identifying or describing their own emotional and mental states than individuals with low vmHRV (e.g., Fukunishi et al., 1999; Panayiotou and Constantinou, 2017). However, the association between inter-individual differences in vmHRV and inter-individual differences in alexithymia seem to be more pronounced among younger (e.g., Fukunishi et al., 1999; Panayiotou and Constantinou, 2017) than older (e.g., Virtanen et al., 2003; Zohar et al., 2013) individuals. Future studies should, therefore, investigate this association among individuals showing a wider age range than those individuals that have been included in the present study. These studies should also employ alexithymia questionnaires with psychometrically sound subscales to explore whether inter-individual differences in vmHRV are differentially associated with distinct dimensions of alexithymia as suggested by previous studies (e.g., Fukunishi et al., 1999; Panayiotou and

TABLE 3 | Association between inter-individual differences in heart rate variability and inter-individual differences in alexithymia across all participants.

	Alexithymia (TAS-20[a])		
Predictors	R^2	ΔR^2	β
Step 1	0.09	0.09	
Age (years)			−0.29
Body mass index (kg/m^2)			0.08
Physical activity (h/w)			0.04
Respiratory activity (Log-pHF-HRV, Hz)			0.10
Step 2	0.13	0.04*	
Age (years)			−0.29**
Body mass index (kg/m^2)			0.04
Physical activity (h/w)			0.09
Respiratory activity (Log-pHF-HRV, Hz)			0.60
Heart rate variability (Log-HF-HRV, ms^2)			−0.22*

Log-pHF-HRV = log-transformed peak of high frequency heart rate variability, Log-HF-HRV = log transformed high frequency heart rate variability, TAS-20 = Toronto Alexithymia Scale 20 (Bagby et al., 1994a,b).
[a]*Data was available for 89 participants.*
*$p \leq 0.05$, **$p < 0.01$.*

Constantinou, 2017). In the present study, we were unable to perform the respective analyses because of the problematic subscale structure of our alexithymia questionnaire. Taken together, the findings of the present and previous studies suggest that inter-individual differences in vmHRV are associated with inter-individual differences regarding the ability to share and understand emotional and mental states of others and the self.

Assuming an association of inter-individual differences in vmHRV with inter-individual differences in empathy and alexithymia may help to explain why individuals with high vmHRV are more successful in establishing and maintaining positive relationships than individuals with low vmHRV (e.g., Kok and Fredrickson, 2010; Beffara et al., 2016; Lischke et al., 2018). Individuals with high vmHRV may be more efficient in simulating and interpreting emotional and mental states under a self-other awareness than individuals with low vmHRV, which may increase the likelihood of mutual understanding that is necessary for the establishment and maintenance of positive relationships. Inter-individual differences regarding the regulation of cognitive and emotional processes that are relevant for the simulation and interpretation of emotional and mental states, like, for example, the control of emotions (e.g., Geisler et al., 2010, 2013; Williams et al., 2015) or the allocation of attention (e.g., Hansen et al., 2003; Segerstrom and Nes, 2007; Luft et al., 2009), may contribute to these differences. In this respect it is noteworthy that individuals with high vmHRV outperform individuals with low vmHRV on tasks that require the inference of others' states on basis of facial and/or vocal cues (e.g., Cote et al., 2011; Quintana et al., 2012a; Lischke et al., 2017), indicating the plausibility of the aforementioned assumptions.

With respect to the neurobiological mechanisms mediating the association of inter-individual differences in vmHRV with inter-individual differences in empathy and alexithymia, it is important to note that a similar set of prefrontal and (para-)limbic brain regions is engaged during the simulation and interpretation of emotional and mental states as during the regulation of cardiac activity (Bernhardt and Singer, 2012; Thayer et al., 2012; Wingbermuhle et al., 2012). Of these brain regions, the anterior cingulate cortex, the insula and amygdala are of particular relevance because functional and structural changes in these brain regions are associated with changes in empathy and alexithymia (e.g., Singer et al., 2004; Moriguchi et al., 2007; Reker et al., 2010; Banissy et al., 2012; Klimecki et al., 2012; Bernhardt et al., 2014; Grabe et al., 2014; Goerlich-Dobre et al., 2015) as well as with changes in vmHRV (e.g., Gianaros et al., 2004; Lane et al., 2009; Sakaki et al., 2016; Winkelmann et al., 2017). Following previous suggestions that changes in vmHRV serve as a proxy for changes in prefrontal activity and prefrontal-(para-)limbic connectivity (Porges, 2007; Thayer and Lane, 2009; Thayer et al., 2012), we assume that inter-individual differences in vmHRV reflect inter-individual differences in empathy and alexithymia that are due to inter-individual differences in prefrontal activity and prefrontal-(para-)limbic connectivity. More precisely, we assume that individuals with high vmHRV are more empathetic and less alexithymic than individual with low vmHRV because individuals with high vmHRV are more efficient in recruiting prefrontal and (para-)limbic brain regions implicated in the simulation and interpretation of emotional and mental states than individuals with low vmHRV. In this respect it is noteworthy that individuals with autism, a disorder that is characterized by alterations in empathy and alexithymia (Hill et al., 2004; Dziobek et al., 2008), show alterations in a prefrontal and (para-)limbic brain regions (e.g., Baron-Cohen et al., 1999; Dziobek et al., 2006; Silani et al., 2008; Wicker et al., 2008; Ecker et al., 2012) as well as alterations in vmHRV (e.g., Mathewson et al., 2011; Kuiper et al., 2017). Inter-individual differences in vmHRV may, thus, indicate inter-individual differences regarding the recruitment of prefrontal and (para-)limbic brain regions during the simulation and interpretation of emotional and mental states in healthy as well as in mentally disordered individuals, implying that inter-individual differences in vmHRV may indeed serve as biomarker for inter-individual differences in empathy and alexithymia.

The findings of the present study suggest that inter-individual differences in vmHRV are associated with inter-individual differences in empathy and alexithymia, presumably because of inter-individual differences in prefrontal activity and prefrontal-(para-)limbic connectivity during the simulation and interpretation of emotional and mental states. The present findings are not only consistent with findings of previous studies revealing an association between inter-individual differences in vmHRV and inter-individual differences in the regulation of emotional and cognitive processes that are necessary for the simulation and interpretation of emotional and mental states (e.g., Hansen et al., 2003; Segerstrom and Nes, 2007; Luft et al., 2009; Geisler et al., 2010; Geisler et al., 2013; Williams et al., 2015), but also with findings of previous studies suggesting an association between inter-individual differences in vmHRV and inter-individual differences in prefrontal activity and prefrontal-(para-)limbic connectivity during the regulation of emotional and cognitive processes that are necessary for the simulation and interpretation of emotional and mental states (e.g., Gianaros et al., 2004; Lane et al., 2009; Sakaki et al., 2016). Taken together, these findings corroborate our assumption that inter-individual differences in vmHRV are associated with inter-individual differences regarding the ability to share and understand emotional and mental states of others and the self. However, whether inter-individual differences in vmHRV really have the potential to work as a biomarker for inter-individual differences in empathy and alexithymia remains to be determined in future studies that are explicitly designed for these types of investigations (Kapur et al., 2012; Davis et al., 2015). These studies should employ correlational and experimental study designs in a cross-sectional or longitudinal way to investigate the aforementioned associations on the behavioral and neural level in healthy and mentally disordered individuals with performance and questionnaire based measures of empathy, alexithymia and social behavior. Otherwise it will be difficult to determine whether inter-individual differences in vmHRV qualify as a biomarker for inter-individual differences in empathy and alexithymia.

AUTHOR CONTRIBUTIONS

AL, AM-M, and RP designed the study. AM-M and MW collected the data. AL and RP analyzed the data. AL wrote the manuscript. AH, AM-M, HF, HG, MB, MW, and RP contributed to writing, reviewing and editing of the manuscript. All authors approved the final version of the manuscript.

DISCLOSURE

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MINI REVIEW
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Alexithymia as a Transdiagnostic Precursor to Empathy Abnormalities: The Functional Role of the Insula

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Distorted empathic processing has been observed across multiple psychiatric disorders. Simulation theory provides a theoretical framework that proposes a mechanism through which empathy difficulties may arise. Specifically, introspection-centric simulation theory (IST) predicts that an inability to accurately interpret and describe internal affective states may lead to empathy difficulties. The purpose of this review is to synthesize and summarize an empirical literature suggesting that simulation theory provides insights into a cognitive and neurobiological mechanism (i.e., alexithymia and insula pathology) that negatively impacts empathic processing, in addition to how disruptions in these processes manifest across psychiatric disorders. Specifically, we review an emerging non-clinical literature suggesting that consistent with IST, alexithymia and associated insula pathology leads to empathy deficits. Subsequently, we highlight clinical research suggesting that a large number of disorders characterized by empathy pathology also feature alexithymia. Collectively, these findings motivate the importance for future work to establish the role of alexithymia in contributing to empathy deficits across clinical symptoms and disorders. The current review suggests that simulation theory provides a tractable conceptual platform for identifying a potential common cognitive and neural marker that is associated with empathy deficits across a wide array of diagnostic classes.

Keywords: alexithymia, insula, empathy, psychiatric disorders, affective neuroscience

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INTRODUCTION

Behavioral and neural empathy deficits characterize many psychiatric conditions, including autism spectrum disorder (ASD; Minio-Paluello et al., 2009), psychopathy (Decety et al., 2013), borderline personality disorder (BPD) (Dziobek et al., 2011), and narcissistic personality disorder (NPD) (Ritter et al., 2011). This suggests that empathy is a relevant transdiagnostic dimension with implications for functional impairment and treatment development. Empathy refers to sharing an isomorphic affective state to others, to understand their feelings (de Vignemont and Singer, 2006). Introspection-centric simulation theory (IST) predicts that empathy requires introspecting upon an isomorphic internal state (Shanton and Goldman, 2010). Empirical work on alexithymia provides a platform for evaluating whether introspection deficits link to empathy difficulties in clinical and typical populations. Alexithymia describes an inability to articulate and interpret internal feelings (Sifneos, 1973). Since this original conceptualization, multiple alexithymia subtypes have been proposed (Bermond et al., 2007), which has led to a distinction between cognitive (i.e., difficulties verbalizing and identify emotions) and affective (low awareness of emotional arousal) alexithymia.

An IST framework predicts that alexithymia may lead to empathy deficits. That is, while alexithymia and empathy differ in that they pertain to internally versus externally oriented states, respectively, they share common referents (i.e., feelings and emotions). Refer to Bird and Viding (2014) for a theoretical review that proposes the role of simulation in empathy, in the context of autism, psychopathy, and alexithymia. The growing alexithymia literature allows for the evaluation of its effects on empathy at behavioral and neural levels. Therefore, the purpose of this review is to summarize theoretical and empirical work that suggests (1) consistent with IST, alexithymia contributes to empathy deficits (2) the insula is a biomarker of alexithymia deficits, and (3) alexithymia presents as a candidate contributor to empathy deficits across multiple psychiatric disorders.

Simulation theory posits that simulation is leveraged as a predictive device, such that a social agent simulates what they might do in a comparable situation, or simulates a matching internal state, then utilizes that information to adopt another's perspective (see **Figure 1**; Goldman, 1992). Multiple forms of simulation theory have been proposed (see Shanton and Goldman, 2010 for a discussion of alternative simulation theory perspectives). IST posits that generating and introspecting upon a matching internal state is required for empathy (Goldman, 2006). Therefore an IST account suggests that since alexithymia involves a distorted representation of internal affective states, empathy deficits should co-occur.

BEHAVIORAL FINDINGS LINKING ALEXITHYMIA WITH DECREASED EMPATHY

Consistent with IST, behavioral findings suggest that alexithymia is correlated with and leads to empathic deficits. Silani et al. (2008) found correlations between alexithymia and empathy across both typical and clinical populations (see Supplementary Table 1 for a summary of research findings included in this review). Links between alexithymia and empathy have also been found in the context of empathizing based on facial expressions. Specifically, in a study by Moriguchi et al. (2006), participants were asked to rate the experienced pain of individuals based on their facial expression. High alexithymia participants ascribed less experienced pain, suggesting that difficulties perceiving one's internal affective state may blunt the perception others' affective states. Alexithymia also mediated the relationship between one's ability to describe and act with mindful awareness and empathy (MacDonald and Price, 2017).

THE ROLE OF THE INSULA IN ALEXITHYMIA AND CONCURRENT EMPATHIC DEFICITS

Alexithymia is a complex neurofunctional phenomenon arising from multiple brain regions (Moriguchi and Komaki, 2013). It is not the purpose here to claim that the insula is the only region underlying alexithymia. It is out of the scope of this review to evaluate the functional role of all regions within the context of IST, alexithymia, empathy, and psychiatric disorders. Given the large body of research suggesting the insula plays a functional role in inner affective experience awareness [Lang, 1994; Craig, 2009; Zaki et al., 2012; Damasio and Carvalho, 2013; Bird and Viding, 2014), we focus our review on the insula.

Empirical work suggests that insula pathology is associated with alexithymia. Specifically, increased left insula glutamate concentrations positively correlated with alexithymia (Ernst et al., 2013). Increased insula dopaminergic receptor availability also positively correlated with alexithymia (Okita et al., 2016). Additionally, alexithymia is associated with decreased gray matter insula volume (Goerlich-Dobre et al., 2014; Laricchiuta et al., 2014). Finally, voxel-based morphometry studies suggest that insula pathology may lead to a domain-specific deficit in cognitive (not affective) alexithymia (Goerlich-Dobre et al., 2014, 2015).

To date, one study assessed for a causal link between insula pathology and alexithymia. Hogeveen et al. (2016) measured alexithymia severity across three groups characterized by increasing insula damage. Insula damage severity predicted increased alexithymia.

Within an IST account, given that accurate processing of internal affective states is requisite for empathy, and given that the insula is implicated in alexithymia, it would be expected that insula pathology should cause empathic deficits. One neuroimaging study assessed the modulating role of alexithymia on insula responsiveness and empathy (Bird et al., 2010). In this fMRI study, participants empathized with a partner who experienced physical pain. Left anterior insula activity was positively associated with level of empathy. Furthermore, the association between left anterior insula response and empathy was weaker in high relative to low alexithymia participants.

Overall, empirical work spanning structural, neurochemical, and functional neuroimaging modalities suggests that insula pathology may lead to alexithymia and associated empathy deficits. Furthermore, very preliminary work provides clues that insula pathology may be associated more with difficulties identifying, analyzing, and verbalizing feelings (i.e., cognitive alexithymia). Replication across structural and functional neuroimaging modalities are needed to support the possible functional specificity of the insula in the context of alexithymia.

THE ROLE OF THE INSULA IN ALEXITHYMIA AND EMPATHY DEFICITS ACROSS PSYCHIATRIC DISORDERS

The literature reviewed thus far suggests that alexithymia leads to empathy deficits in typical populations. This suggests that IST provides a framework for assessing whether alexithymia leads to empathy deficits in clinical populations. To date, while little empirical work has assessed whether empathy deficits source from alexithymia across disorders, we review a body of work suggesting that a variety of psychiatric presentations featuring empathy deficits, exhibit co-occurring alexithymia. This literature highlights the importance for future work to establish

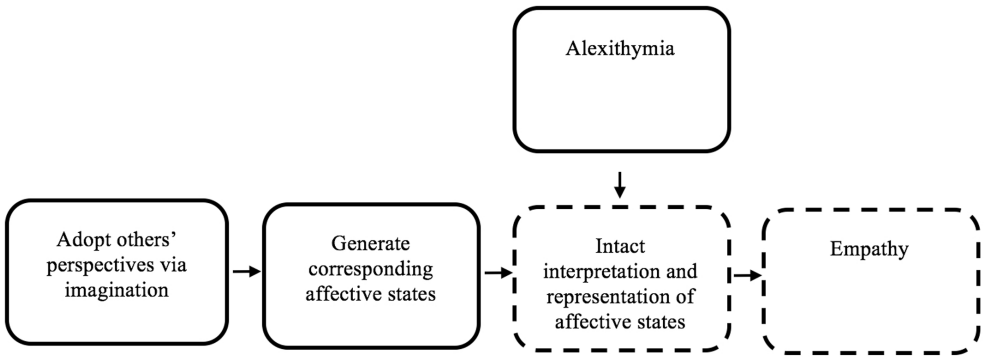

FIGURE 1 | The role of alexithymia in empathy deficits, in the context of introspection-centric simulation theory. This figure represents a schematic simplified version of Goldman's simulation theory (Goldman, 1992). Alexithymia is added in the figure, to clarify how alexithymia might yield empathy deficits. Imagination is used to simulate the perspective of an individual. Then, affective states are generated that follow from the simulated state. Those affective states are then represented in the 'simulator,' yielding empathy. Alexithymia may cause a disruption in the accurate interpretation and representation of affective states, causing empathy deficits. Dotted-lines indicate nodes within an IST framework that may plausibly be negatively impacted by alexithymia.

the mechanistic role of alexithymia in contributing to empathy deficits across clinical presentations.

Autism Spectrum Disorder

Alexithymia prevalence amongst ASD is higher than in the general population (Hill et al., 2004). ASD may also be characterized by greater deficits in cognitive, relative to affective forms of alexithymia (Berthoz and Hill, 2005; Silani et al., 2008). This is interesting given an emerging body of research suggesting that ASD is also characterized by greater struggles with cognitive empathy (i.e., comprehending and adopting the emotional perspective of others), relative to affective empathy (i.e., actually feeling others' emotional state; Deschamps et al., 2014).

Empathy deficits have also been observed in ASD (Baron-Cohen and Wheelwright, 2004; Sucksmith et al., 2013). Regarding a link between alexithymia and empathy deficits in ASD, Bird et al. (2010) operationalized empathy as insula activation magnitude while observing others experiencing pain. Insula activation negatively correlated with alexithymia during the empathy condition. After controlling for alexithymia severity in ASD and controls, no group difference in empathy was evident. The authors concluded that alexithymia, rather than ASD severity, drives empathic deficits. Given that alexithymia estimates are disproportionately higher in ASD (Hill et al., 2004), this suggests that alexithymia may be an important mechanism accounting for empathy deficits in this population.

Silani et al. (2008) also found that the insula was implicated in alexithymia and diminished empathy in ASD. Specifically, for both groups, during affective introspection, a positive correlation between bilateral insula parameter estimates and empathy, and a negative correlation with alexithymia were observed. In addition, at a more relaxed statistical threshold, ASD adults demonstrated hypoactivation of the anterior insula while rating how pleasant or unpleasant they felt after viewing negative affective images.

Overall, these findings suggest that alexithymia and related insula processing in ASD may be associated with decreased empathy. Furthermore, results suggest that the subgroup of ASD individuals high in alexithymia, may be specifically characterized by the cognitive subtype. Preliminary results should therefore not be interpreted as attenuated arousal to emotional events, but rather a specific difficulty with identifying and verbalizing feelings.

Psychopathy

Psychopathy refers to personality traits characterized by callousness, lack of concern about performance, and diminished affect (Blair, 2013). Given that diminished empathy is a core feature of psychopathy (Hare, 1980), IST provides an inroads to assess whether empathic deficits partly source from alexithymia. Psychopathy has been associated with alexithymia (Kroner and Forth, 1995; Louth et al., 1998). Regarding a link between alexithymia and empathy, results are inconsistent with respect to IST. Specifically, alexithymia has been associated with 'secondary' psychopathy, which is not typically characterized by empathy deficits (i.e., emotional instability, risk-taking behavior, and impulsivity) and less with 'primary' psychopathy (i.e., empathy deficits, manipulativeness, fear insensitivity, callousness; Grieve and Mahar, 2010; Lander et al., 2012). However, studies show that both primary and secondary psychopathy are associated with reduced affective empathy (Wai and Tiliopoulos, 2012). Currently, no studies directly address the cognitive/affective alexithymia and cognitive/affective empathy relationship, making it difficult to draw structured conclusions.

Consistent with IST, Jonason and Krause (2013) found that increased psychopathic traits were associated with increased alexithymia, and decreased empathy. Specifically, while deficits existed across multiple alexithymia subdomains, only externally oriented thinking (i.e., preference to attend to external information rather than internal states) was related to affective empathy (i.e., feeling others' emotional states). It is unknown whether alexithymia mediates the relationship between psychopathy and empathy, however, alexithymia mediated the

relationship between criminal aggression and empathy (Winter et al., 2017).

No psychopathy studies have assessed whether insula pathology causes alexithymia. However, research suggests that the insula plays a role in empathic reasoning in psychopathic populations. Specifically, when imagining others in pain, high psychopathy predicted diminished insula activity (Decety et al., 2013; Marsh et al., 2013). High psychopathy individuals also showed attenuated insula response while identifying a perpetrator's emotional state (Decety et al., 2015), and when observing affection or exclusion toward others (Meffert et al., 2013). Insula response to empathy for pain may also be differentrially dependent on facets of psychoapthy. Specifically, affective-interpersonal psychopathy traits were negatively associated with insula response while empathizing, where as lifestyle-antisocial trait were positively associated (Seara-Cardoso et al., 2015).

Results suggest a complex presentation of alexithymia and empathy in psychopathy. Specifically, in secondary psychopathy, characterized by disinhibition, cognitive alexithymia is associated with affective empathy deficits. While there is evidence of affective empathy deficits in primary psychopathy, cognitive alexithymia has not been found, suggesting deficits source either from an alexithymia-independent mechanism or possibly a relationship with deficits in affective alexithymia. Furthermore, while there is evidence of attenuated insula response during cognitive and affective empathy tasks, this atypicality seems specific to the social role of the other. Additionally, given the possible causal role of the insula in alexithymia development (Hogeveen et al., 2016), future work in psychopathy should determine whether affective or cognitive empathy deficits and insula pathology are differentially mediated by cognitive or affective alexithymia.

Narcissistic Personality Disorder

Narcissistic personality disorder is characterized by grandiosity, self-admiration needs, and empathy deficits (American Psychiatric Association, 2013). An emerging body of work suggests that narcissism is particularly associated with an alexithymia subtype (i.e., difficulties identifying feelings). Specifically, Schimmenti et al. (2017) found that high levels of narcissistic traits were associated with difficulties identifying feelings, and not with other alexithymia subtypes. Jonason and Krause (2013) found that across the Dark Triad Traits (i.e., narcissism Machiavellianism, psychopathy), narcissism uniquely predicted difficulties identifying feelings. There is also evidence that specific facets of narcissism may be associated with distinct alexithymia subtypes. Specifically, narcissistic defenses (i.e., seeing others as wrong and abusive) correlated with difficulties identifying feelings, whereas core narcissism (i.e., grandiosity and entitlement) was linked to difficulties describing feelings to others. The majority of studies in this area do not leverage clinical NPD samples, but rather assess narcissistic traits in typical samples. However, preliminary work in the form qualitative research does suggest that difficulties identifying feelings extend to clinical NPD samples also (Dimaggio et al., 2007).

While results are mixed, there is growing evidence that NPD may be characterized by emotional empathy deficits (i.e., feeling an emotional response to another person's state), with cognitive empathy being relatively intact (Baskin-Sommers et al., 2014). It should be noted though that cognitive empathy deficits have been found, particularly for the emotions fear and disgust (Marissen et al., 2012). It has become increasingly appreciated that given the tendency of narcissistic individuals to over-estimate their empathic ability, objective measures of empathy that bypass self-report may provide a more valid measure of empathy in this population (Ritter et al., 2011). This suggestion is consistent with the lack of empathy deficits that have been found on measures of self-report (Fan et al., 2011; Marissen et al., 2012) contrasted with pronounced deficits that have been documented using performance-based empathy measures (Ritter et al., 2011).

With regards to insula functioning, NPD evidenced decreased insula gray matter volume, and further, gray matter volume in the insula negatively correlated with empathic ability (Schulze et al., 2013). Fan et al. (2011) found that narcissism symptomatology was associated with increased levels of alexithymia, as well as reduced positive signal change from non-empathy to empathy task conditions in the right anterior insula.

Overall, while no research has yet assessed whether alexithymia leads to empathy deficits in narcissistic individuals, the co-occurrence of these difficulties indicates this may be a promising avenue of research. The particularly pronounced difficulties with describing internal feelings, suggests that this particular alexithymia subtype may be a useful first step in establishing whether a causal role of between alexithymia in empathic difficulties exists.

Borderline Personality Disorder

Borderline personality disorder is characterized by affective impulsivity and instability relating to social relationships and the self (American Psychiatric Association, 2013). Affective dysregulation is a prominent BPD feature (Glenn and Klonsky, 2009). Interestingly, dysregulation may also be mechanistically related to empathic deficits. Specifically, increased arousal has been observed in BPD while empathizing, and further, decreased emotional dysregulation has been associated with diminished empathetic concern (Dziobek et al., 2011; Kalpakci et al., 2016).

With respect to IST, it is possible that emotional dysregulation exacerbates alexithymia, causing empathic deficits. Consistent with this possibility, emotional dysregulation and alexithymia are conceptually and mechanistically related. Specifically, each pertains to the distorted processing of internal affective experience. Furthermore, increased aversive inner tension (which is related to emotional dysregulation) has been associated with difficulties identifying internal emotions in BPD (Wolff et al., 2007). These findings are consistent with Ridings and Lutz-Zois (2014), who found that alexithymia correlated with both emotional dysregulation, and BPD tendencies. Regarding a mechanistic link between alexithymia and empathy, Flasbeck et al. (2017) found that the effect of early life adversity on empathy for psychological pain was mediated by alexithymia in BPD. Overall, while significant work would be required to scrutinize this speculative IST prediction of the link between affective

dysregulation, alexithymia, and diminished empathy, the purpose here is to highlight the utility of IST, and the potential role of alexithymia in BPD empathic deficits.

While no studies currently exist on the neural correlates of alexithymia in BPD, neuroimaging findings suggest that aberrant insula processing may contribute to dysregulated negative affect in BPD, with implications for altered empathic processing. Specifically, BPD has been associated with diminished insula activity while viewing negative social–emotional stimuli (Koenigsberg et al., 2009; Frick et al., 2012), and increased activity to physical pain after social rejection (Bungert et al., 2015). Regarding empathic processing, BPD evidenced increased insula activity relative to controls during emotional (but not cognitive) empathy (Dziobek et al., 2011). Given that no neuroimaging studies currently exist on alexithymia in BPD, further work may assess whether insula dysregulation in BDP might reflect inaccurate or dysregulated appraisals of internal feelings. Consistent with this possibility, preliminary related work suggests that insula pathology in BPD may confer difficulties generating internally and externally relevant social information. Specifically, the insula mediated poorer consistency in rating the self and others in BPD (Beeney et al., 2016). Furthermore, dissociative tendencies in BPD (which reflect detachment from internal experience) were associated with altered functional connectivity in the insula (Wolf et al., 2011).

CLINICAL IMPLICATIONS, LIMITATIONS, AND DIRECTIONS FOR FUTURE RESEARCH

Consistent with IST, research supports a link between alexithymia and associated insula pathology, and empathy deficits in typical populations. Furthermore, multiple clinical presentations exhibit co-occurring alexithymia and empathy deficits. Combined with reviewed preliminary mediation findings in some clinical presentations, these results indicate that alexithymia is a potential transdiagnostic source of empathic difficulties.

There are limitations to this review worth mentioning. Given that a review focus was the insula, many brain regions that have been linked with alexithymia were not discussed (Moriguchi and Komaki, 2013). An additional limitation stems from the small number of mediation studies to comprehensively evaluate IST predictions in psychiatric disorders.

In the future, levering varied alexithymia measurement approaches, in addition to novel measurement development, may elucidate the role of alexithymia subtypes across disorders. The majority of studies reviewed leveraged the Toronto Alexithymia Scale (Taylor et al., 1992) as their alexithymia operationalization. This measure provides nuanced information about cognitive alexithymia, but unlike measures such as the Bermond–Vorst Alexithymia Questionnaire (Vorst and Bermond, 2001), it does not address the cognitive and affective alexithymia distinction.

A central goal of this review was to provide an empirical basis for the significant potential utility in continued research clarifying the transdiagnostic link between alexithymia and empathy. Currently, alexithymia does not form a core treatment component for the disorders reviewed. Alexithymia is a well-specified, empirically measurable construct. Therefore, alexithymia is suited for empirical clinical work into therapeutic mechanisms of change, as well as in clinical practice settings for purposes of treatment outcome monitoring.

AUTHOR CONTRIBUTIONS

AV conceptualized the review. LA, MG, and JR provided significant conceptual refinement. AV, LA, and MG drafted the manuscript. LA, MG, and JR provided critical revisions. All authors approved the final manuscript.

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SUPPLEMENTARY MATERIAL

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The Multifaceted Nature of Alexithymia – A Neuroscientific Perspective

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Neuroscientific studies have mostly employed the 20-item Toronto Alexithymia Scale (TAS-20; Bagby et al., 1994a) for the assessment of alexithymia, a self-report scale that assesses the alexithymia facets difficulty identifying feelings, difficulty describing feelings, and externally oriented thinking. These facets can be considered to capture difficulties in the cognitive processing of emotions associated with alexithymia. However, Nemiah and Sifneos' original conceptualization of alexithymia included also an affective component, a lack of imaginative capacities, which cannot be assessed using the TAS-20. Aiming to capture the entire alexithymia construct, the Bermond–Vorst Alexithymia Questionnaire (BVAQ; Vorst and Bermond, 2001) was developed, a self-report scale which assesses two affective facets (difficulty fantasizing and difficulty emotionalizing) in addition to three cognitive facets. Based on these facets, an affective and a cognitive dimension of alexithymia can be distinguished. By now, several neuroscientific studies have investigated the neural signatures of the different facets and dimensions of alexithymia. Here, I provide an overview of the history of the alexithymia facets and dimensions and review findings provided by functional and structural magnetic resonance imaging (MRI) studies that differentiated between the alexithymia facets and/or its affective and cognitive dimensions. I then provide a synopsis of the current neuroscientific evidence for dissociable substrates of alexithymia facets and dimensions. Finally, the scientific value and clinical implications of these findings are discussed.

Keywords: alexithymia, neuroimaging, facets, dimensions, cognitive, affective

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INTRODUCTION

The term alexithymia was coined in 1973 by the psychotherapist Peter Emanuel Sifneos to describe patients with psychosomatic illnesses, who had several symptoms in common. These patients showed marked difficulty in identifying their feelings, in finding appropriate words to describe them, and in distinguishing feelings from bodily sensations of arousal. Moreover, they patients had little imaginative capacities, reflected in a paucity of fantasies, and a thinking style that was focused on external events, together with a striking avoidance of a focus on inner experiences. Sifneos introduced the word "alexithymia" [from the Greek *a* (no) – *lexis* (words) – *thymos* (emotion); literal meaning "no words for emotions"] to describe "this specific difficulty which appears more likely to be due to a combination of neurophysiological and psychological defects rather than to purely psychological ones." (Sifneos, 1973).

In 1976, alexithymia was the main theme of the 11th European Conference on Psychosomatic Research held in Heidelberg, Germany (Bräutigam and von Rad, 1977). There, a consensus on the definition of the alexithymia construct was reached. Its salient features were defined as: (1) difficulty identifying feelings (DIF) and distinguishing between feelings and the bodily sensations of emotional arousal; (2) difficulty describing feelings (DDF) to other people; (3) constricted imaginal processes, as evidenced by a paucity of fantasy; and (4) a stimulus-bound, externally oriented cognitive style (Nemiah et al., 1976; Taylor et al., 1997; Taylor and Bagby, 2000). Although some individuals with alexithymia appear to contradict this definition as they can be chronically dysphoric or display sudden outbursts of weeping or rage, Taylor and Bagby (2000) note that thorough questioning usually reveals that "they know very little about their own feelings and, in most instances, are unable to link them with memories, fantasies, or specific situations." "At the extreme, alexithymic individuals are virtually organismic automatons functioning in a one- to two-dimensional world, one that is deprived of the fullness of feelings" (Taylor et al., 1997, p. xii).

Although multiple factors are thought to play a role in the etiology of alexithymia (Nemiah, 1977), psychoanalytic theorists have mostly emphasized the contribution of early developmental deficiencies to what is referred to as *primary alexithymia* (Taylor et al., 1997). Alexithymia is considered to be primary when emerging "as a life-long dispositional factor that can lead to psychosomatic illness" (Lesser, 1981). Primary alexithymia may derive from childhood trauma (Krystal, 1979) or from negative primary caregivers interactions (Wearden et al., 2003). Moreover, the genetic polymorphism of the 5-HT transporter-linked promoter region (i.e., L/L alleles) may influence the occurrence of alexithymia (Kano et al., 2012). Hence, primary alexithymia is thought of as a more or less stable personality trait that becomes molded during childhood and early adult years, and that is therefore developmental in nature (Messina et al., 2014; see also Allen and Heaton, 2010). In contrast, secondary alexithymia refers to alexithymic characteristics resulting from developmental arrests, massive psychological trauma in childhood or later on in life, sociocultural factors, or psychodynamic factors (Taylor et al., 1997).

Clinically relevant alexithymia affects approximately ten percent of the general population (Honkalampi et al., 2001; Franz et al., 2008). Individuals with levels of alexithymia experience continuous problems processing their emotions at a cognitive level and regulating them, rendering them prone to develop psychiatric conditions characterized by affective dysregulation. Thus, alexithymia is a major risk factor for psychological distress and chronic psychopathology. Furthermore, emotion processing deficits associated with Autism Spectrum Disorders (ASD), which show high comorbidity with alexithymia, appear to be due to comorbid alexithymia rather than ASD *per se* (for a review, see Bird and Cook, 2013).

Moreover, alexithymia is linked to deficits in empathy, i.e., the ability to take the perspective of others and to understand others' feelings and intentions. In fact, alexithymia has been found to be a transdiagnostic precursor of empathic difficulties (Valdespino et al., 2017). According to simulation theory, people simulate the feelings they observe in others to predict and understand the feelings of the people in their environment. An inability to accurately interpret and describe one's own internal affective states will thus lead to difficulties empathizing with others' feelings. Bird and Viding (2014) explain alexithymia-related deficits in empathy within the framework of their Self to Other Model of Empathy (SOME), whose core conceptual implication is that factors affecting one's own experience of emotion will determine what emotional associations are learned. The authors suggest that the primary impairment in alexithymia lies within the affective representation system, which contains representations of one's current affective state and which is likely localized to the insular cortex and the anterior cingulate cortex (ACC). Such impairment in the affective representation system would lead to an inability to form a consciously accessible representation of one's own affective state, which is consistent with the diagnostic criterion of alexithymia as being aware of having an emotion, yet being unsure as to what emotion one experiences. In line with this, recent findings indicate that alexithymia is linked to a lack of interoceptive awareness (Mul et al., 2018), an important aspect of empathy, and that alexithymia may even be characterized by a general failure of interoception (Brewer et al., 2016; Murphy et al., 2018). However, interoceptive accuracy (a lower, physiological level of emotional awareness, which is often measured using heart beat counts) might be increased in individuals with high levels of alexithymia (Ernst et al., 2013; Scarpazza et al., 2017), in line with their tendency to overly focus on bodily signals.

Taken together, alexithymia bears major relevance for daily social and emotional functioning and for the development of psychiatric disorders and their associated societal and financial burden. Yet, even after four decades of research, the neuroscientific literature on alexithymia is undermined by disagreement regarding the operationalization and assessment of alexithymia, and by equivocal, often conflicting findings. In this article, I aim to (1) present an overview of the existing evidence for the multifaceted nature of the construct, (2) provide future directions for research into its neural substrates, and (3) discuss potential clinical implications of the presented findings.

ALEXITHYMIA – A MULTIFACETED CONSTRUCT

The construct alexithymia evolved an operational meaning with the development of the self-report questionnaire TAS (26-item Toronto Alexithymia Scale); which assessed four features of alexithymia: (F1) difficulty identifying and distinguishing between feelings and bodily sensations; (F2) DDF (i.e., putting feelings into words and verbalize them to others); (F3) reduced daydreaming; and (F4) externally oriented thinking (EOT) (Bagby et al., 1990). Shortly thereafter, the TAS was revised by eliminating six items assessing daydreaming, resulting in the TAS-20 (20-item Toronto Alexithymia Scale) with a three factor structure, which has become the most-widely used tool for alexithymia assessment: (F1) DIF; (F2) DDF; and (F3) EOT (Bagby et al., 1994a,b).

Despite the popularity of the TAS-20 as it provides a brief and easy-to-use tool for alexithymia assessment (which is advantageous especially in neuroimaging studies, which are usually more time-consuming and laborious than purely behavioral studies), caution is advisable.

It should be noted that DIF and DDF usually correlate highly, whereas correlations of EOT with DIF and DDF tend to be lower. Although DDF is specifically designed to capture the verbalization of feelings (i.e., the ability to find words for one's feelings and to express one's feelings to others), which is not explicitly part of DIF, one may argue that in order to identify a feeling, attaching a label to that feeling (in terms of inner language) is necessary. From this perspective, DIF and DDF seem relatively closely related as both explicitly refer to emotions, whereas EOT specifically assesses a style of thinking, i.e., a cognitive mode not necessarily including the experience of an emotion.

Although more objective measures of alexithymia exist, such as the observer-rated Beth Israel Hospital Questionnaire (BIQ; Sifneos, 1973), its modified version (Taylor et al., 1997), and the Toronto Structured Interview for Alexithymia (TSIA; Bagby et al., 2006), the TAS-20 provides a quick, well-validated, and standardized measure of alexithymia and has thus become the most-widely used method for its assessment. This is particularly true for neuroimaging studies as these are usually more laborious and wearisome than behavioral studies. As a consequence, the vast majority of neuroimaging studies conducted up to today relied on the TAS-20 to assess alexithymia and to shed light onto its neural basis.

Moreover, a large part of these studies used a certain TAS-20 cut-off sum score to divide participants into two groups, an alexithymic versus a non-alexithymic group or a group of high-scorers versus a group of low-scorers on alexithymia, respectively. Some studies used a cut-off score of 61, which has been suggested to indicate clinically relevant alexithymia (Taylor et al., 1988; Bagby et al., 1994b; Taylor et al., 1997). However, a number of studies used lower (and variable) cut-off scores, hampering the comparability of such studies' findings. Importantly (regardless of the specific cut-off score applied), those studies treated alexithymia as a categorical variable and often as a unitary construct by restricting their analyses to TAS-20 sum scores. Consequently, their findings provided no insights into the neural correlates of the different facets of alexithymia. Today, however, most researchers agree that alexithymia constitutes a personality trait that is normally distributed in the population and should thus be treated as a dimensional variable rather than a categorical one. Moreover, more recent studies have come to acknowledge alexithymia as a multifaceted rather than as a unitary construct, whose facets seem to be associated with separable neural correlates. Such inconsistencies in alexithymia assessment and data analysis might have contributed to the heterogeneity in findings characterizing the alexithymia literature.

A related problem is that the "golden standard" of alexithymia assessment, the TAS-20, measures only the three abovementioned facets of alexithymia (DIF; DDF: EOT). These can be considered to capture difficulties in cognitive emotion processing in relation to alexithymia. However, Nemiah and Sifneos' original conceptualization of the alexithymia construct included not only a cognitive but also an affective component. Nonetheless, the majority of alexithymia studies relied on the TAS-20, neglecting differences in the subjective experience of emotions. This might have further contributed to the equivocality in the literature on alexithymia.

Aiming to capture both components and thereby the complete alexithymia construct, the BVAQ was developed (Vorst and Bermond, 2001). This self-report scale assesses in addition to three cognitive alexithymia facets two affective facets: difficulty fantasizing (the degree to which a person is inclined to imagine, day-dream, etc), and difficulty emotionalizing (the degree to which a person is inclined to experience emotional feelings and to become emotionally aroused). Using the BVAQ, an affective and a cognitive dimension of alexithymia can thus be distinguished, with the cognitive dimension referring to the processing of emotions at a cognitive level (identifying, analyzing, and verbalizing feelings), and the affective dimension (fantasizing and emotionalizing) referring to the level at which an individual subjectively experiences emotions (Bermond et al., 2007). Moreover, a further differentiation between several types of alexithymia has been proposed (Bermond, 1997; Moormann et al., 2008).

NEUROSCIENTIFIC EVIDENCE FOR DIFFERENT FACETS AND DIMENSIONS OF ALEXITHYMIA

Today, the idea of differentiating between different alexithymia dimensions is still considered controversial, and some empirical studies have failed to support this idea (Bagby et al., 2009; Watters et al., 2016). However, in my eyes the existing evidence suggests that such a differentiation is indeed worthwhile, for researchers and clinicians alike. Meta-analyses of functional and structural imaging studies have identified the amygdala, the insula, the ACC, and regions of the prefrontal cortex (PFC) as key correlates of alexithymia in the brain (van der Velde et al., 2013; Xu et al., 2018). However, whether these correlates are linked to specific facets and dimensions of alexithymia could not be systematically investigated due to the scarcity of evidence. Consequently, it is currently unclear whether the alexithymia facets and dimensions are linked to separable neurobiological mechanisms. Disentangling these mechanisms is critical for the development of more efficient psychological – possibly pharmacological – treatment strategies of empathy deficits and difficulties in emotion recognition and regulation associated with alexithymia. In the following, I provide an overview of the current neuroscientific evidence for separable neural substrates of the different alexithymia facets and dimensions.

FUNCTIONAL IMAGING

The amygdala, a key node of the emotional perception/attention system, is consistently smaller in volume and less activated during negative emotional processing in relation to higher levels

of alexithymia. In two fMRI studies using masked priming paradigms, pictures of emotional (happy or sad) faces were masked with neutral faces for a very brief period of time (33 ms; milliseconds), preventing conscious recognition of the facial emotions (Kugel et al., 2008; Reker et al., 2010). Kugel and colleagues found that specifically the alexithymia facet DIF was negatively correlated with the neural response of the right amygdala to masked sad faces, even when controlling for depressivity and anxiety. Reker and coworkers reported that the TAS-20 total score and the alexithymia facets DIF and DDF significantly and negatively correlated with activation of the left amygdala in response to masked sad (but not happy) faces, controlling for trait anxiety and depression. A further study masking surprised faces with neutral ones after 33 ms found that specifically the DIF facet was negatively correlated with activity in the fusiform face area, parahippocampal gyrus and superior temporal gyrus (Duan et al., 2010).

These findings suggest that particularly the DIF facet (and to some extent also the DDF facet) of alexithymia is linked to hypoactivation in areas that are important for facial emotion processing during automatic (implicit) emotion processing. fMRI studies investigating the conscious (explicit) processing of emotions observed similar patterns of hypoactivation of the amygdala particularly for DIF in response to fear-inducing and disgusting pictures (Leweke et al., 2004) and hypoactivation of the right amygdala in response to fearful body expressions (Pouga et al., 2010). Moreover, a neurofeedback study observed that the ability of the study participants to increase their amygdala activity by recalling positive autobiographical memories was negatively correlated with DIF scores, suggesting that that the more difficulty people had identifying their feelings, the less successful they were in learning how to regulate activity within their left amygdala (Zotev et al., 2011). Taken together, these results indicate that specifically DIF is linked to a dysfunction of the amygdala (and other emotion-related areas) during the implicit and explicit processing of emotions, particularly of those with negative valence.

A PET study on hypersensitivity to bodily signals in alexithymia observed hyperactivity of the right insula and the orbitofrontal cortex (part of the PFC) during colonic distension with increasing alexithymia levels (Kano et al., 2007). Also here a difference between the alexithymia facets emerged: DIF and DDF showed similar patterns of correlation with activation in these areas, whereas EOT was related to hyperactivity in distinct (temporal) areas, which are not related to somatosensory processing. Moreover, only DIF correlated with the participants' subjective perception during the experiment, suggesting that the more difficult it was for participants to identify their feelings, the more stressed and anxious they reported to feel, and the more intensely they experienced unpleasant sensations during colonic distension. Indeed, another study recently confirmed that primarily DIF correlates with experiences of negative affect (Suslow and Donges, 2017).

An fMRI study in patients with depersonalization disorder provided further evidence for distinct neural substrates of the alexithymia facets (Lemche et al., 2013). TAS-20 total scores correlated with neural activity in the dorsal ACC (dACC) while the patients subconsciously perceived sad facial expressions. DIF was associated with responsiveness of the anterior insula and DDF with responsiveness of the posterior cingulate cortex, both regions that are important for emotional interoception. In contrast, EOT was associated with responsiveness of the orbital gyrus, a key region of emotion regulation.

Moreover, a recent study investigating social rejection in relation to alexithymia by means of the Cyberball game observed that reduced activation in the dACC during rejection was specifically linked to the DIF facet (Chester et al., 2015). Thus, the more difficulty participants reported to have identifying their feelings, the less their dACC was activated when experiencing rejection in a social context. Moreover, DIF was the only alexithymia facet that predicted experiences of social rejection in daily life, and reduced dACC activity significantly mediated this relationship. Considering the role of emotions as feedback mechanism to guide one's behavior, this implies that individuals scoring high on the DIF facet of alexithymia may not be able to benefit from emotional signals in terms of adapting their behavior in social contexts.

In line with the findings reported above, the results of a recent fMRI study in our lab provided evidence for distinct effects of the alexithymia facets on the processing of rewards (Goerlich et al., 2017). While participants anticipated social rewards (anticipation phase), DIF scores correlated with activity in the subgenual and perigenual ACC and the adjacent ventromedial PFC. When participants received social rewards (feedback phase), DDF scores were associated with reduced activity in the ventral tegmental area, when they received monetary rewards, DIF scores were associated with higher activity in the right insula. For EOT, no significant associations were observed, neither for (social or monetary) reward anticipation nor for feedback. These findings again highlight the specificity of the alexithymia facets on activity of the ACC, insula, and PFC during socio-emotional processing.

STRUCTURAL IMAGING

A recent large-scale ($n > 1{,}600$) VBM study corroborated the notion of neural separability of the alexithymia facets (Grabe et al., 2014). Controlling for levels of anxiety and depression, reduced dACC volume was identified as the major structural correlate of alexithymia as assessed by TAS-20 total scores. Regarding the TAS-20 factors, the most prominent contributions to volume reductions were found in relation to DIF scores, which were linked to smaller volumes of the dACC, left middle and inferior temporal gyrus, and cerebellum. DDF scores were associated with less gray matter in the fusiform gyrus, inferior temporal gyrus, and left cerebellum. In contrast, EOT scores showed no association with gray matter volumes. These findings demonstrate that the alexithymia facets are associated not only with differences in the function of emotion-related brain regions, but also to differences in their structure.

In a VBM study of our lab, we investigated for the first time whether the cognitive and affective alexithymia dimensions could be differentiated at the structural brain level (Goerlich-Dobre et al., 2014). We found that TAS-20 total scores (indicative of

the cognitive alexithymia dimension) were linked to more gray matter volume in the right posterior insula. In contrast, the affective dimension, specifically the emotionalizing factor of the BVAQ, was related to more volume in the right middle cingulate cortex. In a VBM study purely based on the BVAQ, the cognitive dimension was associated with reduced dACC volume, and the affective dimension with reduced volume of the orbitofrontal cortex (van der Velde et al., 2014). While the results of the two studies are different (probably due to differences in alexithymia assessment and performed analyses), they do suggest that the cognitive and affective alexithymia dimensions are linked to dissociable structural profiles. However, given the relatively small sample sizes of both studies (40 and 55 participants, respectively), their results should be interpreted with caution. In a further VBM study including 125 participants, using the BVAQ for alexithymia assessment, we found that the cognitive dimension was associated with volume reductions in the left amygdala, left insula, thalamus, caudate, hippocampus, and parahippocampal gyrus, whereas the affective dimension was linked to volume reduction in the middle cingulate cortex only (Goerlich-Dobre et al., 2015).

CONCLUSION

Taken together, the currently available evidence suggests that the different facets and dimensions of alexithymia are indeed related to differences in the function and structure of the key correlates of alexithymia. Especially the evidence regarding the three TAS-20 factors seems fairly robust. DIF is associated with impairments in the explicit and implicit processing of facial and bodily expressions of emotions, somatosensory processing, and reward processing. One large VBM confirmed a special role of DIF particularly on volumes of the dACC, a key region for emotional self-awareness. DDF seems to affect somatosensory and facial emotion processing as well, but to a lesser extent. In contrast, EOT appears to show little effect on the function and structure of brain regions involved in emotion processing. However, it should be kept in mind that EOT refers more to a cognitive level of emotion processing, whereas DIF and DDF are (1) closely related, and (2) refer to the subjective experience of emotions, i.e., the affective level of emotion processing. This difference might explain why MRI studies focusing on emotion-related areas in the brain usually found correlations with DIF (and, to a lesser extent, with DDF), but rarely with EOT.

The evidence regarding the structural correlates of the cognitive and affective alexithymia dimensions is currently less clear. While VBM studies have provided evidence for different structural correlates of the alexithymia dimensions, their results are heterogenous. This may be due to differences in alexithymia assessment and sample sizes between studies. It should also be noted that imaging research on alexithymia has heavily relied on self-report scales, which inherently lack objectivity. Further, it could be a consequence of the persisting uncertainty regarding the validity of the two alexithymia dimensions as based on the BVAQ, especially regarding the inclusion of an emotionalizing factor in the affective dimension (Bagby et al., 2009; Watters et al., 2016).

It is thus recommendable that future studies into the multifaceted nature of alexithymia use a multimethod assessment approach as well as large sample sizes to ensure sufficient statistical power. Moreover, it will be important to control for constructs that are closely related to alexithymia, such as negative affectivity, depression, and anxiety, to reach a better understanding of the neural mechanisms that underlie alexithymia and its different facets and dimensions. Such research could have far-reaching clinical implications. In addition to reflecting a fundamental deficit in recognizing and regulating one's own emotions, alexithymia might be associated with a lack of interoceptive awareness, interrupting the process of simulating the emotions of others in order to empathize with them. Empathy deficits are characteristic of a multitude of psychiatric conditions, including borderline personality disorder, psychopathy, narcissistic personality disorder, and ASD. Given the transdiagnostic significance of these problems and their apparent links to specific facets and dimensions of alexithymia, being able to identify their neural markers could substantially improve the neuropsychiatric assessment of people who are at risk of such disorders, and contribute to the development of individually tailored and thus more effective treatment strategies.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and approved it for publication.

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