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Towards a neurobiological understanding of alexithymia

Authors: Nicolás Meza-Concha**[1]**, Marcelo Arancibia**[2,3]**, Felicia Salas**[1]**, Rosa Behar**[4]**, Germán Salas**[1]**, Hernán Silva**[5]**, Rocío Escobar**[1]**

Affiliation:
[1] Escuela de Medicina, Facultad de Medicina, Universidad de Valparaíso, Valparaíso, Chile
[2] Centro de Investigaciones Biomédicas, Universidad de Valparaíso, Valparaíso, Chile
[3] Departamento de Salud Pública, Escuela de Medicina, Universidad de Valparaíso, Chile
[4] Departamento de Psiquiatría, Escuela de Medicina, Universidad de Valparaíso, Valparaíso, Chile
[5] Departamento de Psiquiatría, Escuela de Medicina, Universidad de Chile, Santiago, Chile

E-mail: marcelo.arancibiame@uv.cl

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Abstract

Although the specialized literature on the etiology of alexithymia is controversial, neurobiological research has shown relevant advances. The aim of this review is to analyze the available evidence regarding the neurophysiological bases of alexithymia. A comprehensive review of available articles from Medline/PubMed, EBSCO and SciELO was conducted. Previously, alexithymia was linked to a reduced interhemispheric brain connection. From a childhood traumatic perspective, the right prefrontal cortex and the default mode network would experience alterations, first hypermetabolic (dopaminergic and glutamatergic dysregulation) and then hypometabolic-dissociative (serotonergic and opioid dysregulation), resulting in a distorted interoceptive and emotional awareness. Mirror neurons are the essential neurobiological substrate of theory of mind and social cognition, intrinsically linked to alexithymia, involving parietal, temporal, premotor, and cingulate cortices, and inferior frontal gyrus. Other structures involved are the amygdala (facial expression and emotional reactivity), the insula (interoception, emotional integration and empathy) and the cerebellum (limbic cerebellum and somatosensory awareness). Molecular genetics has detected polymorphisms in genes of the serotonin transporter, in the enzyme genes of dopaminergic metabolism and brain-derived neurotrophic factor, while the role of oxytocin is controversial. To sum up, we found several studies demonstrating the overwhelming evidence of a neurobiological basis underlying alexithymia; nevertheless, research is still inconclusive and must include environmental, traumatic, social, and psychological factors that contribute to the origin of the alexithymia.

Introduction

The term "alexithymia," coined by Sifneos more than four decades ago [1], is etymologically related to a "lack of words to emotional expression." The concept was conceived from the observation of patients with psychosomatic symptoms that did not respond to psychotherapy. In the general population, it has been estimated a prevalence of 10%, being more frequent in men [2],[3] and people who suffer from psychosomatic disorders, where it reaches up to 60% [4]. Likewise, it is considered as a risk factor for depressive disorders, anxiety disorders, eating disorders, substance use disorder, among others [5],[6],[7],[8],[9].

At the same time, it has been related to diseases such as asthma, hypertension, diabetes mellitus, psoriasis, immune-mediated diseases [10],[11],[12],[13],[14] and functional digestive disorders [15], due to the difficulty that people with alexithymia have in distinguishing feelings from bodily sensations related to physiological arousal, and, in this way, demonstrating a higher vulnerability to the development of psychosomatic disorders.

Classically, the construct implies four main dimensions: difficulty in identifying and/or describing feelings and in distinguishing them from bodily sensations of emotional arousal, a reduced or absent symbolic thinking and a cognitive style [16] (lack of capacity to identify, analyze and verbalize feelings) [17]. On this basis, Bermond [18] distinguished different subtypes of alexithymia that would have a neurobiological correlation. According to the author, type I is characterized by a diminished affectivity and a poor cognitive development in relation to emotions. In type II, people with alexithymia could show a normal or even higher affective dimension, but a cognitive impairment. Finally, type III alexithymia is distinguished by a proper cognitive performance but a lesser affective experience.

Currently, etiological research in alexithymia is controversial, given the great number of investigations that link it with different factors. It would be the result of brain structure alterations involved in emotional processing [19], that could have a genetic and/or traumatic background, or even a hereditary pattern [20],[21],[22].

In this paper, we analyze and discuss the available studies in consulted databases regarding to neurophysiological and genetic background of neurobiology of alexithymia.

Methods

An exhaustive bibliographic search was conducted through the available articles on MEDLINE/PubMed, EBSCO and SciELO databases, and on five specialized consulting texts. A total of 117 articles were considered (72 original papers, 37 review papers and 3 meta-analysis), from 1973 to 2016. We included papers whose content was related to the neurobiological bases of alexithymia and which were categorized as more relevant for their contribution to the subject, according to the common agreement of the authors.

Results

Regarding the neurophysiological perspective of alexithymia, we introduce the main findings based on clinical and basic research.

Traumatic dimension of the origin of alexithymia

The genesis of alexithymia has been located in early and critical development stages (conceptualized by some authors as "secondary alexithymia") [23], associated to psychic trauma that emerges from negligence experiences, physical and psychological maltreatment and child sexual abuse.

During the last few years, environmental trauma has gained relevance as a phenomenon that threats mental and physical integrity [24], emerging particular cognitive-emotional processing patterns in early situational coping [25]. Hence, traumatic episodes would represent a diathesis to different psychiatric disorders, from the clinical perspective of both dimensional and categorical approaches [26],[27].

Some authors situate the human unconscious in right prefrontal cortex, due to its function in non-verbal communication and stress and affective regulation. Therefore, child mental trauma would interfere in right cortical development by triggering a regulatory response that becomes and altered response in order to preserve the homeostasis.

This reaction is characterized by an early hypermetabolic state that implies the activation of sympathetic nervous system through the start-up of neuroendocrine axis, which is conducted by the corticotropin releasing factor, the increased catecholaminergic and mineralocorticoid activity, while a dopaminergic and glutamatergic dysregulation occurs [27].

A second response appears as a reaction to the former, which is phenomenologically observed in the course of mental dissociation. Thus, it would provoke a disconnection from external stimuli, countering through a hypometabolic state the former hyperactivity, and reinforcing the parasympathetic response. This subsequent psychobiological phenomenon has been associated to alterations in serotoninergic and endogenous opioids systems [27].

As a consequence of trauma, different states of lack of integration of early sensorimotor experience and functions and reactions that significantly interfere the own representation of the self that are associated to aftermaths on personality development have been defined [28]. Hence, a deficient right cortical evolution would be expressed by a lack of recognition and processing of external stimuli and their integration with internal ones, that is, a distortion of interoceptive awareness. In this line, the default mode network, a group of cerebral regions (prefrontal cortex, anterior cingulate cortex, posterior cingulate cortex, medial prefrontal cortex, inferior parietal cortex and bilateral angular gyrus) [29], has been involved in self-referential processing [30]. In other words, how the individual thinks about himself. The network would be particularly damaged during the early trauma, resulting in a lack of emotional awareness that provokes a difficulty in emotional verbal identification and expression, of own and others, which are core dimensions of alexithymia [31],[32].

Mirror neurons and theory of mind

The main role of mirror neurons, intrinsically involved in the construct known as "theory of mind," is the modulation of social interaction through understanding and prediction of actions, emotions, motivations, beliefs and intentions of others. Therefore, they provide a plausible neurophysiological explanation about complex forms of

cognition and social interaction represented by a metacognitive ability with others [33], which is mediated by their activation to the perception of an action of others [34]. In that way, they achieve the acquisition or "mentalization" the content of others mind.

In humans, their function has been linked to areas from inferior parietal lobule, ventral premotor cortex and inferior frontal gyrus [35]. In addition, mirror neurons have been suggested to be activated to diverse facial expressions, which would suppose that determined neural substrates that are associated to them, would be implicated in conditions where social interaction is altered, such as autism spectrum disorders and alexithymia, but with a lesser severity and depth in the latter. Indeed, a deficient hemodynamic activity in some regions of mirror neurons system in carriers of autism when they observe or imitate facial expressions has been verified, as well as a decrease of neural functioning to theory of mind related tasks [36]. It is remarkable that it has been hypothesized that these patients exhibit high levels of alexithymia [34], with similar results to people with alexithymia without autism spectrum traits when they are appraised.

A decreased activation in dorsal premotor cortex, superior parietal cortex, inferior parietal cortex and supplementary motor area during negative emotional stimuli processing has been corroborated by the evaluation of different facial expressions and by performing mentalization tasks. These areas also would have properties of mirror neurons [19].

Moriguchi *et al*. [37] studied the relation between alexithymia and mirror neurons. They found that the group with higher degrees of alexithymia reported an increased activation of premotor cortex and superior and inferior parietal cortices when compared to the group with lesser degrees. These results indicate an altered functioning of the same neural regions linked to mirror neurons circuit, but in this case, with an increased activity, suggesting an eventual compensatory mechanism that would fail during emotional processing that is responsible of empathy in people with alexithymia [19].

Theory of mind was originally circumscribed to the research of autism spectrum, but it has recently gained importance in the wide range of social cognition [33], a complex process that makes possible the representation of social environment [38]. It has been proposed that responsible brain areas would be temporal regions, such as fusiform gyrus and superior temporal sulcus –what work with amygdala–, orbitofrontal cortex, anterior, posterior and right somatosensory cortices (whose development is altered if an early traumatic event occurs).

The information processing would be guided to an effector system composed by regions of basal nuclei, motor cortex and hypothalamus, making possible the social behavior. Because of that, the impaired nature of mentalization processes evoke the alexithymia, both clinical and etiologically.

On the other hand, some researchers state that it is related to an encoded ability in genetic modules that are activated by environmental keys such as language, a fundamental aspect in alexithymic development [39]. Jointly, from a neurophysiological point of view, the amygdala has been involved in recognizing of emotional prosody, concerning with affects such as anger, disgust, fear, rage and sadness, in order to generate withdrawal responses [40],[41]. At the same time, an activation of bilateral temporoparietal region and medial prefrontal gyrus in visuo-verbal tasks related to emotional attributing has been demonstrated [42].

Brain structures

The role of brain hemispheres

Initially, alexithymia was linked to a reduced interhemispheric connection, that prevents a proper integration between right (non-verbal affective unconscious information) and left (logical-analytical verbal thinking) hemispheric processing [43],[44]. This fact was observed in subjects with agenesis of corpus callosum [45].

Simultaneously, other authors stressed that alexithymia would be associated to a "functional commissurotomy" [46]. Thus, Zeitlin *et al.* [47] verified through digital topognosis tests, a great association between a deficient bidirectional interhemispheric communication and alexithymia. This was reasserted by Romei *et al.,* who provided new findings by the appraisal of magnetic transcranial stimulation [48].

Goerlich-Dobre *et al.* propose that different subtypes of alexithymia display diverse volumetric patterns throughout brain structures related to emotional processing. They report a noticeable reduction of gray matter in different brain regions in types II and III, but a more bulky corpus callosum than in "lexithymic" [49]. However, the mechanisms involved in this phenomenon are still unknown [50].

Other investigations have established a link between injuries in the right hemisphere and alexithymia. Jessimer *et al.* concluded that greater levels of alexithymia were associated to a reduced response in right hemisphere, and a lesser capacity in recognition of emotional facial expressions [51]. In fact, when examining with positron emission tomography during the observation of emotional facial expressions, it was determined that in people with alexithymia there is a lower blood flow in the right hemisphere than in those that do not present it. Nonetheless, diverse studies have reported differences according to sex [52],[53],[54]. In men, the association between great levels of alexithymia and an altered right hemisphere would prevail; while in women, these levels would be linked with bihemispheric alterations [54]. Evidence has even shown a left brain predomination in female alexithymia [52].

Amygdala: facial expression and emotional reactivity

The amygdala, a subcortical structure that is part of the limbic system, is known for its participation on the processing, significance [55],[56] and emotional reactivity [57]. Some explorations show that the amygdala

is involved in the recognition of facial expression, particularly threat [58],[59],[60].

Nonetheless, a study suggests a lack of significant differences in the emotional functioning between a group of patients with injuries on the amygdala and a control one concluding that, even though it is hard to deny that the amygdala is recruited in emotional processing, its participation is not critical for the production of affective states [61]. Therefore, the amount of studies that involve alexithymia with the amygdala are limited.

Some analyses link alexithymia to a hypofunction of the amygdala during the processing of facial expressions [62],[63]. On the other hand, Goerlich-Dobre *et al.* reported that in type I and II there is a reduction in the volume of the gray matter of the left amygdala, meaning that the cognitive dimension of alexithymia is related to a lower volume of the right amygdala, among other structures (left anterior insula, hippocampus, parahippocampus, caudate nucleus and the precuneus) [49]. Likewise, in a review of primary neuroimagenological explorations, it is proposed that the process described above, jointly with a reduction of the activity of the insula and the anterior cingulate cortex, would imply a disruption of the emotional activity when subjects with alexithymia face external stimuli [64]. Thus, it could be hypothesized that a morphological and/or functional abnormality could trigger alexithymic traits.

Anterior cingulate cortex

The anterior cingulate cortex is a cortical formation that is located around the corpus callosum, participating mainly in the emotional processing and behavior towards objectives [65].

A detriment of its function in people with alexithymia is observed in a series of studies [66]. Kano *et al.*[67] demonstrated, using positron emission tomography, a lesser activation of the anterior cingulate cortex in a group of individuals with alexithymia during the visualization of faces with angry expression. Likewise, Karlsson *et al.* [68] reported an association between alexithymia and a reduced activation of the anterior cingulate cortex under emotional induction (positive, negative or neutral) in women, mediated by the visualization of cinematographic films. It was observed a bigger activation of the somatosensory and motor cortex, which may explain the high frequency of somatization in people with alexithymia.

On the other hand, in an exploration of images obtained by magnetic resonance, a positive correlation between the size of the right anterior cingulate cortex and the degree of alexithymia was found in men, whereas in women, it was found an association with withdrawal [69].

It should be noticed that in the findings of Goerlich-Dobre *et al.*, affective alexithymia would correlate with a bigger volume of the subgenual anterior cingulate cortex (Brodmann's area 25) [49].

Insula

The insula is divided in an anterior and posterior region. The anterior region is very important in interoceptive processes with emotional integration [70],[71],[72],[73] and the phenomena related to empathy [73]. Consequently, multiple investigations suggest that an anomaly on the anterior insular cortex is a substrate for alexithymia. In those investigations, it was verified that a decrease of its activity, detected trough images of functional magnetic resonance, is correlated with high alexithymic scores in patients with an inducted high emotional functioning autism spectrum disorder [74]. Likewise, the bearers of alexithymia would display a hipoactivity of the insula in response to faces with angry expressions [67].

However, other surveys report a higher activity of the right insula in response to traumatic imagery [75] and visceral stimulation (colonic distention) [76]. In this sense, Karlsson *et al.* [68] infer the existence of a left insular hyperfunction in women with alexithymia. Goerlich-Dobre *et al.* evidenced an association between a lower left posterior insular volume, among other structures, and cognitive alexithymia [49].

Prefrontral cortex

It is composed by the lateral, medial and orbitofrontal cortex [77], these structures are involved in superior cognitive processes and in some affective functions [78],[79]. Even though, the orbitofrontal cortex is important in the emotional regulations and it possesses multiple connections with the hypothalamus and the amygdala [80],[81],[82], few studies connect it with alexithymia. Kano *et al.* stated that in a reaction to negative stimuli, a diminished activation of the right orbitofrontal cortex is observed [67], but an analysis by Mantani *et al.* could not find significant differences between a group with alexithymia and control subjects, in terms of its activity [83].

Cerebellum

The cerebellum integrates a great variety of sensitive and motor pathways being also linked with cognitive and emotional processing, due to its connections with the limbic system, the prefontal cortex and the temporoparietal region [84],[85].

Some analyses show a cerebellar activation during decision making as a "failure detection" mechanism [86],[87],[88]. Under this view, Clausi *et al.* concluded that the cerebellum participates in the conscious recognition of negative feelings, following a sense of self-responsibility after taking a wrong decision [89]. The findings around the cerebellar emotional processing have been of such importance, that in its most recent topographic-functional schematization, it has been described the " limbic cerebellum" composed by the lobules VI, VII, VIIb, VIII, Crus 1 and Crus 2 [90],[91].

In fact, it has been recognized the cerebellar cognitive-affective syndrome, characterized by executive dysfunction, behavioral disinhibition and emotional flattening [92]. Like so, many neuroimagenological

explorations have exhibited cerebellar alterations on depression, anxiety and personality disorders [93],[94],[95], even though the evidence of its relationship with alexithymia is insufficient.

Kano *et al.* verified an increased left cerebellar blood flow in people with alexithymia [67]. On the other hand, Moriguchi *et al.* reported a decrease of the cerebellar function within the same context [37],[96].

Recently, Laricchiuta *et al.* [97], hold the idea of a positive correlation between the volume of bilateral cerebellar gray matter on Crus 1 lobe and the level of alexithymia. The authors suggest that this finding may be related to an altered corporeality process, resulting in cognitively non processed emotions. This phenomenon is closely related to the concept "alexisomia," that describes the difficulty to build a state of somatosensory consciousness [64]. This would be part of a primitive level of emotional alteration, the precursor of alexithymia.

Genetical considerations

In the late 1970s, Heiberg documented the first findings that suggested the possibility that the origin of alexithymia could be influenced by hereditary factors [22]. In 2001, Valera and Berenbaum approached the problem by examining twins, but with a limited sample size [20]. Subsequently, it was published a more refined investigation that included a bigger population of twins, which established an association between the alexithymia scores obtained in the Toronto Alexithymia Scale or TAS-20, its dimensions and genetical factors [21]. Nowadays, research tries to precisely define what genetical variations would explain the origin of the alexithymic phenotype through the analysis of diverse genetic polymorphisms.

It has been suggested that dopamine plays an important role in the modulation of neural nets that connect cerebral structures involved in emotional and cognitive processing (prefrontal cortex, anterior cingulate cortex, and many others), due to a vast presence of dopaminergic neurons on the substantia nigra [98],[99]. Even more, it has been suggested that the presence of relevant polymorphisms of dopamine (Val66Met and DRD2/ANKK Tag IA), are related to lower volume of the anterior cingulate cortex [100]. Therefore, the dopaminergic role on alexithymia is proposed.

It is known that the Val (108/158) Met polymorphism in the gen that codes for the enzyme cathechol-O-methyl transferase, that is involved on the degradation and release of dopamine, is related to alexithymia [99]. On the other hand, the polymorphism Val66Met in the gen that codes for the brain-derived neurotrophic factor (that plays a critical role on the synaptic plasticity [101],[102] and on dopaminergic pathways [103],[104],[105], as well on recompense processes, learning and motivation [106]), in interaction with the Tag IA polymorphism of the receptor of dopamine DRD2/ANKK1 is associated with a lower volume of gray matter on the anterior cingulate cortex and alexithymia [107].

It has been suggested that oxytocin on people with alexithymia holds a pronounced role on the recognition of complex emotions [108] and that it would produce a higher sense of satisfaction when emotions are shared [109]. Despite this, an investigation conducted on a sample of people affected by obsessive-compulsive disorder, found that a variation on the gen that codes for the receptor of oxytocin did not have relationship with alexithymia [110].

Neuroimagenology has elucidated the relationship between the polymorphism of the promoter region of the gen that codes for the transporter of serotonin and emotional processing. Thus, the bearers of the short allele would show an amygdalin over reactivity during the processing of fearful faces [111]. This allelic variant also has effects on the interaction of the amygdala and the cingulate gyrus [112]. Therefore, the evidence that associates alexithymia with the genetical variations that regulate the cerebral availability of serotonin is controverted.

In the beginning, it was suggested that the genetic polymorphisms of the enzyme catechol-O-methyl transferase was related to alexithymia, dismissing the existence of an association between this enzyme and allelic variations on the promoter region of serotonin transporter [99]. Conversely, Kano *et al.* reported that the decrease of the activity of serotonin transporters in the context of a synaptic decreasing given by a polymorphism of the promoter region previously mentioned, is related to the establishment of alexithymia [113]. Likewise, polymorphisms on the serotonin receptor subtype 1A were correlated with the development of alexithymic characteristics [114]. Nowadays, it has been determined that the bearers of the long variant of the alleles for the serotonin transporter HTR1A-G and 5-HTTLRP, would present a bigger susceptibility to alexithymia [115].

Simultaneously, there are particular findings that pose a relation between alexithymia and polymorphisms of the genes ABCB4, TP53AIP1, ARHGAP32 and TMEM88B, the role of such genes has not been elucidated yet [116].

Discussion

Alexithymia is a construct that has been coined from the psychoanalytic referent to describe essentially psychosomatic characteristics. However, its nature has been progressively discussed due to the evidence that has emerged from neurobiology. Although, in the beginning, the lack of inter-hemispheric communication was related to alexithymia [43],[44],[45],[46],[47],[48],[49], it is likely that certain neural networks responsible for determined brain functions are preferably located in some hemisphere, since actually it is considered that the brain is a plastic organ that does not exhibit, irrevocably, lateralization [117]. Therefore, it is preferred to observe the brain phenomena from a more functional and dynamic perspective, especially in light of the increasing neuronal plasticity research.

Several neuroimaging studies suggest that amygdala participates as a neural substrate of alexithymia,

presenting hypoactivity during the emotional activation in front of different extra personal stimuli [62],[63],[64]. Likewise, they show a volume reduction in alexithymia subtypes I and II, and in its cognitive plane [49]. However, further research on amygdalin emotional processing and on the relation between its morphofunctional alteration with alexithymia is necessary.

On the other hand, cortical structures such as anterior cingulate cortex [67],[68], insula [73] and orbitofrontal cortex [67] would be generally related to alexithymia due to the existence of a hypofunction in any of them. However, certain inquiries contradict this notion. For example, an insular hyperfunction has been reported in patients with alexithymia in traumatic imagery contexts [75] and visceral stimulation [76].

Due to conceptualizations like "limbic cerebellum," the evidence about cerebellar implication in emotional processing is increasingly recognized. For this reason, initially, hypothesis about its intrinsic link with alexithymia could be formulated. However, the findings are still limited and counterproductive, since, although cerebellar function would be altered in people with alexithymia, there is no consensus about the directionality of this alteration (hyper o hypofunction) [67],[37],[96].

Other authors have been more conclusive [97] in correlating positively the cerebellum gray matter volume of Crus 1 with alexithymia level. Also, this could underlie an altered embodiment process, characterized by a deficient construction of the somatosensory state of consciousness. This idea evokes the etiological understanding of alexithymia from a traumatic platform, as an effect of a lack of integration between the early sensorimotor experience and the individual self-representation [28]. That is, the interoceptive consciousness deficit, where the neural network -that includes diverse cortical structures- participates by defect [30]. This would be one of the bases of subjective or phenomenal body: embodiment [118].

In alexithymia, the difficulty in the identification and emotional description, by the processes already explained, would not be merely individual. Rather, it would hinder emotional recognition of another one and, thereby, alter the theory of mind development [33]. Despite this, neural networks that have been identified as part of mirror neuron systems, which could be the neurobiological basis of mentalization phenomena, have not been involved with cerebellum consistently [34].

From an alternative point of view, but probably complementary to the traumatic-environmental one, certain genetic correlations have been established in alexithymia development [20],[21],[22]. In this way, some allelic variants that alter the brain serotonin availability would be involved in its establishment [98],[111],[112],[113]. Similarly, other studies partially rule out the participation of oxytocin receptor polymorphisms in alexithymia onset [110].

On the other hand, results point out that alexithymia may also have a link with other polymorphisms [98],[105],[114]. However, there is still a lack of recognition of the genetic impact in the early neural network structuring involved in alexithymia, as well as the interaction between genetic with environmental level in situations such as psychic trauma during the phenomenon articulation.

A review conducted by Lane *et al.* [119] discussed the emergence of "affective agnosia," concept to refer to alexithymic phenomenon. This, because the "alexithymia" term would be insufficient to signify the phenomenon to which it refers, for going beyond the lack of words for emotional expression. Thus, it is more like a capacity deterioration to represent mentally the affection. In addition, these authors provided a schematization of neural bases of emotional processing, and another one that shows how these networks are altered in an affective agnosia context, without explaining cerebellar function. Although van der Velde *et al.*[19] do not mention in their meta-analysis the cerebellar implication in alexithymia, this work is the only one that exposes quantitatively and in an integrative way the results of a series of publications around brain regions traditionally analyzed in relation to alexithymia.

Conclusions

The available evidence has been synthesized around the neurobiological perspective of alexithymia, from a morphological and functional view at anatomical and genetic-molecular level. Also, it has been verified how an originally psychodynamic conception has been complemented from its neurophysiological knowledge. However, the interdisciplinary integration of the phenomenon is still limited, since multifactoriality is a property of all mental phenomena.

We are in the presence of a series of parallel theoretical conceptualizations (psychic trauma and mental dissociation, lack of somatosensory integration, theory of mind and mirror neurons), which probably are epiphenomena of the same alteration. These are different but intrinsically related phenomena, different facts or a single finding, but with approaches from simultaneous theoretical references. It is mostly relevant to remember that any hypothesis that we can formulate will be an imperfect, and often reductionist, approach, constructing itself as a model and not as reality *per se*.

Notes

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The authors completed the ICMJE conflict of interest declaration form, and declare not having received funding for the preparation of this report, not having any financial relationships with organizations that could have interests in

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Author address:
[1] Angamos 655
Reñaca
Viña del Mar
Región de Valparaíso
Chile