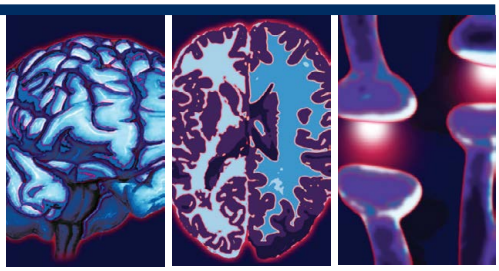
Review



Neurobiological Evidences, Functional and Emotional Aspects Associated with the Amygdala: From "What is it?" to "What's to be done?"

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ABSTRACT

A growing body of neurobiological and anatomic data continues to provide an increasingly detailed understanding of the role of amygdala in cognitive and motor control. We review evidence from past studies showing that the amygdala, which for many years was considered a black box, plays important roles in many neurobiological processes. The amygdala has key connections with the cortical areas, responsible for information processing that subserve emotion (fear, anxiety), learning, motor control, cognition, decision-making and social interaction. We conducted a review of current literature with 169 studies that met inclusion criteria to synthesize findings on amygdala and their influence on the neurobiological aspects. The findings demonstate converging evidence that the amygdala plays a pivotal role in motor, cognitive and emotional functions.

Keywords

Amygdala, Neurobiological aspects, Emotions, Control strategies, Decision-making, Memory, Neurotransmission

Introduction

Amygdala is a complex and unique brain structure surrounded by the hippocampus; deep to the anterior parahippocampal gyrus, particularly, the uncus. This structure is involved with emotional processes, such as fear learning (fear conditioning), and is considered an integrative center of emotion or motivation behaviors and fight or flight response [1]. Neuropsychological pattern experiments have demonstrated that individuals with the damage of the amygdaloid nuclei show impairment of fear conditioning [2,3]. The amygdala is highly

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connected to the prefrontal and frontal areas and coordinates top-down information processing involving the hypothalamus and brainstem, controlling homeostatic responses (i.e., touch, pain sensibility and breathing). Afferent and efferent pathways allow the amygdala to coordinate physiological patterns through cognitive information [4]. Thus, the amygdala is important for the maintenance of the physiological functions. Evolutionary pressures driven by the importance of homeostasis are likely to have played a key role in the circuits formed by the amygdala in humans.

Advances in neuroimaging techniques now make it possible to study the amygdala functioning with improved accuracy [5], which, until recently was seen as a black box. Opportunities to visualize the amygdala's functioning has allowed the present boundaries of knowledge to be crossed [6]. The advancement of knowledge has given rise to a necessity of studies to look ahead to a better understanding of the amygdaloid nuclei, emphasizing its neurobiological functions, mechanisms and their correlations with emotional and psychiatric aspects.

■ Amygdala *vs.* anatomical and neurofunctional aspects

The amygdaloid complex is a deep structure, located in the medial aspect of temporal lobe **(Figure 1)**, which was identified by Burdach in the 19th century [7]. James Papez first identified its role in emotions and learning in 1937. Since then more became known about its functions in the processing and integration of emotion [8,9]. Anatomically, it is a complex of several nuclei with distinct connections and functional characteristics [7,10]. The two main functional divisions, basolateral complex (BLA) and central nucleus (CeA) are connected to the cortical and subcortical areas **(Figure 1)** [9], such as with the mesolimbic pathway responsible for creating sensations/perceptions related to a reward system [11]. However, little is known about the relationship between the localization, function and knowledge of the amygdaloid nuclei. Past studies have shown clinical and biochemical correlations with certain conditions, but few anatomic details were explored; thus, no classical amygdaloid pathways are known [9]. However, even with these limitations, researchers have

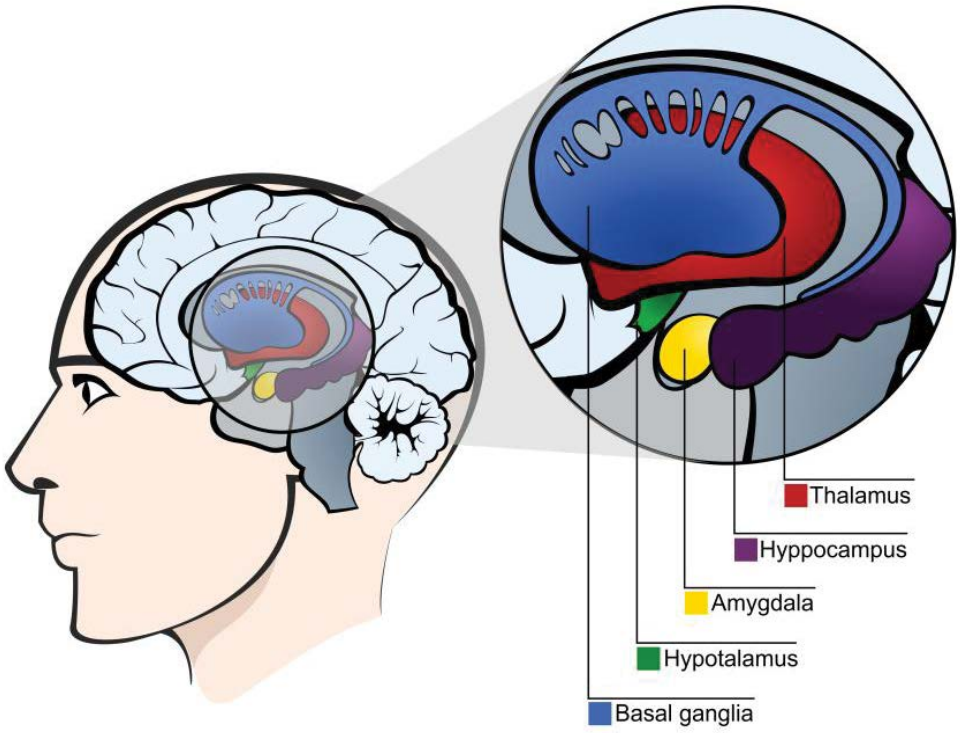

Figure 1: Neuroanatomical positioning of the amygdala. Amygdala is the integrative center for emotions, emotional behavior, and motivation. If the brain is turned upside down the end of the structure continuous with the hippocampus is called the uncus. If you peel away uncus you will expose the amygdala which abuts the anterior end of the hippocampus. Similar to the hippocampus, major pathways communicate bidirectionally and contain both efferent and afferent fibers.

investigated the amygdaloid connections, and their functions. For example, in a study by Linares et al. [12], amygdaloid correlation with sympathetic activation was investigated in individuals with the fear of the spiders (Arachnophobia). Amygdaloid and sympathetic mechanisms were shown to be simultaneously activated in response to the aversive stimulus. In another study, Strawn et al. [13], identified amygdaloid connections with the ventrolateral prefrontal cortex (VLPFC), and reported an anxiety mechanism activation, suggesting that VLPFC modulates anxiety.

Muller et al. [14] reported a decrease in the volume of the amygdaloid gray matter, hippocampus and insula in anxious adolescents. Furthermore, there was the activation of the amygdaloid nucleus when there is emotional perception and possible changes of facial expression within a social context. This is consistent with the defense strategy we observe in the daily social interactions and it is a way of expressing ourselves in response to these stimuli (even if unconsciously). Similar responses occur when a person is exposed to shame and there is a consequent sense of guilt (displeasure of shame followed by guilt). In addition, other areas of the amygdala, near the posterior part of the temporal lobe and the junction in the parietal-temporal groove, are activated [10,15].

Anatomical studies have revealed three groups of nuclei in the amygdala, namely, the basolateral group, the centromedial nucleus and cortical nucleus. The basolateral group is further subdivided into: small dorsolateral cells, large ventromedialis cells, basal accessory and medial subgroup. The anterior part participates in parvocellular and magnocellular pathways, which are preferentially attuned to ambiguous and clear threat respectively. The basal accessory subgroup has extensive hippocampal connections [7]; such connections appear to be relevant in the context of memory and why we feel it is necessary to store some information and but not others [16]. It appears likely that the basal accessory subgroup aided by the hippocampus determines what will or will not be stored in the hippocampus [7,10].

The cortical group of amygdaloid neurons is more superficial and relates to the lateral and accessory olfactory tract. Thus, it seems to be involved with selection of olfactory stimuli. The centromedial nucleus group is related to the globus pallidus, the terminal striae and optic tract, and the optic tract assists in the selection of relevant or not, aversive or stimulating visual stimuli, and if generates fear or anxiety when projecting to the cerebral cortex in the anterior areas [7]. All of amygdaloid groups and subgroups appear to be distributed for the anatomical convenience, but embryologically greater relevance is noted during the development of the basolateral amygdala. These distributions contribute to their greater cholinergic connections with the medial prefrontal cortex (MPFC), which is consolidated during adolescence. This could be due to the increase in glutametrgic N-methyl D-Aspartate (NMDA) receptors, which further stimulates MPFC connectivity with the amygdala as seen in experiments with male rats [17].

■ The processing of emotions (fear and anxiety)

Animal research has helped us to understand the role of the amygdala in emotion, including mediating fear responses [18,19]. Moreover, research with healthy humans subjects has shown that the amygdala and insula mediate responses to emotional stimuli [20]. Sergerie et al. [21], in a review, cited studies that showed diverse roles of the amygdala in processing emotion. The amygdala is argued as a key part of neurocircuitries specializing in rapid and automatic evaluation of stimuli that signal potential threats or danger in the immediate environment [22]. This structure might participate in the processing of signals that may indicate distress other types of environmental information that must be disambiguated [23-25]. In addition, the amygdala processes biologically relevant stimuli regardless of their valence (negative or positive mood) [26].

The amygdala participates in fear learning and plays a special role in the acquisition and expression of conditioned fear response **(Figure 2)** [27]; Misslin, [28]; Rosen, [29]. Various amygdala nuclei are responsible for specific functions, such as, acquisition of conditioned fear and long-term contextual fear memory (lateral/central nuclei) [30], memory consolidation and plasticity in fear conditioning (lateral nucleus) [19], active avoidance behaviors to fear (efferent pathway of the basal nucleus) [31], evaluation of sensory information in the dimensions of emotional valence, vigilance and arousal (basolateral nucleus) [31].

Studies indicate that the amygdala is a part of a complex network that involves cortical and subcortical regions that are especially responsible for mediating and eliciting autonomic responses

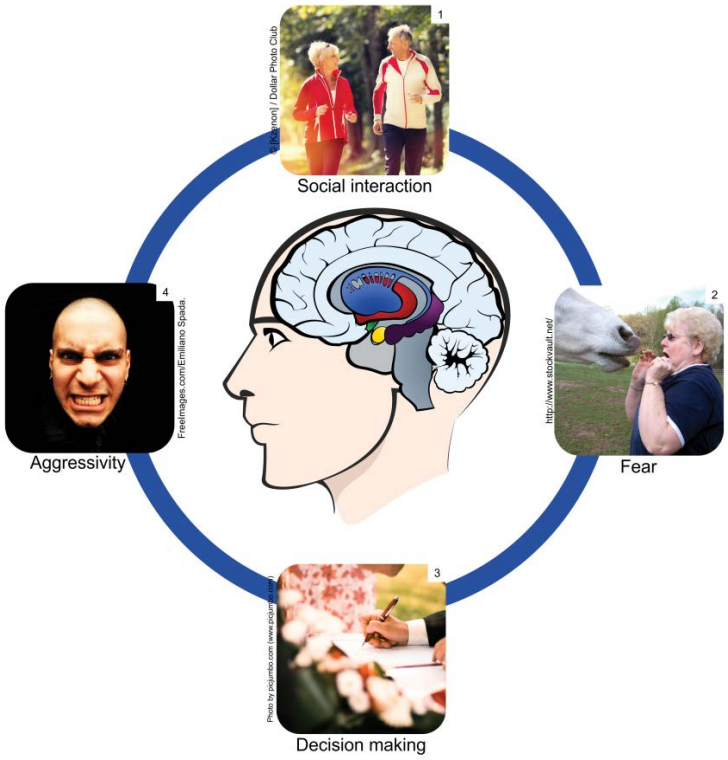

Figure 1: The amygdala is a central core of information that coordinates high-level information processing and emotional processes (fear, aggression), executive function (decision-making) and processes for social interaction.

as well as modulation of emotion, primarily by the prefrontal cortex (PFC) [32-34].

LeDoux [35] has proposed that in emotional processing sensory information may access the amygdala *via* two different routes, called low road and high road. The low road is a direct route to the amygdala from the thalamus, bypassing the cortex, that might promptly elicit fear defense responses without conscious recognition of the threat [36]. By the high road, as soon as the sensory information projects to the thalamus, it is sent to the sensory cortex, insula and PFC for a more complete analysis (conscious awareness of the conditioned stimulus), then this information is sent to the amygdala [36]. Therefore, the amygdala is involved in conscious and non-conscious processing of fear-relevant information [37].

As it was proposed by Gorman et al. [32], from the amygdala the fear-relevant information projects to the effector sites in the brain-stem and hypothalamus, which produce the autonomic, behavioral and endocrine responses of fear [19], such as, increased respiratory rate (parabrachial nucleus), increased norepinephrine release (locus ceruleus), sympathetic discharge (lateral nucleus of the hypothalamus), increased adrenocorticoid release (paraventricular nucleus of the hypothalamus) and additional behavioral responses, such as pain suppression (periaqueductal gray). The hippocampus that has a role in the mnemonic processes that underlie acquisition, consolidation and retrieval of contextual fear [26] - communicates directly with the amygdala [32,38].

Furthermore, the PFC modulates amygdala-generated emotion during conscious evaluation of threat-evoking stimuli [34]. Studies have shown that the reappraisal strategies are related to decreased activity of the amygdala and increased activity of the PFC [39,40]. Reappraisal strategies (cognitive restructuring, for example) might strengthen the ability of the cortical projections, including medial PFC, to inhibit the amygdala activation and, consequently, the automatic physical and behavioral responses [41,42]. The amygdala also participates in fear extinction, along with the medial PFC and hippocampus. It is believed that the medial PFC inhibits the activity of the amygdala, under the modulation of the hippocampus, when the conditioned stimuli is continuously presented [19].

■ Amygdala *vs.* learning process

The effect of emotion on memory storage process was known for a long time before Descartes [43]. Emotional memories are stronger and more easily retrieved. The strength of memory consolidation depends on the amount of emotion attached to a specific event [43-45]. Research during past several decades indicates that the amygdala is the main structure of the emotional network, working as an essential part in many aspects of emotional information processing, such as facilitation of attention with emotion, and behavior. The amygdala can influence the impact of explicit memory in modulating or enhancing activity of other brain regions involved in memory and learning. Its modulatory effect on emotional arousal acts specifically on the consolidation process in memory regions, such as the hippocampus [46]. The amygdala and the hippocampal complexes are linked to two memory systems that work independently. These systems have unique characteristic functions, but they subtly interact. The amygdala modulates the encoding and the storage of hippocampal-dependent memories. The hippocampal complex influences the amygdala response when faced with emotional stimuli by forming the representation of the emotional impact and interpretation of events. Therefore, when emotion meets memory, these two independent systems work together [47].

The anatomical organization of the amygdala can be described divided into more than ten areas and its subdivisions and unique sets of afferent and efferent connections [46]. The influence of the amygdala on memory encoding and consolidation is related to two stages of this process. The first stage occurs when a stimulus is encountered for the first time; several factors can influence how well the stimulus is encoded but one of the most important aspects is the ability to perceive and attend to the stimulus. As mentioned before, emotion can influence attention by capturing it and altering the emotional stimuli, which is processed when attention is limited [45,47,48,]. The amygdala has a relevant part in the facilitation of attention with emotion, and it responds to emotional stimuli in the environment quickly, even before the awareness and regardless of attention focus [47,49-51]. This helps the facilitation of attention and increases vigilance in the presence of emotional stimuli, as shown by Ohman et al. [45]. In this experiment, the participants were exposed to complex visual stimuli and individual images were organized in 3 × 3 and 2 × 2 matrices to verify if participants will be faster at discovering a fear-relevant stimulus against a background with fear-irrelevant stimulus. The second stage of hippocampal memory formation is retention or storage, a very important phase in the learning process; the consolidation happens after encoding and during this time, memories are fragile and vulnerable to loss. It takes a certain time to "settle" the memory and during this time-period, their retrieval is less dependent on the hippocampus. One possible reason for a slow consolidation process is to allow an emotional reaction to an event, and for this, an opportunity to influence the storage of that event [47,52]. In this way, events that evoke emotional responses are more likely to be remembered and are more vivid [47], for example, fear-conditioned memories are quickly acquired and is retained over long periods. In parallel, studies show that stress-related hormones, epinephrine and glucocorticoids affect the amygdala, and that memory is enhanced by the post-training intra amygdala infusions of drugs that activate b-adrenergic and glucocorticoid receptors [53]. A simple form of associative learning that supports the acquisition of this type of information embedded with emotion is the Pavlovian fear conditioning in rats [54], which is relevant due to the evidence that the data in human subjects are consistent with animal studies [53].

■ Amygdala *vs.* storage memory

Amygdala processes sensory information regarding "emotional memory." This processing promotes a cognitive-behavioral response that takes into account the emotional record of previous experiences, which is sub-consciousness, even though it is controlled by the cerebral cortex [55]. One hypothesis is that the amygdala only modulates but it is not necessary for the maintenance or expression of memory [56]. It has a modulating activity of the consolidation memory, interacting with other brain regions including the nucleus accumbens, the insular cortex, the entorhinal cortex, the anterior rostral cingulate cortex, the MPFC, the cerebellum, and both the primary visual and auditory cortex [57].

An extensively studied interaction is that of the BLA with the dorsal hippocampus. The basolateral amygdala activation by stress hormones released by the adrenal glands modulates the consolidation of emotional memories. Epinephrine or glucocorticoids administered after an exposure to emotional

arousal improve the long-term memories consolidation of these experiences. The high circulating levels of stress hormones, however, interfere with the recovery of memory and working memory [58,59]. Nevertheless,it is still unclear that memory could be impaired by the amygdala loss, or that the amygdala is the storage location for emotionally aroused memories [60].

Frey and Morris [61] have described the "synaptic marking" concept that attempts to explain the lasting stabilization of specific synapses underlying long-term memory, suggesting that exposure to a new stimulus from training hours can produce long-term memory for tasks that, otherwise they would not be remembered in the long run. This effect depends on protein synthesis at the exposure time to the new stimulus [62]. Likewise, the "emotional marking" concept has been suggested by results of electrophysiological studies linking hippocampal plasticity with emotional arousal, amygdala activation and memory enhancement [63,64]. Synaptic plasticity in the hippocampus is related to long-term memory only if it is associated with amygdala activity.

Results from neuroimaging research indicate that successful coding of emotional content is associated with enhanced functional connectivity between the amygdala and the hippocampus [65-67]. Evidence from imaging experiments in humans and animals indicates that the influence of emotional activation on memory consolidation involves the interactions of amygdala with the hippocampus and the MPFC. These form the basis of physiological mechanism to promote brain plasticity and rapid memory consolidation for events that influence adaptatison to stimuli related to survival and well-being [60].

■ Amygdala *vs.* neurotransmission

The amygdaloid complex is involved in several circuits of learning, memory consolidation, decision making, emotions, fear and some disorders such as anxiety, aggression, depression, and autism spectrum disorders [68,69]. The amygdaloid complex receives information *via* a direct route from the thalamus that receives data from the external environment (rapid and primitive pathway related to unconscious learning and conditioning) and an indirect path from the cerebral cortex, which is slower and allows cognitive intervention [70]. The dependent learning of the amygdaloid complex depends on the GluN1/GluN2B heterodimers activation present in the basolateral amygdala [71,72]. The GluN1/GluN2B heterodimers are the subunits of N-Methyl-D-aspartate (NMDA) receptors, glutamate-dependent ion channels that play an essential role in the synaptic plasticity that underlies the formation of learning and memory. Since the GluN2B subunit has little impact on NMDA receptor kinetics, it suggests the need for the recruitment of signaling molecules essential for synaptic plasticity [73].

The interactions between the amygdala and the MPFC are fundamental for emotional, motivational and decision-making behavior [74]. BLA stimulation promotes a robust inhibitory effect on the MPFC through local interneuronal circuits. Glutamatergic excitatory neurons from BLA project to the MPFC and activate GABAergic pyramidal interneurons which in turn inhibit pyramidal neurons from the MPFC [75]. These send excitatory impulses to the Ventral Tegmental Area (VTA) that acts antidromically in the MPFC through dopamine and orthodromically in the nucleus accumbens using GABA as neurotransmitters [76,77]. In this way, the amygdaloid complex regulates the mesocortical and mesoaccumbal systems for reward. Injury to the BLA impairs decision making when the risks/benefits to the response are considered relevant, reducing the preference for higher rewards that can be obtained after a more significant physical effort or time to acquire [73,74].

The inhibitory, as well as the excitatory, activity of BLA neurons, is regulated during the developmental stage of the nervous system. Receptors, for instance, γ-aminobutyric ($GABA_A$), cease to be excitatory at birth before becoming inhibitory in adulthood. In BLA, the synaptic inhibition is produced by intrinsic and extrinsic neurons of local interneurons circuits that activate $GABA_A$ receptors and comprise 80-85% of the BLA neurons population. Blocking these receptors promotes fear and anxiety behaviors, while receptor activation attenuates these behaviors [68].

The generation and expression of anxiety and fear is the central role of the BLA. It is noteworthy that the GABAergic inhibition of the activity in BLA is among important pathophysiological mechanisms that result in anxiety disorders. Furthermore, cholinergic receptor hyperstimulation leads to excessive glutamatergic system activity, generating epileptic outbreaks [78]. In addition, cholinergic action is associated with memory consolidation

that is also influenced by the hippocampus, striatum and ventromedial prefrontal cortex. The evidence for increase in cortical and hippocampal acetylcholine (ACh) levels prior to learning experiences support the idea that endogenous ACh release is involved in long-term memory consolidation [78].

■ Disorders *vs.* amygdala-hippocampal complex

Both the amygdala and the hippocampus are linked to memory, each with specific functions, however they act together when emotion meets memory. Also, amygdala-hippocampal interactions are based on how the amygdala can influence, independent of the hippocampus, episodic memory, and emotional stimuli [79]. Adolphs et al. [80] argued that such a structure reinforces episodic memory to obtain the essence of the emotional content at the expense of sensory data, a fact which may be related to attention.

Based on the above, it is assumed that emotional memory is used when evaluating a situation or object, allowing the body to react adaptively. According to the typical conditioned fear paradigm, a subject exposed to a neutral stimulus classifies the event as aversive, concomitantly with the coding of emotional memories with regards to the recognition and interpretation of emotions relative to the physiological expression of emotional responses [81,82]. Accordingly, the role of the amygdala in memory would be the separation between the emotion-object association and the simple response expression, for instance, if a subject goes through an unpleasant experience with a neighbor dog (such as being bitten by the dog), later, when he finds him again, a reaction of fear may be manifested. Thus, this type of learning requires that the hippocampus retrieve memory at the instant the stimulus is available [47].

The voluntary modulation of responses to emotionally evoked stimuli involves interactions between the PFC, the orbitofrontal cortex (OFC), the anterior cingulate cortex (ACC), and the amygdala [83]. On the other hand, the information from various sensory modalities are processed through hierarchically arranged projections. Therefore, the amygdala-hippocampus complex receives information not only from the external world through sensory stimuli but also interoceptive information through subcortical systems about the internal state (including the motivational state) of the organism [84].

■ Amygdala *vs.* control strategies (cognition/motor control)

The amygdala is also important for the movement control strategy [85-88]. On many occasions, we interrupt a motor act to perform another movement due to a potential threat; this relation of fearful stimulus followed by defense motor response is a process that is primarily mediated by the changes in the activities and connectivities of the Central Nervous System (CNS) [89]. In particular, several functions are attributed to the amygdala and are associated with several cognitive factors and sensory modalities widely established by the scientific community [90]. Although it is not well understood how the amygdala modulates motor behavior, when we experience an imminent threat [49,91], there is an association between the amygdala and the PFC modulation [85,86,88], primary motor cortex (M1), ventromedial striatum, supplemental motor area (SMA), subthalamic nucleus and motor nuclei of the brainstem [87,92].

When Sagaspe et al. [93] investigated the influence of threat stimuli on the neural circuits mediating the motor inhibition, they observed that the amygdala participated in the motor response modulation; such findings occurred, directly or indirectly, through functional interactions of the amygdala with the SMA and interconnected motor pathways. Oliveri et al. [94] used the Transcranial Magnetic Stimulation (TMS) and electromyography to investigate whether the SMA would act as an interface between the emotion and the motor system. To test the hypothesis, they presented unpleasant and neutral images for two groups of volunteers. They found increased excitability in the corticospinal tract during the presentation of the unpleasant image as compared to the neutral ones, which was seen when the TMS stimuli were applied in the SMA.

The amygdala has an influence on the preparatory stage of the motor act in emotional states of threat [95,96], being related to the central component of the threat and defense circuit for animate stimuli rather than inanimate ones [97]. To address this question, Coker-Appiah et al. [96] subjected 25 participants to a task that consisted of observing threatening and neutral images, animate (animal) and inanimate (objects). They noted that the amygdala increased its activity only during the presentation of threatening animated images.

Kim et al. [98] also found activity in the amygdala when they analyzed the neural responses to facial expressions of anger and happiness; simultaneously, they observed that the amygdala activity was higher in response to rage than when with happy faces. Interestingly, when they applied botulinum toxin to the corrugator of the eyelashes muscles, the amygdala response to the angry faces was attenuated, which demonstrates that the activity of the amygdala is due to the feedback generated by the facial musculature activation.

In addition, other brain structures are associated with the amygdala. For example, when there is an inhibitory stimulation of the amygdala central nucleus by the fusiform gyrus and the superior temporal sulcus leading to diminished activity in the motor cortex and the corticobulbar pathways, we perceive safe in the environment [99]. On the other hand, when we are confronted with a threat stimulus, and a motor response to fight and/or flight occurs, the amygdala triggers excitatory stimuli on the lateral and dorsolateral region of the periaqueductal gray matter [96], which activate the motor cortex, corticobulbar and corticospinal pathways. Many individuals when they perceive a situation of danger, they remain static. This seems to be more related to the neural impulses coming from the ventrolateral region of the cerebral aqueduct, which activates, through the motor cortex, the lateral corticospinal tract [99].

Finally, beyond the correlation of the amygdala with the motor act presented here, we also highlight that amygdala projection cells located in the face of the magnocellular division of the basal nucleus exert a modulating action on the generation of chewing rhythm. This was observed in monkeys when researchers used an intracortical micro-stimulation in areas related to the maxillary part of the face [99]. In addition, the amygdala participates in the sequences of saccadic movements. Mosher et al. [100], observed that the amygdala in monkeys contains neurons that respond to fixation and contact with the other people eyes, thus demonstrating that the amygdala modulates eye movements when it is necessary to explore and select visual details of scenes that present social and emotional characteristics. These activities also appear to be associated with the lateral portion of the fusiform gyrus and with the posterior region of the superior temporal sulcus since they are related to the visual form and eye movements when we see happy faces and pleasant objects.

■ Amygdala *vs.* social interaction

The fundamental ability for social interaction is defined by emotional expression and behavior **(Figure 2)** [100]. Emotions are unique for each individual. Furthermore, how individuals deal with stressful events is critical in determining their comfort or convenience [101]. Emotional processes are evident at all times, and regulatory strategies can be distinguished during the emotion-generating event [102]. This modulation can be focused on the response or can occur in advance. "Antecedent regulation" modifies the way cognitive interpretation is constructed to lessen the emotional impact of a situation before emotional responses become active [102]. The circuit for emotional regulation may involve the PFC regions, amygdala, hippocampus, hypothalamus, anterior cingulate cortex, insular cortex, and ventral striatum, among other interconnected structures. The mechanism underlying the negative emotion regulation would be possible *via* inhibitory connections of the PFC regions to the amygdala, possibly the OFC [103].

Cognitive re-evaluation strategy studies have identified a cerebral activation pattern, characterized by a significant PFC activation associated with decreased amygdala activation, suggesting that the former could be modulating its activity [20,102,104,105]. Functional Magnetic Resonance allowed the observation of the increase in the lateral prefrontal cortex activity during emotion regulation strategies, specifically during emotion reduction, concomitant with the reduction of the amygdala activity [104]. This suggests that the lateral prefrontal cortex could be modulating the amygdala activity, which is an essential structure for triggering emotional responses. Since the lateral prefrontal cortex does not have direct neural projections to the amygdala, it is believed that this inhibition occurs *via* an intermediate structure activation. This proposal was recently confirmed in a study that investigated the neural circuits associated with the adverse affect regulation [106]. The study showed that the negative affect increase is related to the amygdala activation and ventrolateral, dorsolateral and dorsomedial regions of the PFC. It should be emphasized that above studies suggest inhibition of the neural circuit processing fear due to the influence of the ventromedial prefrontal cortex on the amygdala, and hippocampus. In summary, the present evidence suggests that the ventromedial prefrontal cortex regulates the fear expression

by inhibiting the amygdala, as well as the infralimbic cortex, encoding a relevant aspect of long-term fear extinction [33].

In another lesion study explicitly localized to the left PFC, abnormal cerebral blood flow was observed in the left and right frontal regions, associated with neuropsychological changes in cognitive functions, emotion self-regulation, affection and social behavior. This finding is clinically significant since specific psychiatric disorders (e.g., posttraumatic stress disorder) appear to be related to the PFC dysfunction and its ability to modulate the activity of subcortical structures, such as the amygdala [107]. It should be noted that both pathological fear and anxiety disorders may reflect the abnormal modulation of the amygdala activity and ventromedial prefrontal cortex, as well as their interaction. Accordingly, works investigating the neural circuits responsible for emotion regulation revealed a cerebral activation pattern of the frontal structure activity that would exert an inhibitory control [103,106] over structures more directly related to the emotional stimuli evaluation, such as the amygdala. The hypothesis that unattended stimuli are poorly processed, reinforces the importance of attention to perception; in fact, converging evidences suggest that the perception of the stimuli, which are out of the focus of attention can be attenuated, or even eliminated, under certain circumstances [108,109].

Simons [110] showed that when individuals have their attention focused on a given relevant object or event, they fail to detect the presence of other stimuli. This phenomenon, known as inattentional blindness, can be interpreted by Lavie's theory [108], according to which the stimulus perception may not occur due to the exhaustion of resources in the primary task, which prevents its processing. Some researchers, however, have proposed that an exception to the critical role of attention in perception is the emotional stimulus processing, for which automatic processing has been reported regardless of the voluntary attention allocation [49,50].

In this context, paying less attention to emotional stimuli modulates processing in emotional assessment systems, which include structures such as the amygdala [109]. Taylor et al. [111] showed that amygdala activity decreases when participants paid attention and assessed emotional characteristics of aversive scenes in comparison to the passive view. Thus, the strategy of diminishing attention resources to the emotional stimulus processing may constitute an emotion potential regulation. Accordingly, it is believed that the amygdala is robustly linked to other brain structures, playing a relevant functional role in social interaction. Hence, research that addresses the amygdala influence on social interaction can help develop treatments for a variety of disorders that involve difficulties with social connections such as depression or autism.

■ Amygdala *vs.* decision-making

People are constantly confronted by decisions, which they need to analyze the consequences before choosing the optimal option. At many occasions, the choice is followed by adverse or negative risks. Thus, the decision-making process is featured by the selection process of an action between two or more alternatives. The potential result of one of these choices will be followed by short or long-term consequences [112-114]. The perception/discrimination and the decision-making process are central elements in our daily life **(Figure 2)**. Behavioral researchers have been interested in exploring the attributes of the neural mechanisms of such processes [112,114,115,116]. From a neuroscientific perspective, the decision-making process is a complex process, which requires the organization of multiples cortical and subcortical systems, characterized by a complex network involving prefrontal regions, limbic structures (including the amygdala) and the cerebellum [113].

Primary inducers are stimuli that unconditionally or through learning produce pleasant or aversive stages. Seeing a scary object or lose/win a large amount of money seems to be good examples of primary inducers. However, secondary inducers are characterized by an abstract reference of emotional-event memory. When this event is recovered, it could induce a somatic stage. The amygdala is highlighted as a neural substrate, which initiates somatic responses through primary inducers, but not as an influential source of emotional attributes (retrograde emotions) recovery in order to respond to secondary stimuli [117]. Moreover, beyond the role of the amygdala, studies have shown the involvement of the VLPFC, insula, somatosensory cortex, dorsolateral prefrontal cortex and hippocampus in several aspects of decision-making processes [112,117,118]. In particular, altered activity in the BLA and OFC seems to be an underlying pathological mechanism in neuropsychiatric

disorders, and moreover, these structures are involved in some aspects of the decision-making processes [114,119]. Results of Orsini [114] experiment has shown that the BLA lesions produced an increase of choices for the larger risk reward whereas they observed an opposite effect for the OFC lesions.

Emotion also plays a crucial role in decision-making processes, however, how it is mediated by the brain remains poorly understood and continues to be studied [115]. On one hand, cognitive processes produce emotional response, on the other hand emotion modulates cognition in order to allow adaptive responses to the environment. Therefore, emotion regulates the decision-making and particular regions of the brain involved with emotional states, such as the amygdala, and areas related to cognitive process (for instance, the frontal cortex), which integrate information to make this complex behavioral possible [115,120]. Thus, the amygdala plays an essential role in the decision-making processes, which is sustained by its connection with several cortical regions that include the sensory pathways linking the primary visual cortex to regions involved with memory, such as hippocampus and prefrontal regions (for example, OFC). These features enable the amygdala to receive sensory information about risks and reinforcement allowing the modulation of its activity based on emotional contingencies during the decision-making processes [120]. On a circuit level, the BLA through its extensive afferent inputs from sensory cortical areas is critical for developing the association between the cue and target. Thus, the BLA central nucleus is relevant for mediating the conditioning responses [121].

In an animal experiment, which requires choosing between two options, one which is the easy option provides a smaller reward, however, the one that gives the animal a larger reward also involves higher amount of effort [109]. Furthermore, studies have reported that lesions and inactivation of BLA complex reduce the preference for larger rewards [74,122] and possible increase impulsive choices [123]. In particular, in a study by Ghods-Sharifi et al. [74], rodents were trained to choose between two levers, one that always delivered a smaller reward and other with a probabilistic risk manner to deliver a larger reward. Rodents with BLA lesion demonstrated higher tolerance for the risk-choice suggesting a risk-averse pattern of choice [74]. Another study, which created a temporary inactivation of BLA and the anterior cingulate cortex (ACC) demonstrated an opposite effect of effort-based decision-making. The BLA inactivation increased the time to make the choices, whereas AAC inactivation increased motor impulsivity [124]. Moreover, the role of the BLA and the orbitofrontal cortex (OFC) in the decision-making under risk of explicit punishment was investigated by Orsini and collaborators [114]. In this study, rats perform a risky decision-making process, in which they choose between two levers, small safe reward or larger risk reward, accompanied by punishment (footshock). When compared with control rats, rats with BLA lesions preferred the risk reward. On the other hand, rats with OFC lesions decreased risk-taking. These findings pointed out distinct roles for the BLA and OFC in the decision-making tasks under explicit punishment.

In order to observe human decision-making, the Iowa Gambling task is a psychological task frequently used to simulate the real-life decisions under reward or punishment [117]. Healthy individuals learned to avoid bad decks of cards by deciding to choose reward cards. However, patients with bilateral lesion of the amygdala or with ventromedial prefrontal cortex lesions chose immediate gains cards even the card was no good in the future [109,117,118]. Thus, patients with amygdala lesions show real-life decision-making impairments, they are not able to recognize their own deficit and demonstrate difficulty to evoke compensatory strategies. This is particularly noticed in daily situations even when patients can distinguish between what is right or wrong [125,126].

Neuroimaging studies support the idea that the amygdala is involved with value addition to the decision-making process. In a conditioning task, evoked response in the amygdala by a predictive stimulus was decreased after stimulus depreciation, whereas response to non-devalued stimulus was maintained [127]. A study using fMRI with patients with amygdala damage showed the impairment of ventromedial prefrontal cortex reward representations during a reversal-learning task [128]. Consistent with this, Seymour and Dolan [115] have highlighted that the amygdala-medial prefrontal pathway could be a critical route by which stimulus-specific outcome information is integrated with more sophisticated, goal-directed actions.

■ Amygdala *vs.* stress and training the brain

The stress is one of the major aspects related to emotion processes [129]. Stress leads

to the amplification of the activity of the hypothalamus–pituitary adrenal axis ensuring an increased release of glucocorticoids [130] (cortisol, corticosterone and cortisone) from the adrenal cortex; these hormones influence peripheral target organs as well as the brain [131]. The principal glucocorticoid in human is cortisol [132]. While stress metabolic actions have been well described in periphery, less is known about their effects on brain energy metabolism and evidences suggest that the timeline (varying from minutes to hours) of metabolic regulation is critical to memory modulation by stress [133]. Stress hormones can be released by emotional experiences and play an important role in mediating the effects of emotion on long-term memory through the modulation of the BLA [134].

McIntyre et al. [135] have shown that the extent of long-term memory, in response to a new emotionally arousing experience, is predicted by the levels of the norepinephrine within the amygdala during that experience. Stress does not always impair memory; in fact, the acute stress response is due to facilitated adaptation [130]. Interestingly, while chronic stress impairs memory acquisition and consolidation, mild forms of acute stress can enhance these processes [133]. The effect of acute stress on the facilitation of memory generally presents an inverted-U dose-response curve, parallel to what is observed under other conditions and/or treatments. This modulates memory because acute stress produces a large rise in blood glucose levels, which enhances memory construction. On the other hand, increased blood glucose levels rapidly increase brain glucose supply [133]. The authors have proposed an overview of stress-response, which asserts that a defining feature of stress is the activation of the hypothalamic-pituitary-adrenal axis, which stimulates the renal medulla to secrete epinephrine and cortisol [133].

Thus epinephrine starts short-term responses to cope with stress [133,136] stimulating central afferents connected to the locus coeruleus, which trigger release of norepinephrine in various regions including the BLA [137]. The findings of McIntyre et al. [135] indicated that the degree of activation of the noradrenergic system within the amygdala in response to a novel, emotionally arousing experience predicts the extent of long-term memory for that experience. The findings of McReynolds et al. [138] suggest that the BLA modulates multiple forms of memory and affects the synaptic plasticity when emotional arousal is elevated. Furthermore, noradrenergic activation of the BLA enhances the consolidation of long-term memory of high emotional arousing training experiences [139].

Barsegyan et al. [139] demonstrated that post-training noradrenergic activation of the BLA also boosts the consolidation of memory of object-in-context recognition training, favoring accuracy of episodic-like memories. In that context, Bentz et al. [140] investigated effects of stress on memory processes in a fear conditioning paradigm in healthy human participants. Authors assessed fear memory through a standard differential fear conditioning procedure. Participants underwent a stressful cold pressor test or a control condition on day 2. On day 3, memory retrieval and extinction were tested. Results showed that stress reduces memory retrieval of conditioned fear in men, and suggested that such effects are sex-specific. Furthermore, the results of Quirarte et al. [141] showed that β-adrenergic activation is an essential step in mediating glucocorticoid effects on memory storage and in the BLA occurs the interaction between these two systems. Wong et al. [137] explained that although catecholamines do not cross the blood-brain barrier, circulating epinephrine from the adrenal medulla may communicate with the central nervous system and stress circuitry by activating nerve β-adrenergic receptors to release norepinephrine. As a result, stimulated release is the same from the nucleus tractus solitarius and locus coeruleus. Furthermore, the BLA may stimulate afferents going to the hypothalamus, neocortex, hippocampus, caudate nucleus, and other brain regions.

On the other hand, during a stressful experience, the brain can be led to a memory consolidation state through the release of stress hormones and neurotransmitters, which activate the BLA, permitting a strong consolidation of the event. Moreover, Osborne et al. [133] discussed evidence in a review on stress-response axis and explained that a defining feature of stress is the activation of the hypothalamic-pituitary-adrenal axis, which stimulates renal medulla to secrete epinephrine. The release of epinephrine initiates short-term responses to cope with stress, which stimulates central afferents connected to the locus coeruleus, triggering the release of norepinephrine in various regions including the BLA [137]. Hence, it is suggested that there is a dynamic interaction between the BLA and other brain regions – including the hippocampus and the prefrontal cortex, which

coordinates the antagonizing stress effects on memory consolidation and memory retrieval [59]. Furthermore, glucocorticoids are involved in modulating memory consolidation mediated by β-adrenergic activation [141].

Additionally, animal models have shown that acute stress may impair the continuous inhibition of fear, presumably as a result of PFC function alteration [142]. Blocking noradrenergic activity after aversive learning training does not weaken the consolidation of fear learning, which suggests that only noradrenergic release during training is not sufficient to allow consolidation. Despite this, noradrenergic activity might be required for the enhancing effects of stress-induced glucocorticoids on fear learning [142]. When emotional arousal is elevated, the BLA modulates multiple forms of memory and affects the synaptic plasticity-associated protein Arc in synapses of the dorsal hippocampus [138].

Wolf et al. [131] concluded that higher cortisol levels are associated with a stronger amygdala response to emotional stimuli. Consequently, stimulatory effects of cortisol on this structure might underlie the cortisol-induced enhancement of emotional memory consolidation. This evidence indicates the possibility to train the brain to deal with stressful situations, which can be useful to certain professions in which the individuals have to make decisions, and respond under high levels of stress.

■ Amygdala *vs.* violent behavior

Broadly, regardless of brain size, animals are endowed with the specific ability to react with an immediate aggressive response [103,143]. Experiences conditioned with tasks that simulate danger and aggressive behavior proves such a behavioral event [144]. Two neural systems are relevant in the generation and control of the emotional states, one being the ventral neural system and the other is the dorsal neural system. The ventral system (composed of the amygdala, insula, ventral striatum, ventral regions of the cingulate and OFC) is linked to the identification of the emotional meaning of the stressor stimulus and also to production of the affective states in response to these stimuli. The dorsal system (hippocampus, the anterior cingulate dorsal regions, and the PFC) is related to the regulation of affective states, such as modulation of the behavior appropriate to the context [145].

From the physiological point of view, the stimuli are processed and interpreted according to internal models. However, in circumstances involving survival and high danger situations, this symbolic structuring process is not observed. After initial processing, sensory information is processed in parallel by the amygdaloid nuclei, in the subcortical gray matter of the temporal lobe [9]. The amygdala functions as a hub that is responsible for visceral changes, increased alertness, hormones secretion from the adrenal gland that are fundamental to the anger and fear emotions [146]. According to Consenza and Guerra [147], when a stimulus is detected, there are two forms of emotional interpretation. One follows the cortex sensory pathways and then is sent to the amygdala, where there is identification about "what is" and subsequently investigates the "importance". The other goes directly to the amygdala before it reaches cortex processing and generates emotional and behavioral responses without immediate awareness, also highlighted by Kandel et al. [10]. Two ways of processing emotions provide support to the theory of emotions proposed by the father of functional psychology [148].

According to Almeida [149], the amygdala plays a role in mediation and control of higher order emotions, such as friendship, love and affection, expression of humor and, above all, states of fear, anger and aggression. This regulation is essential for self-preservation by identifying the hazard and generating the feeling of fear, anxiety and alertness. Other areas participate in an amygdala joint function, such as the hippocampus because of its particular connection with memory phenomena, especially the long-term memory (LTM). The thalamus, because relays inputs to cortical structures, allows the regulation of emotional behavior and the hypothalamus plays a role in physical expression of emotions, such as anger and aversion.

The fear, learning, fight-and-flight response, and reward processing is done by three fundamental parts of the amygdala (the medial, central, and anterior core groups). The ability to learn and memory is based on functionally intact amygdala and it involves controlling emotions, especially aggressiveness. The inappropriate responses of the amygdala are associated with aggression, irritability, emotion control loss, short-term memory disruption, and difficulty in recognizing emotions, especially fear [150].

■ Amygdala *vs.* fear consciousness

Exposure to new stimuli and consciousness processes, which allows the human being to

experience and understand aspects of his/her inner and outer world, is related to the amygdala and a network of cortical and subcortical structures essential for learning and memory. Consciousness is necessary for the consolidation of such cognitive aspects [151,152].

Earlier, the hippocampus was at the center of consciousness research and it is now known that the amygdala also plays an important part in specific activities of consciousness [153]. With the neuroimaging use through functional magnetic resonance, circumstances were explored that brought into question the consciousness pattern and responses of the amygdala to stimuli with emotional and neutral images [154]. The results support that such images evoke more activity in the amygdala when presented as a novelty. It suggests an internal representation is necessary for the amygdala-specific responses to novel stimuli [154].

Neural basis of consciousness has been debated for almost 50 years. Most studies focus on perceptual activities to complete the gap in understanding the awareness [155,156]. Since it has repeatedly been demonstrated and seems to be applied to other classical conditioning paradigms, it is evident that individuals learn temporally ordered awareness in response to the shock or traumatic event. To determine the consciousness process and the learning of fear, authors used the magnetoencephalography (MEG) to verify the amygdaloid neural mechanism based on shock stimuli, which triggered rapid responses (~ 170-200 ms) in the amygdala during the stimulus-free period of coping. Such results suggest that unintended coping may serve as signs of imminent threat and that rapid automatic activation of the amygdala contributes to this consciousness process [154].

The amygdala is the emotional sentinel capable of taking the brain control. Fear is a familiar feeling to humans and may be perceived by many other species [157]. According to the Constructivist view, it is necessary to incorporate the conscious experience of fear, where the experience of trauma and indeed the reports of expertise based on this emotional state is a synthesis of high cognitive hierarchy. Somatic knowledge of the body state and its actions, however, is modulated according to context, that is, knowledge stored in memory and information stored in explicit language acquired in a particular culture [158]. Categories of emotions, such as fear, are then seen as highly constructed, rather than primitive or biological, and thus cannot exclude the conscious experience of fear [159].

LeDoux [18] demonstrated that the amygdala acts as an essential component involved in the acquisition, storage, and the expression of fear in the consciousness state. It is important to elucidate how stimuli travel through the amygdaloid pathway by understanding the cellular and genetic mechanisms underlying the conditioned fear by using no-humans models [160]. Cognitive issues also appear to be more addressable than emotional ones, in part, because of the intense subjectivity that hangs over the fear consciousness and emotion themes. Brain processes compute and represent external stimuli without first solving how conscious perceptual experiences occur. Moreover, most cognitive processes occur unconsciously, with only the final products going to consciousness, as in the fear consciousness processes [161,162].

A study by Dannlowski et al. [163] concluded that the amygdala is associated with the limbic circuit participates in the rapid and unconscious facial emotions processing. The increase in amygdaloid reactivity was demonstrated by genotyping functional polymorphism in the serotonin transporter gene (5-HTTLPR) and by functional magnetic resonance concomitant with the detection of emotional features tasks performed by patients with major depression and healthy individuals. The risk allele carriers (S or L (G)) showed higher amygdala reactivity for emotional faces, which in turn was significantly correlated with a chronicity index for depressive individuals. It suggests the existence of unconscious pattern of the amygdala during the emotional images processing. This study suggests that genetic variations of the serotonin transporter may increase the risk of depression chronicity by altering limbic neural activity at a level of conscious processing of emotions [163].

The existence consciouness in other animals (monkeys, rats) is a longstanding question [164, 165,166]. It requires different approach in animals than humans, which depends on language and questioning. Some modern consciousness theories that are functionally adequate for the conscious experience of fear offer testable neurobiological hypotheses which pre-suppose that that the stimuli that communicate or trigger fear can do so even when these stimuli perception is subliminal. This mechanism that involves the amygdala affirms that unconscious fear processing depends on

a particular subcortical route for input to the amygdala [167].

Non-conscious emotions have been proposed as a possibility based on some psychological experiences. Regardless of the empirical status of these dissociations, they highlight the different components of fear experience: (1) one may be aware of inducing stimuli and circumstances (often the object for which fear is directed behaviorally); (2) one can be aware of the bodily changes that accompany fear; (3) one may be aware of his ability to act in response to dealing with the situation, provoking fear; (4) may be aware of the change in cognition; and (5) one may be aware of many associated thoughts and background knowledge related to fear [168].

When people report that they are afraid, they may be aware of any of the fear components. Because the amygdala allows us to quickly orient to the source of potential threat in the environment, which may occur without conscious perception as an evolving mechanism of adaptation. This fear awareness can be observed even in the absence of any behavioral measure as observed by Helmstetter, Parsons and Gafford [169] when checking for brain activation in patients who could not respond to any questions behaviorally, similar to the activation seen in healthy individuals with conscious fear feeling.

Conclusion

In recent decades, significant progress has been made in the delineation of the essential neural circuit and circuit level changes involved in neurobiological aspects asscіated with the amygdala. While the amygdala hypothesis has garnered vast empirical supports based neurobiological evidences of both functional and emotional aspects, there are also incompatible data and alternative hypothesis that require consideration.

The consistency in findings related to neurotransmission in the amygdala underscores the importance of generating hypotheses regarding their participation in emotional memory formation, motor control, execution funtions in cognition. In particular, we propose that the amygdala interacts with the cortical structures to promote enhancement in perceptual processing, semantic elaboration, and attention, which serve to benefit subsequent memory for emotional content. Because of the complexities inherent in understanding the intersection of perception, emotion, memory, decision-making, motor control and stress, more research is warranted that breaks down these gross constructs for more detailed analysis of cognitive subprocesses and underlying neural mechanisms.

Competing Interests

The authors declare that they have no competing interests.

Authors' Contributions

MG, ST, LM, VM, BV, LM, EN, VHB and PR designed the study concept. Studies considered eligible for inclusion were read in full and their suitability for inclusion was determined independently by eight reviewers (MKN, CC, VN, RV, LWDGS, MC, JDG, and JJ). MG, ST, VM, FS, MC, TO, DSG and PR read and finalized the manuscript. All authors read and approved the final manuscript.

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