Impaired orbitofrontal-amygdala circuit and its implications on social behavior in autism spectrum disorder

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Abstract

Social communication and social interaction are essential for human's well-being. For making them successful and rich, one needs to acquire different kind of abilities, together called 'social cognition'. Lack of those skills can cause great suffering for the individual and in many cases to his or her environment. Autism spectrum disorder (ASD) is often characterized with deficits in social communication and social interaction. Its first signs can be seen in infancy and with age, as the complexity of the social world enlarged, the symptoms become more significant. The brain structures involved in social cognition and behavior are being investigated for many years now and still, there is no one accepted theory. However, it has been shown many times in different researches that the amygdala and the prefrontal cortex (PFC), specifically the orbitofrontal cortex (OFC), are crucial brain regions. Here in this assay, we review the relationship between the two regions and the part each of them has in constructing the social world of humans. Finally, we offer an explanation for why the impaired circuit including the Amygdala and the OFC may cause the symptoms seen in people with ASD.

Social behavior and its importance for human lives

Social behavior is one of the most complicated behaviors humans and animals can perform. It can be described by the ability to properly communicate and interact with others, sense, process and interpret social cues [1]. For doing that successfully, one needs to be able to acquire, process, store and use social input from the environment and by that to decide on and take proper social actions, the sum of which is called social cognition [2]. In addition, researches show two skills that are crucial for having successful social interactions. One is mentalization [3] or "theory of mind" [4] that relates to the process of understanding others or one's own thoughts, mental states and feelings [2], and second is emotional regulation which refers to the ability to control the effect of the emotions on our experience while they arise and on the response behavior [5].

The wealth of the Social lives is an integral part of the wellbeing of a human individual. As many Researches show, having proper social and emotional skills is associated with high number of positive psychological and social consequences. For example, people with good social skills or communication competence tend to have higher self-esteem [6] and satisfaction with social interactions [7]. Also, people with good social skills have greater access to social support [8]. People with effective social skills are able to marshal support from their social network when faced with stressors, and that helps to minimize the impact of the stress [9]. As the capability of a person to interact with other people successfully can help him flourish in the world, when a person is lack of those skills it can be a cause for great suffering and ostracism. Individuals with poor social skills may be vulnerable to the development of psychological distress because they have less access to the protective effects of social support [10]. Moreover, it has been shown that deficits in social skills are associated with an extensive list of psychosocial problems such as loneliness, anxiety, and depression [11-13]. Social skills disorders may have effect not only on the individual suffering from them, but also on his close environment. In persons with ASD, it has been found, that its Manifestations are causing great difficulty to the individuals and their families as well [14].

ASD – definitions and symptoms

ASDs are a group of heterogeneous neurodevelopmental disorders characterized according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) by (i) deficits in social communication and social interaction and (ii) stereotyped, repetitive behavior [15] with narrow restricted interests, often accompanied by sensory abnormalities and language development delay or absence [16]. These symptoms must be present in early

childhood and impede the individual's everyday activity. Autism, from the Greek words autos ("self") and ismos ("action"), was described initially by Kanner in 1943 as a congenital lack of interest in other people [17]. In a normative condition, the Signs of first developments of social preferences start at infancy, when newborns show higher attention to human voice and face over other stimuli. In contrast, infants with ASD show no difference in preference between humans and other stimuli [18, 19]. Moreover, Infants with ASD demonstrate impaired joint attention [20], the ability to share eye gaze focus on an object following the alert of one individual to the other by pointing or gazing. In early childhood, the increased ability to communicate verbally with others results in more complex social behavior, including shared play and interactions with other children. these abilities, impaired in children with ASD [21]. Explanations of autism on the psychological level have reflected the view that behavioral manifestations of the disorder are the result of underlying deficits in cognition, affect, or both. Research has provided clear evidence that compared with persons without ASD of similar verbal level, persons with ASD are poorer at reasoning about what others think, know or believe, recognizing emotional expressions and gestures, and making social attributions and judgments, all those are different expressions of social cognition (14). Those deficits in social cognition, found with individuals with ASD, are integral elements for preforming 'theory of mind' and for understanding other person's emotions. Without those abilities, it is hard detecting information about the social world and also, evaluating its functional significance for the self. In those cases, Social Interactions become times of uncertainty and the person is unable to collect and integrate enough information to feel the comfort one needs for this kind of complex situations. This lack of information can help to understand the hyper sensitivity of ASD's to social situation and the anxiety they often feel in those situation [22]. Those strong emotions they often feel can also help explain their inability to regulate their own behavior, which may lead to Inconsiderate or not compatible behavior [23]. That case often leads to the avoidance and deterrence from social situations and interactions with strangers [15, 24].

Theories of neurophysiological deficits in ASD

Brain abnormalities with people suffering from ASD are expressed in many different brain areas including the brainstem, cerebellum, frontal lobe, and limbic structures. Still, there is not yet a single, well-accepted neurodevelopmental model for autism. In contrast, different Researchers offered various explanations. For example, viewing autism as a disorder of sensory modulation affecting cortical mechanisms of selective attention, Ornitz (1983) and Courchesne et al. (1994) have hypothesized involvement of the cerebellum, parietal cortex,

brainstem, thalamus, and striatum [25, 26]. Alternatively, Damasio and Maurer (1978) have speculated that there is dysfunction in bilateral neural structures that include mesolimbic cortex in the mesial frontal and temporal lobes, neostriatum, and anterior and medial nuclear groups of the thalamus, structures that are targets of dopaminergic mesencephalic neurons [27]. This fronto-limbic dysfunction in autism was also posited by Bishop (1993) [28]. The wide variety of theories involved during many years of research is not surprising consider the many different symptoms expressed with different individuals on the spectrum. More recent, based on neuroimaging studies, researches focused on theories related to different aspects of social cognition which involves the superior temporal gyrus, the amygdala, and the OFC or the anterior cingulate area [29-31]. Another recent theory tries to explain ASD as a social motivation deficit, suggest that impaired motivation to engage in reciprocal social interaction leads to the ASD-like social deficit. Social motivation includes three main brain regions that are all highly connected: orbital and ventromedial regions of the prefrontal cortex, the amygdala, and the ventral striatum [32]. We can see in the recent theories that the amygdala and OFC appear as factors under different explanations. For better understanding of the mechanisms involved in ASD, we examined in this assay, the structure and roles of the amygdala and the orbitofrontal cortex and their implications on the behavior of humans. In addition, we focused on the Characteristics of the neural circuits including both areas, and tried to explain how its impairments lead to the symptoms seen in patients with ASD.

Amygdala and OFC neuroanatomy and function

The amygdala, an almond shaped brain region is composed of 13 different nucleuses and it is part of the limbic system [1]. The amygdala has integral part in Processes involving emotions of fear and anxiety, like the acquisition and expression of conditioned fear which can be seen in many studies [33, 34]. Moreover, it takes part in emotional reactions, memories and visual social stimuli; creation and control of anxiety; and recognizing social emotion from faces [35]. The various interconnections between the amygdala and many cortical and subcortical regions make it linked and influential to many different processes in the brain. The lateral nucleus receives sensory inputs, including visual information from faces and facial expressions, gaze direction, body postures and movements, as well as auditory information from specific vocal sounds and intonations [36, 37]. Throughout the basal nuclei the amygdala creates reciprocal relation with cortical regions, which allow affective states to modulate the cortical processing of sensory stimuli. These feedback projections from the amygdala, not only to high association cortical areas, but also to

primary sensory cortical areas allowing emotional states to influence sensory inputs at very early stages in their processing, by weighting the emotional significance of sensory information. The central nucleus is attached to areas like the brainstem and hypothalamus and thought to influence the autonomic and endocrine manifestations of emotion, respectively. Via this pathway, sensory stimuli could influence and activate Emotional reactions [38]. Moreover, the amygdala interacts with the hippocampus means it can act upon and modulate stored information and influence past and emerging memories [39, 40]. The orbital region of the prefrontal cortex is a mesocortical area that occupies the ventral surface of the frontal lobe. Like the amygdala, it receives highly-processed information from all sensory modalities (visual, somatosensory, visceral, olfactory, and gustatory) and based on the pattern of its connectivity; it has been divided into medial and lateral networks. The medial area has strong Connections with the hippocampus and associated areas of the cingulate, retrosplenial, and entorhinal cortices. The lateral area is widespread and interconnected with many different regions in the brain including the amygdala [41, 42]. Generally, the OFC is highly associated with response inhibition and regulation. It receives information about all aspects of the external and internal Environment and makes bi-directional connections to different regions which make it involved and influential with various processes throughout the brain [42]. Studies show that the OFC is involved in the engagement of interpersonal relationships, moral behavior, including value based decisions and social aggression [43-46]. Moreover, Lesions within the medial OFC enhance the response to stressors or fear conditions stimuli [47] resulting in severe impairments in social behavior [48-50] and difficulties in identifying social signals from facial and voice expressions [48, 51]. The OFC contributes to the anticipation of reward and adjusts behavioral responses when the reward values of stimuli have changed, as showed in go/no-go tasks [52], on object reversal and extinction tasks in that they continue to respond to an object that is no longer rewarded [53-55] and also been demonstrated by electrophysiological recording during similar behavioral tasks [56, 57]. Thus, the failure to respond normally after damage to the OFC by adapting behavior when reinforces have changed may be a fundamental deficit that underlies impulsiveness, disinhibition, inappropriate responses to other people's moods, and inadequate self-regulation of social–emotional behavior.

Amygdalar-OFC circuit

The amygdala and the OFC have interesting and important relationship. The amygdala, which is known to have been well-conserved across evolution, is in charge of primary behaviors that are important for survival of the individual. For example, conditioned fear is

the mechanism through which the animal learns to avoid aversive or dangerous situations. In humans lives, avoiding dangerous situations is not the only crucial ability for survival and passing the genes to the next generation. Social skills are essential Feature for human lives [58]. The complexity and diversity of those skills require more sophisticated regulating mechanisms. The PFC in general, which is most elaborated in primates, and the OFC specifically is associated with these kinds of mechanisms. The OFC is related to higher processes, which modulating fear and anxiety in the amygdala is one of the [14]. Brothers (1990) [59], relying on single-cell recording studies [60] and neurological studies [61], was first to offer a neural basis of social intelligence including the OFC, amygdala and superior temporal gyrus (STG). she also relied later on animal lesion studies [62]. Together, she postulated that these comprise the `social brain'. In more recent studies, researches mostly add the medial pre-frontal cortex (mPFC) as another important component of the 'social brain', although still with the OFC and the amygdala as key factors [63, 64]. Studies have shown that the medial OFC projects to the amygdala and that these projections are thought to influence emotional expressions [65, 66]. Furthermore, it has been shown that there is High inverse correlation of hyper activation of the amygdala with orbitofrontal reactivity during the suppression of negative emotions [67] and presence of threatening stimuli [68], in generalized anxiety disorder [69] and posttraumatic stress disorder [70]. In addition, reduced orbitofrontal activation was observed in patients with social anxiety disorder (SAD) during public speaking [71, 72] and in healthy subjects during anxiety-provoking tasks [73, 74] as well as in patients suffering from specific phobia [75]. Hence, a hypoactive medial OFC has been associated with a failure of fear and anxiety inhibition, while a hyperactive lateral OFC seems to be relevant in anxiety-laden cognitions [76, 77]. The circuit between the amygdala and OFC is involved in recognition and perception of emotional response [65, 66], fear extinction [78] and together with the thalamus is responsible for the assessment of threat-related information [79]. It was shown that early developmental disruption of the amygdala-prefrontal circuit indicates an attentional bias toward threats and leads to the development of pathological anxiety [80, 81]. Also, reduced functional coupling within the network between OFC and amygdala was reported in anxiety-prone subjects [82, 83] and corresponding white matter deficits of the OFC–amygdala connection were shown in patients with SAD [84].

Conclusions and hypothesis

As it can be seen from the facts showed in this assay, it is safe to claim that the circuit which includes the amygdala and the OFC is deeply involved in regulation of behavior due to

changing environmental stimulations, specifically in the social world of the individual. In that circuit, the amygdala determines the significance and motivational meaning of the stimulus, that is whether it is dangerous, threatening etc. Furthermore, the amygdala helps to understand different cues like face expressions, body postures, and tone and to indicate whether a change in behavior is needed or we can 'keep on going' with no fear. The OFC is in charge on regulation of the behavior due to the signals coming from the amygdala. In addition, the flexibility in behavior governed by the OFC, is allowing fast adaptation to changes in the situation and by that can help decreasing the stress levels carried out by the amygdala. The OFC acts as a regulator for both behavior and amygdala activation. Thanks to the work of the amygdala-OFC circuit we can manage social situation with comfort, despite the complexity it withholds. People with ASD impaired the ability to sustain social life. They have low capacity for social cognition which means they cannot understand emotions of others and are not able to perform 'theory of mind' and they suffer from high levels of anxiety when present in social interactions. All that makes them act in inappropriate ways which in turn, leads to rejection and finally avoidance and loneliness. I will try to explain, by using the existing knowledge presented in this assay, the way which the damaged circuit may be causing the symptoms we see in ASD concerning only to the social ones. There are many others as well, Though we won't deal with them here. The impairment in the amygdala-OFC circuit, whether caused by deficit in the amygdala or the OFC themselves or whether caused by deficit in the connection between them, means the white matter, is leading to lack of ability to process the information coming and changing constantly in different social situations. The data from the amygdala cannot properly pass to the OFC, which damaging the capability of the individual to adapt to the changing situation and to act accordingly. This by turn prevents the OFC to signal back to the amygdala that 'everything is under control' and that the stress levels can go down to normal. The person with ASD is being in a state of high anxiety and has no capability of decreasing it, which makes the option of handling the situation correctly almost impossible. In addition, being in a state of uncertainty, due to the lack of information, is enough for causing great anxiety with people from all kinds [22, 85]. The hypothesis offered here is sufficient to explain why people with ASD show high anxiety, lack of reward signs and avoidance in and from social interactions.

Future directions

Today, our knowledge about the regions and mechanisms involved in the symptoms seen in ASD is still scarce. As a result, our capacity to understand the autistic experience is not sufficient. Yet, due to improvement in technological research tools, we can collect more

information and with higher accuracy about those regions and mechanisms. For future direction, it is recommended to investigate more the circuit presented in this assay, for its deep involvement in creating the symptoms also presented here. Better understanding of this circuit and others, will help us figuring the reasons for the behaviors seen in cases of ASD and, hopefully, will also help us deepening our capacity to grasp the autistic experience. With that, we can try to develop better treatments and create better environments for people with ASD.

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