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Editorial

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Update on Limbic Connections in Human Brain: A Possible Closer Relationship Between Brain Processes and Visceral Information

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The limbic system includes cortical and subcortical brain structures involved in several functions, first of all emotional and memory processes and integration. Two key structures of the limbic network are hippocampus and amygdala; their connections with the other brain regions are allowed through a number of white matter pathways, including cingulum, uncinate fasciculus and fornix.[1] All these pathways were studied by means of invasive approaches in animals as well as by means of MRI techniques, e.g. diffusion based tractography. These methods resulted very useful for the non-invasive study, *in vivo*, of these limbic brain connections,[1] as well as to show new possible pathways, e.g. the cerebellar limbic one.[2] Recently, new insights regarding possible limbic functions came from a study conducted by means of advanced tractographic algorithms.[3] The main goal of the latter paper was to investigate subtentorial limbic connections in healthy humans; this was an interesting point, since these connections were previously investigated only in animals by means of viral tracing techniques.[4] These previous studies revealed extensive connections of both amygdala and hippocampus with brainstem nuclei, as well as connections with the periphery of the body through spinal projections.[5,6] By means of constrained spherical deconvolution (CSD)[7] based tractography, Arrigo and colleagues[3] reported and described hippocampal and amygdalar connections with midbrain, pons and bulb as well as connections with cervical spinal cord (Figure 1). These represented novel findings in humans, suggesting that functional speculation based on animals studies might be adopted also in human brain. Amygdalar connections with brainstem were proposed to be related with faster answers to fear stimuli, in order to establish a more efficient alerting mechanism.[8-10] Based on findings provided by animal studies, other authors proposed a role of amygdalar-brainstem pathways in the visceral control as well as in the control of the appetite.[11,12] With respect to hippocampal-brainstem pathways, these were previously reported in animals[13,14]; those results allowed to advance the hypothesis of a larger learning and memory connectivity network, involving also brainstem structures, which might influence the limbic system during memory and learning elaboration.[15] In this context we might advance the hypothesis that information

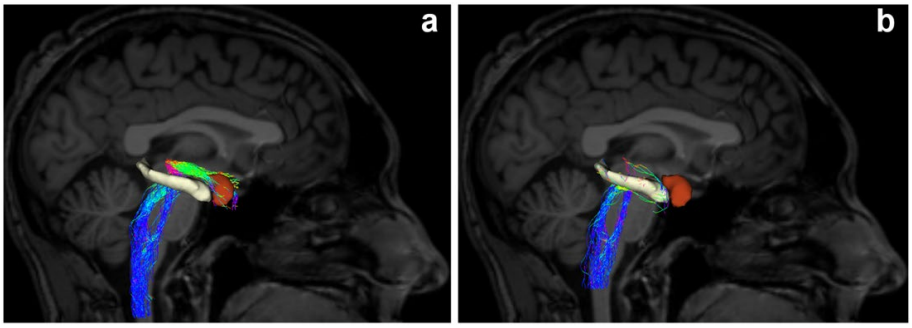

Figure 1: Sagittal view of amygdalar (a) and hippocampal (b) connections with cervical spinal cord. Amygdala and hippocampus are represented by brown and white regions of interest respectively.

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regarding the visceral state in a given moment might influence or take a role in memory and learning processing.[16] Regarding spinal-limbic connections, very little is known about their functional involvement in brain processes. Also in this case, these pathways were supported by previous studies conducted in animals.[5-6] A number of hypotheses might be advanced about the functional meaning of these bundles; an interesting point is related with the possibility that these connections represent a faster way of transmission of nociceptive information and visceral ones, thus making possible faster responses to dangerous or noxious stimuli.

Although, further studies are needed definitely to demonstrate the existence of these connections, i.e. dissection studies, as well as to define their functional meaning, these white matter bundles open new interesting perspectives both in physiological and pathological contexts. Indeed, it might be interesting to study the role of brainstem and the periphery of the body in learning and memory processes, as well as in emotional state integration. Moreover, these pathways might provide further anatomical basis to better define pathophysiological features of a number of psychiatric and syndromic conditions, e.g. bipolar disorder[17,18] and anti-Ma2-associated syndrome.[19,20] In these kind of patients a strong involvement of the limbic system was demonstrated, with concurrent alterations of brainstem nuclei. Furthermore, another interesting future perspective might regard the deeper study of what is known as gut-brain axis, i.e. a bilateral network connecting the periphery of the body both with central and enteric nervous systems.[21] This bidirectional path of connections was described to influence and/or stimulate a number of responses involving nervous, immune and endocrine systems[21]; its alterations was hypothesized to have a role in the pathophysiology of a number of disorders, including functional and inflammatory gastrointestinal disorders, and eating disorders.[16] In particular, with respect to irritable bowel syndrome, previous studies demonstrated alterations of brain functional connectivity, including supra-tentorial limbic circuits.[22,23] Future studies should be conducted in order to understand if an involvement of subtentorial limbic connections occurs in all these contexts.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

DISCLOSURES: None.

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