Brief report

Neurocircuitry of emotion and cognition in alcoholism: contributions from white matter fiber tractography

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Chronic alcoholism is characterized by impaired control over emotionally motivated actions towards alcohol use. Neuropathologically, it is associated with widespread brain structural compromise marked by gray matter shrinkage, ventricular enlargement, and white matter degradation. The extent to which cortical damage itself or cortical disconnection by white matter fiber pathway disruption contribute to deficits in emotion, cognition, and behavior can be investigated with in vivo structural neuroimaging and diffusion tensor imaging (DTI)-based quantitative fiber tracking. Tractography in alcoholism has revealed abnormalities in selective white matter fiber bundles involving limbic fiber tracts (fornix and cingulum) that connect cortico-limbic-striatal nodes of emotion and reward circuits. Studies documenting brain-behavior relationships support the role of alcoholism-related white matter fiber degradation as a substrate of clinical impairment. An understanding of the role of cortico-limbic fiber degradation in emotional dysregulation in alcoholism is now emerging.

 Dialogues Clin Neurosci. 2010;12:554-560.

Keywords: *neuroimaging; DTI-based quantitative tractography; white matter fiber; limbic system; basal ganglia; emotion; cognition; alcoholism*

Emotions influence behavior and decisions. They are vital in evaluating whether perceived information is harmless or dangerous, for making appropriate responses, and for making rational decisions.[1-3] The ability to regulate emotions is thus essential for controlling actions, and difficulty with emotion regulation is a key factor of alcoholism.[4] For example, alcoholics exhibit deficits in decoding emotional facial expressions[5-10] and in controlling impulsivity, and they exhibit behavioral disinhibition whether sober or drunk.[11,12] Selective brain systems that engage the amygdala play a crucial role in a tendency to experience negative emotion and in promoting alcohol intake.[13-15] Patients with selective damage to the amygdala have shown impaired recognition of negative emotions,[16] such as fear[17-19] or disgust.[20,21] Chronic alcohol consumption is associated with widespread brain structural compromise, marked by gray and white matter shrinkage and ventricular enlargement seen in animal studies,[22,23] human neuroimaging studies,[24-27] and with postmortem examination.[28,29] The observed emotional deficits and evidence for brain compromise suggest that the structural neurocircuitry of emotion and cognitive control may be affected in chronic alcoholism.

Neurocircuitry of emotion and cognition

Since the first demonstration of specific brain sites involved in pleasure,[30] extensive animal research has

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identified striatal and midbrain areas and their dopaminergic and glutamatergic projections to other brain structures as key components that regulate the reward circuit (for reviews see refs 31,32). Researchers using neuroimaging techniques recently confirmed the basic anatomy and pathways of cortico-striatal reward (eg, refs 33,34) and cortico-limbic emotion circuits in humans (eg, refs 35-38). The limbic system, located on the medial surface of the cerebral hemispheres, includes the rostral anterior cingulate cortex, hippocampus, and amygdala.[36,39] The structures comprising the limbic system are controversial, and structures such as the hypothalamus, thalamus, basal ganglia, dentate gyrus, entorhinal, piriform, and orbitofrontal cortices have been considered to be part of the limbic system by some but not all investigators. The amygdala directly mediates aspects of emotional learning and facilitates memory operations in other regions, including the hippocampus and prefrontal cortex *(Figure 1)*. For example, neural plasticity in the amygdala was associated with encoding of the emotional component of memories,[40] with mediating aspects of reward learning, and with facilitating memory operations in other limbic regions involving hippocampus and prefrontal cortex.[41,42] Within this neurocircuitry, the medial prefrontal cortex appears to exhibit inhibitory control over emotion- and reward-processing regions to prevent spontaneous and inappropriate emotional responses. This concept was confirmed by functional neuroimaging studies showing inverse activity levels in the medial prefrontal cortex and the amygdala.[43-46] Thus, it is not a single brain region, but rather the interaction of various interconnected structures, that enables emotional control.

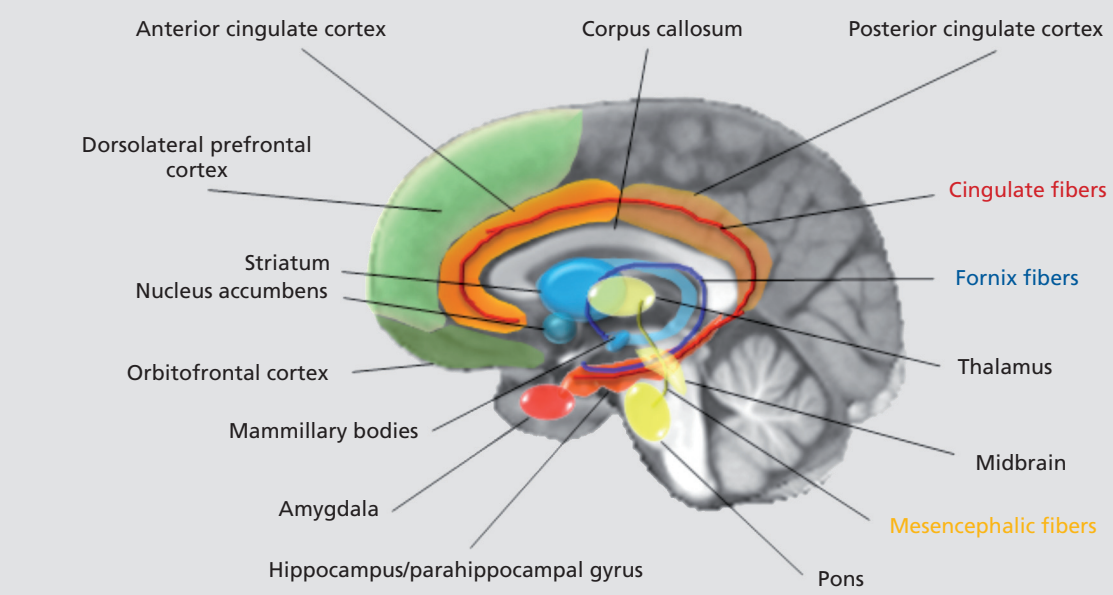
Functional and structural connectivity in cortico-limbic-striatal circuits

To test the functional relevance of interconnected limbic system structures, Cohen et al[35] combined measures of DTI-based fiber tracking with functional magnetic resonance imaging (fMRI)-based connectivity in healthy subjects. Their results yielded two dissociable amygdala-centered brain networks: (i) an amygdala-lateral orbitofrontal cortex network involved in relearning following a rule-switch; and (ii) an amygdala-hippocampus network involved in reward-motivated learning. Support for a role of cortico-limbic-striatal brain networks in both emotion and reward processing in alcoholism comes from recent fMRI studies indicating blunted amygdala activation to socially relevant faces in alcoholics[47] and enhanced ventral striatal activation to alcohol-related stimuli.[48] Further evidence for an interaction of emotion and reward systems in alcoholism comes from an fMRI study showing that anxiety ratings predicted parahippocampal activation to emotionally negative images, but not when these images were presented together with alcohol stimuli,[49] suggesting that alcohol cues attenuated the brain's responsiveness to fearful emotions.

Compromise of anatomical connections may impair neural signal transmission between brain regions involved in emotion processing and attentional bias toward alcohol cues in alcoholics.[50] Using white matter fiber tractography to understand how impaired integrity of neuroanatomical structural connectivity in cortico-limbic-striatal circuits affects emotions and reward learning can explain how the effect of chronic alcoholism on these brain systems can mediate emotion, cognition, and behavior. Conditions such as the persistent preoccupation with alcohol,[10,51] the inability to learn from negative consequences, and the lack of control over drinking behavior[52,53] can be studied.

DTI fiber tractography

DTI has enabled quantitative fiber tracking for in vivo noninvasive mapping of inter-regional white matter fiber connections and the segmentation of axonal tracts in normal[54-56] and degraded brain systems[57,58] (for a review see ref 59). DTI permits examination of the integrity of the microstructure of cerebral white matter by measuring the orientational displacement and distribution of water molecules in vivo across tissue components.[60] Water diffusion modeled with DTI is represented mathematically by an ellipsoid on a voxel-by-voxel basis. In fibers with a homogeneous or linear structure such as healthy white matter, the ellipsoid is long and narrow and has a preferential orientation, presumed to indicate the course of white matter fiber tracts. As such, DTI-based fiber tracking represents an indirect in vivo measure of neuronal pathways in the brain. DTI metrics include fractional anisotropy (FA) and the apparent diffusion coefficient (ADC) or mean diffusivity (MD), which can be decomposed into two components, the longitudinal or axial diffusivity (λl) and transverse or radial diffusivity (λt). High axial diffusivity is taken as an index



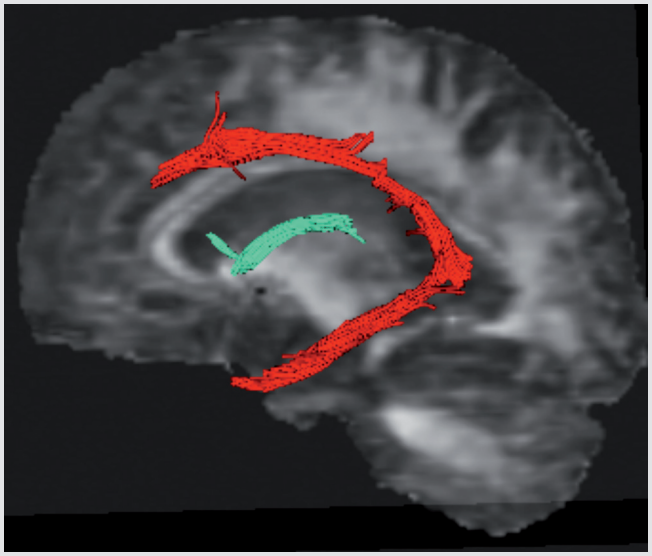


Figure 1. Top: The cortico (green)–limbic (orange, red) emotion system consists of several brain regions that include amygdala, hippocampus, parahippocampal gyrus, anterior cingulate, and dorsolateral prefrontal cortex. It is involved in emotion, memory, emotional learning, and motivation with prefrontal cortices employing attentional and executive control over emotionally motivated actions. The cortico (green)–striatal (blue, yellow) reward system involves mesolimbic and mesocortical pathways from the ventral tegmental area (VTA, midbrain) to the striatum, particularly the ventral striatum (nucleus accumbens). The ventral striatum is connected to the thalamus and receives input from orbitofrontal and anterior cingulate cortices. Cortico-limbic and cortico-striatal circuits are partially overlapping and closely interconnected. Among the brain fiber bundles compromised in chronic alcoholism are cingulate (red) and fornix (blue) fiber bundles of the limbic system,[27] corpus callosum fiber bundles connecting cortical sites in the two cerebral hemispheres,[69] and mesencephalic (yellow) fibers connecting the pons to the midbrain.[67] Bottom: Parasagittal functional anisotropy image of a 67-year-old healthy man with fiber tracking of the cingulate bundle (red) and the fornix (green) superimposed.

of degradation of axonal health or integrity and radial diffusivity indexes the fibers' myelin sheath integrity.[61-63] This information can be used to determine which fiber tracts are and are not affected by chronic alcohol consumption; whether fiber compromise is due to axonal damage, a breakdown of the myelin sheath, or both; and how fiber microstructural integrity may relate to brain functional compromise.[64-66]

DTI-based quantitative fiber tracking in alcoholism

Until recently, few studies had investigated alcohol effects on microstructural integrity of fiber tracts by using DTI-based quantitative fiber tractography (chronic alcoholism[27,67-69]; fetal alcohol spectrum disorder[70,71]; for review see ref 72). In our laboratory, we tracked 11 major white matter fiber bundles in 87 alcoholic and 88 control men and women.[27] Alcoholics demonstrated the greatest abnormalities in frontal, ie, frontal forceps, internal and external capsules, and more superior bundles, ie, fornix, superior cingulum, and superior longitudinal fasciculus, whereas posterior and inferior fibers were relatively spared. Tracking corpus callosum fibers, we found stronger alcohol effects for FA and radial than axial diffusivity, suggesting alcohol-related myelin degradation consistent with previously reported alcoholism-related neuropathology that included demyelination and loss of myelinated fibers.[28] Structure-function relationships between poorer performances on cognitive tests and DTI signs of regional white matter compromise in several fibers indicated that fiber degradation in alcoholism affects cognitive functions, and specifically cognitive processing speed.[27,69] The role of alcoholism-related fiber degradation as a substrate of cognitive and also motor impairment was further supported by a double dissociation between functions and neuroanatomically defined callosal fiber bundles. In particular, prefrontal and temporal callosal fiber bundle integrity predicted psychomotor speed in a working memory task but not the ability to balance on one foot with eyes closed, and parietal fiber bundle integrity selectively predicted balance performance but not psychomotor speed.[69]

Chanraud et al[67] used DTI to investigate the effects of chronic alcoholism on mesencephalic fibers connecting the midbrain to the thalamus and the midbrain to the pons in 20 alcoholic and 24 control men. Alcoholics had fewer fibers than controls for midbrain–pons bundles but not for midbrain–thalamus bundles. The midbrain–pons fiber deficit in alcoholics was predictive of poorer cognitive flexibility. This relation is consistent with the idea that cognitive functions and abilities are both mediated and constrained by the anatomical characteristics of the underlying white matter tracts interconnecting gray matter nodes of complex cortico-subcortical circuits,[73] and that disruption of selective (eg, mesencephalic) fiber bundles impairs cognition, such as mental flexibility.

Among the fiber tracts showing alcoholism-related microstructural compromise are the fornix and the cingulum,[27] two major fiber tracts of the limbic system. The fornix connects the hippocampus with hypothalamic regions including the mammillary bodies, and is involved in memory formation.[74-76] The cingulate bundle of the limbic system has long and short fibers that surround the corpus callosum and course along cingulate cortex and parahippocampal gyrus. The cingulate bundle connects orbitofrontal, dorsolateral prefrontal, and medial frontal cortices with parietal, temporal association, and medial temporal cortices including hippocampus and amygdala. The cingulum has been associated with several brain functions including pain and emotion,[77] cognitive and motor control,[25] memory,[78] and spatial orientation.[79,80] Whether the degradation of fornix and cingulate fibers connecting cortico-limbic-striatal nodes of emotion and reward circuits is directly and selectively related to deficits in component processes of emotional regulation, cognitive control, reward learning, and the urge to drink in alcoholism remains to be investigated. Neuroimaging studies in alcoholism are beginning to link craving and binge drinking to cortico-limbic structural and functional integrity.[81-85]

Conclusion

The recent advance of neuroimaging techniques such as DTI and fMRI have provided the opportunity to study structural and functional compromise of brain networks in chronic alcoholism. These studies provide clear evidence for brain-behavior relationships that support the role of alcoholism-related white matter fiber degradation as a substrate of cognitive and motor impairment.[27,67-69] There is, however, limited understanding of the role of cortico-limbic fiber degradation on emotional dysfunction and impaired cognitive control of emotionally motivated actions in alcoholism. Thus, fiber tractog-

raphy together with functional neuroimaging is an ideal combination to explore the role of regional cortico-limbic-striatal connectivity in emotion and cognition and their dysregulation in alcoholism. ❑

Acknowledgements: This work was supported by NIAAA grants AA018022, AA010723, AA017168, and AA012388. We thank Margaret Rosenbloom, MA, and Fiona Baker, PhD, for comments on this manuscript.

Circuitos neurales de la emoción y de la cognición en el alcoholismo: aportes de la tractografía de fibras de sustancia blanca

El alcoholismo crónico se caracteriza por un deterioro del control de las acciones motivadas emocionalmente para el uso del alcohol. Neuropatológicamente se asocia con un amplio compromiso de la estructura cerebral caracterizado por reducción de la sustancia gris, aumento de los ventrículos y degradación de la sustancia blanca. La extensión en la que el daño cortical en sí mismo o la desconexión cortical producida por disrupción de las vías de fibras de sustancia blanca contribuyen a los déficit en la emoción, la cognición y la conducta se pueden investigar en vivo con neuroimágenes estructurales e imágenes con tensor de difusión (ITD) basándose en el trazado cuantitativo de fibras. La tractografía en el alcoholismo ha revelado anormalidades en haces específicos de fibras de sustancia blanca que incluyen tractos de fibras límbicas (fórnix y cingulado) que conectan nódulos córtico-límbico-estriatales de la emoción y circuitos de recompensa. Hay estudios documentados de las relaciones entre cerebro y conducta que dan soporte al papel de la degradación de fibras de sustancia blanca en el alcoholismo como sustrato del deterioro clínico. Actualmente está emergiendo una comprensión del papel de la degradación de las fibras córtico-límbicas en la falta de regulación emocional en el alcoholismo.

Circuits neuronaux de l'émotion et de la cognition dans l'alcoolisme : contributions de la tractographie des faisceaux de substance blanche

L'alcoolisme chronique se caractérise par une altération du contrôle des actes d'origine émotionnelle sous l'emprise de l'alcool. Sur le plan neuropathologique, il associe des lésions structurelles cérébrales étendues marquées par une contraction de la matière grise, un élargissement ventriculaire et une dégradation de la substance blanche. La neuro-imagerie structurelle in vivo *et l'imagerie en tenseur de diffusion (ITD) basée sur le suivi quantitatif des faisceaux permettent d'évaluer dans quelle mesure la lésion corticale elle-même ou la déconnexion corticale par rupture des faisceaux de substance blanche participent aux déficits émotionnels, cognitifs et comportementaux. La tractographie a révélé dans l'alcoolisme des anomalies des faisceaux sélectifs de substance blanche impliquant des faisceaux limbiques (fornix et cingulum) qui connectent des noyaux cortico-striato-limbiques de l'émotion et des circuits de récompense. Des études sur les relations entre le cerveau et le comportement confortent le rôle des dégradations de substance blanche liées à l'alcoolisme, qui seraient des substrats de la détérioration clinique. Nous commençons à comprendre le rôle de la détérioration des faisceaux cortico-limbiques dans le dérèglement émotionnel observé dans l'alcoolisme.*

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