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Brain effects of ketamine: implications for clinical practice

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Recent progress has been made in the understanding of the effects of anesthetic agents on brain function, and particularly on the mechanisms sustaining consciousness. Several functional changes during anesthesia-induced alteration of consciousness are common to all anesthetic agents. Anesthetics preferentially disrupt higher-order consciousness networks, with a breakdown of fronto-parietal connectivity within those networks, while lower-order sensory networks are relatively preserved. Long range communication between brain regions is also inhibited by anesthetics, and the spatio-temporal complexity of the interactions between brain regions decreases [1], with a limitation in the number of possible connectivity configurations. Anesthetics also modify network topology, by reducing their global efficiency, increasing node clustering, disrupting major hubs such as the posterior parietal hub, and reconfiguring network structure. The net result is a reduction in the capacity of the brain to generate and integrate information [2].

Not surprisingly, because already known to have distinct pharmacologic and electrophysiologic effects compared to other general anesthetics [3 4], ketamine appears to partly differ in terms of functional brain effects [5]. It induces global brain hyper-connectivity and reorganization of sensory networks [6 7], possibly leading to unconstrained cognition. At doses producing unresponsiveness, ketamine disrupts fronto-parietal communication [8 9], but relatively preserves connectivity within the executive control networks, the ones involved in perceptual, somesthetic processing, and ability to respond to an external event. Between-network interactions also seem to be altered by ketamine [5]. Its effects on the salience network, involved in judgment of an event salience, conflict monitoring, information integration, response selection, interoceptive processes, and the emotional counterpart of pain, are not uniform [5]. Regarding sensory processing, ketamine diminishes connectivity between sensory networks, that remain active, and regions responsible for pain sensing and affective processing, and increases connectivity with regions involved in the descending inhibition of pain [6]. These observations may be in relation with the dissociative state produced by ketamine, characterized by an isolation from the external environment, while still experiencing intense dreaming. The ketamine-induced dissociative state can be qualified as a state of disconnected consciousness, of interest to the study of the different components of consciousness. This state displays a specific electroencephalographic signature [10], and a complexity of cortical communication close to the one observed during waking [11]. It is not associated to an ability of the subject to perceive information arising from the environment, and must be distinguished from other peculiar consciousness states such as connected consciousness, and disconnected unconsciousness.

Ketamine affects other brain functional systems. Small doses decrease connectivity between the default-mode network (the network of self-awareness, autobiographical memory, mind wandering, and unconstrained cognition) and other networks involved in depression pathophysiology [12]. These effects carry over in the long term, and justify the use of ketamine for treating depression disorders [13]. Ketamine alters the dorsolateral prefrontal cortex connectivity that relates to working memory [14], in a transient manner.

Aside from the above-mentioned long term effects on depression, the recently evidenced properties of ketamine may have some implications for clinical practice, in terms of consciousness fluctuation during anesthesia, recovery, and postoperative delirium. In addition to putting a damper on N-methyl-D-aspartate receptor-mediated glutamate neurotransmission and favoring neuronal hyperpolarization through the enhancement of hyperpolarization-activated cation channels, ketamine activates excitatory neuromodulators, including amines and acetylcholine [15], which may account for its somewhat paradoxical properties. When added to a basic anesthetic regimen in animals, it first deepens anesthesia but then hastens recovery [16]. Putting together the currently known biochemical and functional properties of ketamine, and undertaking future research to disentangle the remaining uncertainties will certainly help explaining the conflicting results about the ability of this medication to prevent postoperative delirium [17], or not [18], and its possible implication in the occurrence of connected consciousness episodes during anesthesia [19].

Among anesthetics, the black sheep ketamine offers a unique insight into consciousness modulation and the elucidation of involved mechanisms.

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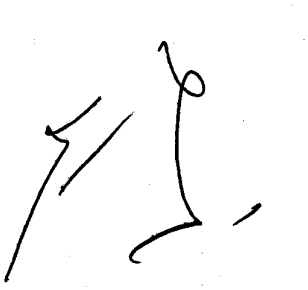

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