



# BRAIN IMAGING AND CATAPLEXY

by Regina Patrick RPSGT

Cataplexy, the temporary sudden loss of skeletal muscle tone, affects an estimated 70 percent of people who have the sleep disorder narcolepsy. At its worst, a cataplexy attack may cause a person to suddenly fall to the floor. The person appears unconscious but, in actuality, remains aware of all that is going on around him or her while frightened onlookers may call emergency medical personnel. Within minutes, the person's muscle tone returns and he or she is able to resume activity.

Less dramatic forms of cataplexy may involve only certain muscles becoming momentarily weak in response to a strong emotion. For example, some narcoleptics note that only their arm muscles become weak during an attack. Although cataplexy can be triggered by anger or other strong emotions, it is most commonly triggered by humor. Brain imaging studies indicate that humor may be processed differently in the brain of a narcoleptic who has cataplexy (cataplectic-narcoleptic) than in a person without narcolepsy.

For example, viewing humorous images normally results in increased activation of limbic and nearby structures such as the hypothalamus and certain regions in the frontal lobe, but this activation is more greatly increased in cataplectic-narcoleptics. Alterations in brain activation, especially that of the hypothalamus in cataplectic-narcoleptics, is helping scientists understand a little more about this debilitating symptom.

Narcolepsy is a syndrome consisting of four symptoms:

- Excessive daytime sleepiness and/or uncontrollable attacks of sleepiness that are relieved by short naps
- Sleep paralysis - a temporary inability to move just as one is awakening or going to sleep
- Hypnagogic hallucinations - vivid, realistic imagery occurring just as a person is falling asleep
- Cataplexy

A person does not have to have all four symptoms to be diagnosed with narcolepsy. Only about 10 percent to 25 percent of

narcoleptics have all four symptoms. Because most narcoleptics do not have all four symptoms, it can take a physician several years to accurately diagnose narcolepsy. Most people struggle with symptoms for 10 or more years before finally being diagnosed.

When a person finds something humorous, brain structures such as the amygdala, nucleus accumbens (part of the "reward center"), the ventral tegmental area (VTA, part of the reward center) and the hypothalamus become activated. Scientists believe that activation of these structures results in the pleasurable sensations associated with humor.

Activation of the hypothalamus is of particular interest because it plays a role in sleep regulation. The hypothalamus modulates the switch between wakefulness and sleep. Its role in sleep regulation depends on proper brain levels of hypocretin (also called orexin), a neuroexcitatory peptide that is synthesized by special cells in the hypothalamus. Scientists believe that improper levels of hypocretin may play a role in narcolepsy. Supporting this belief is the finding that animals that lack the hypocretin gene, and therefore are unable to synthesize hypocretin, have impaired sleep rhythms. About 92.5 percent of cataplectic-narcoleptics who have the genetic marker HLA-DQB1\*0602 have extremely low or undetectable levels of hypocretin in their cerebrospinal fluid.

Because lack of hypocretin may result from hypothalamic dysfunction, Stanford University researchers hypothesized that functional magnetic resonance image (fMRI) scans would reveal abnormal hypothalamic activity in cataplectic-narcoleptic subjects.<sup>2</sup> Their study involved 10 cataplectic-narcoleptic subjects who all had low hypocretin levels and 12 non-narcoleptic controls. The subjects and controls were shown 30 humorous cartoons and 40 non-humorous cartoons. Each individual selected cartoons that he or she found "funny" in the humorous group and which he or she found "not funny" in the non-humorous group. Afterward, only those cartoons that each individual had found funny or not funny were used during their fMRI scan.

In both the controls and the subjects, a humorous cartoon increased activation of the thalamus, amygdala, VTA, nucleus accumbens, hypothalamus and the right inferior frontal gyrus (IFG, a convolution on the cortex of the lower frontal lobe that may play a role in inhibiting one's motor responses to humor). However, the cataplectic-narcoleptic subjects had a greater activation than did the controls in three areas: the nucleus accumbens, hypothalamus and right IFG.

From these results, researchers suspect that humorous stimuli may initially over-activate the pathways linking the amygdala, cerebral cortex and limbic/basal ganglia, which then



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induces a compensatory inhibition of the same pathways. Because some of these pathways impact motor control, the result of the inhibition is the sudden loss of muscle tone (muscle atonia).

An unexpected opportunity to scan a cataplexy attack occurred in the study when one cataplectic-narcoleptic subject had an attack while being scanned. The researchers noted that the subject's hypothalamic activity decreased very dramatically during the attack. Brain scans of a cataplectic attack in progress is rare because attacks occur unpredictably. However, status cataplecticus — difficult-to-control episodes of cataplexy — can give researchers a unique opportunity to study brain activation changes during an attack.

In a 2007 case study, French researchers reported their results from single photon emission computed tomography (SPECT) scans of an elderly female patient with status cataplecticus. The patient was a 68 year-old woman whose cataplexy attacks had been well-controlled with medication for three years. She abruptly stopped taking one medication, clomipramine, after developing glaucoma. The result was disabling, frequent, rebound cataplectic attacks. The frequent attacks had persisted for two months before she was admitted for inpatient treatment. Emotional stimuli was not necessary to induce an attack. The entrance of a nurse or doctor into her hospital room often triggered one. If she were sitting on her bed, she would stutter, not speak, drop her head and fall back onto her pillow for one to two minutes.

She underwent two SPECT scans. One scan was performed during a cataplectic attack and the second scan during an asymptomatic period, in which she had been attack-free for eight hours. Comparison of the SPECT scans revealed that four areas became hyperactive during the cataplectic attack: the cingulate gyrus (an enfolding of brain tissue located deep within the cerebral fissure); the left and right orbitofrontal cortices; the right temporal cortex; and the right putamen (a basal ganglia structure). No areas became hypoactive during the cataplectic attack.

The French researchers' finding of increased activity in these areas contrasts with that of a Korean research team who, in their SPECT study, found decreased activation in these areas. They also found decreased activation in the anterior hypothalamus and other areas of the brain that have hypocretinergic pathways (neural pathways activated by hypocretin).

Korean researchers concluded that the reduced brain activity in these areas may explain cataplexy and other symptoms — attention deficit and emotional instability — in people with narcolepsy. However, their subjects had been scanned while awake but not having an attack. In light of this, the French researchers proposed that what may be occurring is that the decreased activation noted by the Korean team may be a cataplectic-narcoleptic's "normal" state, and that these and other brain areas become hyperactive during a cataplectic attack.

Cataplexy is often described as rapid eye movement (REM) sleep muscle atonia suddenly intruding into wake.<sup>3</sup> Muscle atonia during REM sleep results from increased activation of specialized neurons in the medulla, which inhibit motor signals from traveling down the spinal cord. But recent research indicates that cataplexy may involve a different mechanism, although it may share some of the brainstem-spinal pathways involved in REM sleep.

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Stanford researchers noted that both narcoleptic and non-narcoleptic dogs have a REM sleep period every 30 minutes during sleep. The researchers induced a prolonged cataplexy attack in narcoleptic Doberman dogs. During this induced cataplectic state, they noted that rapid eye movements occurred cyclically every 30 minutes. They concluded that the generator for REM sleep appeared to be active even though the dogs were in a cataplectic state. The researchers pointed out that, unlike REM sleep, the occurrence of cataplexy has no rhythmicity. They therefore proposed that the mechanisms that induce cataplexy may be different from the mechanisms responsible for REM sleep, and that cataplexy may represent a dysfunction in the maintenance of vigilance rather than an abnormal manifestation of a REM sleep phenomenon.

The amygdala may play a role in the mechanism behind cataplexy. The amygdala is a limbic structure involved in processing emotions. It becomes activated during REM sleep and, as brain imaging studies indicate, during cataplexy. The amygdala has connections to the hypothalamus, through which it may modulate one's responses to humor. Hypocretinergic hypothalamic neurons may have reciprocal projections into the amygdala and modulate the amygdala's activation. The loss of hypocretin in narcolepsy may therefore impact the activation of both brain structures setting the stage for cataplexy. For example, the loss of hypocretin may allow the amygdala to be hyperactive in the face of reduced hypothalamic activity.

An alternate mechanism for cataplexy may involve hypocretinergic pathways from the hypothalamus to the VTA in the upper brainstem. This pathway may play a role in wakefulness by modulating proper amounts of the excitatory neurotransmitter dopamine in the prefrontal cortex and anterior cingulate cortex. Activation in the prefrontal cortex and anterior cingulate cortex during wakefulness may normally suppress activity in the amygdala. But if hypocretin levels are reduced, dopaminergic activity in the prefrontal cortex and anterior cingulate cortex could be impaired. This in turn may allow the amygdala to become overly activated and result in cataplexy.

Cataplexy can be dangerous if it occurs while driving or doing other activity requiring attention. It can negatively impact one's quality of life if attacks are frequent. Currently, drug therapy with sodium gamma-hydroxybutyrate (Xyrem®) can reduce cataplectic attacks by 70 percent. However, the drug is highly addictive and therefore stringently regulated to ensure that it is being taken correctly and not abused. For example, a patient taking GHB for narcolepsy must first be on an FDA-monitored registry before being legally allowed to take the drug. Some cataplectic-narcoleptic people fearing addiction may choose a less effective treatment for their cataplexy.

A treatment that would not involve the fear of addiction but that could effectively reduce episodes of cataplexy could bring welcome relief to the great number of narcoleptics who struggle with cataplexy. Brain imaging studies may lead to such a treatment by helping scientists understand the exact roles of hypocretinergic pathways, as well as the hypothalamus, amygdala, inferior frontal gyrus and other brain structures in cataplexy.

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