Too much excitement can create painful hallucinations

Researchers found that excess glutamate can result in cortical spreading depression, and this can promote neuroplasticity in the primary motor cortex of the brain and potentially induce migraine with aura (Conte et al, 2010).

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Research in the area of migraine often makes a distinction between migraine with aura and migraine without aura. Put simply, aura is a broad term encompassing many symptoms that present themselves during a migraine attack. Some research articles acknowledge the differences between migraine with aura and migraine without aura, but many seem to lack an explanation behind the neurophysiology involved in migraine with aura. Therefore, the purpose of this paper review is to describe the neurophysiological processes involved in creating aura for some migraine patients, as this can be beneficial in formulating a more effective treatment for them. Research conducted by Conte et al. has found that the migraine aura may be linked to a more restless brain.[1] Furthermore, they found that excess glutamate (a neurotransmitter, or messenger in the brain) may be responsible for this restlessness.[1]

Before diving into what it means to have a restless brain, it is important to understand what migraine is, what aura is, and what neurological changes result in the manifestation of aura. First off, migraine is a severe and painful type of headache that is usually localized on one side of the head, and the pain is often described as being pulsating/throbbing.[2] This severe pain can also present with other signs and symptoms, such as nausea, vomiting, and an increased sensitivity to light and sound.[2] Things get more interesting, however, when aura is present. Aura is essentially an umbrella term that encompasses a variety of symptoms experienced during, or sometimes right before, a migraine. Aura commonly refers to visual illusions or hallucinations, and other cortical disturbances, but the umbrella has also been expanded to include other symptoms, as well.[3] In terms of visual disturbances, the most common types include flashes of light, blurry vision, blind spots (scotomas), or the presence of jagged/zigzagging lines that interfere with vision.[4,5]

Additionally, symptoms can also include difficulties with motor function (dyspraxia), sensory function (tingling or numbness), and the ability to effectively speak or process one's thoughts.[4,6,7] Olfactory hallucinations and problems with memory can also occur, with the latter being more common.[6] In terms of what produces the aura in the first place, one common belief is that migraine aura results from cortical spreading depression (CSD).[8] Several more studies support that CSD is the mechanism behind migraine aura, and it is described as a slow, self-propagating wave of neuronal depolarization that moves throughout the brain.[9,10,11,12] All that being said, what exactly causes CSD is not well understood at this time, but one possibility will be discussed below.[12]

When an excessive amount of glutamate is released into a synapse, especially when not properly removed afterwards, it binds to the NMDA receptors in the brain and produces too

much excitatory stimulation, resulting in a hyper-excited brain. This hyper-excitability can trigger CSD, which is likely the cause of migraine aura, as mentioned earlier.[13] Interestingly, a study found that migraine patients with aura have a more "restless" primary motor cortex (M1) than those without aura. This is likely due to the difference in glutamate dependent short-term M1 synaptic potentiation between migraine patients with aura and those without it.[13] This study sheds some light on the possibility that synaptic plasticity, specifically short-term potentiation, can be a mechanism behind migraine aura.

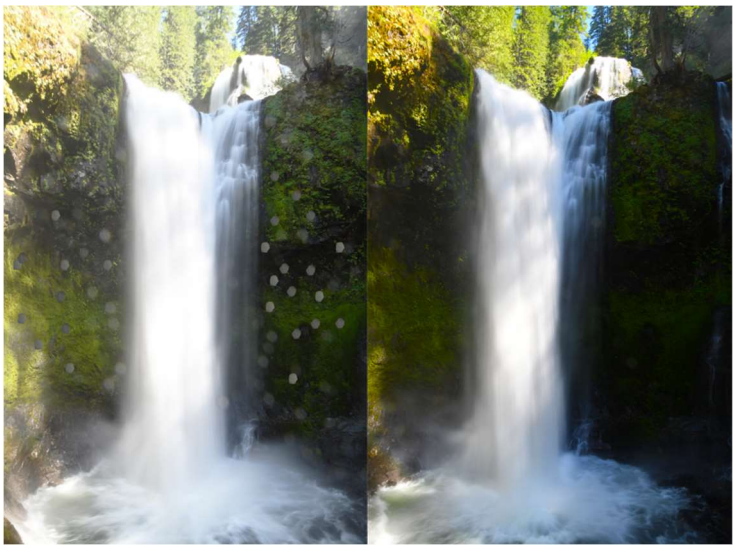

Figure 1: The figure above shows what it is like to see the environment during migraine aura (left) and without migraine aura (right). Additionally, the text below shows what it is like to see words during migraine aura (left) and without migraine aura (right). This is just one example of an aura related visual hallucination, called scotomas (blind spots), but other visual hallucinations may occur as well.

In order to arrive at this conclusion, researchers had to gather a sample of migraine patients with aura (MA), migraine without aura (MwoA) , and also patients without migraines (to serve as a control). All the patients had brain MRIs done on them, and the scans were normal. Before starting the experiment, it was also noted that the participants were not on any medication three days prior to the study, and this was important in terms of reducing a potentially significant confounding variable. Participants then underwent repetitive transcranial magnetic stimulation (rTMS), with the muscle between their thumb and index finger, called the first dorsal interosseous (FDI) muscle, being stimulated and the TMS train (a series of electrodes) being placed on the head. Stimulation was done on their right hands. All patients were studied at rest and when they contracted their FDI muscle for several seconds, and electromyogram (EMG) recordings were collected by measuring activity from electrodes placed on the left hemisphere of the brain. The two rTMS recordings that were measured via EMG were peak-to-peak size of motor evoked potentials (MEPs) and cortical silent period (CSP) duration evoked by each stimulus. All patients were studied when they were not having headaches, with the exception of three patients who had a spontaneous migraine attack (they were studied after their visual aura ended).[1]

While understanding the reason behind using MEP size and CSP duration as measurements is not necessarily important for this paper review, it was found that first MEP size and first CSP size were similar for all three groups (MA, MwoA, and control). That being said, it was also found that rTMS stimulation over the primary motor cortex (M1) resulted in easier glutamate dependent short-term synaptic potentiation in MA patients than MwoA patients or the control patients.[1] The results may be a bit confusing to understand, but essentially, all this means is that the main problem in patients with MA is that they have defects in the "tuning" of their cortical circuits. The rTMS stimulation resulted in hyperactivity of the M1 because of this problem/deficit. Ultimately, the research in this paper supports the hypothesis that glutamatergic transmission differs in patients with MA and patients with MwoA. The patients with MA have an excess of glutamate, which results in an increase in CSD, and this is believed to result in the symptoms

associated with aura. It is also thought that the previously mentioned defects in tuning could be altering how cortical neurons in the M1 interact with other cortical neurons, such as those in the visual cortex, and this could be an important mechanism behind the causes of visual auras.[1] That being said, further studies need to be looked at to better determine how strong the relationship between cortico-cortical projects from the M1 are to the visual cortex, and how this could tie into experiencing visual auras.

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