Effects of Cutaneous Allodynia on Fine Motor Function and Dexterity:

In the Context of Central Sensitization in Migraine Subjects

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Abstract

The global prevalence of headache disorders, according to the World Health Organization (WHO) is about 50%, with symptoms occurring at least once in the last year[1]. Migraine headaches, a primary type of headache disorder, are characterized by unilateral, pulsating pain, often moderate to severe in intensity that lasts from 4 to 72 hours[2]. Approximately 17.6% of women and 5.7% of men in America experience a migraine headache during the course of a year[3]. Because of the symptomatic features, many health organizations, including the Migraine Research Foundation, have determined migraine headaches to be the world's 8th most disabling illness[4]. This assessment is supported by the common side effects associated with migraine such as photophobia, phonophobia, and allodynia[3]. Overall, it is estimated that over 12% of the global population suffers from migraine headaches, yet it is more common during the ages of 25 to 55 years[2]. This paper proposes the investigation of fine motor function and dexterity in migraine subjects who experience cutaneous allodynia, a side effect typically experienced in the migraine population during a migraine episode. This proposed study would improve the understanding of allodynia and its associated peripheral symptoms in the context of central sensitization in migraine subjects.

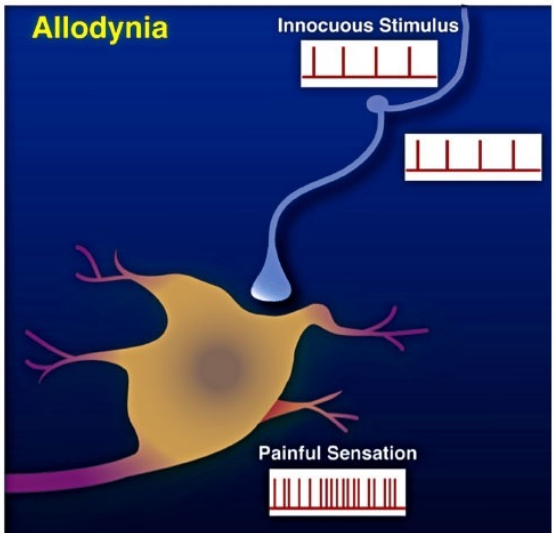

Figure 1: Allodynia is shown as the perception of pain from innocuous stimuli. It is due to the up-regulation of peripheral nociceptors as a result of central sensitization.

Introduction to Migraines and Cutaneous Allodynia

Migraine headaches are known to be a common, neurovascular disorder, that cause patients to typically suffer moderate to severe head pain and associated symptoms[2]. These symptoms may include nausea, sensitivity to light (photophobia), sensitivity to sound (phonophobia), or sensitivity to touch and pressure (allodynia)[2,3].

Allodynia, specifically, is characterized by the perception of pain from a normally non-painful stimulus and is considered a common side effect of an occurrence of migraine[5] [see Figure 1]. For the purposes of

this proposal, cutaneous allodynia will be the focus of investigation. Cutaneous allodynia is defined as the perception of pain from light touch and/or pressure exerted on a migraine sufferer's skin, most likely at the forehead, temples, and arms[6]. Such occurrence of altered processing of sensory input is closely tied to the process of central sensitization (see next section), which has been theorized as the process underlining the progression of a migraine headache[5].

Introduction to Central Sensitization Theory

To fully understand the process of central sensitization, it is imperative to evaluate migraine pain. Migraine pain is a unique type of pain, unlike pain experience from trauma, whereby the intensity of the pain sensation more or less matches the extent of the physical injury. Instead, migraines and other headache disorders, are categorized as dysfunctional or dysmodulatory pain[5]. Therefore, the pain experienced during migraines and the pain associated with allodynia cannot be sourced to physical nor neuronal injury. Rather, central sensitization proposes that migraine pain and allodynia are due to altered function of the nociceptive (pain) system in the brain[5].

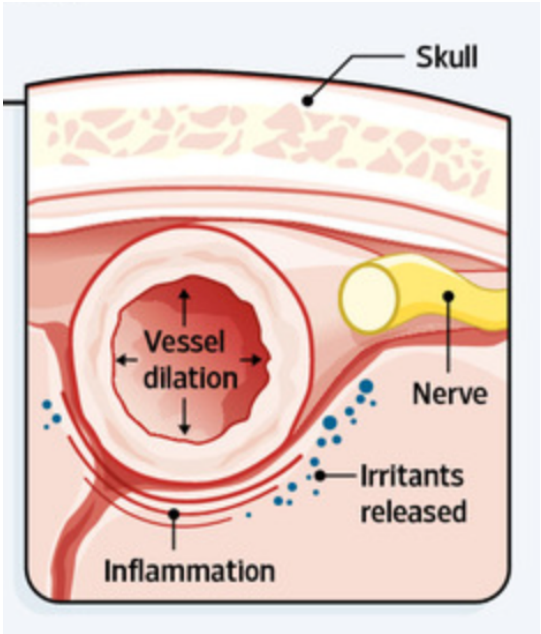

Figure 2: Irritation of the trigeminal nerve causes blood vessels in the meninges of the brain dilate, leading to inflammation and the irritation of nearby nerves.

The progression of a migraine headache is underlined by the process of sensitization, whereby "the stimulus needed to generate a response decreases over time, while the amplitude of the of the response to any given stimulus increases"[5]. In the brain, central trigeminovascular neurons receive sensory input from the meninges and the periorbital (around the eyes) tissues. However, pain signals originating from meningeal nociceptors may be misinterpreted by the central neurons as originating in the periorbital tissue. Referred pain around the forehead and eyes, common of a migraine attack, may result from this misinterpretation. When a migraine attack begins, blood vessels in the meninges dilate due to inflammation [see Figure 2], which activates and sensitizes meningeal nociceptors after 5-20 minutes. Sensitization causes meningeal nociceptors to send increasingly frequent and stronger

signals to the central trigeminal nerve nucleus, thus triggering a throbbing pain in response to the pulsation of the meninges[5] [see Figure 3]. The central neurons of the trigeminal nerve become sensitized (central sensitization), occurring between 20 minutes and 2 hours from the onset of a migraine. Cutaneous allodynia is experienced as these neurons begin to respond to innocuous stimuli such as touch and pressure, primarily around the face, scalp, and arms[6]. At this point, slight stimulation of these areas may induce a pain response.

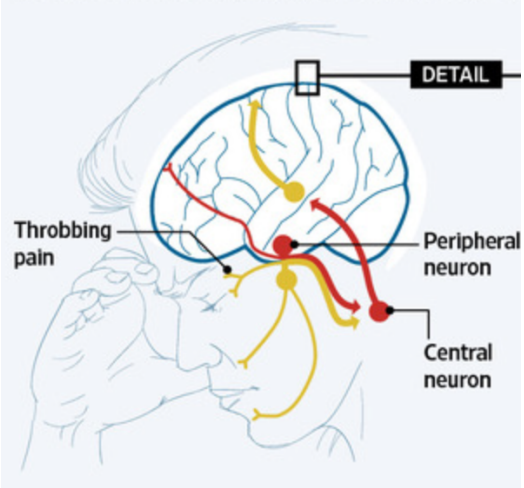

Figure 3: The trigeminal nerve caudalis (TNC) is sensitized during a migraine episode. Throbbing pain is experienced at the periorbital area due to repetitive meningeal nociceptor signalling.

Cutaneous Allodynia in Migraineurs

According to the Berstein et al., investigation in 2000, cutaneous allodynia has been found to occur in 79% of 42 migraine subjects tested[6]. Subjects in this study were initially tested during the interictal phase (phase between migraines without symptoms) using Qualitative Sensory Testing (QST) to determine their pain thresholds in three modalities: cold, heat, and pressure (mechanical) stimuli. These pain thresholds were then reevaluated 3 to 4 hours in the each subject's subsequent migraine attack[6]. If their pain thresholds decreased by one standard deviation from the "baseline threshold" (determined during initial phase of testing) in one or more modalities, that subject was deemed as presenting with cutaneous allodynia[6]. QST was conducted on the bilateral periorbital skin of each subject, as well as bilaterally on the forearms. Heightened sensitivity often occurred during the migraine phase of testing ipsilaterally (same side) to the migraine pain[6].

Findings of cutaneous allodynia in the periorbital area alone or in conjunction with cutaneous allodynia present in the forearm area, ipsilateral to the migraine pain, can also be linked to the process of central sensitization. Berstein et al. speculated that the presence of cutaneous allodynia at the forearm area may be due to additional sensitization of the third-order trigeminovascular neurons[6]. These peripheral nociceptors become upregulated, sending more frequent and stronger signals to the trigeminal nerve caudalis (TNC) as a result of external stimulation[5].

Hypothesis and Proposal

I hypothesize that due to the peripheral sensitization of nociceptors associated with central sensitization of the trigeminal nucleus caudalis (TNC) and migraine, leading to cutaneous allodynia, would cause fine motor skill and dexterity to be diminished during the migraine phase of a migraine subject.

I propose to investigate the association of central sensitization, which results in cutaneous allodynia in migraine subjects, and fine motor function and dexterity during the migraine attack period. I intend to further build upon the foundational basis provided by Dodick and Silberstein, and the investigation into cutaneous allodynia and migraines by Berstein et al. By extending QST to assess pain thresholds at the bilateral periorbital area, bilateral forearm, and the bilateral dorsal area of the hands, it allows for the evaluation of fine motor function and dexterity. Fine motor skills utilize the coordination of small muscles in the hands and fingers with muscles in the forearms and movements of the eyes[7]. This assessment would be conducted within two phases, as mirroring the Berstein et al. study, and would progress as follows:

Methodology and Analysis:

Initial Phase of Testing

In congruence with the study presented by Berstein et al., I will conduct my study in two phases. The ideal goal would be to have 80 healthy subjects, from 18 to 65 years of age, that meet the classification for recurrent migraine headache outlined by the Headache Classification Committee. The evaluation would involve first determining the status of the prospective subjects' headaches and whether they fit the criteria for migraine — i.e. one-sided, throbbing pain, lasting 4 to 72 hours, with associated symptoms like photophobia, phonophobia, nausea, vomiting, fatigue, etc[2].

After subjects are selected, the first phase of testing will involve QST during the interictal period, while the migraine subjects are not currently experiencing a migraine, any prodrome symptoms, or any symptoms associated with migraine[8]. Therefore, the initial phase will take place at least 5 days after each subject's previous migraine attack.

Initial QST is needed to determine the pain thresholds of each subject during the interictal period at each of the six bodily locations outlined earlier (each side of the periorbital area, each forearm, each dorsal hand area). For every, individual location, three modalities of QST will be assessed in order to determine pain thresholds: cold, heat, and pressure (mechanical). One's initial pain threshold to cold and heat is concluded by first using a 30mm^2 thermode (Thermal Sensory Analyzer 2001)[6]. Skin that is being tested is first adapted to a specified temperature (32°C) for 5 minutes, then cooled or warmed at a constant rate (1°C/sec) until the subject experiences a painful sensation[6]. For pressure, a set of 20 calibrated von Frey hairs (VFH), each monofilament having an increasing amount of force (g) is exerted on the subject's skin[6]. "Each monofilament is applied to the skin three times for 2 seconds, and the smallest VFH number capable of inducing pain in two of the three trials [is] considered a threshold"[6].

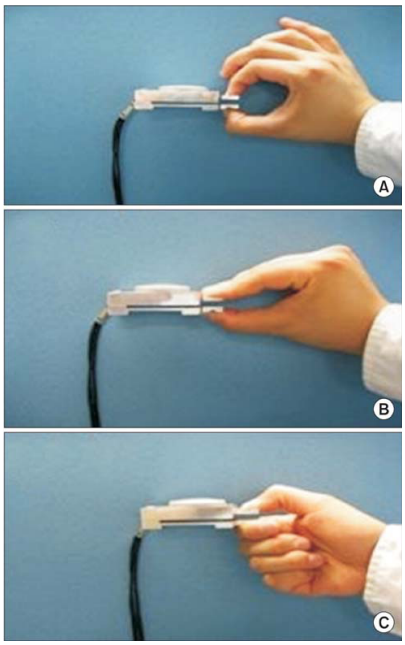

Figure 4: (A) The tip (pulp) pinch. (B) The palmar pinch. (C) The lateral pinch. Each shown being measured by a hydraulic pinch gauge (kg).

After pain baseline thresholds are determined during the initial phase, fine motor skills and dexterity is assessed for each subject. To evaluate one's fine motor function, various grip strength and dexterity examinations will be conducted. First, each subjects' hand grip strength (utilizing all five digits) will be measured by quantifying the amount of static force the hand can exert on a calibrated, hydraulic dynamometer, measured in kilograms[9]. This assessment will be carried out with subjects seated, arms at their sides, elbows in a 90 degree angle, and with a neutral wrist position[8]. Similar to the pain threshold assessment, three trials will be conducted to calculate a mean force (kg) and will be conducted for each hand. In additional to hand grip strength, the force of three pinch grips will be assessed: the tip (pulp) pinch, the palmar pinch, and the lateral pinch [see Figure 4]. Each will be assessed for both hands, using hydraulic pinch gauges, and measured in kilograms. The mean of three trials will be taken for each assessment.

I will also be conducting a further examination of the migraine subjects' dexterity by administering the Grooved Peg Board Test[7]. Each peg has a ridge on one side and therefore "must be oriented correctly to fit into a hole on the pegboard"[7]. The necessity for correct orientation requires visual attention to coordinate thumb and index finger manipulation of each peg. Therefore, the Grooved Pegboard Test, which measures how quickly (seconds) a subject can orient each peg into the holes on the pegboard, has proven to be a reliable and valid method of measuring dexterity in adult populations[7].

Secondary Phase of Testing and Analysis

Migraine subjects assessed during the initial phase of testing will be asked to return 3 to 4 hours into their subsequent migraine attack, of moderate to severe intensity. At this stage of the experiment, pain thresholds will be reevaluated using QST at each of the six locations outlined previously[6]. Hand grip, tip (pulp) pinch, palmar pinch, and lateral pinch force will be administered again using the same methodology as in the initial phase of testing as well. Finally, the Grooved Pegboard Test will be administered once more during this stage.

At this point, we will be determining whether the pain thresholds of each subject have decreased by a margin of one standard deviation or more. According to Berstein et al., "if, during a migraine attack of a given patient, the pain threshold of one or more modalities (heat, cold, pressure), measured on the ipsilateral head alone or on the ipsilateral head and one or more of the other three skin locations, was reduced by 1 or more standard deviations of the respective baseline control threshold… the presence of cutaneous allodynia was inferred"[6]. For subjects that do not experience a decrease of baseline pain threshold, subject was considered non-allodynic[6].

Concerning the whole hand grip assessment, a significant decrease in performance will be inferred if the subject's exerted force (kg) lowers by 1 or more standard deviation from the mean recorded in the initial phases of testing[9]. This standard issue of measurement will be applied for the following tip (pulp) pinch, palmar pinch, and lateral pinch evaluation. If a subject shows sign of declined performance in 2 or more of the 3 pinch assessments, it would be considered statistically significant for our study concerning pinch

grip force exertion. A decrease in performance on the Grooved Pegboard Test would also be determined by a decrease in 1 or more standard deviations (seconds) from the mean previously calculated in the initial phase of testing[7].

Predicted Results

As per the study conducted by Berstein et al. in 2000, I predict that around 70% to 80% of the migraine subjects that return for the secondary phase of testing will meet the outlined criteria for cutaneous allodynia. Differences between allodynic subjects and non-allodynic subjects may be due to the age of the subjects or the number of years they have experienced migraine headaches[6].

I predict that migraine subjects that experience cutaneous allodynia, not only on the ipsilateral periorbital area, but also in the ipsilateral forearm area or dorsal harm area, will causes these subjects to have decreased performance in grip/pinch strength and dexterity demonstrated in the Grooved Pegboard Test[6,7,9].

Limitations and Discussion

Not all subjects selected for the initial phase of testing may return to the secondary phase of testing due to the severity of their experienced migraine. As indicated by the Berstein et al. study, 44 out of 60 (approximately 74%) subjects returned during a migraine attack.

Because this experiment primarily deals with dexterity performance in relation to pain thresholds and cutaneous allodynia, subjects participating within the experiment may not be allowed to take any pain medication or triptan medication for their migraine episodes for the duration of the experiment. Also due to the nature of this proposed study, each phase of testing would have to be staggered to accommodate the timing of the subjects' migraine attacks.

Statistical measures concerning age, age at onset of migraines, and frequency of migraines would be gathered for each subject in order to compile demographic data for each sub-group of the study. Subjects

that do not exhibit cutaneous allodynia (according to the criteria previously outlined) in any of the 6 locations and do not exhibit diminished performance on grip/pinch strength or dexterity task would be considered unaffected, for the purpose of this study, in regard to the process of central sensitization. Yet, non-allodynic subjects that *do* exhibit decreased task performance may be attributed to transformed sensory integration or altered visual processing. This result would not be highly expected, but these subjects could be experiencing decreased dexterity and grip/pinch strength due to a specific presentation of central sensitization in which the subject experiences photophobia yet no other forms of hypersensitivity such as allodynia[5]. Such a presentation would result in altered processing of visual input and therefore altered multi-sensory integration, potentially making coordination tasks more difficult[10].

If subjects that exhibit cutaneous allodynia on the ipsilateral head alone also exhibit decreased performance on grip/pinch strength and dexterity tasks, you could argue that these results may be related to the process of *central* sensitization occurring during the subjects' migraine attack. Again, due to altered processing of multi-sensory integration in migraineurs, subjects that exhibit ipsilateral periorbital allodynia may be experiencing impaired coordination of visual input and small muscle movements[9,10]. This may be the result of the intensity of the migraine pain being associated with greater aversion to visual stimulation and light. In other words, greater central sensitization in the TNC is identified with greater trigeminal nerve pain (referred migraine pain in the periorbital area), which may lead to altered processing of visual input and cutaneous allodynia at the forehead and eye area[10]. These features combined may lead to decreased performance on dexterity tasks.

If subjects exhibit cutaneous allodynia on the ipsilateral head and one or more of the other two locations (forearm and hands) while also exhibiting decreased task performance, it may be attributed to peripheral sensitization. Now, peripheral sensitization is a result of central sensitization, as stated previously[5]. Therefore, hypersensitivity to touch in the arms and hands would be associated with decreased grip strength and dexterity due to up-regulation of peripheral nociceptors in the process of central and peripheral sensitization. Stimulation of the nociceptors in the arms and hands 3 to 4 hours into a moderate or severe migraine attack would result in repeated and progressive pain signals being sent to the brain[5].

Hence, grip, pinch, and dexterity tasks may be uncomfortable and more difficult to perform during a moderate to severe migraine episode.

Conclusion

Understanding central sensitization and its role in migraine episodes is essential for improving the cognition of chronic pain and migraine pathology. Furthermore, investigation into hypersensitivity to touch and pressure, especially at remote sites from the migraine pain, is imperative for expanding our recognition of the effects of central and peripheral sensitization and its effect on motor functioning.

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