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Application of auditory stimuli with movement cue in Ecuadorian patients with severe and acute left-sided neglect, 2020.

.

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Application of auditory stimuli with movement cue in Ecuadorian patients with severe and acute left-sided neglect, 2020.

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RESUMEN

La negligencia hemiespacial es un síndrome neurológico profundamente incapacitante, que se produce debido a una lesión unilateral en el lóbulo parietal, y que afecta a la habilidad de prestar atención al lado contralesional del espacio. Este déficit, a su vez, causa muchas complicaciones para ejecutar actividades de la vida diaria y representa un enorme desafío para los pacientes que se ven afectados por este. Por esa razón, el desarrollo de nuevos tipos de herramientas y estrategias de rehabilitación es de suma importancia para contribuir a la mejora de los estilos de vida de los pacientes con un diagnóstico de negligencia hemiespacial. Así pues, tomando esto como referencia, en la presente propuesta de investigación se busca diseñar una metodología para poner a prueba y llevar a cabo una terapia basada en estímulos auditivos, en pacientes diagnosticados con negligencia hemiespacial severa y aguda. Se reclutarán aproximadamente 24 pacientes afectados por este síndrome, quienes todavía estarán en la unidad de accidentes cerebrovasculares, y se los colocará o bien en el grupo de intervención (12) o en el grupo de control (12). De este modo, se espera que los síntomas de negligencia de los participantes se reduzcan después de este tratamiento en comparación con la condición del grupo de control. Esto se demostrará posteriormente mediante un análisis cuantitativo del nivel de rendimiento de los participantes en diferentes pruebas diagnósticas.

Palabras clave: Negligencia Hemiespacial, terapia basada en estímulos auditivos, rehabilitación, accidente cerebrovascular, fase temprana-aguda.

ABSTRACT

Hemispatial neglect is a deeply disabling neurological syndrome, which occurs due to a unilateral injury of the parietal lobe and affects the ability to pay attention to the contralesional side of the space. This deficit, in turn, causes many complications in carrying out activities of daily living and represents a huge challenge for those affected by it. For that reason, the development of new types of rehabilitation tools and strategies is of utmost importance to contribute to the improvement of neglect patient's lifestyles. Thus, taking that as a reference, the current research proposal will seek to design a methodology to test and put into practice an auditory-based therapy in acute and severe neglect patients. Approximately 24 patients affected by this syndrome and still in the stroke unit, will be recruited and placed in either the intervention group (12) or the control group (12). On that basis, it is expected that the participants' neglect symptoms will be reduced after this treatment in comparison to the control condition. This will be later examined through a quantitative analysis of the level of performance of participants in different diagnostic tests.

Key words: Hemispatial neglect, auditory-based therapy, rehabilitation, stroke, early-acute stage.

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INTRODUCTION:

Description of the disorder:

Hemispatial neglect is a common and characteristic outcome after a unilateral hemispheric lesion, manifested as a failure of awareness towards the contralesional side of the affected person's space (Corbetta, 2014), and frequently taking place at the ventral-dorsal stream of the posterior parietal lobule of the brain (Rizzolatti & Matelli, 2003). This neurological syndrome appears predominantly after a stroke and less commonly due to other conditions such as neurodegenerative diseases, neoplasia, and trauma (Li & Malhotra, 2015). Other brain areas have also been linked to neglect symptoms, these being the superior temporal gyrus (STG), inferior frontal gyrus (IFG), middle frontal gyrus (MFG) and the anterior insula (Corbetta & Shulman, 2011). Similarly, further studies have shown that white matter and subcortical nuclei injuries could also lead to the manifestation of neglect (Corbetta & Shulman, 2011). It is also known that affectations to the right hemisphere are responsible for more serious and persistent symptoms, possibly because of the major role that the right hemisphere exerts on the brains' attentional processes (Li & Malhotra, 2015). Thus, left-sided neglect, after right-hemispheric lesion, appears as a much more common and challenging phenomenon.

In terms of the symptomatology, this condition can be recognized because patients fail to attend and process sensory stimuli coming from the neglected side of the room; exhibiting a behavioral bias directed to the ipsilesional side, and a lack of exploration of mental representations of space (Rode et al., 2017). This reduced awareness occurs exclusively due to an attentional impairment, not due to a sensory loss; and it can be directed towards the extrapersonal space of the patient, causing allocentric symptoms; as well as towards its personal space, resulting in egocentric symptoms, asomatognosia or somatoparaphrenia (Parton et al., 2004). Both aforementioned types of symptoms could co-occur, and its

appearance depends on each individual and on the lesion type. Likewise, a typical neglect patient will show a deviated body and head posture directed to the non-neglected side (Rode et al., 2017), in addition to an ipsilesional oriented gaze (Li & Malhotra, 2015). Some neglect patients may display directional hypokinesia as part of their symptomatology, causing in consequence, a reduced bodily movement for actions guided in the direction of the contralesional side of the space (Buxbaum et al., 2004)

Regarding auditory neglect, symptoms of this syndrome variation are characterized by a deficiency in responding and localizing single sounds coming from the contralesional side of the space. One of the most common manifestations of this neglect subtype is alloacusis, which is the act of behaving as if the auditory stimuli coming from the contralesional side of the space would come from the ipsilesional one (Pavani et al., 2003); in other words, this is a deficit characterized as a diminished ability in recognizing where do the sounds come from in combination with an ipsilesional perceptive bias. Another identified type of auditory neglect manifestation is called extinction, which is basically ignoring and omitting the sounds coming from the contralesional side of the space when an ipsilesional stimulus is simultaneously presented (Clarke & Thiran, 2004). Both aforementioned auditory insufficiencies are triggered by a specific injury to certain auditory streams. Thus, “auditory extinction” is known to be the outcome of a lesion in the ventral stream, implicated in the identification of sounds; and the “auditory spatial localization deficit” (alloacusis), is apparently caused due to an impairment to the dorsal stream engaged in sound localization (Rode et al., 2017).

Moreover, neglect can also be exhibited through imagery and memory tasks. This type of neglect manifestation is called representational neglect and it describes the act of ignoring stimuli from the contralesional side of the space when the neglect patient is imagining or remembering different types of visual and spatial stimuli, i.e. not necessarily only when the affected person is perceiving and in contact with these stimuli in real-time (Bisiach & Luzzatti, 1978). The inability to recall contralesional stimuli involves losing skills in

constructing a frame of reference to the environment, resulting in a spatial orientation impairment (Ortigue et al., 2001). This means that the abilities of mentally reconstructing images, as well as the skill of orienting oneself around the space, can also be affected by the characteristic lack of awareness from this symptom.

This all being said, it can be stated that hemispatial neglect is both a multimodal and a heterogeneous syndrome, that can be expressed in a visual, auditory, somatosensory, representational, and in a motor way. However, symptoms can go beyond the above-mentioned manifestations to simultaneously provoke several difficulties in a wide array of activities of daily living (ADL), such as shaving, putting on makeup, eating, reading, walking, etc… (Drive, 2001). Turning, in consequence, hemispatial neglect into a highly disabling disorder which appear to predict a poorer outcome after stroke and can affect different domains of a person's life including their ability to be independent to even causing shoulder-hand problems; therefore, a large number of neglect patients will need constant supervision and rehabilitation (Wee & Hopman, 2008).

Basic concepts of attention:

Attention has been studied under the scope of different perspectives, and for that reason, it has become a construct made up of several dimensions. However, despite the considerable amount of information available about this topic, this cognitive function can be briefly defined as the "ability to focus on specific stimuli or locations" (Goldstein, 2015). However, this definition explores only the tip of the iceberg, as attention also enables us to actively process small parts of the information that hits our senses, that is available to our memory, and that is the subject of many thought processes (Jäncke, 2013). Hence, attention comprises different elements and mechanisms working with each other.

The field of neuropsychology established a specific taxonomy in order to be able to classify these attentional mechanisms. At a cortical activation level, attention has been divided into different components or cortical activation states, this being: arousal, alertness,

and vigilance. In the cognitive neuroscience area, the term vigilance refers to the ability to sustain attention; arousal refers to the state of being awake or conscious, and alertness is a term that overlaps with arousal, but that additionally includes cognitive processing (Oken et al., 2006). Further divisions of attention include selective attention, which refers to "the differential processing of simultaneous sources of information"(Johnston & Dark, 1986), in other words, the ability to direct our awareness to relevant stimuli while ignoring irrelevant information. Divided attention is another fundamental element of attention, which denotes the capacity of paying attention to more than one stimulus at the same time (Goldstein, 2015), and last but not least executive attention which refers to "the ability to maintain attention on critical tasks and to avoid having attention captured by either internally generated thoughts or externally generated events that lead to thoughts that compete with performance on the task" (Engle, 2018). This type of attention is deeply connected with control processes such as planning, problem-solving and inhibition of behavior; furthermore, it is characterized as being one of the principal components of working memory and the mechanism that works as a provision of conscious will (Jäncke, 2013).

Visuospatial attention is another crucial dimension of awareness. It is known that by certain circumstances attention seems to be evenly distributed across space, englobing therefore the whole picture (Eriksen & St. James, 1986). However, there are some other circumstances in which our attention gets focalized into specific stimuli of our visual field; literature about this topic has stated two important concepts that have tried to explain how this branch of selective attention works. One of these hypotheses is the well-known spotlight metaphor proposed by Posner et al. (1980). This theory compared the ability to fixate the gaze in a specific target while excluding information from other regions of the space, with the light emitted by a spotlight when it illuminates and selects only one area of the stage while shadowing the rest of it (Cave & Bichot, 1999). The second important theory that seeks to explain this dimension of attention is the zoom lens model by Eriksen and James. This theory

suggests that unlike a spotlight that only focuses on a single target, visuospatial attention can be focused on two or more stimuli that are relevant at the same time. Thus, it was proposed that our attention works like a camera lens that can be adjusted to capture and process more than one stimulus or to capture a specific and single detail depending on the need of the observer (Müller et al., 2003).

To perform visual searches and make use of visuospatial attention eyes are major tools for directing awareness. When attention is directed by means of eye movement this process is called overt attention, and when the attention is shifted while eyes are kept stationary, this mechanism is called covert attention (Goldstein, 2015). Neglect patients normally only look at the side on which the lesion is located (ipsilesional side); therefore, when right-sided neglect patients have to search the space in front of them for certain objects, their gaze movement is clearly shifted to the right (Jäncke, 2013).

Selective attention has also been proved to be greatly impaired in patients suffering from neglect syndrome. This has been attested through visual discrimination tasks in which neglect patients failed to perceive and recognize the target stimuli when distractors similar in appearance where presented. These results suggest that neglect patients might have an inability to focus on critical and specific stimuli when the demands of selective attention are elevated. This is believed to happen due to reduced attentional capacity in high workload tasks; namely, an impairment in the top-down processing of information (Rapcsak et al., 1989).

Models of attention related to neglect

Since the discovery of neglect, multiple researchers have sought an explanation to understand this syndrome better. Thus, attention itself has been extensively explored over the years, and in consequence, some models have been proposed in order to comprehend more deeply how this brain function works and how it can be affected by parietal lesion preceding neglect. One of these hypotheses is the well-known “hypothesis of attention” proposed by

Posner et al, “the representational hypothesis”, “the transformational hypothesis” and the Marcel Kinsbourne model.

Hypothesis of attention. This hypothesis assumes that in terms of spatial attention, there are different types of subprocesses that collaborate and interact with each other in order to compound the human ability to attend. Thus, in the case of neglect, this hypothesis suggests that for this syndrome to appear, at least one of these subprocesses must be impaired. According to this theory, three core subprocesses are relevant regarding covert attention, namely: Attentional disengagement, shift of attention, and focus of attention. Research on this topic suggested that neglect in parietal lesions could be either attributed to a damage to the attentional disengagement subsystem, which allows attention to be shifted to new targets and also help to avoid fixation towards a single target or to a preponderance and persistence of automatic orientation of attention in the direction of the damage (Keller et al., 2003). However, whether this hypothesis corresponds to reality still remains in discussion.

Representational hypothesis. In this hypothesis, the neglect is not explained by insufficient processing of sensory stimuli. Rather, an incorrect mental representation of the outside world is assumed. In other words, neglect is a disturbance of the imaginary, mental spatial representation of the environment. The conscious perception of stimuli is preceded by a mental representation of sensory impressions. If this is missing, neglect can be the result. The aforementioned limitation of the ability to imagine one side of the space when a patient has been diagnosed with neglect has also been explained taking into account this hypothesis (Keller et al., 2003).

Transformation Hypothesis. According to the transformation hypothesis, neglect is based on a disturbance of the neuronal egocentric space coordinate system. Afferent signals from various peripherical sensory organs are transformed into an egocentric, body-related reference system necessary for action and orientation in space; the neglect is based on an impairment of this transformation, which shifts the entire egocentric reference system to the

side of the impairment. This is supported by the fact that experimental manipulation of the perceptions by cue stimuli or a changed orientation of the trunk can partially compensate for the neglect symptoms. These methods influence the afferent processing of spatial information in the parietal cortex and thereby reduce the severity of symptoms (Keller et al., 2003).

Marcel Kinsbourne model. According to Kinsbourne, each of our two halves of the brain generates an attentional shift to the opposite side of the outside world. At the same time, the activity of the other brain hemisphere is inhibited. Due to this mutual inhibition, both brain hemispheres are in an activity balance. When a lesion occurs in one hemisphere, the inhibitory influence of the undamaged hemisphere on the damaged one increases. Conversely, the influence of the damaged hemisphere on the healthy one decreases. Consequently, in the case of a lesion of the right hemisphere, the inhibitory influence of the damaged hemisphere on the left one decreases. This results in a stronger inflow of the left hemisphere; in other words, in a left-hemisphere bias, and in attention to be increasingly directed to the right (Jäncke, 2013).

Epidemiology

Hemispatial neglect occurs very often in patients who have suffered a stroke and that have had their parietal area of the brain compromised. According to previous research on this topic, this syndrome has been reported to occur in an 82% in right-hemisphere lesion patients and 65% in left-hemisphere lesion, but the incidence varies from 33% to 65% in right hemisphere patients and 0% to 24% in left hemisphere patients (Stone et al., 1993). Other studies have indicated a lower incidence of 48% in right hemisphere patients, but evidence of a greater probability of motor impairment, sensory dysfunction, visual extinction, basic attention deficit, and anosognosia in comparison to stroke patients without neglect (Buxbaum et al., 2004). Additional research found that a total of 43.5% of the tested patients showed some degree of neglect on at least one of the measures used for diagnosis (Beis et al., 2004). This data suggests that the number of patients showing neglect symptomatology after stroke

comprises a significant percentage. However, an exact number of affected patients have not been estimated since this is a syndrome that manifests itself in such different ways, and therefore, it is complicated to calculate the exact number of people who suffer from it.

In terms of the gender differences of this syndrome, an interesting study explored this topic comparing the performance of a large sample of both men and women who suffered from an ischemic stroke in a variety of neuropsychological tests that aimed to measure neglect severity and visuospatial abilities. The results of this assessment showed that the consequences of a unilateral parietal lobe stroke on attentional abilities appear to be analogous between genders, and that both neglect rate of occurrence and its severity are also similar between men and women (Kleinman et al., 2008). On the other hand, in terms of the ages at which this syndrome normally occurs, it can be inferred in line with all the above-mentioned literature, that a stroke responsible for neglect symptoms could appear with more likelihood between 40-80 years old. However, it is known that in general, the stroke risk between those ages is higher for men than for women and it seems that being a woman is a protective factor until the ages between 75 - 85 years, for after that age this protection appears to be reversed. After the age of 79 years, no gender difference could be found between different types of stroke patients (Sealy-Jefferson et al., 2012).

Neglect Severity assessment

Hemispatial neglect divides itself not only for its type, but it can also be classified for its severity. The severity of neglect is interconnected with the damage magnitude of stroke and the level of disability caused by it. The most immediate way to recognize neglect symptoms is by paying attention to the patient's head and eyes, which might display an ipsilesional bias, and may cause the patient to respond to the biased side even when the stimulus does not come from that direction. Further signs of neglect are ignoring food on one side of the space and bumping into furniture, doors frames and other obstacles (Adair & Barrett, 2008).

However, one way to detect how disabling this syndrome for a person is, is by the usage of neuropsychological assessment. The two most common tests for measuring neglect severity are the cancellation task and the line bisection task tools (Molenberghs & Sale, 2011). The score of these tests serves to identify how severe the neglect symptoms are and to classify patients in either the acute or in the non-acute phase. In other words, the more omissions and the larger the distance from the true center of the line is, the more severe and disabling the symptoms are.

For the purposes of this study, only patients in the acute phase will be evaluated and treated. The main reason for this decision is that in Ecuador there are not special rehabilitation units for neglect/stroke patients to receive treatment and, therefore, no facilities to provide them with therapy once they have left the hospital, namely once they have been medically stabilized and no longer in an acute phase. Furthermore, a second reason consists of the existing evidence that points out and suggests that the earlier any targeted treatment is initiated, the better the outcomes for stroke patients are, and the shorter the time of hospitalization is (Maulden et al., 2005).

The Turgut et al. study, corroborates that statement by having shown through their research that the participants who were part of the intervention group and that received adapting cueing therapy for neglect earlier, displayed better rates of recovery and fewer symptoms of neglect in different testing instruments used to assess this syndrome severity and extent of impairment, in comparison to the control group that received the therapy about one and a half months after (2018). In other words, although both groups developed improvement derived from the therapy, the intervention group that received the therapy before the control group, showed a more significant and substantial improvement; suggesting that working with patients in the acute phase of neglect could benefit their recovery levels in a greater way.

Situation in Ecuador

As mentioned before, facilities to provide neglect patients with rehabilitation in Ecuador are nonexistent, as well as studies describing the development of this syndrome in the country. However, what can be described is the scenario of patients affected by stroke and the impact of this disease in Ecuadorian patients; however, in general terms this topic has been poorly explored in Ecuador. According to the available literature, between 1991 and 2015 cerebrovascular disease was ranked as the leading cause of death in Ecuador, surpassing Influenza and Pneumonia, Diabetes, coronary-vascular diseases and even traffic accidents (Moreno-Zambrano et al., 2016). Moreover, another study that explored stroke patients who were assisted at the biggest public hospital in Guayaquil, Ecuador confirms the assertion that Hispanics might be at higher risk of suffering from cerebrovascular disease and concludes that this situation could be explained through different factors such as genetics, the environment, and dietary habits. Likewise, this study reported that in contrast to white stroke victims who have shown a higher prevalence of putaminal hemorrhages, participants in this study shown predominantly lobar hemorrhages that could be explained through possible self-medication practices and alcohol abuse (Del Brutto et al., 1993).

As can be seen, the situation regarding stroke in Ecuador is not very encouraging, as it seems to be highly prevalent in Ecuadorian territory. Furthermore, problems in the country in terms of public health such as the shortage of specialist doctors, mainly due to the lack of postgraduate studies, the lack of protocols and the population's lack of knowledge about the disease, as well as the conflict over treatment adherence (Moreno-Zambrano et al., 2016), may also keep increasing the likelihood of Ecuadorian population to suffer a stroke.

Treatment

Some of the most commonly used treatments to assist neglect patients consist of top-down and bottom-up procedures such as visual scanning, optokinetic stimulation, neck-muscle vibration, caloric and galvanic vestibular stimulation (Kerkhoff & Schenk, 2012), prism adaptation (Scheffels et al., 2019), transcranial direct current stimulation (tDCS)

(Turgut, Miranda, et al., 2018), adaptive visual cueing (Turgut, Möller, et al., 2018) and auditive cueing (Schenke et al., 2020).

Visual scanning. is one of the most common treatments used to ameliorate neglect syndrome symptoms. This method was firstly developed in 1977 and then later further explored by Pizzamiglio et al. in the ‘90s (Luukkainen-Markkula et al., 2009). The principal aim of this therapy is to encourage neglect patients to improve their visual scanning skills and to explore and pay attention to stimuli coming from the contralesional side of the space. In order to do so, operant conditioning is carried out through the reinforcement of correct scanning movements in different visual scanning tasks. Likewise, at the beginning of the therapy, compensatory strategies are often used, and different types of cues and feedback are consistently delivered. However, as the sessions progress, it is recommended to increase the difficulty of the tasks and to reduce the presence of cues and feedback. This therapy was originally conceived to last at least 40 h during an 8 weeks period, and has proven to be quite effective (van Kessel et al., 2013).

Optokinetic stimulation. is a technique based on visual motion tasks, involving a screen with dynamic background patterns moving towards the neglected hemifield of the space and then back towards the contralesional side (Keller, 2016). The idea behind this therapy is to evoke the perceptive impression that the body rotates to the opposite side of the direction originally presented on the screen. In this way, the body naturally compensates this perceived rotation by reorienting it to back to the original direction presented (Kerkhoff & Schenk, 2012). For instance, a patient suffering from left-sided neglect will have to visually follow a moving pattern shifting back and forth from right to left (Keller, 2016), which will ultimately lead to a left reorientation of perception. Results from multiple pieces of research show that this therapy reduces significantly neglect symptoms, exhibiting a two-weeks follow up improvement maintenance (Kerkhoff & Schenk, 2012). Likewise, it has been found that slower-moving background patterns lead to better results and to a larger compensation

phenomenon, compared with faster motions (Keller et al., 2003). It has been therefore possible to corroborate with scientific evidence that this is an effective therapy for treating patients affected by neglect.

Neck muscle vibration. is a method in which a perceptive illusion is created through vibrations applied over the neck muscles. Our body normally understands that we are looking straight when both neck muscles are stretched equally (Kerkhoff & Schenk, 2012). Therefore, the effect is based on the fact that the vibration stimulates specific stretch receptors in the muscles and tendons of the neck, which leads to an apparent rotation of the head (Keller, 2016). In this way, when vibrations are applied to the left side of the neck, this stimulation will produce the impression that the head is rotated to the right and on some occasions that the trunk is rotated to the left. This technique has been proved to reduce neglect perceptual bias and hence, neglect symptoms (Kerkhoff & Schenk, 2012). Normally such therapy needs to be performed at least 30 to 40 minutes per session, depending on the patient's condition. Additionally, a total of at least 15 therapy sessions are necessary to achieve a lasting effect.

Caloric vestibular. stimulation consists of the irrigation of warm and Ice-cold water on the external auditory canal (Bottini et al., 2013), as a mean of producing a vestibulo-ocular reflex in patients, due to the change of temperature. Ice-cold water produces a slow phase of nystagmus (involuntary eyeball movements) towards the stimulated ear, and warm water an opposite effect, which means, a quicker phase of nystagmus (Rubens, 1985). This effect, in turn, leads to sensations of virtual body rotations, which consequently reduces for about 10 to 15 minutes the characteristically hemispatial neglect symptomatology, as well as the imbalance of the body posture, and the unawareness of hemiplegia (Kerkhoff & Schenk, 2012). Galvanic vestibular stimulation, on the other side, uses electrodes placed above the mastoids, to stimulate through small intensities of current the vestibular system. Depending on the polarity of the electrodes, a primary right hemispheric stimulation is achieved with right cathodic stimulation and a bilateral activation with left cathodic stimulation (Keller,

2016). The literature has shown that the results of GVS are very similar to the ones achieved by CVS, however, to what extent a lasting improvement can be achieved by repeated application of such training remains still open.

Prismatic adaptation. is a bottom-up technique that consists of the performance of a visuomotor task (pointing to an object) in combination with the usage of prism goggles that produce a visual shift effect. This effect generates, at the same time, a motor error in the direction in which the movement (pointing) is directed (Adair & Barrett, 2008). After a few attempts with the motor task, a visual adaptation is produced, and the hand position is ultimately realigned with the target, which causes the directional error to disappear. After the adaptation occurs, the goggles are removed, and a pointing error directed to the other side of the space is produced. Eventually, this aftereffect will also disappear. This procedure induces approximately 1 hour of improvement on multiple neglect deficits, however, a prolonged exposure to this treatment can reach an improvement in the symptoms of neglect for up to a month (Corbetta, 2014).

Transcranial direct current stimulation (tDCS). is a non-invasive treatment that is based on the usage of electrodes that are designed to induce a polarity-specific activity modification in the human brain (Sunwoo et al., 2013). The procedure consists on positioning a cathode (positive electrode) on the affected hemisphere and an anode (negative electrode) on the healthy hemisphere. The current flow is transmitted from the positive pole to the negative one; causing an anodal excitation and a cathodal inhibition. This treatment has a duration of maximum 20 minutes. Applied to the parietal lobes, this strategy has proven to reduce neglect symptoms, especially the egocentric domain of neglect (Turgut, Miranda, et al., 2018).

Adaptive visual cueing. is an approach that seeks for a more independent orientation on the patient's behalf, for the implementation of tasks with a more direct connection to activities of daily living, and for a personalized treatment protocol depending on neglect's

symptoms severity. Adaptive visual cueing therapy is therefore, based on different types of cues that are used to direct the patient's attention towards the neglected side of the space, and to enhance visual exploratory behavior. Turgut, Möller, et al., designed a methodology in which both exogenous and endogenous cues where used to stimulate patients. Cues consisted on novel visual stimuli as well as on verbal instructions that where provided while patients were executing a reading task. During the therapy sessions both endogenous and exogenous cues, as well as the reading task, were firstly adjusted to the patient's necessities, and afterwards, to their rate of adaptation and improvement. Thus, cues were reduced when patients were showing a better performance. This research yielded significant results showing improvement in both activities of daily living and in neglect symptoms (2018).

Auditive cueing. is a relatively new, low cost, non-invasive, and under-explored technique that uses music or auditory stimuli such as audiobooks, equipped with a cueing effect, to induce a perceived drift movement from the ipsilesional side towards the contralesional side of the space. The tracks and the cueing effect are displayed through headphones and are personalized depending on patient's music preferences and depending on their processing speed. This drift acts as a dynamic cue which aims to draw the patient's attention towards their neglected side. As part of the therapy, patients are instructed to mentally follow the sounds provided, and to identify from which side of the headphones do they come from. This procedure should take around 30 minutes, and depending on the progress of the patients, and the number of times they identify where the sounds are coming from, the speed and duration of the music track or auditory stimulus will be readjusted, increasing the level of difficulty. This approach has proven to be effective in decreasing neglect symptoms after three weeks of therapy and in remaining stable up to three days after the last session. Furthermore, this therapy has a high level of applicability even in patients belonging to an early-acute phase of stroke, making its implementation very promising (Schenke et al., 2020).

Study justification

Giving that neglect prevalence is high among stroke patients (Demeyere & Gillebert, 2019), it is imperative to keep working on finding much more practical and effective strategies in order to improve neglect symptoms. All previous studies were conducted on patients in a post-acute stage several weeks or sometimes months after stroke. However, no results exist if patients could decrease their neglect symptoms already few days after stroke. New methods need to be developed, since in an acute stage mobilization to the wheelchair for table based cognitive training is not possible. Patients with larger lesions are not suitable for stimulation therapy like tDCS due to the strict exclusion criteria (Turgut, Miranda, et al., 2018). Therefore, a new procedure is developed using save auditory stimuli with a movement cue to the neglected side. The use of headphones does not require mobilization into the wheelchair but can be used in bed instead. Furthermore, it can be conducted even when the room is shared with several other patients, which is the usual case in Ecuadorian units.

As stated above, this syndrome affects many areas of daily life functioning, and has, therefore, become for the field of neuropsychology a huge challenge to find rehabilitation methods that can contribute to the long-term improvement of these patients. This study aims to contribute to the mission of improving neglect patients' quality of life, and to the further development of more inclusive and less invasive treatments. Likewise, this research looks forward to validating the empirical transcendence of the auditive-cueing procedure as a potential non-invasive treatment option for treating neglect, providing patients in acute phases of neglect with a treatment that is easy to apply and does not require mobilization or devices that are difficult to bring into the therapeutic space.

METHODS:

This investigation proposal has been reviewed and accepted by the ethics committee of the Universidad San Francisco de Quito. In this way we ensure the safety and well-being of all potential research participants as the primary consideration to get this project started.

Design:

The current research proposal is of a quantitative nature and makes use of an independent group-design. In other words, two groups with different participants — which share the same inclusion criteria— will be compared. The intervention group receives the auditory movement cues, whereas the control group receives the usual therapy on a stroke unit in Ecuador. To be able to perform the blind for the control group, those participants will be given headphones, with music without the characteristic drift of the therapy. In that way, biases within this group will be avoided. The randomization will be done by a third person, who will randomly assign each patient to one of the conditions and give notice to the co-investigator to perform the therapy or just provide music without drift to the patients in the control group.

Participants:

In order to collect the required data for this experiment, 24 neglect patients will be recruited, half of them receiving auditory movement cues. No study was published using auditory movement cues in neglect patients on a stroke unit, therefore a sample size calculation was not performed. However, based on previous rehabilitation studies using visual cues, we have considered that the minimum of 12 participants for each group will be necessary.

Inclusion Criteria	Exclusion Criteria
Patients showing left-sided neglect resulting from a large right hemispheric brain lesion.	Patients showing neglect after left hemispheric brain lesions (aphasia)

Patients should also have a minimum age of 18 years	Patients in minimal responsive state
Capacity of being awake for at least 20 minutes (therapy time)	Patients previously diagnosed with dementia
	Patients which develop hydrocephalus

Table 1: Inclusion and exclusion criteria

Materials:

Music will be played through a tablet via headphones (the version and further descriptions of each of these devices cannot yet be specified, as they have not been purchased). Due to hygienic reasons headphones will be covered with disposable sanitary headset covers (Latex Free), which will be replaced after every session.

Assessment and diagnostic:

The "Line Bisection test" is a standard diagnostic instrument to assess neglect severity. It consists of several lines of different angles and that can also vary in length, located on a sheet of A4-size paper. Participants will be asked to bisect those lines with the unaffected hand, where they think the midpoint of the lines is (Molenberghs & Sale, 2011). An exacerbated deviation either towards the left side or the right side will be an indicator of neglect (Verdon et al., 2010). In the case of this test, the further the division of the line drawn by the patient is from the actual center, the more severe the damage is.

A clinical assessment of body posture will also be executed. In this way, the neuropsychologist will evaluate patients spontaneous head, eye and trunk position as well as the body position after cuing the patient with three questions. A 3-point scale is normally used for spontaneous and cued body posture: normal position= 0, moderate ipsilesional deviation = 1, distinct ipsilesional deviation = 2; (maximum score = 6).

Additionally, an experimental Auditory Test will also be performed. Thus, 10-15 sounds will be presented on the right and/or left side of the headphone. The patient will have

to point to the direction where the tone is perceived. Omissions and errors will be counted. The exact amount of sounds as well as the duration of presentation is still in development.

Finally, a clinical assessment of Spatial Working memory in which the patient will have to allocate two pencils, which were previously shortly presented together and afterwards separated, will also be done.

Primary variables
• Clinical assessment of body posture (with cues/without cues)
• Line Bisection Test
• Secondary variables:
• Experimental Auditory Test
• Clinical assessment of Spatial Working memory

Table 2: Primary variables

Procedure:

Patients will be contacted at the neurology department (Stroke unit) of the Hospital Eugenio Espejo in Quito, Ecuador. The Neurologist in charge is Mr. Dannys Rivero, diagnosing left-sided hemispatial neglect and contacting the principal investigator if no exclusion criteria is present. The patient is contacted by a neuropsychologist/Psychologist, asked for participation and informed about his/her rights (see consent form). The patient is asked to sign the consent form. The Co-investigator is responsible for the randomization and allocates the patient either to control or intervention group.

Neglect severity at Baseline (Pre-condition) will be assessed by a blinded neuropsychologist, using the clinical assessment of body posture (with cues/without cues), the Line Bisection Test and an experimental Auditory test. After Baseline testing is completed, the treatment phase will begin. The Intervention group will receive auditory stimuli (music), moving from the right to the left, which is expected to induce an attentional shift towards the

neglected left side of patient's space. The auditory stimuli will be based on the individual preferences to increase compliance. They will be conducted through tablets connected via Bluetooth to noise-canceling headphones to enable the highest comfort since the sessions are conducted bedside. Auditory stimuli with drift will be conducted daily for a minimum of 20 minutes per session during the whole stay of the patients in the hospital. The control group receives the standard treatment of a stroke unit in Ecuador. Before the patient is discharged from the Stroke unit, a blinded neuropsychologist is assessing the neglect severity (Post-condition) using the same procedure as in Baseline.

Data analysis

The statistical analysis will be conducted using IBM Statistical Package for the social sciences (SPSS). Based on the data distribution and scaling of the variable, independent t-test will be used if parametric criteria are given. In case of parametric violation Mann-Whitney-U test will be used.

DISCUSSION

Based on the auditive cueing research performed by Schenke et al., (2020), it was hypothesized that the participants' neglect symptoms would be reduced after this intervention in comparison to the control condition. The present research proposal sought to validate the usage of auditory stimulation towards the neglected side as a potential rehabilitation method for very severe left-sided neglect patients, and to prove the extent of improvement (or if there is any improvement) in the symptoms of the aforementioned population by using an auditory-based therapy. Likewise, it was contemplated as part of this study to use the level of performance of participants in different diagnostic tests as an indicator of neglect symptoms variability.

Furthermore, this research sought to contribute in the field of Neurorehabilitation which in Ecuador is almost non-existent. On the first hand, patients were going to receive a possible treatment in an early stage without any additional costs. The conduction of auditory stimuli was not going to require mobilization, in order to provide as much comfort as possible, while using auditive stimuli, without annoying cables or large devices. On the other hand, this research can provide important information, to analyze if an improvement in symptoms already is possible in such an early stage. Moreover, since neglect is a syndrome that affect a large number of stroke patients with severe consequences in ADL both for patients and their caregiver, a possible new therapy method could have a significant impact on patient's life and the society. Hence, contributing to the rehabilitation process of patients affected by hemispatial neglect, exploring the scopes of a promising and innovative therapy that could help individuals who have not been able to benefit from the current treatments available, and defining the duration of the possible effects of this therapy, were the main objectives of this investigation.

It was planned to share the results of this study in neurorehabilitation journals for the community. Unfortunately, due to the COVID-19 worldwide emergency, it was impossible to carry out the practical portion of the current research; leaving this experimental design as a proposal. Eugenio Espejo hospital facilities were destinated to assist coronavirus patients, making our contact with stroke patients very difficult. However, it has been planned to continue this research when this sanitary emergency allows us to do so. Similarly, another limitation within this research is that in terms of the inclusion criteria, participants must be able to speak and maintain a specific level of concentration during therapy, making it difficult for all patients in an early-acute phase of this syndrome to benefit from the results of this type of rehabilitation.

However, the literature on this approach offers great hope for further research into the functionality of this therapy. Schenke et al., proved a three-day symptom's improvement

maintenance (2020), yet, possible modifications of the present therapy, or different combinations made up with other types of approaches, may also give us a better idea of the new scenario for hemispatial neglect rehabilitation. In addition, taking into account the multimodality of this syndrome (Corbetta, 2014), it is also important to explore multimodal forms of therapy. Much more research is needed to make the most of the available treatments, however, moving the focus from only visual oriented therapies, towards rehabilitation methods involving other senses and different perspectives, is already a major advance for this field.

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ANEXO A: FORMULARIO DE CONSENTIMIENTO INFORMADO

Comité de ética de investigación en seres humanos

Formulario de Consentimiento Informado por escrito, para participantes adultos

Título de la investigación: *Application of auditory stimuli with movement cue in Ecuadorian patients with severe and acute left-sided neglect, 2020.*

Organizaciones que intervienen en el estudio: *Universidad San Francisco de Quito, Hospital Eugenio Espejo*

Investigador Principal*: Nergiz Turgut, Universidad San Francisco de Quito, nturgut@usfq.edu.ec*

Co-investigadores: *María José Ortega, Universidad San Francisco de Quito, mjortega@estud.usfq.edu.ec*

DESCRIPCIÓN DEL ESTUDIO
Introducción *Debe tomarse en cuenta que el lenguaje que se utilice en este documento no puede ser subjetivo; debe ser lo más claro, conciso y sencillo posible; deben evitarse términos técnicos y en lo posible se los debe reemplazar con una explicación*
Este formulario incluye un resumen del propósito de este estudio. Usted puede hacer todas las preguntas que quiera para entender claramente su participación y despejar sus dudas. Para participar puede tomarse el tiempo que necesite para consultar con su familia y/o amigos si desea participar o no. La presente investigación sobre el uso de una terapia auditiva para tratar los síntomas de lo que se conoce como "negligencia hemiespacial" — un síndrome que ocurre después de un accidente cerebrovascular y que afecta la capacidad atencional hacia un lado del espacio — es realizada por Nergiz Turgut PhD, catedrática de la Universidad San Francisco de Quito, y su estudiante de pregrado María José Ortega. Usted ha sido invitado a ser parte de esta investigación ya que después de haber sido evaluado neurológicamente por su médico tratante, se ha concluído que usted presenta la sintomatología de el síndrome ya antes mencionado, y que ha perdido su capacidad de atender hacia el lado izquierdo del espacio. Al ser una persona mayor a 18 años que puede mantenerse despierto por un periodo mayor a 20 minutos, usted cumple con lo que se necesita para ser parte de esta investigación.
Propósito del estudio Incluir una breve descripción del estudio, incluyendo el número de participantes, evitando términos técnicos e incluyendo solo información que el participante necesita conocer para decidirse a participar o no en el estudio

Esta investigación de naturaleza cuantitativa es un estudio que busca indagar sobre el funcionamiento de una terapia con enfoque auditivo que se ha desarrollado para pacientes diagnosticados con el síndrome de negligencia hemiespacial. Este estudio pretende proveer a la comunidad de un nuevo método para la rehabilitación de pacientes diagnosticados con problemas para atender hacian un lado del espacio, y a su vez, validar a través de la ciencia la validez de la mencinada terapia. Los síntomas del síndrome de negligencia hemiespacial serán evaluados antes y después de la terapia y a través de estos resultados podremos saber que tan efectivo es este método que tiene como base el uso de movimientos auditivos. Para este estudio necesitaremos de 24 participantes que cumplan con el perfil ya antes mencionado.

Descripción de los procedimientos para llevar a cabo el estudio Breve descripción de cada actividad en la que participarán los sujetos y el tiempo que tomará. No describir procesos en los que los participantes no tomarán parte.

Se contempla que la terapia durará un mínimo de 20 minutos durante el tiempo en usted se encuentre internado en el hospital, y la misma será llevada a cabo en las camas que el hospital le haya asignado.

1. La primera parte consiste en dar instrucciones y explicar al paciente sobre como se llevará a cabo la terapia.
2. En segundo lugar, se colocan los audífonos al participante y se da comienzo con la reproducción de canciones de acuerdo a los gustos musicales de cada uno de ellos.
3. Mientras el paso dos sigue en marcha, se le preguntará cuatro veces al paciente que señale con la mano que no está afectada en qué lado (izq. o der.) percibe que se encuentra el sonido, mientras el terapeuta que también está escuchando las pistas musicales, califica la precisión del participante.
4. Si el paciente acierta las cuatro veces que se le pregunta sobre su percepción del sonido, se subirá la velocidad del movimiento auditivo en la próxima sesión.

Estos pasos serán repetidos hasta finalizar con la fase terapéutica.

Riesgos y beneficios Explicar los riesgos para los participantes en detalle, aunque sean mínimos, incluyendo riesgos físicos, emocionales y/o sicológicos a corto y/o largo plazo, detallando cómo el investigador minimizará estos riesgos; incluir además los beneficios tanto para los participantes como para la sociedad, siendo explícito en cuanto a cómo y cuándo recibirán estos beneficios

Riesgos:
Dado que se trata de una terapia no invasiva, los riesgos serán mínimos. Usted podría cansarse durante o después de recibir los estímulos auditivos.

Cómo se minimizarán:
Para minimizar el riesgo del cansancio, por lo menos un psicólogo lo supervisará constantemente durante la exposición a los estímulos auditivos, para así evitar la sobrecarga y el agotamiento. Además, usted tiene derecho a pausar o detener la estimulación cuando lo requiera.

Beneficios individuales:

- El paciente recibe un potencial tratamiento en una fase temprana sin ningún costo adicional.
- Por el hecho de que la reproducción de estímulos auditivos no requiere movilización, intentamos proporcionar la mayor cantidad de comodidad posible utilizando estímulos auditivos basados en las preferencias individuales y sin el uso de molestos cables o grandes dispositivos.

Beneficios sociales:

- Este estudio contribuirá al campo de la Neurorehabilitación que lamentablemente en Ecuador es casi inexistente. Se ha previsto compartir los resultados de este estudio en revistas de neurorehabilitación para la comunidad. También ofrecemos enviar una versión por correo electrónico cuando este estudio se publique, a todos aquellos interesados en conocer más detalles sobre los resultados del estudio, incluyendo a pacientes y cuidadores.
- Proporciona información importante, sobre si una mejora en los síntomas de negligencia hemiespacial es posible en una etapa temprana, muy poco tiempo después del accidente cerebrovascular.
- Además, dado que la negligencia es un síndrome que afecta a un gran número de pacientes con accidente cerebrovascular y que tiene consecuencias graves en las actividades del día a día de los pacientes y sus cuidadores, un posible nuevo método terapéutico tendría un impacto no solo en la vida de los pacientes, sino también en la sociedad que los acompaña.

Confidencialidad de los datos *Debe describirse cómo se protegerá el anonimato de los participantes, y también cómo se garantizará la seguridad de los datos en todas las etapas del estudio: reclutamiento, ejecución, análisis, publicación, postestudio (almacenamiento). Es importante explicar quién será el custodio de los datos recolectados..*

Para nosotros es muy importante mantener su privacidad, por lo cual aplicaremos las medidas necesarias para que nadie conozca su identidad ni tenga acceso a sus datos personales:
1. La información que nos proporcione se identificará con un código junto con su nombre y se guardará en un lugar seguro donde solo los investigadores mencionados al inicio de este documento tendrán acceso. Una vez finalizado el estudio se borrará su nombre y se mantendrán solo los códigos.
2. Se removerá cualquier identificador personal que permita la identificación de usted y sus estudiantes al reportar los datos.
3. Su nombre no será mencionado en los reportes o publicaciones.
4. El Comité de ética de la investigación en seres humanos (CEISH) de la USFQ, podrá tener acceso a sus datos en caso de que surgieran problemas en cuando a la seguridad y confidencialidad de la información o de la ética en el estudio.
5. Al finalizar el estudio los datos serán almacenados en las computadoras del instituto de neurociencias de la USFQ durante los siguientes 5 años. Al finalizar con ese periodo de tiempo, todos sus datos serán eliminados del sistema.

Derechos y opciones del participante

Usted puede decidir no participar y si decide no participar solo debe decírselo al investigador principal o a la persona que le explica este documento. Además aunque decida participar puede retirarse del estudio cuando lo desee, sin que ello afecte los beneficios de los que goza en este momento.
Usted no recibirá ningún pago ni tendrá que pagar absolutamente nada por participar en este estudio.
Para poder revocar la validez del consentimiento informado y a su vez su participación en el estudio, se le pedirá firmar la revocatoria de aquel documento, la cual está ubicada en el mismo formulario de consentimiento informado.

Procedimientos para verificar la comprensión de la información incluida en este documento

- ¿Puede explicarme cómo va a participar en este estudio?

• ¿Qué hace si está participando y decide ya no participar? • ¿Cuáles son los posibles riesgos para usted si decide participar? ¿Está de acuerdo con estos riesgos? • ¿Qué recibirá por participar en este estudio? • ¿Hay alguna palabra que no haya entendido y desearía que se le explique?
Información de contacto
Si usted tiene alguna pregunta sobre el estudio por favor envíe un correo electrónico a nturgut@usfq.edu.ec
Si usted tiene preguntas sobre este formulario puede contactar al Dr. Iván Sisa, Presidente del CEISH-USFQ USFQ, al siguiente correo electrónico: comitebioetica@usfq.edu.ec

Consentimiento informado para participar en el estudio	
Comprendo mi participación en este estudio. Me han explicado los riesgos y beneficios de participar en un lenguaje claro y sencillo. Todas mis preguntas fueron contestadas. Me permitieron contar con tiempo suficiente para tomar la decisión de participar. ☐ **Acepto voluntariamente participar en esta investigación y me entregaron una copia de este formulario.** ☐ No acepto participar en esta investigación	
Nombres y apellidos del participante: Firma /huella del participante	Fecha CC
Nombres y apellidos del testigo: Firma /huella del testigo	Fecha CC
Nombres y apellidos del investigador: Firma del investigador	Fecha: CC
Revocatoria del consentimiento	
Nombres y apellidos del participante: Firma /huella del participante	Fecha CC
Nombres y apellidos del testigo: Firma /huella del testigo	Fecha CC
Nombres y apellidos del investigador Firma del investigador	Fecha CC

ANEXO B: FORMULARIO DE ASENTIMIENTO INFORMADO

Título de la investigación: *Application of auditory stimuli with movement cue in Ecuadorian patients with severe and acute left-sided neglect, 2020.*

Hola, mi nombre es María José Ortega Vásquez y estudio en la Universidad San Francisco de Quito. Estamos realizando un estudio para tratar los síntomas de lo que se conoce como "negligencia hemiespacial" — un síndrome que ocurre después de un accidente cerebrovascular y que afecta la capacidad atencional hacia un lado del espacio.

Usted ha sido invitado a ser parte de esta investigación ya que después de haber sido evaluado neurológicamente por su médico tratante, se ha concluído que usted presenta la sintomatología de el síndrome ya antes mencionado, y que ha perdido su capacidad de atender hacia el lado izquierdo del espacio. Al ser una persona mayor a 18 años que puede mantenerse despierto por un periodo mayor a 20 minutos, usted cumple con lo que se necesita para ser parte de esta investigación.

Su participación en el estudio consistiría en escuchar a través del uso de audífonos, diferentes tipos de pistas musicales, al mismo tiempo que responde a algunas preguntas. Usted puede decidir no participar y si decide no participar solo debe decírselo al investigador principal o a la persona que le explica este documento. Además, aunque decida participar puede retirarse del estudio cuando lo desee, sin que ello afecte los beneficios de los que goza en este momento.
Usted no recibirá ningún pago ni tendrá que pagar absolutamente nada por participar en este estudio.
Para poder revocar la validez del consentimiento informado y a su vez su participación en el estudio, se le pedirá firmar la revocatoria de aquel documento, la cual está ubicada en el mismo formulario de consentimiento informado.

Toda la información que usted nos proporcione, al igual que las evaluaciones neurológicas que realicemos, nos ayudarán a monitorear su progreso, y se utilizarán únicamente para fines de investigación científica-académica. Para nosotros es muy importante mantener su privacidad, por lo cual aplicaremos las medidas necesarias para que nadie conozca su identidad ni tenga acceso a sus datos personales:

Si acepta participar, le pido que por favor coloque un visto (✓) en el recuadro que dice "Sí deseo participar" y que por favor escriba su nombre.

Si no desea participar, no coloque ningún visto (✓), ni escriba su nombre.

☐ Sí deseo participar Nombre: _____

Nombre y firma de la persona que obtiene el asentimiento: Fecha:

ANEXO C: PRUEBAS NEUROLÓGICAS

Line Bisection Task