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Multisensory integration in different states of consciousness

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<u>Summarv</u>

Our experience is embedded in a dynamic world. We are surrounded by different stimuli sensed by specific sensory channels, giving us a multisensory experience, which increases our chances of survival. (Fetsch, Deangelis, & Angelaki, 2013; Lewkowicz, David J, Kraebel, 2004; Lewkowicz & Ghazanfar, 2009). This process is called multisensory perception and is defined as the process by which inputs from two or more senses are combined to form a product that is distinct from, and thus cannot be easily deconstructed to the component from which it is created (Stein, Stanford, & Rowland, 2014).

In recent years our understanding of multisensory integration has been deepening. Since the first research, a fundamental principle was established in the area. The probability of perceiving something as a multisensory object increases if the sensory modalities are close in space and time (Stein & Meredith, 1993)). However, much of our knowledge of these principles come from cats' superior colliculus (Binns & Salt, 1996; Wallace, Meredith, & Stein, 1998). In the last years, new non-humans models (Cloke, Jacklin, & Winters, 2014) and advances in electrophysiological techniques in human studies have increased our knowledge about the phenomenon (Keil & Senkowski, 2018).

Multisensory human research has shown the involvement of Gamma, Beta and Alpha frequencies. (for review (Keil & Senkowski, 2018)). Multisensory coordinated stimuli elicited gamma-band increases even under unisensory stimulation in a task where the participant was required to answer to a target presented in any involved modality. These increases in the Gamma band were observed in occipital and medial-frontal areas (Senkowski, Talsma, Grigutsch, Herrmann, & Woldorff, 2007). Changes in Gamma were also observed when subjects had to take multisensory training; when the subjects underwent audio-visual coherence training, a synchronization of Gamma and Beta in the coherence visual task post-practice was observed (La Rocca, Ciuciu, Engemann, & van Wassenhove, 2020). In a task where the instruction was to detect whether the current stimulus (visual, tactile, both) matched with a previous one, Beta activity increased when the detection was correct. Additionally, when the task involved a judgement of coherence between an audio-tactile stimulus, the power of Alpha-band increased when the response was correct (Göschl, Friese, Daume, König, & Engel, 2015). An increase in the Beta band was also observed in a study relating cognitive load and multisensory perception. The participants were exposed to an n-back task and the sound-induced flashy illusion (SIFI). The results provide evidence that the susceptibility to the SIFI increases at a higher cognitive load, accompanied by suppression in Beta power. (Michail, Senkowski, Niedeggen, & Keil, 2021). Finally, in a task where the subjects were required to detect a visual grating stimulus while a sound was played (continuous noise or adjusted to the target), a better performance was observed with sound than without it. This task was concurrent with decreased occipital Alpha and central Beta (Gleiss & Kayser, 2014). In the case of perception of simultaneity, when a subject perceives something as belonging to the same perceptual object, a decrease of alpha activity correlated with the perception.

This decrease was absent when the audio-visual stimulus was separated in time. (Bastiaansen, Berberyan, Stekelenburg, Schoffelen, & Vroomen, 2020).

All these results were obtained in awake subjects. However, a study shows multisensory integration (odour-sound) during NREM sleep (Arzi et al., 2012). When falling asleep, there is a series of changes in the electrical dynamic of the brain, such as a decrease in Alpha and Beta, along with the emergence of slow-wave activity (Akeju & Brown, 2017; Brown, Basheer, McKenna, Strecker, & McCarley, 2012). As the brain dynamics changes during falling asleep, it is natural to wonder how these changes affect the process of multisensory integration.

Unfortunately, there is no behavioural response to the environment when the subjects are sleeping. However, a temporal transition window called drowsiness, where the subject falls asleep but still can generate behavioural responses (Bareham, Manly, Pustovaya, Scott, & Bekinschtein, 2014; Jagannathan et al., 2018a). This state is a helpful tool to examine how the multisensory integration behaves in the transition to sleep and better understand the phenomenon's neuronal substrates. Through a multisensory task with an auditory and visual stimulus which could be synchronous or not, we examine the electrical activity associated with the presentation of the stimulus while the subject falls asleep.

Introduction

Why Multisensory integration

All animals live in a complex and dynamic sensory environment in which many events must be detected, interpreted and acted accordingly (Fetsch, Deangelis, & Angelaki, 2013). Biologically significant events are often registered by more than one sense. Given that each sensorial channel independently transmits specific information, more accurate perceptual evaluations and behavioural decisions can be made by synthesizing their different sensory signals (Stein, Stanford, & Rowland, 2014). This process, called multisensory integration, is central to adaptive behaviour. It allows us to perceive a world of coherent perceptual entities and take advantage of the increased salience created by multisensory redundancy. (Lewkowicz & Ghazanfar, 2009). For instance, like other animals, humans perform better in tasks that involve attention and discrimination when the information is multisensorial than when it is not (Lewkowicz, David J, Kraebel, 2004). For instance, in the perception of flavour, the gustatory and olfactory cortex inputs are integrated into a single perception. If we inhibit one, the perception of taste cannot happen (Spence, 2015).

The principal assumption is that multiple sources of information can provide a perceiver with a more veridical picture of the world (Lewkowicz, David J, Kraebel, 2004). In other words, the brain must alter its reaction to external events when it integrates information across the senses in a way that could reflect the coherence of the data transmitted from the unisensory channels (Stein, Stanford, Ramachandran, Perrault, & Rowland, 2009). This assumption can be viewed from a statistical perspective. One of the most fundamental aspects of the sensory inputs is uncertainty, defined as the imperfect mapping between events in the world and the sensory representation. This uncertainty is reduced when we can combine data from multiple sources. (Chandrasekaran, 2017). This variety of sources gave the possibility, for instance, to a predator to catch prey easily. After all, it knows how it smells, looks, and sounds, because all of these features are part of the same percept, in this case, the prey (Lewkowicz, David J, Kraebel, 2004).

In short, integrating different sources of information into a single perception is fundamental to increasing the probability of survival in a dynamic environment.

What is multisensory integration?

Multisensory integration has been defined as the process by which inputs from two or more senses are combined to form a distinct product. This combination cannot be deconstructed to reconstitute the component from which it is created (Stein & Meredith, 1993). Operationally, from the perspective of behavioural and neuronal studies, it is defined as a statically significant difference between the response evoked by a crossmodal combination of stimuli and that evoked by the most effective of its components individually (Stein et al., 2009).

There are different forms of experiencing multisensory integration. The first is the cases where various senses provide redundant information about specific properties (Deroy et al., 2016). It means that the inputs from different sensory channels are integrated into a single object representation (The perception of a ball in our hands as proprioceptive and visual roundness) (Deroy, Chen, & Spence, 2014). This combination also includes the cases in which the multisensory experience looks like something new and different from its components, as with flavour (Deroy et al., 2016; Spence, 2015).

The other is when modality-specific features, such as visual and sound elements, are perceived together as part of the same object (Deroy et al., 2014). For instance, the perception of a dog barking is faster if the sound of the bark is congruent with the picture of the dog compared with other incongruent noises (Chen & Spence, 2010). Here, the contents can stay uni-sensory, but the multisensory awareness seems to be related to the same object (Deroy et al., 2016).

Finally, we can distinguish a third form of multisensory integration, where two or more different modalities are experienced as part of the same and congruent scene (Deroy et al., 2016).

What is the relationship between multisensory integration and awareness?

At first glance, it seems that all our experience is multisensory. We have sensors that constantly monitor our environment (Exteroception) and supervise the states of our bodies (Interoception), creating a unified multisensory world (Blanke, 2012; H.-D. Park & Tallon-Baudry, 2014; Roy Salomon et al., 2017). It has been suggested that consciousness is responsible for this integration and coordination of processes that otherwise will only occur in isolation (Baars, 2002; Dehaene & Changeux, 2011). One of the most likely models of multisensory integration proposes that these processes occur due to interactions between the frontal cortex, temporoparietal regions, and primary cortices (Senkowski, Schneider, Foxe, & Engel, 2008). Sharing this different information between various areas is a critical element of the most crucial consciousness theories (Dehaene, Charles, King, & Marti, 2014; Tononi, Boly, Massimini, & Koch, 2016). For example, being aware of a single sensory stimulus can increase the conscious perception of another unconscious stimulus. For instance, visually sensory information, invisible to perception, can reach consciousness if it is congruent in time with a sound (Alsius & Munhall, 2013; Chen & Spence, 2010; Deroy et al., 2014; Palmer & Ramsey, 2012). Also, an audio-tactile stimulus can generate many different outcomes in visual perception. First, it can facilitate visual search, influence the dominance of visual stimulation, or affect the conscious access to a visual stimulus (Lunghi & Alais, 2015; Lunghi, Binda, & Morrone, 2010; Lunghi, Morrone, & Alais, 2014; Ngo & Spence, 2010; Roy Salomon et al., 2016). Proprioception also influences rendering invisible visual stimulus visible when the stimulation is shown congruent with the participant's hand than when it is not (R. Salomon, Lim, Herbelin, Hesselmann, & Blanke, 2013). The same phenomenon is valid for the vestibular system, which allows conscious access when the visual stimulus is congruent with the movement of the head (Roy Salomon, Kaliuzhna, Herbelin, & Blanke, 2015).

State of consciousness

We oscillate between different degrees of alertness, from a vigil condition to deep sleep. These states involve certain features that are present when the subjects are awake or lose consciousness. For example, in the unresponsive conscious state, we can observe a metabolic dysfunction of a widespread cortical network that involves medial and lateral prefrontal cortices and parietal multimodal associative areas. These subjects show cerebral activation but are only limited to subcortical regions and low level primary cortical areas and disconnected from frontoparietal networks and thalamic-cortical connectivity (Laureys et al., 2000; Steven Laureys et al., 1999; Steven Laureys, 2005). Furthermore, there is evidence that the equilibrium between excitatory connectivity and the feedbacks projections towards the posterior cingulate cortex is disrupted (Crone et al., 2015).

Subjects can also lose their consciousness as a result of anaesthesia. For instance, in the presence of propofol, subjects lost responsiveness to an auditory stimulus, showed an increase in low-level frequency power, loss of coherent occipital alpha oscillations along with the appearance of spatially coherent frontal alpha oscillations changing again when the participants recover consciousness (Purdon et al., 2013). Furthermore, when subjects are under the effects of midazolam to induce loss of consciousness, the triggered responses to Tomography Magnetic Stimulation (TMS) of cortical activity measured with an EEG last for least 300 ms compared with awake subjects with more prolonged activity (Ferrarelli et al., 2010).

Finally, a third case is when subjects fall asleep naturally. Consciousness fades when we fall asleep. It has been shown that when you stimulate the brain with TMS when the participant is sleeping, the cortical activity is reduced to short and local activation or a burst of an explosive and specific response, producing a full-fledged slow-wave (Tononi & Massimini, 2008).

All these states have compromised the amount of integration and complexity, as shown with Principal Component Index (PCI) measures. This measurement calculates the level of complexity and integration of the brain after a TMS exposition. This measure can discriminate accurately between different states. It shows that either NREM sleep, anaesthesia or clinical conditions (like unresponsive wakefulness syndrome and minimally conscious state) shows reduced PCI values compared with awake subjects. The lower PCI means that there is a breakdown in all these cases on the cortical connectivity (Casali et al., 2013), specifically of thalamocortical circuits that sustain long-range differentiated patterns of activation (Massimini, Ferrarelli, Sarasso, & Tononi, 2012).

Drowsiness

Nevertheless, there is another state of consciousness that is significantly different. In the transition to sleep, the subjects still can make motor responses but gradually lose conscious control of their environment. (Bareham, Manly, Pustovaya, Scott, & Bekinschtein, 2014). The transition to sleep is not something that happens suddenly. Instead, it is a continuous interlaced series of changes that begin in relaxed drowsiness and continue to stage 1 and 2 (Ogilvie, 2001). This transition period has been studied, and nine different stages have been identified (Hori, 1985; Tanaka, Hayashi, & Hori, 1996). At first, it can be seen the appearance of slow rolling eye movements (SEM) during the state of drowsiness, which cease before the first sleep spindles (Magosso, Ursino, Provini,

& Montagna, 2007; Ogilvie, 2001). Also, there is a decrease in muscle tone, body temperature and heart rate due to parasympathetic dominance (Baharav et al., 1995; Šušmáková & Krakovská, 2008; Van Den Heuvel, Noone, Lushington, & Dawson, 1998).

Furthermore, we can find certain EEG features in this transition which are:

Elements of drowsiness

- 1. Alpha wave intermittent (< 50%)
- 2. EEG flattening (amplitude $< 20 \,\mu$ V)
- 3. Decrease of occipital Alpha and increment on frontal Alpha
- 4. Increment of theta, especially in the central and temporal regions
- 5. Low voltage theta waves (ripples) with amplitude around $20 \,\mu V$ -50 μV

Graphoelements

- 1. Vertex sharp waves (Sharp negative discharge followed by a positive one; maximal in parietal and frontal regions)
- 2. Spindles (12-16 Hz with a minimum duration of 0.5 sec; prominent in temporal and frontal regions)
- 3. K –complexes (Starts with a sharp positive wave followed by a large negative wave, with an asymmetrical duration (shorter at first); prominent in frontal, temporal and parietal regions)

(Goupil & Bekinschtein, 2012; Jagannathan, Nassar, Jachs, Pustovaya, & Corinne, 2017)

From a behavioural and phenomenological perspective, this transition is marked by a progressive loss of the ability to respond to external stimuli. These can be seen in longer reaction times and loss of accuracy. Also, the subjects report a gradual loss of awareness, control of their thoughts correlated with the loss of responsiveness at the behavioural level (Goupil & Bekinschtein, 2012). The particular characteristic of this state of transition is ideal to study state-dependent cognitive processes because it does not need an alteration of the stimulus (De Graaf, Hsieh, & Sack, 2012).

Is consciousness necessary to generate multisensory integration?

At this moment, it should be clear that there is a relationship between multisensory integration and consciousness. It seems that multisensory integration needs communication between different brain areas and that this is achieved when the person is awake and conscious (Dehaene & Changeux, 2011; Steven Laureys, 2005; Senkowski et al., 2008; Tononi & Massimini, 2008).

Nevertheless, some recent findings challenge this conclusion. In the first place, it is possible to condition a behavioural sniff response to the pairing between pleasant and unpleasant odours and sounds when the subjects are in REM and NREM sleep. Even when the subjects were unaware of this when they woke up, they still had the conditioned behavioural response (Arzi et al., 2012). Furthermore, when subjects classify words as animals or objects, an event-related potential associated with the motor preparation remains during sleep (Lateralized Readiness Potential) (Kouider, Andrillon, Barbosa, Goupil, & Bekinschtein, 2014). Nevertheless, it is challenging to control stimulus awareness during sleep, and the stimulus was consciously perceived but forgotten when the subjects awake (Faivre, Mudrik, Schwartz, & Koch, 2014).

Despite this, some studies have tackled this question by measuring subliminal stimuli. In audio-visual integration, two sensory inputs (letters) were presented subliminally to the subject. They had to discriminate if the stimulus were congruent or incongruent (Sound of a letter B with the visual presentation of the letter M for the incongruent condition). Even though the subjects report not seeing nor hearing anything, they still could accurately discriminate between both conditions (Faivre et al., 2014). Furthermore, subjects were subliminally exposed to semantically complex tasks with two male names paired with a creative or a non-creative profession. After, they must classify between two jobs, preceded by name subliminally paired. They show that inverse priming occurred when test pairs were concordant, with significantly slower classification judgements (Scott, Samaha, Chrisley, & Dienes, 2018). Outside the field of audio-visual stimulus, there is an alteration of the detection and response times to tactile stimulation when a visual ball, rendered invisible through continuous flash suppression, enters the peripersonal space (Roy Salomon et al., 2017). Finally, it was reported in a case study that a patient with posterior cortical atrophy, which is a condition where the patient is unable to perceive stimulus consciously, have a multisensory enhancement in a detection task, with reaction times and variability similar to control subjects (Barutchu, Spence, & Humphreys, 2018). Finally, the heartbeats of a subject can also predict if the participant will detect a faint visual grating or not (Park, Correia, Ducorps, & Tallon-Baudry, 2014).

It seems that some kind of multisensory integration can be achieved without conscious awareness of the stimulus. Although these experiments address the behavioural aspect of the phenomenon, the neuronal mechanisms involved remain poorly understood.

Neural mechanisms of Multisensory integration

In the first place, we need to address the multisensory integration from the individual neuron. The first studies were made in the superior colliculus of cats, and it was possible to understand some principles of the multisensory integration (Stein & Meredith, 1993). The first two involves space and time and conclude that when two cues from different sensory modalities are in close spatial and or temporal proximity, it produces an enhancement on the activity of multisensory neurons or depression if they are separated (Kadunce, Vaughan, Wallace, & Stein, 2001; Meredith, Nemitz, & Stein, 1987). The third principle is that more significant effects are present for cross-modals cues when weaker sensory input. This principle is called inverse effectiveness and refer to the fact that the magnitude of multisensory integration is inversely related to the efficacy of the stimuli being integrated (Stein et al., 2009). Finally, there is the principle of superadditivity, subadditivity and additivity. There is a superadditivity activity if the multisensory response is higher than the sum of the individual sensory inputs. When the

multisensory answer is lower, there is a subadditivity activity, and when there is approximately the same activity, it is called additive. Generally, the additivity principle correlates well with behaviour on multisensory tasks (Chandrasekaran, 2017).

These principles were intimately related to the association cortex (Ectosylvian cortex) and the rostral lateral suprasylvian sulcus. In the absence of these structures, the multisensory neurons of cats are unable to integrate different sensory cues and mediate over multisensory behaviours (Jiang, Jiang, Rowland, & Stein, 2007; Stein, 1998; Stein et al., 2014).

Brain areas related to multisensory integration in humans

The search for the areas involved in multisensory integration in the human brain has resulted in extensive work. First, multisensory integration is related to activity in the frontal lobe, temporoparietal and intraparietal sulcus. A convergence of different sensory inputs could happen in these higher hierarchical areas (Kayser & Logothetis, 2007; Rohe & Noppeney, 2015). Other areas involved are the superior temporal gyrus, the supramarginal gyrus and the cerebellum (Baumann & Greenlee, 2007; Beauchamp, Argall, Bodurka, Duyn, & Martin, 2004). It has also been reported that the insula shows activation in response to audio-visual and visual-tactile information (Amedi, Von Kriegstein, Van Atteveldt, Beauchamp, & Naumer, 2005).

Nevertheless, there are some problems with these findings. First, it seems that the localizations involved could be related to the nature of the task. For instance, the superior temporal gyrus and the intraparietal sulcus integrated identity and spatial information. (Calvert & Calvert, 2001). Furthermore, there is increasing evidence that some "low hierarchy" areas can also have an earlier multisensory integration (audio-visual). An example of this earlier integration is the auditory belt, where is activity related to visual stimulus. (Ghazanfar & Schroeder, 2006; Kayser & Logothetis, 2007; Macaluso, 2006). However, maybe this integration observed are ruled by different principles. For instance, in primary visual cortices, spatial disparity of the stimulus controlled the influence of auditory signals or other non-visual signals (Rohe & Noppeney, 2016)

Finally, related with areas activated with meaningful semantic stimulus in audiovisual paradigms, there is evidence pointing out to an implication of the temporal lobe in the audio-visual integration of semantically congruent and the frontal lobe to an incongruent audio-visual stimulus (Doehrmann & Naumer, 2008)

Evidence from manipulation of neural activity

There is a considerable amount of evidence related to the manipulation of neural activity and multisensory integration. Anodal Direct Current Stimulation can speed reaction times for detecting auditory, visual and bimodal audio-visual targets when applied over the right posterior parietal cortex (Bolognini, Olgiati, Rossetti, & Maravita, 2010). Also, TMS targeting the right angular gyrus reduces subjects' susceptibility to the auditory-sound induced flash illusion (Bolognini, Rossetti, Casati, Mancini, & Vallar, 2011; Kamke, Vieth, Cottrell, & Mattingley, 2012; Shams, Ma, & Beierholm, 2005). Related to proprioception, we can find an enhanced sensitivity to induction of phosphenes with TMS when there is an unattended touch to the hand that is spatially coincident (Bolognini & Maravita, 2007). Additionally, the enhancement produced in tactile

perception when coupled with visual information is disrupted when the TMS was applied in the anterior intraparietal sulcus, suggesting a multisensory mechanism modulating tactile processing (Konen & Haggard, 2014). Finally, when transcranial direct current stimulation is applied over the visual cortex, tactile perception is enhanced in spatial orientation. When it is over the auditory cortex, it enhances the tactile perception of temporal frequency (Yau, Celnik, Hsiao, & Desmond, 2014).

Neurodynamic of multisensory integration

Multiple paradigms show the neurodynamics involved in multisensory integration. Beta frequency power (13-30 Hz) over frontal, occipital, central and sensory regions depends on a multisensory discrimination task (Senkowski, Molholm, Gomez-Ramirez, & Foxe, 2006). Furthermore, in a sensory gating paradigm, the salience of the multisensory stimuli involving tactile, visual and auditory stimulation modulated EEG beta power (Kisley & Cornwell, 2006). According to bimodal evoked potentials, an activity is produced in the theta range over frontal regions and a gamma activity over central, parietal and frontal areas (Sakowitz, Quiroga, Schürmann, & Ba Ar, 2001; W. Sakowitz, Schürmann, & Başar, 2000). The exciting element is that the changes in the power of all these frequency bands were modulated in time, with theta frequencies appearing earlier and Alpha appearing approximately 200 ms after stimulation. In contrast, beta and Gamma seem unpredictable (Sakowitz, Quiroga, Schürmann, & Başar, 2005).

In the sound-induced illusory flash, it was observed that when the subject report saw a second flash, it was accompanied by an earlier modulation of the visual cortex (30-60 ms) and an increment on gamma band (Bhattacharya, Shams, & Shimojo, 2002; Shams et al., 2005). An early ERP is localized on the auditory and polymodal cortex of the temporal lobe in a detailed analysis. It was accompanied by a gamma burst on the visual cortex (Mishra, Martinez, Sejnowski, & Hillyard, 2007; Mishra, Martinez, & Hillyard, 2008). Finally, the difference in the frequency of the occipital Alpha is fundamental to perceiving or not the second flash. Slower frequencies (8 Hz) increase the time window (100 ms) of perception of the illusion while faster alpha frequencies (12 Hz) decrease the time window for the perception of the second flash (Cecere, Rees, & Romei, 2015; Kerlin & Shapiro, 2015)

In tasks related to the McGurk effect, it has been observed an increment in gamma band activity associated with visual discordance with the auditory stimulus, with maximum amplitude at 270 ms over occipital areas and at 320 ms over left inferior frontal cortex (Kaiser, Hertrich, Ackermann, Mathiak, & Lutzenberger, 2005). In an oddball paradigm, an audio-visual discordance was related with an amplitude at 80 Hz between 250 - 350 ms over occipital cortex. These changes support the idea that high-frequency oscillatory activity over sensory areas is fundamental for the perceptual experience (Kaiser, Hertrich, Ackermann, & Lutzenberger, 2006).

The temporal presentation of an auditory and visual stimulus is related to changes in oscillatory gamma-band responses. In an experiment where the onset of the auditory and visual stimulation was modified, the gamma band was incrementally when the asynchrony between was lower (Senkowski, Talsma, Grigutsch, Herrmann, & Woldorff, 2007). Also, according to the semantical elements, when the subjects have to classify pictures and sound as congruent or incongruent, there is an increment in gamma band responses for the incongruent conditions (Yuval-Greenberg & Deouell, 2007). This gamma-band involvement can also be seen when subjects are presented with coherent stimuli separate in time. There was facilitation on recognition in the congruent trial and an increment on gamma-band between 120 – 180 ms following the auditory stimulus onset compared to incongruent trials (Schneider, Debener, Oostenveld, & Engel, 2008). Similar gamma-band responses are seen on the binding of symbols and sound at 152 ms after stimulus onset (Widmann, Gruber, Kujala, Tervaniemi, & Schröger, 2007). In the case of perception of simultaneity, when a subject perceives something as belonging to the same perceptual object, a decrease of alpha activity correlated with the perception. This decrease was absent when the audiovisual stimulus was separated in time. (Bastiaansen, Berberyan, Stekelenburg, Schoffelen, & Vroomen, 2020). Also, the amount of low-frequency (7-13 Hz) long-range coherence between the visual and sensorimotor cortex is related to an increase in performance in matching tasks (Hummel & Gerloff, 2005).

Finally, using steady-state potentials, the power associated with the specific frequencies, which in this experiment was 11 Hz for the auditory input and 10 Hz for the visual information, was higher when the stimulus was congruent compared when they were incongruent (Nozaradan, Peretz, & Mouraux, 2012).

Summary

Our worlds are multisensorial, and studies about this phenomenon shed light on the areas involved in integrating our sensory world. We observe long-range communication through frequency and amplitude in frequencies such as alpha, beta, and gamma (Keil & Senkowski, 2018) when the participants are awake. This state is critical because it provides a system status to observe connections through neural synchrony across different areas (Koch, Massimini, Boly, & Tononi, 2016). It is not so difficult to infer that multisensory integration and this state of consciousness are deeply involved; nevertheless, other research raises the question about their relationship (Faivre, Arzi, Lunghi, & Salomon, n.d.). The mayor characteristic of the neurodynamics of the phenomenon are increases in power in beta and gamma and decrease in alpha (Bastiaansen, Berberyan, Stekelenburg, Schoffelen, & Vroomen, 2020; La Rocca, Ciuciu, Engemann, & van Wassenhove, 2020) and perturbation in connectivity. We expected to observe an alteration in these frequencies due to the change of the system's state in where the activity is less widespread (Casali et al., 2013). To achieve this, we presented an audio-visual stimulus and observed how the neural dynamics and behaviour change while the subject is falling asleep.

Objectives

General objective

Describe the behaviour and neural dynamics of multisensory integration in alertness and drowsiness

Specific objectives

- a) To evaluate and compare the reaction times and accuracy of multisensory integration between the waking state and the drowsy state
- b) To evaluate and compare neural synchrony in Alpha, Beta and Gamma in multisensory integration between the waking state and the drowsy state
- c) To evaluate and compare the power in Alpha, Beta and Gamma in multisensory integration between the waking state and the drowsy state
- d) To evaluate and compare the multisensory condition with the uncoordinated presentation of auditory and visual stimuli
- e) Integrate the neuronal and behaviour activity in a model of multisensory integration in drowsiness.

Hypothesis

General Hypothesis

While we are awake, the sensory inputs processed in their respective primary cortexes interact with the association cortexes, allowing us to generate multisensory perceptions. On the other hand, when we begin to fall asleep, the interaction capacity between the primary cortexes and the association areas is progressively lost, which does not allow us to have a multisensory perception.

Specific Hypothesis

When we are falling asleep, the interaction between different cortexes begins to be progressively lost:

a) Preventing the subject to perceive a multisensory stimulus, increasing reaction time and decreasing accuracy.

b) Which is observed in a decrease of the long-range synchrony in Alpha, Beta and Gamma.

c) Which prevents an increase in Alpha, Beta and Gamma power associated with multisensory integration.

Methods

Stimuli and procedures

The audio-visual stimulus (figure 1) was presented simultaneously as a pulse in the multisensory coordinated condition. In contrast, in the multisensory uncoordinated condition, one of the sensory modalities changed the presentation frequency (figure 1 C, D, E). Fifty per cent of the coordinated trials were presented for 1000 milliseconds (ms) with a fade-in of 100 ms and a fade-out of 860 ms (figure 1, A). The other half had a duration of 700 milliseconds with a fade-in of 87 ms and a fade-out of 572.5 ms (figure 1 B). In the uncoordinated condition, one of the sensory modalities was presented with a different frequency, making the auditory or visual stimuli change at 700 ms.

The audio was created using Matlab (MathWorks, Inc., Natick, MA). It consisted of a 333.3 Hz pure tone and amplitude modulated using a Hanning function (The same fade-in and fade-off values as the visual stimulus) between 0 and 1. The envelope of the pulse sound was either 0.7 Hz or 1 Hz (Nozaradan et al., 2012). Meanwhile, **the visual** stimulus was created using psychopy (Pierce, 2007), forming a square of 1920 x 1080 (same as the screen's resolution) with a luminosity of 100%. Then the audio-visual stimulus was presented using the software "Virtual desktop" in a virtual reality device (Rift, 2015) at a distance of 2.30 meters with a curve screen at 85%. The Rift headsets emitted the sound at 40% of the max sound capacity.

The task consisted of two blocks of 220 trials, and each block had fifty per cent coordinated trials and uncoordinated trials (figure 1, F). In the first block, the presentation of the stimulus was continuous for 45 minutes, and the second one was nine blocks of five minutes with a self-administer rest. The longer first part of the experiment was intended to provoke drowsiness, and the second part to encourage alertness. There was an intertrial interval of 4 - 5 seconds. The stimulus was presented until the volunteers responded. Right-click indicating coordinated, and left-click indicating uncoordinated stimulus. The right and left buttons were exchanged in fifty per cent of the subjects. If the person did not respond, the stimulus ended at 5 seconds of presentation.

The informed consent was delivered and filled out at the volunteer's arrival. Afterwards, participants were seated in a comfortable chair. The virtual reality device and the electrodes were installed, the instructions given, and any question related to the task comprehension answered. The volume was adjusted to 25% and modified according to the participant's comfort. The virtual reality device was adapted to the head.

Justification of the methodology and design

This study was intended to explore the neural correlates of multisensory integration in drowsiness. So, our dependent variables were the behavioural, neurophysiological and neurodynamics correlates of multisensory integration. We were interested in the reaction times, accuracy, frequency band and neural coherence associated with multisensory integration. Our independent variable was manipulating the state of consciousness, where the participants were divided into alert and drowsy.

We presented the audio-visual stimulation to the participants in two blocks, an extended one of 45 minutes (220 trials) and nine short-ones of five minutes (220 trials) with self-administered rest in between (figure 1, E). The result was a two-by-two design (Keppel & Wickens, 2004), as shown in Table 1.

Drowsiness is one of the best models to tackle this research question. In drowsiness, subjects gradually lose conscious control of their environment, but they still can respond (Bareham et al., 2014). Thanks to these characteristics, we can explore the neural mechanism without altering the stimulus, isolating the changes due to consciousness and not isolating changes corresponding to stimulation changes (De Graaf et al., 2012). There are changes in Delta, Theta, Alpha and Beta power when people close their eyes (Geller et al., 2014). The participants were with their eyes closed the entire experiment to avoid any muscular electrical noise in the transition of conscious states.

Finally, the experiment was created following the principles of multisensory integration defined by Stein and Meredith (1993), of spatial and temporally synchrony and with unisensory conditions to evaluate multisensory enhancement. The instruction was created according to Deroy et al. (2016) recommendations, which indicate that for an element to be considered multisensorial, each sensory input must be perceived as belonging to the same perceptual object.

Detailed description

Participants

A sample of thirty university students (22 females and eight males; average age = 25; SD = 3) participated in this study. All participants were recruited from different universities in Santiago of Chile through social media and the fulfilment of a questionnaire to assess eligibility.

All volunteers were native Spanish speakers who had no history of psychiatric or neurological disorders, neither their first-degree relatives nor photo sensibility. They were instructed to refrain from coffee consumption before the experiment.

One subject was excluded from the final EEG analysis due to the absence of response on an entire block (Trials of coordinated Alert 700 ms visual = 0 responses)

The ethics committee of the Pontificia Universidad Católica de Chile approved this study. All the procedures were done under written consent from the volunteers and according to the Helsinki declaration standards.

Material and instrument

Psychophysiological recordings

Continuous EEG and cardiac activity recordings were obtained using Biosemi \mathbb{R} ActiveTwo System (http://www.biosemi.com/) with 64 EEG electrodes mounted in an elastic cap according to the extended 10 – 20 system + 4 external channel (ECG, mastoids). Electrode impedance was kept below five k Ω . Continuous data were sampled at 2048 Hz and stored offline for further analysis.

Software and Hardware of presentation of stimulus

We used a head-mounted display (HMD) Oculus Rift (<u>https://www.oculus.com/rift/</u>). This virtual reality device is an immersive display with 2160x1200 resolution, 90 Hz refresh rate, and 110°. The Rifts employed integrated microphones and in-ear earbuds to block ambient noise and transmit stereo audio (Smith & Neff, 2018).

Stimuli were presented, and responses were recorded using the Psychopy module for Python (Peirce, 2007, 2008) (<u>http://www.psychopy.org/</u>). To show the screen to the virtual reality device, we used Virtual Desktop® (<u>https://www.oculus.com/experiences/rift/911715622255585/</u>). Finally, the response was reported by an ergonomic joystick of Microsoft Xbox 360® (<u>https://www.xbox.com</u>)

Instruments for data analysis

Signals were analyzed using EEGLAB plugin (Delorme & Makeig, 2004) (<u>http://sccn.ucsd.edu/eeglab</u>), Fieldtrip (Oostenveld, Fries, Maris, Schoffelen, 2011), and customized scripts for MATLAB R2017a (Mathworks ©) (<u>http://www.mathworks.com/products/matlab/</u>). Statistical analysis was performed using R (<u>http://www.r-project.org/</u>).

Data analysis

Behavioural Analysis

We excluded the non-answer responses. We used Grubb's test to remove outliers. Next, we calculated the accuracy (correct answer rate according to the intended condition) and the reaction times mean and standard deviations. We performed an ANOVA test analysis with a p-value of 0.05.

EEG recording and classification

EEG recording was acquired through 64 Ag/AgCl electrodes mounted in an elastic cap according to the international 10-20 system connected to a Biosemi Active Two device (Biosemi, Amsterdam, Netherlands). Additionally, two mastoid electrodes were added as a reference for later analysis and two cardio electrodes to monitor the hearth activity during the task. The impedance was maintained under 15 k Ω , and the digital signal was recorded at a sampling rate of 2048 Hz.

All data was preprocessed using Matlab (MathWorks Inc. Natick, MA), the EEGLAB toolbox (Version 14.1.2) and the Matlab FieldTrip toolbox (Oostenveld, Fries, Maris & Schoffelen, 2011). First, we bandpass filtered the signals between 1 - 100 Hz,

re-referenced them to mastoids and downsampled them to 1024 Hz. Finally, epochs were created between -4000 ms to 4000 ms using the onset of the stimulus as 0.

The first step was to separate alert and drowsy trials. The sorting was achieved through an algorithm of classification by Jagannathan (2018). The preprocessing includes filtering between 1 - 30 Hz (phase shift-free Butterworth filter; 24 dB/octave slope), resampling to 250 Hz and the electrodes interpolated according to the guidelines before running the algorithm in the baseline between -4000ms to 0 (Jagannathan et al., 2018a). The classification divided the trials into alert, drowsiness and severe drowsiness. Severe drowsiness trials were excluded from subsequent analysis.

For time-frequency analysis

The time-frequency analysis was performed using the Matlab Fieldtrip Toolbox (Oostenveld, Fries, Maris & Schoffelen, 2011)), filtering the data between 1 - 100 Hz and segmented from -4000ms to 4000ms. We epoched according to coordinated or uncoordinated conditions. The uncoordinated conditions were separated if visual or auditory changed at 700ms. Those conditions were divided into alert and drowsiness states, and then the power spectrum was calculated. We applied an overlapping Hanning window of 500 ms with a step of 50 ms with the mtmconvol function of the ft_freqanalysis of Fieldtrip (Oostenveld, Fries, Maris & Schoffelen, 2011). We used a decibels normalization with a baseline between -2500ms - 500ms. We then plotted in a 300 ms window between 700 ms - 3100 ms after the onset of the stimulus.

For connectivity analysis

The connectivity analysis was performed using the Matlab Fieldtrip Toolbox (Oostenveld, Fries, Maris & Schoffelen, 2011)). First, the data was segmented between - 4000 ms to 4000 ms and separated between alert status and multisensory condition. The data were resampled to 521 with a baseline of -2500 to -500 ms filtering between 8 to 12 Hz.

We applied a Hilbert transformation over the segmented data and used a phase-locking value (Cohen, 2014). We then plotted in a 300 ms window between 700 ms - 3100 ms after the onset of the stimulus.

Results

Sorting of states

The alert and drowsy conditions were separated by a classification algorithm (Jagannathan et al., 2018b).EEG was recorded from thirty subjects, yielding a total of 13500 trials. The number of non-answer trials was 40 (\Box = 1.36 SD = 2.37) and excluded from the analysis. A total of 13460 trials were analysed. The classification processing yielded 7324 alert trials and 6136 as drowsy. The proportion of trials was 54.4% alert and 45.6% drowsy state. The average number of trials by participant and state were \Box = 244.1 SD = 139.5 for alert and \Box = 204.5 SD = 140.4 for drowsy (Figure 2 and 3).

Behavioural results

Response time (rt) and accuracy were assessed for coordinated and uncoordinated stimuli during alert and drowsy states, excluding any trial with a non-answer response and any outlier (Uncoordinate visual stimuli at 700 ms or 1000 ms with Grubb's test). We did not control by sleep hours. The rt and accuracy mean and standard deviations by alertness state, conditions and the combinations were summarized in Tables 2 and 3. During the alert condition no statistical difference was found between coordinated and uncoordinated conditions in rt (f = 0.031, p = 0.861) or accuracy (f = 0.459, p = 0.5). The same was found for the drowsy state, where there was no difference between the coordinate and uncoordinated condition in rt (f = 0, p = 0.998) or accuracy (f = 0.099, p = 0.754). Next, we evaluated the difference between the states of consciousness. For the coordinated alert state versus the coordinated drowsiness states, we did not find any statistical difference for rt(t = 0.38, p = 0.69) or accuracy (t = 0.76, p = 0.44). The same was for the uncoordinated 700 visual stimuli offset between alert and drowsy rt (t = 0.36, p = 0.71) or accuracy (t = 1.07, p = 0.28) and for the uncoordinated 1000 visual offset between alert and drowsy rt (t = -0.28, p = 0.77) or accuracy (t = 0.94, p = 0.34) (figure 2-5).

We questioned if a certain frequency band could explain these results. We run a mixed model analysis to the accuracy and reaction times (table 4). To the accuracy values, we did not find modulation effects in the power of beta (t = -0.711, p > 0.05), alert status (t = 1.885, p > 0.05), or condition (t = 1.400, p > 0-05). We did find a modulation of reaction times to the power of beta (t = 3.95, p < 0.00) and to the alert status (t = -5.166, p < 0.00) but not to the condition (t = 0.186, p > 0.05) (figure 6).

Differences by sensory modalities on each state

We performed an electrode by electrode comparison with a permutation test with extreme values correction between the conditions and alert-states in Alpha (8-12 Hz), Beta (13-29 Hz), and Gamma (30 – 48 Hz) power. During alert state, coordinated vs uncoordinated visual conditions did not show statistical differences in Alpha, Beta, or Gamma power (p > 0.05). The coordinate and uncoordinated visual condition within the Drowsiness state did not show statistical differences in Alpha, Beta, or Gamma power (p > 0.05) (Figure 7). Finally, we compared the coordinate vs uncoordinated auditory condition within the Alert state did not show statistical differences in Alpha, Beta, or

Gamma power (p > 0.05). Similarly, the coordinate vs uncoordinated auditory condition within the Drowsiness state did not show statistical differences in Alpha, Beta, or Gamma power (p > 0.05) (Figure 8).

Oscillatory differences between alertness states in coordinated conditions were found on Alpha and Gamma bands. We performed an electrode by electrode comparison with a permutation test with extreme values correction in the same condition (coordinated or uncoordinated) but differentiating according to the conscious state (alert vs drowsiness). The first comparison was between coordinated condition between alert and drowsiness state in Alpha power in the range of 300 ms from the onset of the stimulus. We observed statistical differences in each time range (700 ms to 3100 ms) in the electrodes P1, PO7, PO3, CP3, CP1, P3, O1, Iz, Oz, CPz, Cz POz, Pz, P2, P4, P6, P10, PO8, PO4, O2 (p < 0.05) with variations on each time windows (figure 9). Next, we performed the same statistical analysis on beta power but did not find statistical differences in the electrodes F5, FT7, FC5, FC3, C3, C5, T7, TP7, CP5, CP3, F4, F6, F8, FC4, FC6, C4, C6, T8, CP6, CP4, P6 (p < 0.05) (Figure 9).

Then, we evaluated the variatons between alertness and drowsiness state in the uncoordinated conditions. We found differences in Alpha and Gamma accordingly to the sensory modality which change its frequency first. When the visual stimulus change its frequency at 700 ms we find a statistical difference between alert and drowsy state on Alpha power (figure 10) in C1, CP1, P1, P3, P5, P7, PO7, PO3, 01, Iz, Oz, POz, Pz, CPz, Cz, C2, C4, CP6, CP4, CP2, P2, P4, P6, P8, P10, PO8, PO4, 02 (p < 0.05). We did not find a difference in Beta power or Gamma power (p > 0.05). When the auditory stimulus changed its frequency first we did not find any statisyical difference in Alpha power (p < 0.05). In Beta power, we did find a consistent difference in two electrodes (T7, AF8) at 2500 ms - 3100 ms (supplementary figure 3). We also observed a difference from 1900 ms to 3100 ms in Gamma power (figure 11) in the electrodes F7, FT7, FC3, C3, C5, T7, CP5, CP3, Fpz, AF8, FT8, C6, CP6 (p < 0.05).

Synchrony activity

We calculated the Phase Locking Value between each condition and alert state and an electrode by electrode comparison with a permutation test with extreme values correction. We observe Alpha (8-12 Hz), Beta (13-29 Hz), and Gamma (30 – 45 Hz) frequency. The coordinated compared to the uncoordinated visual at 700 ms within the alert state did not show statistical differences in Alpha, Beta, or Gamma power (p > 0.05). The coordinated compared to the uncoordinated visual at 700 ms within the drowsiness state did not show statistical differences in Alpha, Beta, or Gamma power (p > 0.05). Finally, we compared the coordinated to the uncoordinated auditory at 700 ms within the Alert state and we did not observe statistical differences in Alpha, Beta, or Gamma power (p > 0.01). Similarly, the coordinated to the uncoordinated auditory at 700 ms within the drowsiness state did not show statistical differences in Alpha, Beta, or Gamma power (p > 0.01). In conclusion we did not find any differences in phase locking value in Alpha, Beta or Gamma between coordinated and uncoordinated conditions.

Next, we performed an electrode by electrode comparison with a permutation test with extreme values correction in the same condition (Coordinated or Uncoordinated) but differentiating according to the conscious state (Alert vs Drowsiness). We did not find any statistical differences in Beta or Gamma between in any conditions considering the alert state (p > 0.01). Nevertheless, we find statistical differences in Alpha band between coordinated alert state and uncoordinated drowsiness state. We observed a desynchronization in the electrodes Fp1, AF7, AF3, F1, F3, F5, F7, FT7, FC5, C5, Fpz, Fp2, AF8, AF4,, AFz, Fz, F2, F4, F6, F8, FT8, FC6 (p < 0.05) with variations across time windows (figure 12 a) (supplementary 5).

Then we evaluated Uncoordinated visual stimulus at 700ms between alert and drowsiness on Alpha. We also find a desynchronization in electrodes AF7, F5, F7, FT7, Fpz, F8 (p < 0.01) (figure 12 b). In the uncoordinated auditory stimulus at 700ms, we find a desynchronization in Alpha in the electrodes Fp1, AF7, F5, F7, FT7, FC5, Fp2, AF8, F8, FT8, P10 (p < 0.01) (figure 12 c). We did not find differences in connectivity in Beta or Gamma frequency (p > 0.01).

Discussion

What does it mean the power changes?

Multisensory integration studies are usually made with alert subjects, but how the activity changes when people lose contact with their surroundings when they fall asleep has been poorly understood. As we classified the trials between alert and drowsiness, we observed that while the subjects were alert and the stimulus was coordinated, there was a diminished power in Alpha in occipital electrodes and a bilateral activity of Gamma parietal-temporal electrodes. This activity was different when the presentation was uncoordinated. We observe a diminished Alpha power in occipital electrodes when the visual stimulus changes before the auditory stimulus. By contrast, when the auditory stimulus change first, we observe an increment in Gamma bilateral.

Research dealing with multisensory integration generally disregard which sensory modality changes first. We found that the sensory modality initiating the discoordination does matter. We observed differences related to which sensory modality change first when we are alert and drowsy. We found changes in the alert coordinated and uncoordinated condition in Alpha. Alpha is a critical element of attention (Foxe & Snyder, 2011). For example, when subjects have to change between exogenous or endogenous attention in a Gabor rotation discrimination task, there was a decrease of Alpha in occipital lateralized electrodes independently of the location of the attention. (Keefe & Störmer, 2021). Also, Alpha has been related to a multisensory integration temporal window through the phase of the frequency band in a task where a visual stimulus moves closer in time with auditory stimulation, showing that Alpha predicts the simultaneity perception. (Bastiaansen et al., 2020). We could observe this alpha modulation present in coordinate and uncoordinated conditions between states. However, this modulation is absent when the auditory stimulus changes first.

We observe a different modulation in the auditory condition, where Alpha is gone, and Gamma takes its place. We observe changes in the coordinated condition between alert and drowsiness state and the uncoordinated condition when the auditory signal changes first. How can we explain these changes? Gamma has been related to auditory processing (Ikegaya et al., 2019; Schadow et al., 2007). For example, when subjects had to listen to a music sample, Gamma was present in the superior temporal sulcus (STS), predicting the appearance of Alpha in the auditory processing. (Potes, Brunner, Gunduz, Knight, & Schalk, 2014). The absence of Gamma in the uncoordinated condition when visual modality changes first and the lack of Alpha when the acoustic modality change rather could be a sign that there is a different mechanism that changes accordingly with the sensory modality guiding the discoordination.

The different frequencies related to the uncoordinated stimulus are not coherent with the absence of behavioural differences. We propose that these differences exist because when some sensory modality change first, that information guides the perception of a multisensory stimulus. This approach corresponds with the "Modality Appropriate Hypothesis", which posits that the sensory modality which fits better with the task will guide the multisensory integration process (Guttman, Gilroy, & Blake, 2005; Kitagawa & Ichihara, 2002; Talsma, Senkowski, Soto-Faraco, & Woldorff, 2010; Welch & Warren, 1980). The process behind this change could be related to a recalibration guided by the

sensory modality that changes. Recalibration is a mechanism proposed to ensure a coherent perception of our surroundings (Bruns & Röder, 2015). In this task, the recalibration could start when the audio-visual stimulus is uncoordinated in time. Alpha will influence the perception of a coordinated audio-visual stimulus and when the visual element changes first. Gamma will contribute to the same recalibration effect when the auditory element changes first.

But what happens explicitly when we are drowsy? Alpha shows only an increment between 2.3 - 3.1 ms and a decrease of gamma-band during the task (see supplementary figure 4) in the coordinated and visual uncoordinated condition. The increment of Alpha activity could be related to disengagement from the task after the multisensory judgement has been made. On the other hand, the increase of Alpha has been seen in the early stages of sleep transitions (e.g., Hori 1 and 2 (Goupil & Bekinschtein, 2012)) and in the unconscious state induced by anaesthetics (Hight, Voss, Garcia, & Sleigh, 2017). So it is possible that before the subjects respond, Alpha would be related to attentional processes that end when the subject responds, rapidly returning to the EEG characteristics of drowsiness state. Another possible explanation for the increase in alpha power is shifting attention from the exterior to the interior. Some studies have reported that when subjects disengage from an external task, there is an increment of alpha power related to inhibition from bottom-up processing and more focused on the internal states of the subject (Benedek, Schickel, Jauk, Fink, & Neubauer, 2014; Fink & Benedek, 2014). Nevertheless, due to a lack of systematic data according to the participants' answer strategies, it is not easy to interpret which of these two options is a better explanation.

In the case of gamma-band activity, when we compare alert versus drowsiness, we can see an increment in the alert condition (Figures 1 and 3). But a closer analysis separating each state shows us no Gamma activation when the subject is alert; instead, there is a stronger decrement during the drowsy state in coordinated and visual uncoordinated conditions (supplementary figure 4). Decreases of gamma power have been related to habituation due to exposure to an overtrained task (Madhavan et al., 2015). In this paradigm, the subject was confronted with the same combination of sequences for a considerable amount of time (90 minutes). When we explored the activity of Gamma before the stimulus change (0 – 700 ms), we found that there was a significant decrease of Gamma (p < 0.05) in this range of time. So Gamma activity could be related to learning the sequence of the task. Inhibition of Gamma has been reported to be linked with the continuous exposure to the same task and could be unrelated to multisensory processes (Choi, Lee, & Lee, 2018; Robinson & Sloutsky, 2004),

One significant limitation of this study is the nature of the task. The absence of any substantial difference between the uncoordinated and coordinated presentation of an audio-visual stimulus could be related to how easy was the task to perform. Because the time needed to complete the task was long (90 minutes), and the task itself was repetitive. The time required to complete a task has been inversely related to the engagement on a task. A more extended task is related to more fatigue perceived (Rosenbaum & Bui, 2019). After completing the experiment, the subjects systematically report the tediousness of the task. Second, after being exposed to the same stimulus variation, an anticipatory state improves the performance on the different variations of the task, especially in the reaction times (McKinney & Euler, 2019). Finally, but not less important, is the decision to create this kind of stimulus. One big problem in multisensory studies is the number of different approaches to the phenomenon, from speech analysis (Lin, Liu, Liu, & Gao, 2015), to animals (Chen & Spence, 2010). These complex objects could contaminate the neural activity of the multisensory perception, which could be more related to the content

of the stimulus than to the phenomenon itself (Boncompte & Cosmelli, 2018), so we decided to present the most straightforward stimulus. These three elements, the amount of time on the task, the anticipatory state, and the stimulus's nature, could be related to the null differences between conditions.

Finally, even when we do not have behavioural differences, we have differences in the brain's electrical activity. To summarise, we have changed between Gamma and Alpha during the state of the subject. Why we do not have behavioural differences between states, but we do have differences in neural activity? To tackle this problem, we will be referred to the decision-making process in a multisensory approach. It has been reported in several studies that early sensory cortices respond to different sensory modalities (For review, Kayser & Logothetis, 2007). For instance, one study trained a monkey to discriminate the coherence between an audio-tactile stimulation. Even when they found the activity of neurons in opposite sensory cortices (e.g. auditory cortices responding to tactile stimulation), these activities did not inform the multisensory decision about the coherence nature of the stimulus (Lemus, Hernández, Luna, Zainos, & Romo, 2010). There is a difference between the activity of neurons and the perceptual multisensory decision. It means that different steps in multisensory processing constantly interact (Bizley, Jones, & Town, 2016). These elements could create a compensatory effect while awareness fades. Specifically, Gamma would be involved in maintaining a performance due to repetition of the task, while Alpha would be related with the visual processing and possibly enhancing the auditory features of the stimulus (Barutchu, Spence, & Humphreys, 2018; Faivre, Mudrik, Schwartz, & Koch, 2014).

These results suggest that these compensatory mechanisms could play a role when consciousness fades, giving the subject a degree of control before falling asleep. Nevertheless, a more complex stimulus is needed to examine these mechanisms more closely.

The relationship between behaviour and beta power in multisensory integration

We measured the reaction times and accuracy of the participants to the multisensory presentation. We did not find any statistical difference between coordinated and uncoordinated presentation or alertness versus drowsiness. Nevertheless, we did find that the power of beta was correlated with the reaction times. Specifically, we observed that the reaction times were fastest at the stronger beta frequency (13 - 16hz).

These behavioural results are not the expected results in multisensory integration experiments. Accordingly, with the redundancy paradigm, the presentation of a single stimulus through different sensory modalities should increase the response to the stimulus, and this could be measured as reaction times. The coordinated multisensory stimulation would produce the fastest reaction times (Colonius & Diederich, 2017). These quicker reaction times are present in different multisensory paradigms relating Beta and Gamma band with the behavioural response (Barutchu et al., 2018; Harrar, Harris, & Spence, 2017; Krebber, Harwood, Spitzer, Keil, & Senkowski, 2015; Senkowski et al., 2006).

How can we explain this absence of reaction times facilitation? We did not find any differences in reaction times in coordinated stimulus presentation, but also we did not find differences in beta. Why is beta essential? First, power variations in beta are associated with multisensory integration (Gleiss & Kayser, 2014; Göschl, Friese, Daume, König, & Engel, 2015; La Rocca et al., 2020; Michail, Senkowski, Niedeggen, & Keil, 2021). Furthermore, when subjects respond whether a red circle is simultaneous with a specific sound, the reaction times are faster in coordinated presentation. These faster reactions are related to an increase in frontal, central and occipital beta power. These results concluded that beta mediated behavioural response to multisensory stimulus (Senkowski et al., 2006). We did not find differences between coordinated or uncoordinated neither in behaviour nor beta power. Nevertheless, we found a negative correlation between reaction times and beta power (supplementary figure x).

What is the relationship between the reaction times, beta activity and multisensory integration? Beta has been closely related to motor preparation. This beta activity could be modulated by reward (Savoie et al., 2019) or even by the degree of uncertainty of the task (Tzagarakis, West, & Pellizzer, 2015). It is unclear how beta is generated or whether the motor components are part of this. Nevertheless, the phenomenon's hypothesis suggests a possible network of coordination between frontal and parietal areas mediated by beta due to top-down processes (Khanna & Carmena, 2015). These attentional processes could affect the reaction times of a subject directly. It has been shown that increases in "low beta" will maintain the current movement generating faster reaction times and decreasing slower reaction times (Chandrasekaran, Bray, & Shenoy, 2019). Our results indicate a negative correlation between low beta and alertness state in reaction times, which, according to the beta attentional hypothesis, will be related to increased engagement with the task when the subjects were awake. The fact that neither the reaction times nor beta power show statistical difference between states could be due to the maintenance of beta during the transition inducing faster reaction times. Beta has been related to cortical arousal during non-rem sleep (Wu et al., 2013) and could function as a compensatory mechanism (Bruns & Röder, 2015), supporting the motor response and maintaining the subject's performance.

Relationship between the alertness state of the subject and connectivity

We performed a Phase Locking Value (PLV) analysis of the data to assess changes in connectivity between conditions (Coordinated and uncoordinated) and state (Alert versus drowsy). We did not find any statistical differences between conditions; nevertheless, we did find statistical differences between states across all conditions. There was a higher desynchrony of alpha activity in frontal electrodes when the subjects were alert.

What is Alpha desynchronization? The synchronization of brain rhythms (Buzsáki, 2009) has been closely related to cognitive functions (Varela, Lachaux, Rodriguez, Eugenio, & Martinerie, 2001). Nevertheless, the phenomenon of alpha desynchronization is poorly understood. On the one hand, it has been defined as a decrease in power due to a higher load of cognitive functions (Benedek, Bergner, Könen, Fink, & Neubauer, 2011) and better behavioural performance (Phukhachee, Maneewongvatana, Angsuwatanakul, Iramina, & Kaewkamnerdpong, 2019). But also as a reduction of connections in eyes-closed compared to eyes-open conditions (Gómezramírez et al., 2017).

It has been argued that alpha desynchronization is related to opening the eyes due to the influence of light on the system. This open-eye condition will be translated into the involvement of the reticular activating system (Barry, Clarke, Johnstone, Magee, & Rushby, 2007) or a higher level of alertness (Gómez-ramírez et al., 2017). Nevertheless, we argue that it is more related to attentional processes. Decreases of alpha power have been related to increased performance on attentional tasks due to a suppression of nonrelevant events (Phukhachee et al., 2019). One example is the decrement of performance in patients with brain injury in frontal areas related to an absence of variations in alpha power (Dockree et al., 2004).

The alpha role seems to be a pivotal element to sustain attention, specifically in tonic alertness, which is defined as the readiness to respond maintained in time. This definition differentiates voluntary attention related to the participant's implicit commitment to respond (Hayward & Ristic, 2018). Considering that the fluctuations found in alertness are strongly correlated with alpha variations (Sadaghiani et al., 2010), we infer that the desynchronization of Alpha on the alert state could be a marker of a higher degree of alertness. The decrease in alpha power is related to the inhibition of other nonrelevant stimuli, increasing voluntary attention in the dorsal attentional network (Gómez-ramírez et al., 2017; Sadaghiani et al., 2010). Our results would be more closely related to an attentional phenomenon than to a change in the eyes' openness because our participants were with the eye closed for the entire task. This process would be independent of the synchronization of multisensorial stimulus, reflecting a state of the system responsiveness to the task more than to the influx of light to the retina. This interpretation holds since alpha desynchronization is absent when the participant is drowsy.

To summarize, the desynchronization of Alpha in an alert state would reflect a state of the attentional system to respond to the influx of information of the multisensorial stimuli, decreasing this ability in drowsiness. This activity will be more related to task engagement than to a condition of the eyes, making the Alpha desynchronization a neurophysiological marker of tonic and sustained attention.

Conclusion

Our objective was to characterize the multisensory integration on the transition to a different state of alertness. We based our research on the assumption that every integration of sensory information must need a long-range connection between the areas involved. Nevertheless, our results indicate different elements according to this alertness modulation of multisensory integration.

First, we have to address the fact that the behavioural paradigm was too easy for the participants. We can see this in the outcomes of reaction times and accuracy with faster responses and high precisions. Nevertheless, we observe how the beta power predicts the reaction time to the task. This modulation of beta could be related with an engagement to the task accordingly with the alert status, reduced drowsiness but not enough to make a difference between conditions but strong enough to act as a compensatory mechanism that sustains the motor response.

Secondly, we have the difference in power, which is different accordingly with alert status and sensory modality in the uncoordinated conditions. The involvement of alpha and gamma are critical to show the difference in the dynamic of cerebral activity and the possible compensatory effects in front of uncoordinated presentations of a multisensory stimulus. The interplay between these two frequency bands could sustain the perception of a stimulus accordingly to the sensory modalities involved.

Finally, we have the desynchrony of alpha, which could be directly related to an attentional mechanism, which could be associated with the system's state to the influx of information. These results reinforce the knowledge about the nature of alpha desynchrony. This neurophysiological activity could be a marker of alertness independently of the content of the stimulus.

These results indicate that we facilitate the influx of information due to alpha desynchronization when we are awake in front of multisensory stimuli. Differences between conditions are modulated between alpha and gamma. In coordinated conditions, both appear in response to the audiovisual stimulations and differentiate each other in uncoordinated conditions related to the sensory modality that change. Even when almost all these mechanisms decrease drowsiness, we argue that beta is vital in sustaining the response. Nevertheless, we cannot exclude the effect of the task on the performance due to the nature of the task. The participants' performance was good enough, independently of the condition of status. We observe a tendency to increase reaction times and decrease precision, but not enough to show a statistical difference. These results demand a more challenging task that could throw us into the light of the mechanism which sustains behavioural response and confirm the relevance of beta in this compensatory mechanism.

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Figure 1. Audio-visual stimulation with different frequencies. A) The fade in and fade out of the short audio-visual pulse. B) The fade in and fade out of the long pulse. Both are in the same pulse length in coordinated conditions, and they mix in uncoordinated conditions. C, D, E) The phases of presentation of the audio-visual stimuli in coordinated and uncoordinated conditions. E) Description of the timeline of the task presentation with an extended modality (increase drowsy) and with self-administered rest (Increase alertness).



Figure 2. The distribution of trials of alertness and drowsiness by participants. The number of trials by participants was 450. The minimum amount of trials by each state was 9 in alertness and 19 in drowsiness. The average of trials of each state was of 244 (s 139) for alertness and 204 (s = 140) for drowsiness in 30 participants.



Figure 3. Total proportion of trials across participants. When we observe the total distribution of trials we observe a close proportion of trials in each state. We performed

a t test between the trials by state and we did not observed significant difference (p < 0.05)



Figure 4. There are no statistical differences between states in reaction times. The X-axis show the reaction times and, in the Y-axis, the different states. In red, we observe the boxplot of alert and in blue the drowsy state. The differences between both are not significant.



Figure 5. There are no statistical differences between conditions in reaction times. The X-axis show the reaction times and, in the Y-axis, the different conditions. In red, we observe the boxplot of coordinated presentation, in blue the uncoordinated auditory presentation and green the uncoordinated when visual changes first at 700 ms. The differences between both are not significant.



Figure 6. There are no statistical differences between states on accuracy. The X-axis shows the accuracy of the perceptual decision, the objective presentation, and the different states in the Y-axis. In red, we observe the boxplot of alert and in blue the drowsy state. The differences between both are not significant.



Figure 7. There are no statistical differences between conditions on accuracy. The X-axis shows the accuracy of the perceptual decision, the objective presentation, and the different states in the Y-axis. In red, we observe the boxplot of coordinated presentation, in blue the uncoordinated auditory presentation and green the uncoordinated when visual changes first at 700 ms. The differences between both are not significant.



Figure 6. The mixed model reveals modulation effects over reaction times due to beta power and status. In the Y-axis, we see the effects of alert or drowsiness (Status), beta power and interaction. In the X-axis, we see the estimates of the reaction times. We observe the values of prediction between beta power (p < 0.00) and alert status (p < 0.01) in the reaction times are significant, but not in the interaction between variables.



Figure 7. Non-Statistical differences reported in power in coordinated and uncoordinated visual presentation of multisensorial stimli. In the first column we observe the power of coordinated (a), uncoordinated (b) and the difference score between them (c) in alert-state. The differences observed did not reach statistical difference. In the second colum we observe the power of coordinated (d), uncoordinated (e) and the difference observed did not reach statistical difference. In the second colum we observe the power of coordinated (d), uncoordinated (e) and the difference score between them (f) in the drowsy state. The difference observed did not reach statistical difference.



Figure 8. Non-Statistical differences reported in power in coordinated and uncoordinated auditory presentation of multisensorial stimli. In the first column we observe the power of coordinated (a), uncoordinated (b) and the difference score between them (c) in alert-state. The differences observed did not reach statistical difference. In the second colum we observe the power of coordinated (d), uncoordinated (e) and the difference score between them (f) in the drowsy state. The difference observed did not reach statistical difference.



Coordinate alert vs drowsiness

Figure 9. Changes in Alpha and Gamma to coordinated stimulus between alert and drowsiness. We calculate the difference between alert and drowsiness in the coordinate condition. Each asterisk in red is an electrode with a statistical difference of p < 0.05. There is a decrease of occipital Alpha through the task since the start of the task and an increment of Gamma starting at 1000 ms (see supplementary figure 1).



Uncoordinate visual alert vs drowsiness

Figure 10. Changes in Alpha to an uncoordinated stimulus where the visual stimulus change at 700 ms between alert and drowsiness. We calculate the difference between alertness and drowsiness in the uncoordinated visual condition. Each asterisk in red is an electrode with a statistical difference of p < 0.05. There is a decrease of occipital Alpha through the task since the task's start and as in the uncoordinated condition (see supplementary figure 2).



Uncoordinate auditory alert vs drowsiness

Figure 11. Changes in Gamma to uncoordinated stimulus where the auditory stimulus change at 700 ms between alert and drowsiness. We calculate the difference between alertness and drowsiness in the uncoordinated auditory condition. Each asterisk in red is an electrode with a statistical difference of p < 0.05. There is an increment of lateralized Gamma throughout the stimulus (see supplementary figure 2).



Figure 12. Alpha desynchronization is present in all conditions and is higher in an alert state. We observe the connectivity of Alpha in frontal electrodes thorough the task. In red, we observe the drowsy state and in blue the alert state. The grey area is the standard deviation. We can observe an increase in connectivity in drowsy versus alert across all conditions.

<u>Tables</u>

Table 1

Conditions for the experiments

		Alert	Drowsy	
	Coordinated	Behavioural,	Behavioural,	
neuro		neurophysiology and	neurophysiology and	
		neurodynamics	neurodynamics	
Participant		measures	measures	
	Uncoordinated	Behavioural,	Behavioural,	
		neurophysiology and	neurophysiology and	
		neurodynamics	neurodynamics	
		measures	measures	

Table 2

Reaction Times means and standard deviations by state and conditions in ms

	Mean	SD
Alert	2367.621	389.7170
Drowsy	2354.279	371.0277
Coordinated	2319.450	357.9575
Uncoordinated visual	2417.218	418.6109
Uncoordinated audio	2346.695	358.5908
Alert coordinated	2336.945	346.6259
Alert uncoordinated visual	2400.924	416.6270
Alert uncoordinated audio	2366.132	415.5073
Drowsy coordinated	2301.954	374.4709
Drowsy uncoordinated visual	2400.924	427.5505
Drowsy uncoordinated audio	2327.953	300.3009

Table 3

Accuracy means and standard deviations by state and conditions

	Mean	SD
Alert	0.517	0.432
Drowsy	0.504	0.411
Coordinated	0.513	0.447
Uncoordinated visual	0.508	0.409
Uncoordinated audio	0.510	0.410
Alert coordinated	0.525	0.460
Alert uncoordinated visual	0.513	0.428
Alert uncoordinated audio	0.513	0.421
Drowsy coordinated	0.502	0.422
Drowsy uncoordinated visual	0.503	0.397
Drowsy uncoordinated audio	0.507	0.407

Table 4

Mixed models of beta power and alert status in reaction times

Fixed effects					
	Estimate	Std. Er	ror df	t value	Pr(> t)
(Intercept)	2659.543	98.391	27.555	27.030	< 2e-16 ***
Alert Status	96.347	31.127	27.577	3.095	0.00448 **
Beta	-101.323	19.614	22.478	-5.166	3.31e-05 ***
Alert Status : Beta	0.356	1.909	7746.550	0.186	0.85209

Supplementary figures

Supplementary

AlphaImage: Definition of the second second

Supplementary 1. Changes in power in the coordinate condition between alert and drowsiness in Alpha, Beta and Gamma throught the task.

Coordinated alert vs drowsiness

Uncoordinated visual alert vs drowsiness



Supplementary 2. Changes in power in the coordinate condition between alert and drowsiness in Alpha, Beta and Gamma throught the task.

Uncoordinated auditory alert vs drowsiness



Supplementary 3. Changes in power in the coordinate condition between alert and drowsiness in Alpha, Beta and Gamma throught the task.



Supplementary 4. Characterization by condition and state of power related with Alpha and Gamma against the baseline.



Supplementary 5. Phase Locking Value topoplot across time, status and conditions.