Assessing the oscillatory properties of functional connections between sensory areas during crossmodal illusions: A correlational and causal investigation.

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Contents

General Abstract:

A comprehensive investigation on multisensory integration is presented whereby three complex studies investigating the role of neuro-oscillatory processes in tactile-visual and auditory-visual illusory tasks were conducted. Utilising EEG scanning we first replicated previous evidence of a correlation between individual alpha frequency and the auditory-induced Double Flash Illusion (DFI). We also provided evidence of a previously unreported correlation between individual beta frequency and the corresponding tactile-induced DFI. In two follow-up studies evidence is also provided of a causal relationship between beta processes and the tactile-induced DFI using a variant of paired associative TMS known as cortico-cortical Paired Associative Stimulation. Here we demonstrated by temporarily reducing occipital beta speed we can subsequently produce reliably predictable changes in the temporal profile of visuo-tactile multisensory processing. Using two control measures across two investigations we provided evidence suggesting that the stimulation that we utilised was both frequency specific and hemisphere specific. From this we concluded that multisensory processes are facilitated by the oscillatory properties of network-specific (auditory-to-visual or somatosensory-to-visual) neural connections favouring optimal, directional neural communication and integration between the senses.

1. Chapter One: General Introduction:

1.1. Introducing unisensory and multisensory processing:

Simplistically speaking, our senses act as something of a bridge connecting our mind with our environment. These allow us to perceive stimuli occurring outside (and within) our body to promote efficient perception and navigation of our world.

It is commonly stated in popular literature that we have five senses (often listed as sight, hearing, touch, taste and smell). However, this assertion is erroneous; in truth we have many more. This of course, includes the well-known five, alongside other less obvious senses. These include nociception (the sensation of painful or harmful stimuli, (Snider & McMahon, 1998)), proprioception (the sensation of knowing where our limbs and body parts are without necessarily seeing them, (Graziano, 1999)), interoception (the awareness of how your body feels physiologically (Craig, 2003)), and even chronoception (the perception of the passing of time, (Rao, Mayer, & Harrington, 2001)).

Despite the large number of senses we have at our disposal, typically within the literature, studies mainly focus of the five "classical" senses, compared to the other less obvious domains, and critically, they are mostly investigated in isolation. Only relatively recently has literature started to shed light on the relevance of how our senses interact to produce an integrated, multisensory percept (Kayser & Logothetis, 2007; Kayser & Shams, 2015). Of particular relevance have been investigations of the sensation of sight, hearing and touch, which will represent the main area of investigation in the current report and will be introduced in greater detail, mainly from a multisensory perspective.

The sensation of vision was once thought of as the dominant sensory domain (Heron, Whitaker, & McGraw, 2004; Posner, Nissen, & Klein, 1976). In fact it is still probably

thought of as one of (if not) the most important domain when it comes to interacting with one's environment. Visual information is processed in the visual cortex within the occipital lobe, an area situated in the posterior part of the brain. This area is segmented into 5 different visual areas (Visual area 1 (V1) – Visual area 5 (V5)), with each area processing more complex information than the last. This essentially acts to build up a complex picture of our environment involving shapes, colours, textures, contours and movement (Grill-Spector & Malach, 2004).

Unisensory auditory information is processed in the auditory cortices, these are located just above the ears in the temporal lobe. Interestingly these areas of the brain appear to be primarily tasked with conscious sound perception only. This means that when this area is damaged subjects can often lose the ability to perceive sounds. Research has shown however that these individuals can still demonstrate a reactionary response to loud noises. This is because some basic auditory information is also processed in the mid brain and the brainstem (Skoe & Kraus, 2012; Strait, Kraus, Skoe, & Ashley, 2009).

Tactile information is processed in the parietal lobe; this area of the brain houses the somatosensory cortex. This area is predominantly tasked with the perception of physical sensations, this can include perceiving touch, pain, texture and temperature (Franzén, Johansson, & Terenius, 1996; Robles-De-La-Torre, 2006). The primary somatosensory cortex is itself often stated as being functionally linked to the motor cortex, which is often referred to as the sensorimotor cortex. Perhaps unsurprisingly given its name this area of the brain also allows the processing of motor information, allowing us to move effectively and efficiently throughout our environment.

These sensory systems were once thought to perform their processes early and in isolation. Only at a later point in time and in higher order areas was it thought that this information was integrated to form multisensory precepts of the world. Hence, each area has long been investigated as exclusively processing unisensory information (Kayser & Logothetis, 2007). However, it has increasingly become clear over the past few decades that instead of processing sensory information in isolation we must instead use a specific process to combine complex environmental multisensory information into one logical perceptual whole. This idea is highly logical when you look at real life examples of interacting with one's environment. Take, for example, the act of knocking on a door: whilst we see our outstretched hand in front of us we also feel the pressure on our knuckles as they strike the door and hear the resulting sound that this action makes. Clearly these three sensory events are related, but how does our brain combine these into a single logical percept? There must exist a mechanism to integrate the different sensory components so as to allow the perception of multisensory events as being a single multisensory whole as opposed to a series of unrelated unisensory sensations. So how does it work that despite being separated in different physical locations in the brain our senses are eventually integrated together?

Initial models of multisensory integration postulated a late integration process. Here it was believed that each unisensory system initially processes information in isolation and only at a later point integrates the separate sensory events into an integrated whole (Ghazanfar & Schroeder, 2006; Kayser & Logothetis, 2007). However, recent research has provided empirical evidence against this serial late model, in favour of early multisensory integration (Alais, Newell, & Mamassian, 2010). This has even been shown to occur within what have been generally considered unisensory areas of the brain (Giard & Peronnet, 1999; Molholm et al., 2002; Watkins, Shams, Tanaka, Haynes, & Rees, 2006).

To truly appreciate how important the multisensory system is, one must consider the adverse effects on mental and physical health when the system becomes damaged. Indeed, the loss of even just a single sensory domain can cause a feeling of detachment from one's environment or a feeling of detachment from one's self, when compared with healthy controls, subsequently affecting an individual's mental health (Jauregui-Renaud, Ramos-Toledo, Aguilar-Bolanos, Montano-Velazquez, & Pliego-Maldonado, 2008). However, those suffering with the loss of (or at least some form of damage to) their capacity to integrate unisensory information into a single multisensory percept, have been shown to exhibit perhaps more serious consequences. A condition known as Sensory Integration Dysfunction (SID) (Goldstein & Morewitz, 2011) typified by a poor ability to integrate multisensory information, has been linked with learning difficulties, and extreme anxiety or panic attacks. What is more, this condition is surprisingly common, with 15% of children experiencing the condition to some degree at some stage during their development. Whilst most sufferers tend to grow out of it, this condition can often result in delayed learning and noticeable difficulties later in adult life (Stepp-Gilbert, 1988).

There is also another condition that highlights the potential fallibility of multisensory integration, this is named synaesthesia. This condition is a sensory disorder that was at first thought to be very rare, but research now suggest may affect around 2 – 4% of the general population (Brang & Ramachandran, 2011; Simner et al., 2006). In this case, multisensory connections become scrambled, creating seemingly impossible and highly illogical pathways. This in turn can lead to a bizarre effect whereby the presentation of stimuli in one sensory domain may also result in the perception of another stimulus appearing in a secondary (unrelated) domain (Cytowic, 2002). For example, individuals have been reported who experience visual distortions, including colours, geometrical shapes and even words

when tasting food. These irrelevant perceptions also tend to appear reliable, with different tastes and flavour reliably inducing the same visual distortions across different times (Richer, Beaufils, & Poirier, 2011). Many other examples of this condition have been presented within the literature, including an individual who experienced skin tingling when presented with certain sounds (Beauchamp & Ro, 2008), another who could perceive sounds when presented with a visual flash (Saenz & Koch, 2008) and also an individual who could feel a touch sensation on their skin, when viewing another person being touched upon the same area (Blakemore, Bristow, Bird, Frith, & Ward, 2005).

These conditions demonstrate the importance of the integrity of multisensory processing and what happens when something goes wrong. However, multisensory processing also has been found to not just influence low level sensory perception but to represent the basis for a number of developmental and psychiatric disorders. Indeed, recent evidence has suggested that unisensory and multisensory degradation may also play some role in other, seemingly unrelated conditions. These include schizophrenia (Ross et al., 2007), autism (Foss-Feig et al., 2010; Kwakye, Foss-Feig, Cascio, Stone, & Wallace, 2011; Woynaroski et al., 2013) and even eating disorders such as anorexia nervosa (Gaudio, Brooks, & Riva, 2014) and obesity (Scarpina et al., 2016).

The pertinent issue here however is that furthering our understanding of both unisensory and multisensory processing is hugely important. By increasing our understanding we may be able to further inform our knowledge of these conditions, potentially developing therapies or treatments that exploit the brain's natural plasticity. This would be done with a view to ultimately facilitating normal functioning behaviour. Understanding multisensory information is not just important in our overall understanding

of neurological or physical conditions. We use this information regularly in our daily life to ensure prompt and efficient readouts of our environment.

What is often thought of as the seminal paper on multisensory integration provides a great example of how we use this system to make sense of our environment. In this investigation researchers investigated what role multisensory integration might play in simple speech comprehension. Sumby and Pollack (1954) looked at participants' overall efficacy in comprehending speech when a speaker's mouth was hidden compared to when their mouth was shown, essentially comparing unisensory speech comprehension (using just sound) with multisensory speech comprehension (using both sound and visual information). These researchers were able to demonstrate that when the person who was speaking had covered their mouth participants performed significantly worse in a test of speech comprehension (less than 20% words identified correctly). This was compared to the condition where the person who was speaking did not cover their mouth (with on average 40 – 80% of words identified correctly). What Sumby and Pollack (1954) demonstrated was that we simply find it easier to comprehend speech when we can make use of both auditory and visual information in combination than when compared to simply using auditory information alone. This large (and increasing) body of research highlighting the importance of the multisensory system leads us to ponder how and where exactly is this information processed and combined within the brain?

It is commonly accepted that one of the most important brain areas in multisensory processing is the superior colliculus (Meredith & Stein, 1986a; Meredith & Stein, 1986b). Research using cats has suggested that several types of sensory information may be processed here (Meredith & Stein, 1983; Meredith & Stein, 1986a; Meredith & Stein,

1986b). Interestingly there is also an increasing body of empirical evidence to suggest that brain areas that were once thought of as being strictly unisensory in nature can in fact also process information from a number of different domains. For example, the primary visual area, has also been shown to respond to other senses, such as touch (Amedi, Malach, Hendler, Peled, & Zohary, 2001).This point can be particularly pertinent when a person loses their ability to see and has to rely on their sense of touch in order to read. Braille is a reading system created by Louis Braille in 1824. It is a system specifically developed for visually impaired individuals, enabling them to read text via a series of raised, coded bumps that they feel with their fingers. Essentially it allows visually impaired individuals to bypass their disabled visual system and allows them to utilise their intact tactile processing to compensate for their inability to read. However, whilst this seems to be a simple process of learning which set of bumps correspond to which letter, the process is far from as simple as it seems. Here the brain is instead utilising its natural plasticity for it to process this new information.

Research conducted by Sadato et al. (1996) utilised Positron Emission Tomography (PET) to investigate the neural activity of visually impaired participants whilst they were asked to read passages of Braille. Whilst it was found that the somatosensory cortex displayed the normal levels of activation one would expect, surprisingly, an increased level of activation was also observed in the early visual areas. This is consistent with what you would expect should the participants be reading via their visual system as normal. In other words, the visual system has been engaged in those activities typical of reading by using a sensory input other than vision, but effectively to serve the same function. Interestingly this effect has been found to be relatively easy to induce in sighted participants. Unimpaired participants were asked to learn to read Braille over a relatively short time. While

blindfolded, brain activation was recorded during Braille reading. Eventually this resulted in the same level of visual cortex activation as the blind participants, even after just 5 days of learning (Pascual-Leone & Hamilton, 2001).

This effect is far from exclusive to the visual and the tactile domains. Research has demonstrated something of a counterpart to this effect in auditory and in visual areas. In this case visual, (or even in some cases somatosensory) information provokes a response in the auditory cortex of congenitally deaf adults (Karns, Dow, & Neville, 2012). Essentially, when communicating with hearing impaired patients via the use of sign language, these individuals' brains actually appear to "hear" the sign language, with higher levels of activity once again being observed in the auditory cortex (Nishimura et al., 1999). Researchers hypothesise that the neural plasticity of the brain enables it to exploit multisensory pathways (possibly via the lateral geniculate nuclei) in order to provide this compensatory tactic and effectively enable the blind to "see" (Sadato et al., 1996) or the deaf to "hear" (Nishimura et al., 1999).

One other possible explanation for this would be for the senses to essentially work as plug-ins to the corresponding neural systems. For example the eye is the best plug-in for processing visual information, however, it is not the only one. In the absence of a visual plug-in (for example blindness), other sensory domains can take over to inform what was classically processed as visual, thus maintaining the same level of specificity. One example of this would be for the visual domain to have the capacity to process spatial information over other sensory modalities, as would also be the case temporal information in the auditory domain.

In addition to the superior colliculus and (so called) unisensory areas of the brain, other regions have also been implicated in the processing of multisensory information. These include fronto-temporal regions (Giard & Peronnet, 1999) and parieto-occipital regions (Molholm et al., 2002). This is in addition to areas of the ventral premotor cortices, intraparietal cortices and the cerebellum (especially in the processing of visual and tactile multisensory combinations) (Ehrsson, Holmes, & Passingham, 2005).

Essentially what this evidence suggests is that there is a general lack of consensus on exactly where and how multisensory information is processed in the brain, with no key universal *multisensory cortex* having been uncovered. Instead of one single functional area, multisensory integration appears to take the form of a complex multisynaptic network spanning many areas of the brain (Cuppini, Magosso, Serino, Di Pellegrino & Ursino, 2007; Rowland, Stanford, & Stein, 2007).

Given the general lack of understanding in terms of how we process multisensory information and the surprisingly high occurrence of unisensory and multisensory conditions, such as SID (which may account for severe learning difficulties in children) investigating such a mechanism could be hugely beneficial. This is coupled with the co-occurrence of multisensory degradation and a number of psycho-physical conditions, a greater understanding of this seemingly complex system is vital. One very convenient way in which we can further investigate key properties of individual multisensory processing is by exploiting the functionality of multisensory processes with extreme situations whereby integrating incongruent information from different senses can lead to the perception of illusions. When presented with congruent sensory information our brains can easily combine this information to make sense of its environment. When however, this

information is incongruent, the brain often attempts to simplify this confusing information by outputting what it assumes to be the most logical percept. This often creates a scenario whereby the percept does not make logical sense or contradicts the actual nature of the stimuli. By presenting multisensory illusions to participants this enables researchers to carefully manipulate the parameters associated with these illusions as a way of uncovering new information about multisensory integration processes.

The following section will now look to describe some of these illusions in greater detail and to clarify their importance in the understanding of multisensory integration.

1.2. Illusions as a way of investigating multisensory perception:

Illusory tasks are a very convenient way in which we can investigate key properties of our underlying multisensory mechanisms. When presented with incongruent sensory information an individual's brain will attempt to understand what it is they are experiencing; this results in what it assumes to be the most logical outcome. In a laboratory setting, the parameters regarding the presentation of this incongruent information can be carefully manipulated (i.e. altering the intensity of one or both of the stimuli or changing the timings of the presentations). Manipulating these parameters can give us more precise information as to the situations in which these illusions occur. This in turn can allow us to uncover information such as specific timings associated with multisensory integration or what precise conditions allow this information to be combined and what do not.

Perhaps one of the most striking examples of these illusory effects is known as the McGurk effect (McGurk & Macdonald, 1976). Like Sumby and Pollack's (1956) investigation, this effect once again demonstrates the important role of combining sensory information in

speech comprehension. This time however as opposed to helping speech comprehension the effect demonstrated here shows how the multisensory system can also be fooled into mistakenly perceiving incorrect information. For this effect to occur participants are presented with footage of a person mouthing the nonsense phrase “Ga-Ga”, the footage is recorded without sound and overdubbed with a recording of a person saying “Ba-Ba”. Interestingly when viewing this scene and asked what they believe the person is saying, participants will often tend to amalgamate this incongruent information (due to the visual information’s effect on that of the auditory) and report hearing “Da-Da”. Clearly despite being incorrect this percept is what the brain appears to assume is the most logical one (McGurk & Macdonald, 1976).

Similarly, another illusion, known as the ventriloquist effect, also demonstrates the influence of incongruent visual information on our sense of hearing. In this illusion participants are forced to mislocate the source of speech due to the addition of an incongruent mouth movement presented alongside it (Bertelson, Vroomen, de Gelder, & Driver, 2000). By removing the visual information of a person’s mouth moving whilst they are speaking and using another actor (or a *ventriloquist’s dummy*), an individual can be forced to misattribute the location of the source of the sound to the other actor (or dummy) rather than the actual speaker (Bertelson et al., 2000).

In the research conducted by Sumby and Pollack (1956) it was demonstrated that by pairing auditory information with congruent visual information you can facilitate the comprehension of speech. Conversely the previous two illusory examples demonstrate that when auditory information is paired with incongruent visual information we see the emergence of auditory illusory effects as our brain attempts to make sense of the

contradictory information on display. However, this is not just the case for hearing. Another example presented here demonstrates the influence that incongruent visual information can have on the sensation of touch. This effect is known as visual capture, with one famous example being dubbed the *Rubber Hand Illusion*. In this example a participant's arm is hidden from view and stroked by the experimenter, providing tactile information. However, in place of the hidden real arm a fake one is placed in view of the participant and stroked synchronously with the strokes on the real hand. This acts to provide incongruent visual information. After a brief period of this, participants have been reported to begin feeling a sense of dissociation with their real arm, eventually appearing to accept the fake arm as their own (Botvinick & Cohen, 1998; Pavani, Spence, & Driver, 2000).

As stated previously, vision was once regarded as the dominant sensory domain. This is perhaps why we tend to see a plethora of illusory effects whereby vision is shown to influence hearing or touch (Heron et al., 2004; Posner et al., 1976). However, depending on the features of the stimuli being presented, vision can also be influenced by other senses giving rise to multisensory-induced visual illusions. Indeed several examples whereby vision is influenced by other domains have now been demonstrated within the literature (Shams & Kim, 2010). One such example is provided by Sekuler, Sekuler and Lau (1997). In this example participants are presented with two computerised balls (identical in size and colour) that slowly converge towards one another, overlap and continue their path. Participants were subsequently asked whether they thought the balls had collided and bounced off, or simply streamed through one another (the nature of the stimuli made this entirely ambiguous). Indeed the vast majority of participants believed the balls had streamed through one another (Sekuler, 1999). This can be explained by the visual systems preference for continuity and smooth uninterrupted motion (Vitello, 2010). However, a

striking difference was observed when researchers paired the moment the balls touched one another with a brief tone. Here, despite the identical visual stimulus, the change was noticeable with a much larger percentage of participants now stating that the balls had collided and bounced away instead of streaming through one another. What occurs here is that the sound has been integrated with the visual information, with the participants combining it into one perceptual whole. Subsequently participants now assumed the sound occurred because of a collision between the balls, hence their change in answer (Sekuler et al., 1997).

Another auditory induced visual illusion was provided by Shams, Kamitani and Shimojo (2000). This effect was later developed upon by Shams, Kamitani and Shimojo (2002) and Violentyev, Shimojo and Shams (2005) the latter of which also uncovered a tactile induced counterpart to this effect. The effect is known as the Double Flash Illusion (DFI). The auditory-visual effect has recently begun to demonstrate its importance as a tool in uncovering some of the fundamental aspects of the multisensory system (Cecere, Rees, & Romei, 2015; Ferri, Venskus, Fotia, Cooke, & Romei, 2018; Haß et al., 2017). Yet the tactile-visual counterpart has remained relatively under-utilised. Both the auditory-visual and a corresponding tactile-visual version will form the basis for the current research being discussed in this report, with the main focus being on the tactile version. These key effects will be discussed in greater detail in the following chapter, including its overall importance in researching general properties of multisensory integration and in the investigation of neurophysical mechanisms.

1.3. Introducing the Tactile-Induced and the Auditory-Induced Double Flash Illusions:

In the original paper presenting the DFI (Shams et al., 2000), participants were presented with a single flashing disc that could flash upon the screen at a variable number of times (up to 4 times). They were subsequently asked to state how many times they believed the disc had flashed upon the screen; the disc could flash up to a maximum of 4 times. However, the flashing disc was also concurrently paired with several brief tones. Interestingly, on trials when the disc only flashed once participants consistently perceived the number of flashes as being more when it was also paired with more than one beep sound. It appears that participants erroneously extrapolated the number of beeps to the number of flashes, this often appeared to lead to them perceiving multiple illusory flashes. This illusion is specifically known as a 'fission effect', whereby a single flash is split into multiple flashes. Another version of this illusion highlighted in this original paper is called a 'fusion effect', this means that 2 (or indeed more) flashes essentially fuse together when paired with a number of beeps that is lower than the actual number of flashes; subsequently causing the illusory perception of fewer flashes than are actually present. Interestingly the fission illusion appears to be very robust (in those that perceive it at least), with prior knowledge of the effect or feedback training appearing to have very little effect in terms of its perception (Rosenthal, Shimojo, & Shams, 2009).

Alongside this auditory-induced DFI, researchers also later provided a corresponding tactile-induced counterpart (Violentyev et al., 2005). The procedure was almost identical; however in this case the auditory stimuli are replaced by tactile stimuli, presented upon the participant's finger. As with the auditory-induced DFI this was shown to induce a reliable fission effect when one flash can be split into multiple flashes when presented synchronously with multiple taps to the index finger. As with the auditory version, the

tactile version also induced a corresponding fusion effect (Violentyev et al., 2005). Further research has also demonstrated a similar effect with active touch-based tasks, whereby participants pressing a key on a keyboard twice alongside the presentation of the flash also demonstrated the perception of a second illusory flash (Kunde & Kiesel, 2006).

The important aspect here is the use of multiple incongruent stimuli (i.e. the number of beeps or taps). By carefully manipulating the Inter-Stimulus Interval (ISI) separating these beep or tap pairs, it is possible to uncover information regarding the temporal profile for these illusions. This profile is often referred to as the Temporal Window of Integration (TWI). In this case, a TWI refers to a temporal profile that determines when the illusion occurs and when it does not. Shams et al., (2002) demonstrated that, for the auditory-induced effect, typically when the beeps were spaced apart by a delay of 100 ms or more, the illusory effect begins to degrade. This means that the auditory-induced DFI has a TWI of on average 100 ms. Unfortunately to date, there is no corresponding study for the tactile version of the illusion providing a TWI; this is something that will be investigated in the current report.

The use of these DFI tasks (most often the auditory-induced version) has in recent years formed the basis for many interesting investigations (Cecere et al., 2015; Ferri et al., 2018; Haß et al., 2017). However as yet there is little understanding as to the general mechanisms behind these illusions. More specifically we have little information on exactly what processes the brain uses to combine both auditory and visual and tactile and visual information in order to create a single perceptual whole. Our understanding of the mechanisms behind multisensory integration is as yet lacking, and ultimately our investigation looks to provide more details on this. We already know multisensory

integration appears to happen early in the processing of sensory information, often in areas once thought to be unisensory in nature (Giard & Peronnet, 1999; Molholm et al., 2002; Watkins et al., 2006). But as yet we do not know exactly how these areas combine to process and integrate this information. More specifically we do not know whether multisensory binding uses universally similar processes, regardless of the individual domains (i.e. tactile-visual or auditory-visual) or tasks differing in their individual domains are processed differently within the brain.

One mechanism that perhaps could be important in the processing of multisensory information are neuro-oscillatory processes. But what exactly are these processes and how could they possibly relate to the DFI itself and the integration of sensory information in general? The following section will look to answer this question and provide some further details on this interesting topic.

1.4. A brief introduction to neuro-oscillatory processes:

The brain is thought to contain between 85 and 100 billion neurons (Herculano-Houzel, 2009), resulting in trillions of connections between them. Of course this results in a lot of activity occurring in brain. Neuronal activity is typified by electrochemical responses known as action potentials. Here, when any kind of stimulus elicits a response within the brain information propagates from one neuronal cluster to the next. In response to the signal from an adjacent neuron, electrical activity is passed through a neuron via its axon, eventually reaching the cell's synapses. At this point chemical signals are transferred from these synapses to reach those connected to an adjacent neuron's dendritic branches, hence perpetuating the transfer of information. Typically the cell body of the neuron is electrically

polarised, but in response to synaptic inputs from adjacent cells the membrane potential of the neuron becomes depolarised or hyperpolarised, hence resulting in a rise or a fall in the membrane potential of the neuron, thus resulting in an action potential. An increase in action potentials across a neuronal cluster is said to be excitatory whereas a reduction of these results in an inhibitory effect (Hodgkin & Huxley, 1952).

From here, multiple (excitatory or inhibitory) postsynaptic potentials at the dendritic branches of relatively large groups of neurons firing synchronously can be detected and visualised by methods of neuro-investigation producing a complex waveform. This complex waveform can then be segmented into different frequency bandwidths, the predominant frequency in individual recordings can then be linked to different mental states, behaviours or to different regions of the brain (Britton et al., 2016). These frequency bandwidths are what are referred to as neuro-oscillations, more commonly known as brain waves.

Across the brain these different frequency bands can be plotted across a spectrum. This spectrum of frequencies is typically separated into different distinct wavebands that are often linked to different behaviours, areas of the brain and mental states. These include Alpha (7 – 12 Hertz (Hz)), Beta (12 – 30 Hz), Theta (4 – 7 Hz), Delta (0.5 – 4 Hz) and Gamma (25 – 100 Hz) frequencies. As this report aims to investigate typically in the alpha range and the beta range these two wave bands will be introduced in further detail, explaining their general function and their overall importance to investigating our hypotheses.

Alpha activity (first identified by Hans Berger (1929)), typically seen in the band covering frequencies from 7 to 12 Hz (although different reports use slightly different frequency ranges) is a very stable wave band (Grandy et al., 2013) that appears to be the predominant rhythm in the resting human brain (Britton et al., 2016). Its general properties

appear to have a very strong heritability, with genetic factors appearing to be a very large influencer in terms of their peak frequencies (Bodenmann et al., 2009; Van Beijsterveldt & Van Baal, 2002). Alpha activity was once thought of as being predominantly associated with cortical idling, that is it was thought to represent a state of reduced neuronal activity in the brain (Pfurtscheller, Stancak Jr, & Neuper, 1996) or as having an inhibitory effect on attention (Payne, Guillory, & Sekuler, 2013). Typically, it was once believed that a heightened level of alpha activity would lead to an inhibitory response, as such high levels of alpha in one area of the brain would lead to the suppression of activity within this area (van Diepen & Mazaheri, 2017). For example during a motor suppression task one would expect to see higher levels of alpha activity present within the motor cortex.

The general consensus on this topic is that this alpha influenced suppression of neural activity could be used as a gating process (most often for sensory information). This means that areas of the brain that are less relevant to the task at hand tend to be suppressed, allowing a heightened activity in the more relevant areas. This subsequently enables the correct area of the brain to perform the processing, thus enhancing the efficiency of the processing itself (Zumer, Scheeringa, Schoffelen, Norris, & Jensen, 2014). Research also suggests that alpha activity tends to increase alongside the workload of the working memory. This again may point to this frequency being used as a way of diverting attention by suppressing it to interfering inputs and focusing it more on the relevant tasks (Jensen, Gelfand, Kounios, & Lisman, 2002).

Traditionally alpha also been associated with simple sensory processing, specifically they tend to have a strong association with the processing of visual information (Dugue, Marque, & VanRullen, 2011; Ergenoglu et al., 2004; Hanslmayr et al., 2007; Minami &

Amano, 2017; Romei, Gross, & Thut, 2010; Romei, Rihs, Brodbeck, & Thut, 2008; Ronconi, Busch, & Melcher, 2018; Samaha & Postle, 2015; Van Dijk, Schoffelen, Oostenveld, & Jensen, 2008; Wutz, Melcher, & Samaha, 2018; Wutz, Muschter, van Koningsbruggen, Weisz, & Melcher, 2016). Furthermore research has also linked alpha activity to the processing of auditory information (Dohrmann, Weisz, Schlee, Hartmann, & Elbert, 2007; Katalin Dohrmann, Elbert, Schlee, & Weisz, 2007; Frey et al., 2014; Fujioka, Mourad, & Trainor, 2011; Gleiss & Kayser, 2014; McKee, Humphrey, & McAdam, 1973; Mercier et al., 2013; Teplan, Krakovská, & Štolc, 2003; Weisz, Hartmann, Muller, Lorenz, & Obleser, 2011). As part of the stimuli that we are investigating in this report is concerned with a combination of visual and auditory information, these associations will be particularly important in this current research.

As previously stated we do not know whether multisensory binding uses universally similar processes, regardless of the individual domains (i.e. tactile-visual or auditory-visual) or tasks differing in their individual domains are processed differently within the brain. One way in which different multisensory tasks differ in their processing could be at the neuro-oscillatory level. Research already exists that has linked alpha processes with the auditory-induced DFI (Cecere et al., 2015). Researchers were able to demonstrate the role that alpha oscillations play in determining the temporal profile of the auditory-induced DFI. They found a direct correlation between the peak occipital alpha frequency and the TWI for the auditory effect. Furthermore by entraining these alpha frequencies (using transcranial Alternating Current Stimulation (tACS)) they were able to directly reduce or increase the overall speed of the alpha wave. This subsequently led to a decrease or increase in the size of the TWI respectively. Given that both auditory and visual information appears to be associated with alpha frequencies this effect may not be entirely surprising. However, this also means that

we are unable to infer exactly what processes are being used here to set the fate for the illusion. On the one hand local oscillatory activity in the occipital regions could account for this effect, alternatively properties of the functional connection between the auditory and the visual cortices may also play a role here. As logically speaking both mechanisms could give rise to an influence of alpha, and we do not know which of these mechanisms are at play here. Thus, one method in which we theorised would allow us to tease apart these two alternative hypotheses was to investigate a different version of the DFI (in this case the tactile effect). We would do this in order to see whether it also appears to be influenced by alpha properties (i.e. local visual processes). Alternatively it could also be that this effect is influenced differently, in this case it may be via the functional connection between the somatosensory, and the visual cortices. As evidence has implicated beta frequencies in the processing of somatosensory information, these frequencies may be of particular interest to us here.

Beta oscillations are wave forms that are present over a relatively large range of frequencies, (12 – 30 Hz), however they are often segmented into low, medium or high beta. These waves are thought to be less stable than alpha frequencies and are often associated with the motor cortex and subsequently motor, tactile or somatosensory functions (Baumgarten, Schnitzler, & Lange, 2015; Brovelli et al., 2004; Engel & Fries, 2010; Foffani, Bianchi, Baselli, & Priori, 2005; Kilner et al., 2003; McFarland, Miner, Vaughan, & Wolpaw, 2000; Paus, Sipila, & Strafella, 2001; Rubino, Robbins, & Hatsopoulos, 2006; Salenius & Hari, 2003; Zhang, Chen, Bressler, & Ding, 2008). This, however, is far from exclusive and research has linked low levels of these processes (those in the 12 to 15 Hz range) with other emotional and cognitive functions. These include anxious thought and

active concentration (Baumeister, Barthel, Geiss, & Weiss, 2008) as well as other general cognitive tasks (Ray & Cole, 1985).

As stated, typically beta oscillations are associated with motor or tactile tasks, typically studies associate these with response preparation or motor suppression (that is the conscious prevention of a reactionary movement) (Zhang et al., 2008) or the maintenance of steady movements or muscle contractions (Brovelli et al., 2004). Research has also demonstrated that both real movements, and simply imagining these movements also correspond to these processes (McFarland et al., 2000). Beta frequencies also appear to have a complex relationship with the neurotransmitter gamma aminobutyric acid (GABA). This neurotransmitter plays an important role in coordinated movements and maintaining muscle tone. Research has demonstrated that drugs that decrease cortical GABA effectivity (and hence interfere with regular motor responses) tend to also result in heighten cortical beta activity (Feshchenko, Veselis, & Reinsel, 1997; van Lier, Drinkenburg, van Eeten, & Coenen, 2004).

As has been stated, previous research has suggested that alpha processes appear to be related somehow to the mechanisms underlying the auditory-induced DFI. However we are unsure as to whether this would also be the case for the tactile-induced effect. We theorise that this depends on the exact form of the underlying mechanism behind these illusions. Understanding this further may allow us to understand better the mechanisms underlying multisensory integration. If the auditory-induced DFI is driven exclusively by local oscillatory activity, then one would indeed expect to see a relationship with alpha processes. This is due to their association with visual processes (Dugue et al., 2011; Ergenoglu et al., 2004; Frey et al., 2014; Gleiss & Kayser, 2014; Gulbinaite, van Viegen,

Wieling, Cohen, & VanRullen, 2017; Lange, Keil, Schnitzler, van Dijk, & Weisz, 2014; Mercier et al., 2013; Minami & Amano, 2017; Romei, Brodbeck, et al., 2008; Romei et al., 2010; Romei, Rihs, et al., 2008; Ronconi et al., 2018; Samaha & Postle, 2015; Van Dijk et al., 2008; Wutz et al., 2018; Wutz et al., 2016). Of course this is exactly what tends to be found (Cecere et al., 2015). If this is the case for the auditory effect, we would also expect it to be the case for the tactile effect. In this case, if it was once again being driven by local visual processes we should also expect to find a comparable correlation between the temporal profile of the tactile-induced DFI and these alpha processes. However as yet we are unsure of whether this is indeed the case, or if the effect is instead being driven by properties of the functional connection between the two remote but interconnected areas of the brain. In the case of the auditory-induced effect, the connection between the auditory and the visual cortices may be subtended by the oscillatory processes associated with the influencing domain, in this case audition. Yet again this would result in a correlation between alpha processes and the temporal profile for this particular task. As with the visual processes, auditory processes also appear to be linked to alpha activity (Dohrmann et al., 2007a; Dohrmann et al., 2007b; Frey et al., 2014; Fujioka et al., 2011; Gleiss & Kayser, 2014; McKee et al., 1973; Mercier et al., 2013; Teplan et al., 2003; Weisz et al., 2011). However in the case of the tactile-induced effect what we might expect to find here could be somewhat different. As research tends to associate somatosensory processing more with beta oscillations (Baumgarten et al., 2015; Brovelli et al., 2004; Engel & Fries, 2010; Foffani et al., 2005; Kilner et al., 2003; McFarland et al., 2000; Paus et al., 2001; Rubino et al., 2006; Salenius & Hari, 2003; Zhang et al., 2008), here we might expect to see more of an influence of these beta processes in setting the parameters of the tactile-induced effect. In turn this

would manifest as a significant correlation between the temporal profile of the tactile-induce DFI and visual beta processes.

Something else that may be considered here is the existence of the mu wave, and its association with motor tasks. Mu waves typically represent a wave band within medium-high alpha to very low beta (typically 8 – 13 Hz (Hobson & Bishop, 2017)). This rhythm is associated bilaterally across the precentral motor cortex and typically has been associated with many motor processing tasks and mirror neuron functioning in this region (Hobson & Bishop, 2017; McFarland et al., 2000; Oberman et al., 2005; Pineda, 2005). As such rather than finding an association between alpha frequencies or beta frequencies we may instead expect to find an association with these mu frequencies, hence still providing a differentiation in frequency between the two illusory tasks. It is important to note that typically mu rhythms are suppressed during motor or tactile tasks (Hobson & Bishop, 2017; McFarland et al., 2000; Oberman et al., 2005; Pineda, 2005), as a result we may indeed see no influence of this frequency at all. Hence we believe that we are more likely to see an association with beta frequencies rather than mu frequencies. As a result we will not focus on this narrow waveband, however this could be something that we wish to consider in future investigations.

Currently the main aim of this investigation is to provide information as to how these individual illusions may be processed differently. This will also help to inform our current knowledge of the mechanisms underlying multisensory integration in general. Before discussing the individual experiments in more detail one must first wonder why these oscillatory processes subtending the functional connection between the two cortices could play such a large role in determining the properties for these illusions in the first place.

One explanation for this could be a model called the *Communication through Coherence* (CTC) framework (Fries, 2005, 2015). Here, neural communication is subserved by neural synchronization between remote but functionally interconnected areas. Specifically, such neural synchronization is the result of alignment of post-synaptic neural activity to pre-synaptic input, creating temporal windows of optimal, preferred communication between involved areas. In this case, the auditory- and tactile-induced DFIs could be the result of top down directed influences (feedback connection) directly from the influencing domain. In the case of the auditory-induced DFI this could be the auditory cortex (associated with alpha processes), and for the tactile effect this could be the somatosensory cortex (associated with beta processes). These would then act to shape the final illusory outcomes for both tasks respectively.

From this perspective, if a crossmodal stimulus (in our case auditory or tactile) phase aligns with oscillatory activity in visual areas, it will define the temporal windows corresponding to such oscillatory cycle lengths, within which two consecutive stimuli may give rise to the illusory percept (in this case the TWI of the illusion). The illusory phenomenon will be engendered by a second crossmodal phase alignment attempt induced by the second cross sensory stimulus reactivating the visual trace being still processed by the ongoing phase alignment induced by the first multisensory pair. Thus, an individual's frequency peaks could characterize the temporal resolution of interregional synchronization within which the TWI phenomena arise.

Another closely related framework has been introduced by Klimesch, Hanslmayr, Sauseng, Gruber and Doppelmayr (2007). These researchers propose that communication between two remote, but interconnected areas of the brain can be achieved through what

are commonly known as *travelling waves*. These are neural oscillations that facilitate the transfer of information as measured through the propagation between electrodes via a neural network (Klimesch et al., 2007; Muller, Chavane, Reynolds, & Sejnowski, 2018). According to this framework, local oscillatory activity (i.e. resonance frequency) in auditory (alpha) or somatosensory (beta) cortices will propagate towards the visual cortex accounting for the specific differential impact of alpha and beta oscillations on the auditory- and tactile-induced DFIs, respectively. This mechanism would allow for prompt rescaling of temporal sampling across the senses, optimizing cross sensory communication efficiency.

With this in mind it is clear that there is some ambiguity here. Are the properties of these illusory effects set by local *visual* oscillatory process, or are the differential effects of *auditory* or *somatosensory* processes at play here?

Experiment One looked to investigate this further, by using both the auditory-induced and the tactile-induced DFI tasks. In his case we intended to tease apart these two hypotheses and determine whether local activity or functional connectivity is important in the processing of this multisensory information.

1.5. An introduction to Experiment One:

In Experiment One we intended to investigate both the auditory- and tactile-induced DFI further (focusing mainly on the latter). We wished to provide details, for the first time, on the temporal profile of the tactile-induced effect. The ultimate aim here however was to compare it to the auditory-induced effect with a view to determining the underlying mechanisms behind these effects. We hope that by investigating these particular illusions

we were able to provide some interesting new information, furthering our overall understanding of how multisensory information is generally processed in the brain.

As has already been discussed, the role of neuro-oscillatory processes in sensory processing has been highlighted in recent reports. For example, oscillations in the alpha band tend to be associated with visual processes (Dugue et al., 2011; Ergenoglu et al., 2004; Frey et al., 2014; Gleiss & Kayser, 2014; Gulbinaite et al., 2017; Lange et al., 2014; Mercier et al., 2013; Minami & Amano, 2017; Romei, Brodbeck, et al., 2008; Romei et al., 2010; Romei, Rihs, et al., 2008; Ronconi et al., 2018; Samaha & Postle, 2015; Van Dijk et al., 2008; Wutz et al., 2018; Wutz et al., 2016). Alpha activity has also been linked to auditory processing (Dohrmann et al., 2007a; Dohrmann et al., 2007b; Frey et al., 2014; Fujioka et al., 2011; Gleiss & Kayser, 2014; McKee et al., 1973; Mercier et al., 2013; Teplan et al., 2003; Weisz et al., 2011). Somatosensory tasks however, have more often been associated with slightly faster bands, predominantly in high alpha or low beta bands (Baumgarten et al., 2015; Brovelli et al., 2004; Engel & Fries, 2010; Foffani et al., 2005; Kilner et al., 2003; McFarland et al., 2000; Paus et al., 2001; Rubino et al., 2006; Salenius & Hari, 2003; Zhang et al., 2008).

Research has since shifted into looking at the neuro-oscillatory processes that associate with multisensory processing. Perhaps the most influential report here in terms of this current research was produced by Cecere et al., (2015). As has been briefly touched upon, these researchers utilised the auditory-induced DFI task to further investigate the neuro-oscillatory properties of multisensory integration (Cecere et al., 2015). They discovered a tight relationship between a person's peak Individual Alpha Frequency (IAF) in the visual area, and the temporal profile of the auditory-induced TWI. Essentially it was

found that a higher IAF (faster occipital alpha speed) was shown to predict a smaller TWI while conversely, lower frequencies predicted larger TWI values.

These researchers also provided evidence of a causal link between visual IAF and the auditory-induced TWI. Researchers utilised a transcranial Alternating Current Stimulation protocol by stimulating slightly above (+2 Hz) or below (-2 Hz) the IAF value. Theoretically what they aimed to do here was to entrain these oscillatory processes to the stimulation frequencies that were higher or lower than each individual participant's natural visual alpha frequency. For this particular study no post-stimulation EEG was provided, so arguably no direct evidence of this change is present, however other research using similar techniques has confirmed that this method can indeed be used to manipulate the speed of these oscillatory processes (Minami & Amano, 2017). The overall aim here was for the researchers to essentially increase or decrease the speed of occipital alpha for each individual participant. What they found was that when stimulating at 2 Hz above the IAF (i.e. increasing processing speed) participants demonstrated a temporary reduction in the magnitude of their auditory-induced TWI. Similarly, they found that stimulating at 2 Hz below the IAF (i.e. decreasing processing speed) resulted in an increased TWI size. These findings and subsequent line of reasoning has formed the basis for the current investigation.

Previous research has focused almost exclusively on the auditory-induced DFI often neglecting the tactile-induced effect. Hence we have a lot of existing information regarding the temporal profile of the auditory-visual illusion, however, there exists very little in terms of its tactile-visual counterpart. To the best of our knowledge no reports exist detailing the average value of the TWI for the tactile-induced DFI, and how this compares to that of the auditory-induced effect.

We also wished to make use of the less favoured tactile-induced effect in order to provide further details of the underlying mechanisms behind multisensory integration. Our reasoning here is that we did not know the exact nature of the underlying mechanism subtending these specific illusions. One theory is that this mechanism could be determined by local network rules. In other words it could be the properties of the visual cortex that also set the properties of the temporal profile of the DFI. Conversely the illusion's properties may depend on longer-range communication networks (Fries, 2015). In other words, the properties of both the tactile-induced and auditory-induced illusions may be determined differently. This would be because the way the two domains (auditory or somatosensory) communicate with the visual cortex is different to one another (Romei, Gross, & Thut, 2012). In this case we wanted to find out if multisensory visual illusions are strictly determined by *visual* oscillatory constraints alone, or by the oscillatory properties of the functional connection *between* sensory modalities. Testing both the auditory-induced effect and its tactile counterpart may provide an elegant way of teasing these two hypotheses apart.

Simply using the auditory-induced effect tells us very little as to which of these theories is correct. If the effect is determined by local *visual* processes then we would expect alpha to play a role in determining its properties (Dugue et al., 2011; Ergenoglu et al., 2004; Frey et al., 2014; Gleiss & Kayser, 2014; Gulbinaite et al., 2017; Lange et al., 2014; Mercier et al., 2013; Minami & Amano, 2017; Romei, Brodbeck, et al., 2008; Romei et al., 2010; Romei, Rihs, et al., 2008; Ronconi et al., 2018; Samaha & Postle, 2015; Van Dijk et al., 2008; Wutz et al., 2018; Wutz et al., 2016). Alternatively if the functional connectivity between the two cortices sets the fate of the illusion (i.e. it depends more on *auditory* processes) then yet again we may also expect alpha to play a role (Dohrmann et al., 2007a;

Dohrmann et al., 2007b; Frey et al., 2014; Fujioka et al., 2011; Gleiss & Kayser, 2014; McKee et al., 1973; Mercier et al., 2013; Teplan et al., 2003; Weisz et al., 2011). Thus what is needed here is a similar illusory effect whereby visual processes are being influenced by those from another domain (different from audition).

In the case of the tactile-induced DFI, visual processes are being influenced by somatosensory process, these are often associated with beta frequencies (Baumgarten et al., 2015; Brovelli et al., 2004; Engel & Fries, 2010; Foffani et al., 2005; Kilner et al., 2003; McFarland et al., 2000; Paus et al., 2001; Rubino et al., 2006; Salenius & Hari, 2003; Zhang et al., 2008). This is important as if we had found local *visual* processes to be important here we should once again have found an influence of alpha processes. However if it is indeed the properties of the connection between distant yet interconnected cortices, more specifically the properties set by *somatosensory* processes, then here we might have expected to see a correlation with beta frequencies instead.

In this research we looked to provide details on the temporal profiles of the both the auditory-induced and the tactile-induced DFIs. We first looked to replicate the results demonstrated by Cecere et al., (2015) and investigate whether we could also find a significant correlation between the auditory-induced TWI and visual alpha processes. Subsequently we then looked to perform a similar investigation of the tactile-induced TWI. Reasoning that if we could find a correlation with visual alpha processes then we could take this as evidence for both the auditory and tactile effects being determined by local oscillatory frequencies. If, however we had found a correlation between this illusion and visual beta processes (as well as replicating that between alpha and the auditory effect), we could then perhaps take this as tentative evidence for these illusions instead being

determined by properties of the functional connectivity between cortices. In other words the fate of the illusion is being set by somatosensory processes in the tactile effect and auditory processes in the auditory effect rather than simply visual processes for both.

In this research we did indeed find evidence of this relationship between beta processes and the tactile-induced DFI (as well as replicating the relationship between the auditory effect and alpha processes). This aligned to our second hypotheses and would suggest to us that rather than being subtended exclusively by local activity (in the visual cortex), these multisensory effects appear rather to be influenced by properties of the functional connectivity between the two separate regions of the brain that are working together to process the two illusory tasks. We took this as an opportunity to move forward with the data and further provide evidence to support this theory.

1.6. An introduction to Experiment Two:

Based on the findings of the previous experiment we then aimed to develop these further. In this research we wished to provide more details on the illusory effects. More specifically we looked to focus on the underlying mechanisms behind the tactile-visual illusion. We then used this information to expand our overall knowledge of the general mechanisms behind multisensory processing. Our overall aim here was to use a novel method of neuro-stimulation known as cortico-cortical Paired Associative Stimulation (ccPAS) to modulate the functional connectivity between the two remote but interconnected areas of the brain that we believe to be driving the illusory effect. By stimulating this network we wished to modulate the beta frequencies subtending this connection. Essentially we intended to manipulate the processing speed and the time it

takes for information from the somatosensory cortex to reach the visual cortex. By fine-tuning this network we wished to produce a reduction in its processing speed, manifesting as a reduction in low beta frequencies as measured at the visual cortex. We expected that any modulation of these beta processes that we were able to achieve would subsequently result in a further modulation of the temporal profile for the tactile-induced DFI. In other words a reduction of beta processing speed should subsequently manifest as an increase in the size of the TWI for the illusion.

The previous research conducted by Cecere et al., (2015) on the auditory-induced effect focused exclusively on modulating *local* oscillatory activity, this subsequently means that using tACS as a method of modulation was perhaps a logical choice. This method however would not have been appropriate in our research; this is because we wished to exclusively modulate the functional connectivity *between* remote areas of the brain. So the question is what method may best allow us to test our hypothesis?

The method that we decided to utilise here is a variant of Transcranial Magnetic Stimulation (TMS), this particular method is known as cortico-cortical Paired Associative Stimulation. Crucially this method has been demonstrated in the literature to stimulate functional connectivity. Taking into account what we proposed, in terms of properties of the functional connection between the somatosensory and the visual cortex determining the properties of the tactile-induced DFI, this appeared to be the perfect method for us to use. Incidentally, prior to this current investigation, this method had not yet been utilised as a way of inferring anything about the oscillatory function of the connections between remote areas. As a result, our research also acted as a novel investigation as to the capabilities of this method.

The ccPAS method uses slow-rate repetitive TMS pulses to stimulate opposite areas of the motor cortex, aiming to enhance cortical excitability in a conditioned hand. (Rizzo et al., 2009). Theoretically this was thought to evoke Hebbian like principles of Long Term Potentiation (LTP) in the interneurons of the contralateral motor regions (of the conditioned hand) that received transcallosal inputs from the ipsilateral motor region (Buch, Johnen, Nelissen, O'Shea, & Rushworth, 2011; Hebb, 1949; Rizzo et al., 2011). LTP (and its counterpart Long Term Depression (LTD)) is where the connection between neuronal clusters are created (or suppressed), essentially resulting in learning. This not only demonstrates our ability to manipulate the plasticity of the brain, it enables us to temporary manipulate certain properties of functional neuronal connections. In the present work we used ccPAS by testing a novel and unprecedented assumption. We tailored the cortical to cortical timing to a period resembling the duration of one single oscillatory cycle that we had previously found to be associated with the perception of the illusion (i.e. beta processes). This will be done with the aim of modulating the temporal properties of the functional connectivity, ultimately aiming at modulating its efficiency in predicted directions.

Specifically we proposed that the connectivity between these areas are facilitated by low-beta frequencies (as these are most associated with the (pre-synaptic) somatosensory cortex (Baumgarten et al., 2015; Brovelli et al., 2004; Engel & Fries, 2010; Foffani et al., 2005; Kilner et al., 2003; McFarland et al., 2000; Paus et al., 2001; Rubino et al., 2006; Salenius & Hari, 2003; Zhang et al., 2008)). As such we believe that optimal communication is linked tightly to activity in this waveband. In other words, the time it takes for information to leave the somatosensory cortex and reach the visual cortex corresponds to one beta cycle length. This means it would take approximately 50 – 80 ms for information to leave

the somatosensory cortex and arrive at the visual cortex, thus facilitating the communication of these two areas.

If our postulations were correct and the communication between cortices are dependent on the wave frequency travelling between them, stimulating at, or around the beta frequency should possibly allow us to demonstrate an ability to modulate these functional connections simply by modulating the specific wave frequencies associated with them. Here we looked to base our stimulation spacing directly upon this beta frequency; however in this case we used a slightly reduced value so as to attempt to fine-tune the system and induce a reduction in the speed of the beta processes that are subtending the connection between the two cortices.

Utilising these reduced beta frequencies means that the average spacing between ccPAS coil pulses was approximately 60 - 100 ms in this study. The exact value of which depending entirely on each person's Individual Beta Frequency (IBF). The distance covered by the stimulated network (somatosensory to visual) and the length of time between pulses was unprecedently long. As a result, prior to this investigation we were unsure whether modulation would indeed be successful. Subsequently, this investigation also acted as a way of ascertaining the true capability of the method that we are utilised.

Thus, the ultimate aim of using this method was to attempt to reduce the speed of the beta processes subtending the connection between the two cortices involved in the tactile-induced DFI. We expected this to manifest as a lower IBF value in occipital regions after the ccPAS protocol, which was investigated via the use of EEG. If these processes do indeed set the fate of the tactile-induced DFI (and we did indeed find a reduction of beta speed post-ccPAS), then we would have also expected to see a modulation of the parameters of this

illusion. Specifically, by reducing the occipital IBF value, we also expected to see an increase in the overall magnitude of the TWI for this illusory effect.

Additionally, in this experiment we also tested the illusory effect when the tactile stimuli were applied over both the left hand and the right hand. As we always measured occipital beta whilst each task was taking place (either the left-hand or the right-hand task), two different connections were at play here. One subtending the right somatosensory and the visual cortices (left-hand condition) and one subtending the left somatosensory and the visual cortices (right-hand condition). This should have led to a differentiation of occipital beta tuning depending on which task was being completed. As we were using the ccPAS method to target only the network in use for the left-hand condition (right somatosensory to visual cortices) post-ccPAS measures of the parameters when tactile stimuli were presented to the right hand should have been the same as pre-ccPAS measures. Specifically we expected to see a reduction in post-ccPAS beta speed (and subsequently an increase in the size of the TWI) only when the network involved corresponded to the one targeted by the ccPAS, theoretically showing the state-dependent network specificity of the effect.

In this investigation we first asked participants to take part in two tactile-induced DFI tasks (with stimuli being presented to the left hand in one task and the right hand in the other). Then we performed the ccPAS protocol and measured the TWI for both of the separate tactile tasks and the IBF values associated with them. If our stimulation was indeed successful, we would have expected to find that post-ccPAS measurements of the IBF value would be lower than those taken pre-ccPAS. Furthermore if our conclusions from Experiment One were correct and the beta processes subtending the connection between somatosensory and visual areas set the fate of the temporal profile of the illusion these

changes should have also resulted in a significant increase in the size of the TWI. Crucially we only expected this to be the case when stimuli are presented to the left hand (with no changes in either the IBF or the TWI being expected for the right).

In this experiment we were indeed able to uncover some promising results. Crucially we were able to demonstrate a significant reduction in the frequency of visual beta processes after the TMS protocol took place. We took this as compelling evidence that we were able to explicitly manipulate the properties of the functional connectivity between the somatosensory and the visual cortices using our method. Hence it appears that we were successful in reducing the speed of the beta processes subtending the connection between the somatosensory and the visual cortex. Importantly this effect was only found when the tactile stimuli were presented to the left hand with no changes being found when it was presented to the right. Furthermore, pre- and post-stimulation measurements of the tactile-induced TWI (for when tactile stimuli were presented to the left hand only) confirmed that this reduction in beta frequency also corresponded to an increase in the size of the TWI (with no changes being found when stimuli were presented to the right hand). We take this as further evidence for the role of functional connectivity between cortices in influencing the properties of multisensory integration.

However, despite this promising evidence it may have also been the case that the effect found was the result of a general slowing down of sensory processing, brought upon by inserting incongruent noise into the connection. As a result, at the conclusion of this experiment we were simply unsure exactly as to whether the changes that we found could reliably be attributed to the specific temporal parameters of the ccPAS protocol. In Experiment Three we now wished to provide a control condition; here we mimicked the key

aspects of the stimulation in order to directly compare the results. In this case we wished to use the ccPAS method to stimulate using a timing corresponding exactly to that of each persons' IBF (without first reducing this value). As this pulse timing should directly correspond to the normal processing speed of the functional connectivity between these areas, we aimed to allow participants in Experiment Three to experience the same conditions as those in Experiment Two, without changing their beta frequency and without modulating the tactile-induced TWI. This was done with the aim of teasing apart these the two alternative explanations for our findings here.

1.7. An introduction to Experiment Three:

Based on the promising results of Experiment Two we wished to investigate the phenomenon further by providing a second control condition to our experiment. More specifically we wanted to include a condition in which the ccPAS protocol was mimicked superficially yet with parameters manipulated so that no changes were expected. This was something that ideally would have been completed as part of Experiment Two, but the time constraints of an already lengthy experiment meant that this was difficult, if not impossible to perform. As such despite the promising results that we uncovered in the previous experiment we could not exclude alternative explanations for the change in beta frequency and the subsequent change in TWI size. In this case, instead of the specific temporal parameters of the ccPAS pulse timing (i.e. utilising a reduced beta frequency to base the timings on) inducing this change in processing speed, it could alternatively be a marker of a general sensory processing slow-down. This could be as a result of simply inserting incongruent noise into the system. This means that we still did not exactly know if the

specific properties of our stimulation resulted in this change or if by blindly stimulating this network, using any random pulse timing we would have induced identical changes regardless of the specific properties.

As we did not as yet have compelling evidence to determine this one way or another, in Experiment Three we aimed to provide somewhat similar research, yet we manipulated the parameters of the stimulation, so that we would instead have expected no change between pre- and post-ccPAS measurements of both the IBF and the TWI. Our main aim during this study was to once again use the ccPAS method to stimulate the functional connection between the somatosensory and the visual cortices. However in the previous study we attempted to modulate this connection by basing the pulse timing directly on a reduced version of the participant's IBF. This was with a view to fine-tuning the network and subsequently reducing the speed of the oscillations subtending it, ultimately resulting in us observing a reduced occipital IBF value post-ccPAS. As well as a subsequent increase in the relative size of the tactile-induced TWI.

In this current investigation however, we based the timing of the paired TMS coil pulses exclusively on the exact IBF value (in ms). According to our theory, this value corresponds exactly to the time that it takes for the influence of the somatosensory cortex to reverberate into the visual cortex. As we were stimulating at this exact value, and not reducing it, as per the previous investigation, we theorised that this would not have resulted in any reduction in the IBF value. If we were indeed to find this to be the case then we would also have expected to see no change between pre-stimulation and post-stimulation measurements of the tactile-induced TWI.

This study had two overall aims, initially we looked to uncover further evidence as to the underlying mechanisms governing multisensory information. Our second major aim here was to provide further testing to a relatively new method of neuro-stimulation. As we have utilised this method somewhat differently to other researchers we wished to ensure that our methods are carefully thought out and leave as little room for ambiguity as possible. Firstly we looked to stimulate the functional connectivity over far longer-range networks than had previously been demonstrated; as such we aimed to stimulate using much larger pulse delays. Secondly we also hoped to provide evidence for the first time to suggest that this method can also be used reliably to inform our understanding of the oscillatory activity subtending the functional connections that it is stimulating. As such, providing this control condition we hoped to further develop on the compelling evidence that already exists from the previous investigation and to confirm the efficacy of the methods that we used.

If indeed our postulations were correct and the communication between cortices are dependent on the wave frequency travelling between them, stimulating at, or around the beta frequency would allow us to demonstrate an ability to modulate these functional connections simply by modulating the specific wave frequencies associated with them.

Our reasoning behind this investigation is that by stimulating using the exact communication time of this network (and not a reduced time) we would have expected to see no change in beta speed post-ccPAS. Due to the tight link between these beta processes and the tactile-TWI values presented in the previous experiments, we also expected to find no changes in the temporal window of this illusion post-ccPAS.

After participants first completed a tactile-induced DFI task (left hand only) we then performed the stimulation protocol and compared the pre-ccPAS values of the tactile-

induced TWI and the IBF values to post-ccPAS measures. Stimulation once again occurred between electrode C4 (right somatosensory cortex) to Oz (visual cortex), as was the case in the previous study. We then directly compared the change in IBF and TWI seen in Experiment Three with the results seen in Experiment Two. Where we expected to see no change in post-ccPAS IBF or TWI, compared to pre-ccPAS measures.

If our intended findings were confirmed, then we would take this as promising evidence for a frequency specific mechanism subtending the tactile-induced DFI, specifically governing the somatosensory visual functional network giving rise to the studied illusion. Finally, we would also provide evidence that the ccPAS method could reliably be used to experimentally modulate the functional connectivity between longer-range networks (utilising longer pulse delays than what has previously been reported). This would also suggest to us that the method can reliably be used to modulate the speed of neuro-oscillatory process and that this method is both network (left vs. right somatosensory to visual) and frequency specific.

In this experiment we were indeed able to uncover some further promising results. Firstly we were able to provide evidence of the expected correlations. Crucially, we also found no significant change in IBF value after the TMS protocol took place. We took this as compelling evidence that in the previous experiment we were indeed able to explicitly manipulate the properties of the functional connectivity between the somatosensory and the visual cortices using our method. We take this as promising support to our initial postulations, and only by stimulating this network using the specific parameters that we used (i.e. a reduced IBF value) could we replicate the results. Furthermore, pre- and post-stimulation measurements of the tactile-induced TWI confirmed that no change in the

magnitude of this value took place. We take this as further evidence for the role of functional connectivity between cortices in influencing the properties of multisensory integration. This investigation also provides evidence for the efficacy of the ccPAS method in stimulating longer-range functional connections. It also demonstrates for the first time that the technique can also be used to inform our understanding of neuro-oscillatory processes and how these relate to the communication between two functionally connected areas of the brain.

The follow chapter will now look to assess the ccPAS method in more detail. It will also discuss another technique we are using, namely encephalography as well as discussing some of the wider background of the TMS machine that the ccPAS protocol relies upon.

2. Chapter Two: An introduction to the core techniques and methodologies implemented in the current project:

This section will introduce the two techniques that we employed in the experiments that will be presented in this report. These techniques were Electroencephalography and Transcranial Magnetic Stimulation; in regard to the latter we used a particular variant known as cortico-cortical Paired Associative Stimulation. Here some of the key principles behind these methods will be explained. The reasoning behind their use in these investigations will also be highlighted, as well as some of the safety risks associated with these methods and the measures we have taken to minimise these risks.

2.1. An Introduction to Electroencephalography:

In all the experiments we present in this report we utilised EEG techniques for the evaluation of the neuro-oscillatory activity that we investigated. EEG is a non-invasive method of investigation whereby typically silver chloride electrodes (of which there are often 64, but this number can vary depending on the usage and the resolution required) are situated within a cap. This cap is subsequently placed upon the scalp of the participant. A highly conductive saline gel is then applied between the electrodes and the scalp to reduce the impedance of the signal, ensuring that it is as clean and readable as possible.

EEG works by picking up on the electrical activity occurring within the brain, this activity is facilitated by the chemical transfer of information. These chemical signals are passed from pre-synaptic cell to post-synaptic cell and this acts to create a change in the membrane potential of the post-synaptic terminal. Thus multiple (excitatory or inhibitory) postsynaptic potentials of relatively large groups of neurons firing synchronously can be

detected and visualised by the EEG producing a complex waveform. This complex waveform can then be segmented into different frequency bandwidths, the predominant frequency in individual recordings can then be linked to different mental states, behaviours or to different regions of the brain (Britton et al., 2016).

2.2. The history and usage of EEG:

EEG is a very well established method, having been initially introduced in the late 1800s. At this time the method was very different to what it is today. It was very invasive with electrodes having to be placed directly on the brain of the tested subject (Coenen, Fine, & Zayachkivska, 2014; Swartz, 1998). At this point human subjects were not considered due to this level of invasiveness. Human usage was however eventually initiated by Hans Berger in 1924. It was at this point that the method was also given its familiar name (Haas, 2003). EEG scanning has since become a hugely important tool in medical scenarios. This method is able to detect the onset or even the cause of certain neurological disorders. Typically, it is used as a way of distinguishing between types of epilepsy, to determine the best course of treatment and to arrive at an accurate prognosis (Smith, 2005). The method is also, less commonly, used to diagnose or investigate other conditions, with one example being investigating the early stages of dementia (Adamis, Sahu, & Treloar, 2005; Barber et al., 2000; Roks, Korf, Van der Flier, Scheltens, & Stam, 2008).

EEG is also an invaluable tool for research purposes. This method is a relatively cheap and easy way of investigating brain activity in the form of Event Related Potentials (ERPs). This method is also advantageous as it does not incapacitate the participant as much as other methods that require them to enter into a large scanner unit may do. This includes

such methods as Magnetic Resonance Imaging (MRI), Positron Emission Tomography, Computerised Tomography (CT) scanning or Magnetoencephalography (MEG). This is advantageous as it enables participants to perform numerous computer tasks in controlled conditions whilst researchers can measure these ERPs in real time. Moreover, the method is used to investigate neuro-oscillatory processes. It is particularly useful as different oscillations can be measured depending on the task being undertaken, or the particular area of the brain currently being investigated. As such, we can use this method to actively investigate behavioural tasks in real time. This allows us to associate specific behaviours with specific neural patterns, allowing us to build up a clearer picture of how information is processed in the brain (Brovelli et al., 2004; Buzsáki, 2002, 2005; Buzsáki & Moser, 2013; Ergenoglu et al., 2004; Furman et al., 2018; Jensen et al., 2002; Klimesch, 1999; McFarland et al., 2000; McKee et al., 1973; Payne et al., 2013; Ray & Cole, 1985).

In the research that is presented, we wish to investigate these neuro-oscillatory processes further. We intend to collect this information in association with the auditory-induced or the tactile-induced DFIs. Thus we require real-time scanning to occur whilst participants are undertaking both of these tasks, this is in order for us to uncover further information on the associated neuro-oscillatory processes. Hence why we have decided to make use of EEG scanning in our current investigation.

2.3. Safety concerns, drawbacks and precautions to be taken:

Aside from some mild discomfort, possible claustrophobic feelings associated with wearing a restrictive cap and potential anxiety at the use of the (blunt) syringe used for gel insertion, there are very few risks associated with using EEG. Regardless of this, great care was taken to ensure participant safety and comfort here. In addition to the (mild) safety

risks there is one drawback to the use of EEG that deserves mention, this is its relatively low signal-to-noise ratio. This means that the method is highly susceptible to interference, whether it be electrical, electromagnetic (as in the case of its combined use with TMS) or directly from the participant themselves. This can be due to the electrical activity associated with muscle and body movements, the participant's eye blinks, or even their heartbeat, all of which can interfere with the neuro-oscillatory signals being recorded. Essentially this can contaminate the data and if adequate care is not taken may lead to false conclusions being drawn (Islam, Rastegarnia, & Yang, 2016). Hence, great care should always be taken to reduce interference in the final data file.

With that in mind we attempted to negate as many of these confounding signals as possible. This was by ensuring the ground and reference electrodes were as noise free as possible. Careful artefact rejection was carried out prior to analysing the data. Screening also took place during the recruitment process to highlight any participants with neurological disorders (for example epilepsy). This could have resulted in altered neurological activity that may have confounded our results. Participants were asked to refrain from taking any psychoactive or neuroactive substances (including alcohol) 24 hours prior to participation and try to have a good sleep the night before. If not controlled carefully these factors could also have affected neurological activity. Participants were seated in a room and in a position that was as comfortable as possible. They were also asked to relax and place their feet firmly on the floor and refrain from moving as much as they could whilst the recording took place. It is hoped that by implementing these methods the data that was collected was as clean and as readable as possible and ultimately allowed for us to make an accurate interpretation of the results.

We intended to use this EEG scanning method to track the electrophysical changes to the participant's brain as a result of non-invasive neuro-stimulation. The method of stimulation that we used to modulate neural activity and ultimately behaviour was Transcranial Magnetic Stimulation. The following sections will look to introduce this further, as well as discussing its usage and overall level of safety. Importantly, we will also introduce the specific protocol of stimulation applied in our research and justify its use in our particular investigation.

2.4. The history and usage of TMS:

TMS is often considered an excellent alternative to other methods of neuromodulation including those that utilise electrical stimulation. Despite these methods (that include Transcranial Alternating Current Stimulation or Transcranial Direct Current Stimulation (tDCS)) being developed after the introduction of TMS, the level of spatial specificity and the mechanism of action of this method has ensured that it has remained a popular choice in both research and clinical environments. It is generally regarded as a safe method of producing a transient modulation of areas of the brain (providing safety guidelines are accurately followed).

TMS as a method of neuro-modulation was first proposed by Barker and colleagues in 1985 (Barker, Jalinous, & Freeston, 1985). During a TMS procedure a wire coil is placed against the scalp, as a current is passed through the coil. This in turn produces a magnetic field that passes through the skull with relatively little resistance, which can reach up to 50 – 60 mm into the outer layer of the brain. As the magnetic field passes into the participants brain it produces an electric current through electromagnetic induction. This magnetic

current in turn acts by depolarising the neurons this then can induce transient physiological changes (either excitatory or inhibitory). This subsequently can be used to induce temporary behavioural changes in the participant (Horvath, Perez, Forrow, Fregni, & Pascual-Leone, 2011). The coils that are used often take the shape of a figure of 8, however the first to be used was a simple circular coil whose level of spatial specificity was particularly low. In addition to these figure of 8 coils other shaped coils have also been designed to allow for the stimulation of deeper brain structures. These deeper brain stimulation coils include H coils (Roth, Zangen, & Hallett, 2002), double cone coils (Lontis, Voigt, & Struijk, 2006) as well as the theoretically proposed C coils (Davey & Riehl, 2006) and circular crown coils (Deng, Peterchev, & Lisanby, 2008). As we wished to only stimulate superficial layers of the cortex with a good level of focality, the coils that we used in this investigation were the standard figure of 8 shaped coils.

Over the years, since its conception TMS has become one of the preferred methods of neuro-modulation. This is because after years of development and fine-tuning it can now be used effectively alongside EEG recording (Ilmoniemi & Kičić, 2010), PET scanning (Siebner, Peller, & Lee, 2008) or functional Magnetic Resonance Imaging (fMRI) (Bohning et al., 1999; Ruff, Driver, & Bestmann, 2009), with only a few issues (again, providing guidelines are followed). The method has received widespread use as an experimental way of determining the nature of causal relationships between functional brain activity and behaviour. This usage has led it to become an invaluable tool in cognitive neuroscientific research.

Perhaps the greatest potential application of TMS however comes in the medical field, with certain protocols being used in the diagnosis of Multiple Sclerosis (MS) (Gagliardo

et al., 2007). Other protocols have also been shown to be successful in the treatment of otherwise drug resistant depression (Avery et al., 2010; Blumberger et al., 2018; Chung, Hoy, & Fitzgerald, 2015; George et al., 2000; Kolbinger, Hoflich, Hufnagel, Moller, & Kasper, 1995; Lisanby et al., 2009; Loo, McFarquhar, & Mitchell, 2008). TMS as a treatment of depression has recently become widespread and has been deemed successful enough to be approved for use by the Food and Drug Administration (FDA) in the United States of America (Horvath, Mathews, Demitrack, & Pascual-Leone, 2010). Similarly it has also received approval by the NHS as a tool to treat painful migraines and cluster headaches (Ahmed, Goadsby, Bhola, Reinhold, & Bruggenjurgen, 2015; Brüggenjürgen, Baker, Bhogal, & Ahmed, 2016).It has been proposed that TMS protocols could also have other uses in medical settings. This includes the treatment of OCD (Greenberg et al., 1997), relieving the effects of some brain injuries (Paxman, Stilling, Mercier, & Debert, 2018) or strokes (Naeser et al., 2005) and alleviating some of the symptoms associated with schizophrenia (Jin et al., 2005). It should be noted however that the findings on its efficacy in terms of these treatments often appears mixed, especially for the treatment of schizophrenia and OCD respectively (McIntosh et al., 2004; Sarkhel, Sinha, & Praharaj, 2010). As a result its widespread use in the treatment of these conditions has yet to become a reality. However further investigations of this method could look to ascertain other uses, and perhaps even the emergence of other potential treatments for conditions that we have yet to consider.

TMS can be applied in a number of different ways. Single-pulse TMS involves a protocol in which pulses are presented in isolation or separated by a very long delay (Gagliardo et al., 2007; Pascual-Leone, Walsh, & Rothwell, 2000). Repetitive TMS involves pulses that are rapidly repeated in a series of “trains” (Avery et al., 2010; George et al., 2000; Horvath et al., 2010; Kolbinger et al., 1995). A similar protocol is Theta Burst

Stimulation, in which repetitive TMS trains are punctuated by brief pauses. This results in repeated TMS pulses, whereby blocks of trains are presented at a frequency of ~ 5 Hz, thus mimicking typical theta frequency (Blumberger et al., 2018; Di Lazzaro et al., 2008; Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005; Suppa et al., 2016). Finally Paired Associative Stimulation (PAS) in which pairs of stimuli are separated by a variable interval (Buch et al., 2011; Chiappini, Silvanto, Hibbard, Avenanti, & Romei, 2018; Rizzo et al., 2011; Rizzo et al., 2009; Romei, Chiappini, Hibbard, & Avenanti, 2016; Stefan, Kunesch, Cohen, Benecke, & Classen, 2000). Each of these methods have slightly different effects on the brain and also have a different level of safety concerns. The following sections will look to discuss these common TMS protocols, as well as the one that we intend to make use of in the current investigation.

2.5. Single-Pulse TMS:

Single-pulse TMS is typically used to stimulate single areas of the brain, this is achieved through a short burst of current across the coil that results in a variation in the magnetic field. This in turn leads to a rapid depolarisation of the stimulated neuronal cluster. Depending on certain factors and conditions this can then result in a brief display of the behaviour associated with the area being stimulated. For example, if having their visual cortex stimulated, an individual can (when the conditions are correct) perceive a brief flash of light known as a phosphene. Depending on the area of the visual cortex being stimulated these phosphenes can subsequently be mapped across the visual field. Similar stimulations over the sensorimotor cortex can induce Motor Evoked Potentials (MEPs).These are small muscle movements or twitches that are usually noted in the hand or the finger and can be

measured more objectively via electromyography. These MEPs are vital in determining nerve conduction rates, which in turn can be important in the diagnosis of certain conditions such as MS (Gagliardo et al., 2007). The effects of single-pulse TMS are very short term, lasting no more than a few milliseconds (with each pulse lasting approximately 100 microseconds). This method is thought to be very safe as it merely mimics the change in membrane potential that occurs during normal neuronal firing (Pascual-Leone, Walsh, & Rothwell, 2000). Increased seizure risk has only been observed when participants have been taking neuro-active medications (Rossi, Hallett, Rossini, Pascual-Leone, & Group, 2009), these have been shown to occasionally result in a reduced seizure threshold (Wassermann, 1998) hence demonstrating the need for proper screening to ensure participants are not taking these medications.

2.6. Repetitive TMS:

Unlike single-pulse TMS, repetitive TMS (rTMS) methods can be used to induce longer term effects (Pascual-Leone, Gates, & Dhuna, 1991). Unsurprisingly, given its name, rTMS subjects participants to multiple repetitions of stimulations (of up to 50 Hz) to the same area of the brain. After enough of these stimulations, physiological changes in the participants brain will begin to occur. If stimulation is continued for long enough or repeated often enough, these changes may eventually become semi-permanent (Avery et al., 2010; George et al., 2000; Horvath et al., 2010; Kolbinger et al., 1995).

These long term changes are thought to be the result of functional changes brought on by Hebbian like principles that cause Long Term Potentiation (LTP) or Long Term Depression (LTD) (George, Taylor, & Short, 2013; Ma et al., 2014; Wang, Wang, & Scheich,

1996; Zhengwu et al., 2018), this is the same processes that results in learning. The ability for the brain to change both physically and functionally in this way is known as neural plasticity (Bliss & Cooke, 2011). By repeatedly stimulating neuronal clusters in a fashion that either excites or inhibits them, the physiology of these neurons changes, exciting or inhibiting them respectively for a period of time. This demonstrates the natural plasticity of the connections within our brains and can be very useful in an experimental setting. For example, we can induce these plastic changes upon a specific region of the brain and conduct a series of behavioural tasks post-stimulation. We can then compare performance to pre-stimulation trials in order to observe any behavioural changes. We can subsequently use these findings to infer the degree of causality between activity in the stimulated brain region and the behaviour observed within the task.

This procedure is generally thought to be more dangerous to participants and has been known to cause seizures in otherwise seemingly healthy participants (Rossi et al., 2009). As a result, safety and ethical guidelines must always be followed to maximise the safety of the participant. This includes proper training for the experimenter and vigorous health screening for the participants. This is to ascertain any history of epilepsy or seizures in the participant's own (or their family's) history and to prevent the use of contraindicative drugs during the procedure. All of these factors may go some way to reduce the seizure threshold of the individual taking part (Wassermann, 1998). Thus all efforts should be expended in order to screen participants beforehand to ensure that *at risk* individuals do not take part.

2.7. Theta Burst Stimulation:

Another TMS protocol closely linked to that of rTMS is a method known as Theta Burst Stimulation (TBS). These are patterned rTMS protocols whereby rapid bursts of (typically) 50 Hz rTMS are repeated in shortly interleaved blocks. These rTMS bursts are repeated at a rate in the theta range (~ 5 Hz). The effects of this stimulation can vary depending on whether the stimulation is continuous (cTBS) or intermittent (iTBS). With cTBS having an inhibitory effect on cortical spinal activity and iTBS having an excitatory effect (Di Lazzaro et al., 2008; Huang et al., 2005). The main benefit to using TBS compared to other TMS protocols is that it is remarkably efficient, resulting in non-inferior post-stimulation effects despite the procedure itself lasting a fraction of the time that rTMS requires (Blumberger et al., 2018). This obviously results in a greater efficiency when using it compared to rTMS, especially considering that it has been shown effective in the treatment of major depressive disorder (Blumberger et al., 2018; Chung et al., 2015), meaning that many more individuals can be treated in a day. TBS has also been shown to require a much lower intensity level than that of rTMS to achieve comparable effects (Blumberger et al., 2018). This also acts to increase its safety, as a lower intensity stimulation is linked to lower discomfort and a lower seizure risk (Rossi et al., 2009).

Much like rTMS, TBS demonstrates long term effects, the method is once again thought to exploit Hebbian principles of neural plasticity, those that are present in LTP or LTD. However, unlike rTMS, segmenting the trains into ~ 5 Hz waves, also mimics a firing pattern found in cortical neurons during learning (Otto, Eichenbaum, Wible, & Wiener, 1991). Essentially this evokes a better replication of the processes resulting in LTP or LTD, resulting in a greater efficiency at inducing these changes (Suppa et al., 2016).

In terms of the risks associated with the procedure, evidence suggests that some effects are comparable to rTMS, with participants occasionally experiencing headaches and nausea (among other symptoms), whereas some participants reported a higher level of discomfort during the procedure itself (Blumberger et al., 2018). However, it should be noted that due to the decreased treatment duration and the intensity needed, the overall level of risk may be reduced here (Rossi et al., 2009). It is important to remember here that due to the relative infancy of this method, more research needs to be conducted to ascertain its overall safety. Nonetheless the method remains a potentially exciting alternative to other TMS protocols.

2.8. Peripheral-cortical and cortico-cortical Paired Associative Stimulation:

Paired Associative Stimulation is a dual coil procedure whereby coil pulses are paired with one another, this has been shown to be effective at enhancing the functional connectivity between distant, yet functionally connected regions (Buch et al., 2011; Chiappini et al., 2018; Rizzo et al., 2011; Rizzo et al., 2009; Romei et al., 2016; Stefan et al., 2000).

Peripheral-cortical Paired Associative Stimulation (pcPAS) is the most common form of Paired Associative Stimulation (PAS). Here TMS stimulation upon the primary motor or sensory cortex is paired with electrical stimulation to the contralateral median nerve (Rizzo et al., 2009; Stefan et al., 2000). The TMS stimulation in this case consists of slow-rate repetitive pulses. Again this leads to long term cortical changes, that once again exploit principles of Hebbian plasticity (Rizzo et al., 2009; Stefan et al., 2000). Here when the pre-synaptic region is stimulated before the post-synaptic region, the connection between the

two areas of the brain can be enhanced or weakened (depending on stimulation parameters). This phenomena is known as spike-timing-dependent plasticity (STDP) (Bi & Poo, 1998). This essentially allows for the functional transient facilitation or inhibition of pathways, exploiting the neural plasticity of the brain in order to do so.

Until relatively recently this pcPAS procedure was the only form of PAS receiving widespread attention and use. However a novel approach has since been developed. Instead of cortical stimulation being paired with a second peripheral stimulation, in this application the paired stimulation is applied exclusively cortically. This method, known as cortico-cortical Paired Associative Stimulation, uses these TMS pulses to stimulate synaptic clusters (Rizzo et al., 2009) within the brain. Here the two coils are placed over two distant and yet functionally connected areas. The parameters of the stimulation can therefore be manipulated in order to set directionality (i.e. which region is stimulated first and which second) or the specific timings of the stimulation. By setting these parameters precisely we can theoretically reproduce this effect of Hebbian principles of neural plasticity (Buch et al., 2011; Hebb, 1949; Rizzo et al., 2011) over these cortical regions. This results in STDP which subsequently acts to strengthen or weaken (depending on specific stimulation parameters) the connectivity between regions.

Prior to the current research, the ccPAS method has typically been used to stimulate across short-range monosynaptic connections, typically within local regions (e.g. exclusively between areas of the motor cortex, (Buch et al., 2011; Rizzo et al., 2011; Rizzo et al., 2009). This usually manifests as an average temporal spacing of 8 ms between pulses. These timings were informed by the functional timing connecting areas of the motor cortex (Ferbert et al., 1992). Recently however, research has demonstrated ccPAS to be effective

over even wider distances, still within local areas however (this time within the visual cortex; with stimulation occurring from area V5 to area V1), this manifested as an average time of 20 ms between pulses (Romei et al., 2016). This was informed by the functional timing of the back projections between V5 and V1 (Pascual-Leone et al., 2000; Silvanto, Cowey, Lavie, & Walsh, 2005). We now wish to make use of this ccPAS method in a novel way to investigate properties of the multisensory system. The reasoning behind this will now be discussed in the following section.

2.9. The use of ccPAS in the current investigation:

In this current research we looked to stimulate across connections that span a much wider area of the brain. In this case we presented the stimulation over the connection between the right somatosensory cortex (denoted by electrode C4) and the visual cortex (electrode Oz). We intended to use this method in a novel way, basing stimulation timings exclusively on the timings of the neuro-oscillatory processes subtending these longer-range connections. Recent developments in neurostimulation protocols have proposed a specific information-based approach of non-invasive transcranial stimulation to reflect more closely the biological constraints of the neural network we are investigating (Romei et al., 2016). These theoretical developments have prompted the surge of new protocols aimed at closely mimicking the neural mechanisms subtending a given neural process. In this vein, the aim of the current work inspired by the information-based approaches in neurostimulation was to explore the biological relevance of neuro-oscillatory signatures of functional networks. In this particular case, as will be detailed below, we looked to investigate the relevance of beta oscillations in controlling somatosensory to visual connectivity. Therefore, to the best of our

knowledge this investigation was the first time in the literature that the ccPAS method was used to inform our understanding of neuro-oscillatory processes and how they relate to multisensory behaviour using this information-based approach. Our reasoning for using the ccPAS method in our research is as follows.

Previous evidence has suggested that alpha frequencies are tightly linked to the temporal properties of the auditory-induced DFI (Cecere et al., 2015; Cooke, Poch, Gillmeister, Costantini, & Romei, 2019). In this current report we also provide evidence to suggest that beta frequencies may also play a role in the tactile-induced effect. Here we propose that the functional connections between the key cortices are subtended by different processes depending on the properties of the pre-synaptic regions and their organisation in providing effective communication to post-synaptic regions. In other words we believe that, in the case of the auditory-induced DFI, the information transfers across the connection from the auditory to visual region by means of local activity in the auditory cortex transferred to the visual cortex. Specifically we have reasons to believe that this happens through local organization of alpha waves in the auditory cortex (Dohrmann et al., 2007a; Dohrmann et al., 2007b; Frey et al., 2014; Fujioka et al., 2011; Gleiss & Kayser, 2014; McKee et al., 1973; Mercier et al., 2013; Teplan et al., 2003; Weisz et al., 2011). These are later tranfered to the visual cortex as a way of effective communication between distant nodes of the synchronized network. This mechanism would be an alternative interpretation to a simple visual phenomenon in which discrete auditory signals alter the ongoing local alpha activity in the visual cortex. This connectivity mechanism can explain the differential effect of the tactile-induced effect we have observed in our data, according to which, information transfer between the somatosensory and the visual cortices seem to be driven by beta waves, which are likely originated within the somatosensory cortex (Baumgarten et

al., 2015; Brovelli et al., 2004; Engel & Fries, 2010; Foffani et al., 2005; Kilner et al., 2003; McFarland et al., 2000; Paus et al., 2001; Rubino et al., 2006; Salenius & Hari, 2003; Zhang et al., 2008). In other words, a possible mechanism of action to explain this phenomenon is that the time it takes for information to reverberate from the somatosensory cortex to the visual cortex corresponds to the duration of one complete beta cycle.

This transfer of information could take place via travelling waves. These waves are theorised to facilitate the transfer of information propagating from one sensor to the next (Klimesch et al., 2007). Or alternatively it could be explained via a theory known as the *Communication Through Coherence* framework (Fries, 2005, 2015). Here communication between remote but functionally connected areas could be the result of the alignment of post-synaptic neural activity to pre-synaptic input. This then acts to create a temporal window of optimal communication based on the specific timings of the pre-synaptic regions (i.e. the auditory or the somatosensory cortices). As we find that EEG measurements during the different tasks demonstrate enhanced coherence at different frequencies we can conclude that they are sending information and therefore communicating at slightly different timings. In other words the communication between the auditory and the visual cortices is based upon the alpha frequencies subtending the connection between these regions. Conversely the connection between the somatosensory and the visual cortices is set at a slightly faster frequency, i.e. beta, which acts to facilitate the transfer of information across the network.

Our intention here was to test our model further by modulating the functional connectivity between the somatosensory and the visual cortices, basing the timing on the beta waves travelling between them. As such we required a method that had been

demonstrated to modulate the connectivity between distantly connected regions. Thus we concluded that the ccPAS method would be an ideal way for us to test our hypotheses.

Therefore in Experiments Two and Three we wished to utilise the ccPAS method in a way that has not been previously reported in the literature and base the pulse timings exclusively on the individual beta frequencies subtending the somatosensory to visual connections. We intended to use this method to exploit the natural plasticity of the brain, manipulating the key functional differences and producing momentary changes in the way these two areas communicate with one another. We also aimed to subsequently produce a modulation of the temporal properties of the tactile-induced DFI.

More specifically, in Experiment Two we used an Inter-Stimulus Interval that was slightly longer than this beta cycle duration. Our intention here was to fine-tune the network and produce an overall reduction in the speed of the beta processes subtending it. We also hoped that if this was indeed successful, we should also be able to provide a corresponding widening of the Temporal Window of Integration for this illusion, which has been explicitly linked to these beta frequencies. In Experiment Three we based this ISI on the exact beta frequency value subtending this connection. In other words we were stimulating at the frequency that the system already operates at. We expected this to result in no changes to the beta speed subtending the connection and was intended to act as something of a control condition to the previous experiment. This subsequently led to an average pulse delay between coils of approximately 60 – 110 ms in Experiment Two and 50 – 80 ms in Experiment Three, a pulse delay much longer than anything that has been shown successful in the literature.

Previous research has focused exclusively on short-range monosynaptic networks, mimicking Hebbian rules of pre-to-post synaptic connectivity. In our case rather than looking at these specific *short term* networks we focused more on these *longer term* networks that are not necessarily monosynaptic. These particular regions may be connected indirectly through other intermediate networks. Hence the networks that we are investigating here are potentially more complex and their communication requires longer transmission times, hence the longer delays that we used here. It is hoped that by using this method in a novel way we can inform the literature to further capabilities of the method. We aim to show that the method can be used to stimulate longer-range cortico-cortical networks and that we can indeed use this method to inform our understanding of neuro-oscillatory processes and how these phenomena relate to the communication of multisensory networks.

However before using this method we first had to consider the safety issues that may have arisen in order to ensure that we were doing everything possible for us to keep the risk of injury to the participants as low as possible.

2.10. Safety concerns of ccPAS and precautions to be taken:

In this study, we can confirm that all efforts were taken in order to maximise participant comfort and safety, as ccPAS is a variant of Paired Associative Stimulation we followed the safety guidelines for this particular method as highlighted by Rossi et al., (2009). Whilst this method is thought to be relatively safe with little evidence to suggest a seizure risk we understand that no matter how small the risk, appropriate steps should always be taken to reduce any likelihood of this occurring. In addition to this, PAS has been linked with some discomfort, and whilst this should not have overly affected participants,

their comfort should always be maximised in order to minimise anxiety and reduce drop-out rates. With this in mind experimenters were given full and comprehensive training in the use of the TMS machines and followed the recommended safety guidelines (Wassermann, 1998; Rossi et al., 2009). Participants were also extensively screened for any neurological issues, enabling us to pick up any family history of seizures, history of brain trauma or the use of any contraindicative drugs that may have resulted in a reduced seizure threshold or any other safety concerns for the participants. As previously noted participants were asked to refrain from taking any neuroactive or psychoactive substances 24hrs prior to participation (including alcohol). They were also asked to have a full and restful night sleep before (if possible). These are to ensure that any lowering of the seizure threshold was kept to an absolute minimum.

Another important point to consider here is that using TMS and EEG in conjunction with one another is a potentially delicate operation. As such we always ensured that the EEG caps that were used were specifically designed for the use of these two methods in combination. Failure to do this could have resulted in damage to equipment and even burns upon the participant's scalp.

Finally, participants received constant reassurance throughout the procedure. The overall safety of the method was stressed and further reading, or information was made available to them should they wish to find out more. Participants were assured that despite any discomfort they may feel the procedure is well established and relatively safe. However if they wished to leave the experiment at any time they were always free to do so. This was done to create a relaxed atmosphere and reduce participant stress or anxiety, which may have adversely affected neurological performance, led to increased dropout rates or

resulted in an increased risk of adverse effects. It is hoped that by following this method we significantly reduced any risk of participant injury or discomfort. Subsequently maximising the efficacy of the stimulation and the validity of the results. During the procedure no participant felt uncomfortable enough to leave the experiment, and no adverse effects were recorded from participants during or after the procedure. This is aside from some minor discomfort being reported during the procedure itself, which of course was expected.

3. Chapter Three: Experiment One – Oscillatory properties of functional connections between sensory areas mediate crossmodal illusory perception:

3.1. Experiment One: Abstract:

The presentation of simple auditory stimuli can significantly impact visual processing and even induce visual illusions, such as the auditory-induced Double Flash Illusion. This effect appears to be driven by occipital oscillatory alpha activity. Whether this phenomenon is network specific or can be generalized to other sensory interactions remains unknown. The aim of the current study was to test whether crossmodal interactions between somatosensory to visual areas leading to a similar (tactile-induced) DFI share similar properties to the auditory-induced DFI. We hypothesized that if the effects are mediated by the oscillatory properties of early visual areas then the two illusions should be subtended by similar neurophysiological mechanisms (i.e. alpha frequency speed). Alternatively, if oscillatory activity in visual areas predicting this phenomenon is dependent on a specific neural network, then it should reflect network specific oscillatory properties. In line with the latter, results show a network specific oscillatory profile linking auditory-induced DFI to occipital alpha oscillations and tactile-induced DFI to occipital beta oscillations, a rhythm typical of somatosensory processes. These frequency specific effects are observed exclusively for visual areas and account for auditory-visual connectivity in the alpha band and somatosensory visual connectivity in the beta. We conclude that task dependent visual oscillations reflect network specific oscillatory properties favouring optimal, directional neural communication timing for sensory binding.

3.2. Experiment One: Introduction:

Our senses act as temporal gateways to our environment, allowing continuous information streams within and across senses to be coded into discrete information units (Chakravarthi & VanRullen, 2012; VanRullen, 2016; VanRullen & Koch, 2003). The precise temporal resolution of such mechanisms may allow the brain to temporally bind sensory input over time and across senses into meaningful objects and events (Cecere et al., 2015) thus reducing the overall complexity of our environment (Wutz et al., 2018; Wutz et al., 2016) allowing for accurate and efficient navigation.

More often than not this Bayesian mechanism[1] (Barakat, Seitz, & Shams, 2013; Beierholm, Quartz, & Shams, 2009; Cuppini, Shams, Magosso, & Ursino, 2017; Kayser & Shams, 2015) tends to result in generally prompt and efficient interpretations of the environment. However, when presented with incongruent sensory information, this multisensory system has been shown to often give rise to illusory phenomena, as it attempts to understand and interpret this information. One example of this is the Double Flash Illusion. Shams and colleagues (2000) first discovered that when two or more shortly interleaved beeps are paired with a disc that would briefly flash upon the screen once before disappearing, participants often perceive a second illusory flash (or multiple illusory flashes depending of the number of beeps) (Shams et al., 2000, 2002). Illusions such as this may possibly represent the optimal coherent perceptual resolution of otherwise conflicting sensory information (Cecere et al., 2015).

[1] In this case a Bayesian mechanism refers to the fact that the illusory outcome could be the most probable outcome based on previous experience. This is as generally when a single visual stimulus is presented in association with a single auditory stimulus your brain is hardwired to expect this to occur again. Hence when the second auditory stimulus is presented (this time in isolation) your brain mistakenly believes this to also be associated with a visual stimulus, hence the illusory perception of such.

Incidentally by systematically manipulating temporal intervals between paired beeps, it is possible for us to define a temporal window of integration for the auditory-induced DFI; this represents the time interval in which the illusory flash is perceived. When the temporal spacing of the beeps exceeds this value, the illusory effect tends to degrade. This TWI, first characterised by Shams and colleagues (2002) and once more detailed by Cecere et al., (2015), demonstrates that the illusion tends to decay when the average time between these beep pairs exceeds 100 ms. Cecere et al., (2015) argued that these TWIs, which appear to be highly variable across individuals, are reminiscent of the temporal profile of posterior oscillatory activity in the alpha band (7 – 12 Hz, but with an average of 10 Hz or 100 ms). Employing both correlational and causal approaches, Cecere et al., (2015) found a tight correlation between a person's individual TWI and their individual alpha frequency peak in occipital regions. Here a faster IAF generally predicted a shorter TWI, and a slower IAF predicting a larger TWI.

As yet however, we are unaware whether this mechanism is solely determined by local network rules *per se*; in other words, local occipital oscillatory resonance activity (typically alpha) (Dugue et al., 2011; Ergenoglu et al., 2004; Frey et al., 2014; Gleiss & Kayser, 2014; Gulbinaite et al., 2017; Lange et al., 2014; Mercier et al., 2013; Minami & Amano, 2017; Romei, Brodbeck, et al., 2008; Romei et al., 2010; Romei, Rihs, et al., 2008; Ronconi et al., 2018; Rosanova et al., 2009; Samaha & Postle, 2015; Van Dijk et al., 2008; Wutz et al., 2018; Wutz et al., 2016), or whether it depends on long-range communication networks (Fries, 2015). In other words the way in which a sensory modality (in this case the auditory domain) impacts on visual cortex activity (Romei et al., 2012). The question that arises here is, are cross modal visual illusions strictly determined by typically visual oscillatory

constraints, or do visual oscillations mediating these effects reflect the oscillatory properties of the functional connection between the two sensory modalities?

One way to tease these hypotheses apart, is to investigate the temporal profile and neural underpinnings of a DFI that is induced by a sensory modality other than that of audition and compare these properties with those of the auditory-induced effect. In our case, we utilised the tactile-induced DFI (Violentyev et al., 2005), where we will replace the paired beeps with taps upon the left index finger; this has been demonstrated to elicit a similar visual illusory response (Violentyev et al., 2005). Unfortunately, no previous report of a temporal profile for the tactile-induced DFI exists in the literature. If the induced illusory flash is determined by the local resonance frequency of the visual cortex (here assumed to be alpha), irrespective of paired modality, then presumably a similar illusory phenomena (pairing visual processes with that of a domain other than audition) should also be mediated by these occipital alpha processes. Alternatively, if functional connections between auditory or somatosensory cortices and the visual cortex determine the fate of the illusory experience, then occipital oscillations accounting for the auditory and tactile-induced DFIs may depend on communication specific mechanisms influencing visual cortical processing at the speed of their typical resonance frequency. But why might this be the case?

According to the *Communication Through Coherence* framework (Fries, 2005; 2015), neural communication that is subserved by oscillatory synchronization between remote but functionally interconnected areas could be the result of the alignment of post-synaptic neural activity (in our case the visual cortex) to the pre-synaptic input (either the auditory or somatosensory cortex), thus creating temporal windows of optimal communication.

This hypothesis would already be consistent with evidence that suggests that the auditory-induced TWI is mediated by alpha oscillations. This is because the auditory cortex (pre-synaptic), which is often associated with alpha activity (Dohrmann et al., 2007a; Dohrmann et al., 2007b; Frey et al., 2014; Fujioka et al., 2011; Gleiss & Kayser, 2014; McKee et al., 1973; Mercier et al., 2013; Teplan et al., 2003; Weisz et al., 2011), phase aligns alpha oscillations in the visual cortex (post-synaptic) (Romei et al., 2012). Crucially however, this model would also predict somewhat faster waves to influence the tactile-induced TWI, with tactile processing (pre-synaptic) often associated with beta frequency oscillations (Baumgarten et al., 2015; Brovelli et al., 2004; Engel & Fries, 2010; Foffani et al., 2005; Kilner et al., 2003; McFarland et al., 2000; Paus et al., 2001; Rubino et al., 2006; Salenius & Hari, 2003; Zhang et al., 2008).

As such, we looked to investigate the neural correlates of the auditory-induced and tactile-induced DFI. We expected to be able to replicate previous research linking this effect to alpha processes (Cecere et al., 2015). We were however unsure what to expect for the tactile version of the illusion. If the induced illusory flash is determined by the local resonance frequency of the visual cortex then we should once again have expected to see a positive correlation with the IAF. However, our hypothesis may also be in line with the *Communication Through Coherence* framework, in which case we should have expected to find a correlation with somewhat faster frequency waves, given previous evidence we would assume this to be the individual beta frequency.

3.3. Experiment One: Materials and Methods:

Participants:

A total of 62 participants initially volunteered to take part in the study which was approved by the ethics committee of the University of Essex. Eleven participants were excluded from data analysis as their perceived illusion could not be fitted to the sigmoid function curve leaving us with a total sample of 51.

Forty eight of the 51 participants stated by self-report that they were right handed, out of the remaining 3, 2 stated that they were left handed and 1 stated ambidextrous. The mean age of the sample was 25 years (range: 18 – 44), the sample consisted of 31 females and 20 males. We intentionally used a relatively narrow age range band (only selecting participants between the ages of 18 - 45), so as to reduce variability in oscillatory activity as a result of age (Aurlien et al., 2004), evidence also suggests that age may play a role in DFI illusory susceptibility (Innes-Brown et al., 2011; McGovern, Roudaia, Stapleton, McGinnity, & Newell, 2014).

Prior to taking part, participants completed an extensive screening questionnaire ensuring they had no history of psychiatric or neurological disorders and normal (or corrected to normal) vision, as well as normal hearing and somatosensation by self-report.

Materials and Apparatus:

All visual stimuli were presented on a 17.5 inch cathode ray tube monitor via a Dell Optiplex 960 computer (Windows XP, resolution: 1280x1024) with a refresh rate of 85 Hz. Auditory stimuli were delivered via a pair of speakers placed either side of the monitor

(placement was carefully selected to focus the centre point of the sound's location at the centre of the screen, close to the visual flash). Volume was set so stimuli were approximately 50 dB (SPL) at the location of the participants' head. The tactile stimuli were provided via a tactile controller and mechanical solenoid stimulator (Heijo Research Electronics, London, UK). Which would deliver a suprathreshold tap (upon the participant's left index fingertip) by pushing a blunt plastic point against the participant's skin whenever a current was passed through the solenoid. Exclusively during the presentation of the tactile stimuli, white noise (approximately 50 dB) was played to participants through the speakers to mask the mechanic noise produced by the tactile stimulator and ensure this was not heard by the participants. This was to avoid confounding the tactile experience by also inadvertently presenting participants with auditory stimuli. All experimental stimuli were presented via the software E-prime (version 2.0; Psychology Software Tools, Pittsburgh, PA).

We piloted the experiment in the first 15 participants with EEG recording taking place with a restricted number of electrodes including Electrodes Oz, O2, O1, FP1, FPz and FP2, alongside the ground electrode (located at position AFz) and the reference electrode placed upon the right mastoid bone.

In the remainder of the participants (N = 36), the EEG was recorded from 64 sintered Ag/AgCl electrodes mounted on an elastic cap (Easycap, Herrsching, Germany) alongside the ground electrode (again located at position AFz) and the reference electrode (again placed upon the right mastoid bone). The EEG signals were digitized at 500 Hz and amplified using a BrainVision Professional BrainAmp amplifier through the BrainVision Recorder programme (BrainProducts GmbH, Gilching, Germany). Before the recording began we ensured that all

electrodes were set upon the participant's scalp at an impedance not exceeding 10 Kiloohms (kΩ).

In all trials, participants were presented with a flashing disc with a diameter of 2 cm, displayed just below a central fixation cross (this disc flashed once for a duration of 12 ms). During the auditory-induced DFI task the disc was always paired with a double beep sound, with each auditory stimulus having a frequency of 3500 Hz and a duration of 7 ms. During the tactile-induced DFI task disc presentation was paired with a double tap sensation to their left index finger.

The two brief sensory stimuli were spaced apart by a varying range of Inter-Stimulus Intervals, these ranged between 36 ms and 204 ms increasing with increments of 12 ms, this resulted in in 15 different ISI values. Each ISI was presented 10 times, resulting in 150 randomly ordered trials in each of the two task blocks. The time between trials included the presentation of the stimuli (as described above) plus a varying interval. This corresponded to the elapsed time following the experimenter's input on the keyboard, this was upon hearing the participant's vocal response to the previous trial. This prompted another varying (inter-trial) interval ranging between 1000 ms and 1800 ms (there were 5 different inter trial delays in steps of 200 ms, each occurring 30 times) before the next trial started.

Experimental Design:

Upon EEG cap fitting completion, participants were seated approximately 57 cm away from the screen. EEG recording was manually started prior to the first block of trials beginning. Participants were subsequently instructed to fixate on a cross situated at the

centre of the screen while the 150 flashing discs within the block were presented. This was once in a first block of trials paired with two auditory (or tactile) stimuli, and once again, after a brief resting period, in a second block of 150 flashing discs this time paired with two tactile (or auditory) stimuli. To control for order effects (including fatigue or boredom), the order of the blocks was counterbalanced, with half of the participants performing the tactile-induced DFI task first, and the other half performing the auditory-induced DFI task first. EEG recording was stopped between tasks with recording commencing once the second task begun.

For the tactile-induced DFI block, participants were asked to place their left index finger immediately below the location of the flashing disc (as close as they could get whilst still remaining comfortable) this was in order to maximise spatial co-occurrence of the visual and tactile stimuli.

In all trials participants were asked to verbally report whether they perceived one flash or two flashes, this was done to avoid motor interference from participants using their resting (right) hand to respond to the stimuli, this could have been an issue in the tactile version of the illusion, where focus should only be concentrated on the stimulated left hand. Participants were instructed to provide unspeeded and accurate responses. The verbal report was then input by the examiner via the “1” or the “2” key, which prompted the new trial to begin, only after the variable inter-trial interval.

3.4. Experiment One: Statistical Analysis:

Behavioural data analysis:

The participants' perceived illusory flashes across the different ISIs were used to calculate the auditory and tactile temporal windows of integration separately, this was the ISI in which the visual illusion was maximally perceived. Therefore, we calculated the percentage of illusory trials (trials where two flashes were perceived) and plotted them as a function of the ISIs, this was done separately for both the auditory and tactile-induced DFIs. A psychometric sigmoid function [$y = a + b/(1 + \exp(- (x - c) / d))$; *a = upper asymptote; b = lower asymptote; c = inflection point; d = slope*] was then fitted to each percentage distribution returning a corresponding inflection point (centre c) of the fitted sigmoid representing the point of decay of the illusion, this value was then subsequently taken as an index of the TWI. Ergo we could assume that when stimuli pairs were spaced apart by more than this corresponding centre point the illusory response would begin to significantly decay. If, however, the data would not fit to the sigmoid function then the participant's performance was deemed unreliable and hence discarded. Following this procedure, 11 of the 62 participants were not enrolled in the full experimental procedure because of this issue, they were therefore excluded from data analysis.

EEG data analysis:

Sensor space analysis:

EEG activity was concurrently recorded during task execution, this was subsequently analysed to calculate individual alpha and individual beta frequency peaks, for each participant (as well as individual theta peaks, which we used as part of a control condition).

For each individual this process was done separately for the auditory-induced DFI task and the tactile-induced DFI task.

In the first 15 participants, EEG analysis was performed only on electrode Oz. Depending on which wave band we were interested in, the data was band pass filtered as follows: for alpha, a high pass filter of 3 Hz and a low pass filter of 40 Hz were used (this was identical to filters used by Cecere et al., (2015)); for beta, given the lower power relative to alpha, a more stringent criterium was used, here a high pass filter of 12 Hz and a low pass filter of 25 Hz were used. Finally, for theta we used a high pass filter of 4 Hz and a low pass filter of 7 Hz. The EEG signal was segmented into equal epochs of 2000 ms. As data in this first sample of participants was not synced to stimulus presentation (in other words no triggers were recorded for each stimulus onset and response), the 2000 ms epochs corresponded to consecutive non-overlapping segments independent of the stimulus onset (for a total of approximately 170 epochs on average).

The potential confound of induced and evoked oscillatory responses was controlled for in the second group of 36 participants, where 64 channel EEG was recorded at a sampling rate of 500 Hz. In this group the EEG signal was re-referenced offline to the average of all scalp electrodes. EEG data was subsequently segmented into 2000 ms epochs time locked to and preceding the visual stimulus onset. This resulted in 150 epochs of pre-stimulus oscillatory activity for each of the three frequency bands assessed, this was both for the tactile-induced and auditory-induced DFI tasks. Each single epoch was visually inspected for artefacts, and manually rejected where necessary. For each participant and for all the recorded electrodes a full power spectrum was obtained through Fast Fourier Transform (FFT) with zero padded window (nominal frequency resolution 0.125 Hz). Finally,

for each participant, task (tactile- or auditory-induced DFI) and frequency band (Alpha, Beta or Theta), EEG segments were averaged for calculation of the average peak frequency in the visual cortex, as calculated at electrode Oz. For each frequency band, the peak frequency was determined for each participant as the value corresponding to the maximum peak frequency within their frequency range (alpha: 7 – 12 Hz; beta: 12 – 25 Hz; theta: 4 – 7Hz). Finally, for each participant the duration (in ms) of one single oscillatory cycle was calculated using the peak frequency data (in Hz) obtained in the alpha, beta and theta bands over Oz in the first 15 participants and over 64 channels in the other 36 participants.

Source Space analysis:

All source space analyses have been performed on the second group of 36 participants in which the signal has been recorded from a full set of 64 EEG channels.

Frequency peak analysis in virtual electrodes:

For each participant we calculated the speed (in ms) of one single oscillatory cycle using the peak frequency data (in Hz) obtained in source space in the alpha and beta bands at the visual, somatosensory and auditory cortices. For the purposes of this analysis we did not use theta bands.

Virtual electrodes were computed for three different cortical areas (the visual cortex, auditory cortex and somatosensory cortex) using the linearly constrained minimum variance scalar beamformer (Sekihara, Nagarajan, Poeppel, & Marantz, 2004) implemented in Fieldtrip. First, a 10 mm three-dimensional grid was fitted to the MNI standard brain.

Then, the forward model was created using a standardized realistic head model. The spatial filters were computed for each DFI task using a window of 2000 ms pre-stimulus and 500 ms post second stimulus covariance window, with the regularisation parameter set to 10%. Single trial time series were projected to the cortical surface by multiplying them by the spatial filters weights. The source volume was interpolated with the MNI standard brain to define three regions of interest: right calcarine gyrus (visual cortex), right superior temporal gyrus (auditory cortex), and the right postcentral gyrus (somatosensory cortex). For each participant the IAF and IBF values were calculated in the voxel inside each of the three regions of interest showing a clear peak with the maximal amplitude.

Phase locking value analysis:

We wished to quantify the frequency specificity synchronisation between the visual and the somatosensory cortex in the tactile-induced DFI condition, and between the visual and the auditory cortex in the auditory-induced DFI condition. Thus we computed the Phase Locking Value (PLV) centred in each participant specifically for the IAF and IBF (Lachaux, Rodriguez, Martinerie, & Varela, 1999). The time series in each virtual electrode was filtered with a central frequency equal to that of the IAF or IBF +/- 1 Hz. The instantaneous phase complex representation of the filtered signal was calculated as follows: $e^{i\phi(t)} = s_a(t) / | s_a(t) |$, where $s_a(t)$ is the signal's analytic representation. The phase alignment between the two virtual electrodes was computed using the following formula:

$$PLV_{i,j}(t) = \frac{1}{N} \left| \sum_{n=1}^{N} e^{-i(\varphi_i(t,n) - (\varphi_j(t,n)} \right|$$

Where N is equal to the number of trials.

PLVs were computed separately for trials within each participant´s TWI and outside the TWI and rescaled in respect to a 100 ms pre-stimulus window. Non parametric statistics were used to compute significant differences between each condition (Maris & Oostenveld, 2007). First, temporal clusters of PLVs were calculated based on paired t-test significant time points. Then, Monte Carlo randomisation was performed to obtain the empirical distribution of the maximum cluster statistic, computed as the sum of within cluster t-values. The observed cluster was considered significant if its cluster statistic value was above the 95% of the empirical distribution.

Correlation analyses on behavioural data:

Firstly, we wanted to investigate the behavioural data obtained from all 51 participants for both auditory- and tactile-induced DFIs, for us to compare performances in the two tasks, replicate the temporal profile for the auditory-induced DFI and also characterise, for the first time, the temporal profile of the tactile-induced DFI. Secondly, we assessed the relationship between the known auditory-induced DFI and the previously unexplored tactile-induced DFI temporal profiles.

Correlation analyses between behavioural and electrophysiological data (sensor space):

Next, we performed correlational analyses between the individual speeds (in ms) of each oscillatory cycle (alpha, beta and theta) and the individual temporal width (in ms) of the TWI, this was done separately for the auditory- and the tactile-induced DFI.

Our behavioural and electrophysiological data were used to test the following predictions. Firstly, we aimed to replicate the data from Cecere et al., (2015) providing evidence suggesting that occipital IAF is selectively predictive of TWI size, especially in the case of the auditory-induced DFI. Secondly, we wanted to test the hypothesis that occipital IAF is predictive of both the size of the auditory- and tactile-induced TWI. Or alternatively that the size of TWI is differently accounted for by the occipital IAF in the specific instance of the auditory-induced DFI and by the IBF in the specific instance of the tactile-induced DFI. We tested these hypotheses first in the initial 15 participants over Oz (with epochs not locked to stimulus onsets) and again in the sample of 36, this time using a full array of electrodes allowing for a topographical distribution of Pearson's r (using epochs locked to stimulus onsets). As the preliminary analyses both on behaviour and EEG data showed comparable results between groups, notably excluding at the EEG level the potential confounds of evoked responses in the calculation of individual frequency peaks, data from both groups were pooled together for behavioural and EEG analysis at sensor Oz.

Multiple regression analyses between behavioural and electrophysiological data (source space):

In order for us to test whether any relationship between behavioural and oscillatory data was strictly specific to the visual cortex, a multiple linear regression analysis was used to assess the relationship between: 1) the TWI in the auditory-induced DFI and the IAF and IBF of visual and auditory virtual electrodes; 2) the TWI in the tactile-induced DFI and the IAF and IBF of visual and somatosensory virtual electrodes (Keil, Pomper, & Senkowski, 2016). A

forward step procedure was adopted to fit the regression model. Again for the purposes of this analysis the 15 participants utilised in the pilot study were excluded.

3.5. Experiment One: Results:

Auditory-induced vs. tactile-induced DFI:

We first determined the temporal profile for the auditory-induced and tactile-induced DFI effects. For the auditory-induced DFI we were successful in replicating previous reports (Cecere et al., 2015), finding an average TWI of around 100 ms. The temporal profile of the tactile-induced DFI was found to be very similar to that of the auditory effect in the same participants, a subsequent paired t-test suggested that the two did not significantly differ from each other (*auditory-induced TWI: 99.02 ms (S.E.M.: 3.08); tactile-induced TWI: 102.80 ms (S.E.M.: 3.23); t (50) = - 1.02; p = 0.31*). We then looked to test whether these two measures were correlated with one another. In this case we did indeed find a significant correlation between the TWIs of the two versions of the DFI (*Pearson's r = 0.31, p = 0.03*) which survived robust skipped correlations method (as described by (Pernet, Wilcox, & Rousselet, 2013)) (*r = 0.31, Confidence Interval (CI) = [0.02 : 0.55*]). This can be seen in Figure 1.

We further compared the two sensory versions of the illusion by contrasting the goodness of fit of the sigmoid function curve across the two versions of the DFI. Specifically, measurements were taken for the R^2 value (taken as an indicator of the overall goodness of fit) for each curve across both participants and conditions. We found that the goodness of fit for the tactile-induced illusion ($R^2 = 0.70$) was in fact significantly lower compared to that

of the auditory-induced illusion ($R^2 = 0.83$, $p < .001$), suggesting the tactile illusion is inherently noisier than the auditory version.

Overall, a first interpretation of these behavioural findings is that the auditory and tactile version of the DFI are comparable and might be driven by similar neurophysiological mechanisms. This would be consistent with the significant correlation that we found between the two, and the fact that the two measures were not found to differ from one another.

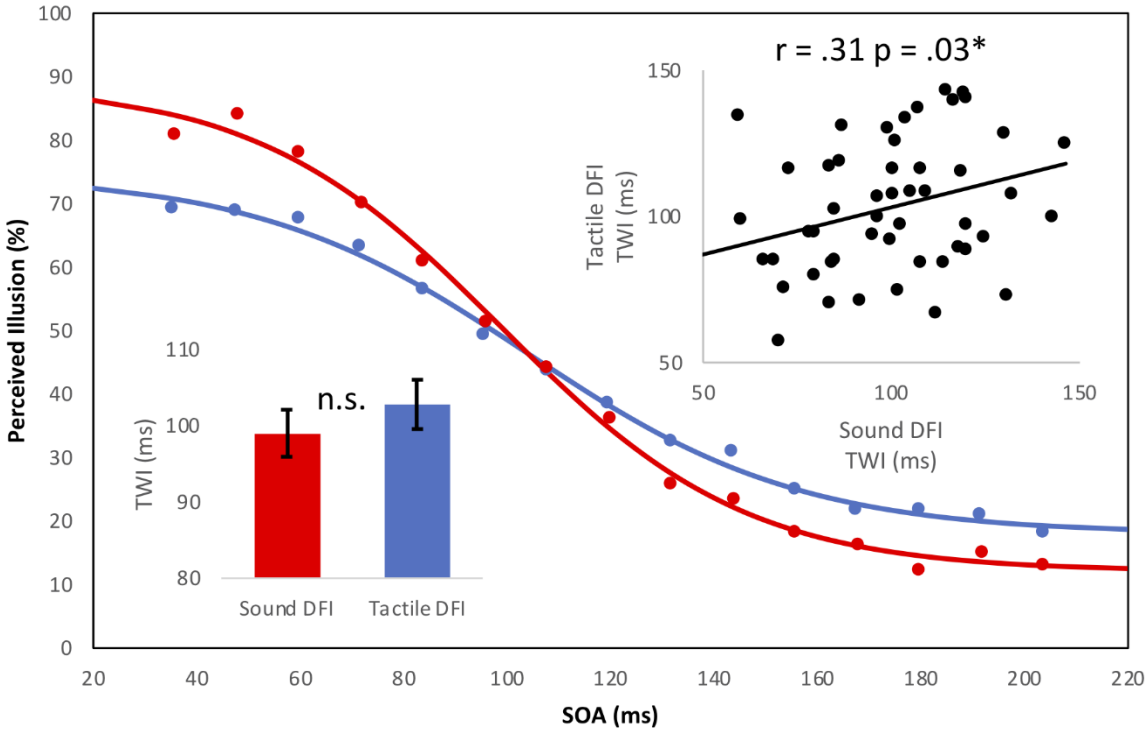

Figure 1. Behavioral data: *Sigmoid curve represents the best fit of the average probability of perceiving the double flash illusion plotted as a function of inter beep (red) and inter tap (blue) delays. Each individual point represents the average percentage of illusory trials at each ISI.*

Upper inset: *Significant positive correlation between respective TWIs for each illusion.*

Lower inset: *Absolute values of the average TWIs for the auditory-induced (red) and the tactile-induced (blue) TWI, respectively. The error bars represent the standard error of the mean, whereas n.s. refers to the non-significant difference between the TWIs of the auditory and tactile-induced DFIs.*

EEG correlates of auditory and tactile-induced DFI:

Sensor space:

We found that occipital IAF (in ms) positively correlates with the size of the TWI in the auditory-induced DFI (*r = 0.52; p < .001*), as before this also survives robust skipped correlations (*r = 0.41, CI = [0.18 : 0.59]*), such that faster IAFs once again appear to account for shorter auditory-induced TWIs, we have essentially replicated the results of Cecere et al., (2015). Pearson's correlation topography (calculated on 36 participants) suggests that this effect is maximal over posterior regions, this effect was found to be strictly frequency specific as no significant correlations could be found for IBF (calculated on 51 participants: *r = - 0.06; p = .69*) (See Figure 2) or for the Individual Theta Frequency (ITF) (*r = - 0.06; p = 0.69*). Crucially, when looking at the tactile-induced DFI, a different pattern of results emerges. Results suggest that the IAF does not seem to have any predictive value on the TWI when the TWI is induced by tactile stimuli (*r = - 0.13; p = .38*). Instead we found that occipital IBF positively correlated with the size of the TWI in the tactile-induced DFI (*r = 0.54; p < .001*), this was also shown to survive robust skipped correlations (*r = 0.54, CI = [0.32 : 0.69]*), such that faster IBFs accounted for shorter tactile TWIs (See Figure 2B). As with the auditory-induced DFI Pearson's correlation topography (calculated on 36 participants) suggests that this effect is maximal over posterior regions. Yet again no effect was found for the ITF (*r = 0.04; p = 0.10*).

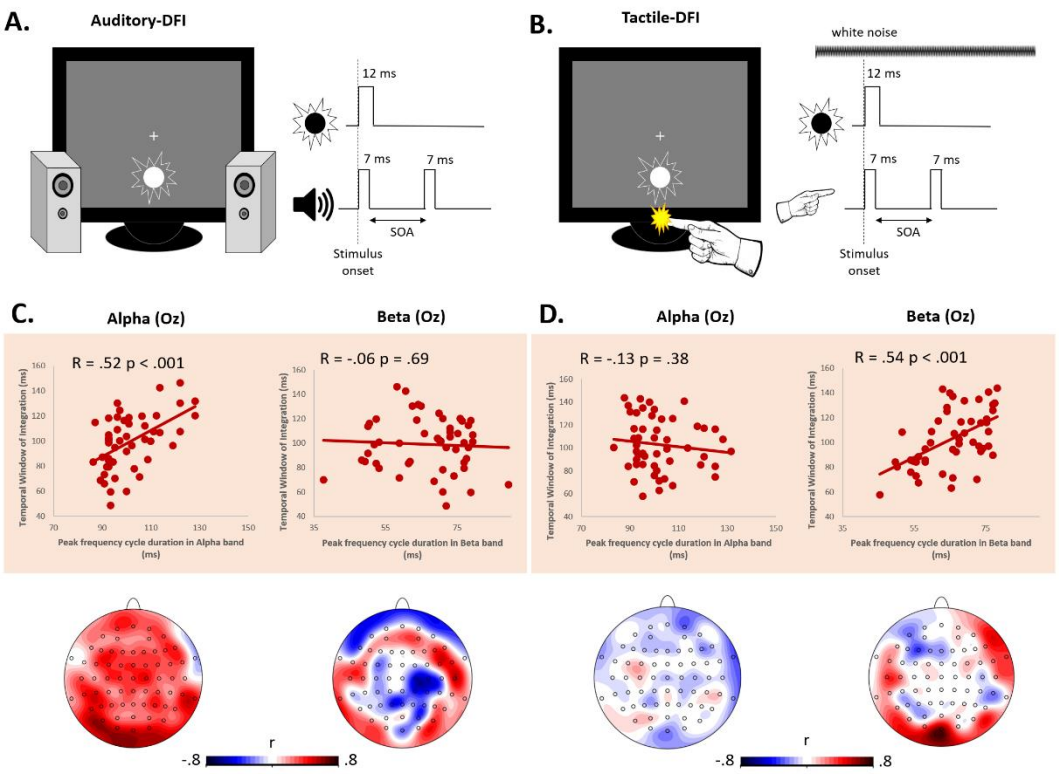

Figure 2. EEG correlates of auditory and tactile-induced DFI.

A. Auditory-induced Double Flash Illusion (Sound DFI): *Whilst viewing the flashing disc (12 ms duration) participants also experienced two 3500 Hz tones (both with a 7 ms duration). These auditory stimuli were separated by a variable ISI (36 ms - 204 ms). Participants were asked to ignore the sound and state aloud whether they perceived one or two flashes.*

B. Tactile-induced Double Flash Illusion (Tactile DFI): *Whilst viewing the flashing disc (12 ms duration) participants also experienced two brief taps to their left index finger (both with a 7 ms duration). These tactile stimuli were separated by a variable ISI (36 ms - 204 ms). Participants were asked to ignore the tactile stimuli and state aloud whether they perceived one or two flashes.*

C. Correlation plots: *For occipital regions (electrode Oz) and Pearson's r topographic distributions (lower panels) between auditory-induced TWI and alpha (left most panel) or beta (right most panel) bands. A selective, positive and significant relationship between the auditory-induced TWI and the speed of alpha oscillations was found suggesting that faster alpha speed accounts for shorter TWI, replicating previous evidence (Cecere et al., 2015; Keil & Senkowski, 2017).*

D. Correlation plots: *For occipital regions (Electrode Oz) and Pearson's r topographic distributions (lower panels) between tactile-induced TWI and alpha (left most panel) or beta (right most panel) bands. A selective, positive and significant relationship between the tactile-induced TWI and the speed of beta oscillations was found suggesting that faster beta speed accounts for shorter TWI.*

Source Space:

Multiple linear regression analysis was conducted on 36 participants (with the 15 pilot participants excluded) whereby the TWI of the auditory-induced task is regressed onto the visual IAF, auditory IAF, visual IBF and auditory IBF. This showed that when the TWI of

the auditory-induced DFI task was predicted it was found that the visual IAF (*Beta = 0.751, p < .01*) was a significant predictor (in line with recent findings by Keil and Senkowski (2017), while auditory IAF (*Beta = 0.040, p > 0.05*), visual IBF (*Beta = 0.020, p > 0.05*) and the auditory IBF (*Beta = -0.05, p > 0.05*) were not significant. The overall model fit was R^2 = *0.184*.

A second multiple linear regression analysis was also carried out whereby the TWI of the tactile-induced task is regressed onto the visual IAF, auditory IAF, visual IBF and auditory IBF. This found that the visual IBF (*Beta = 0.984, p < .05*) was a significant predictor, while the somatosensory IBF (*Beta = - 0.141, p > 0.05*), the visual IAF (*Beta = - 0.020, p > 0.05*), and the somatosensory IAF (*Beta = 0.104, p > 0.05*) were not significant. The overall model fit was $R^2 = 0.16$.

Phase locking value:

Next, we explored whether the frequency specific effects observed at the level of the visual cortex for the auditory-induced DFI and the tactile-induced DFI can be best explained by a network specific mechanism. For this purpose, we measured the PLV in both alpha and beta oscillatory activity for auditory-visual and somatosensory-visual networks depending on first, the performed task (either the auditory or the tactile-induced DFI) and second, the individual TWI, thus contrasting trials within and outside the TWI respectively.

Non-parametric statistical analysis revealed significant differences between trials within and outside the TWI (see Figure 3). Specifically, IAF PLVs between the auditory and visual cortices in the auditory-induced DFI were significantly greater for the trials outside

the TWI in a temporal cluster comprised between 310 ms and 400 ms post-stimulus (*p = 0.046*). On the other hand, IBF PLVs between the visual and somatosensory cortex in the tactile-induced DFI differed between conditions in two temporal clusters comprised between 210 ms and 260 ms and between 280 ms and 360 ms post-stimulus (*p = 0.015 and p=0.03*, respectively).

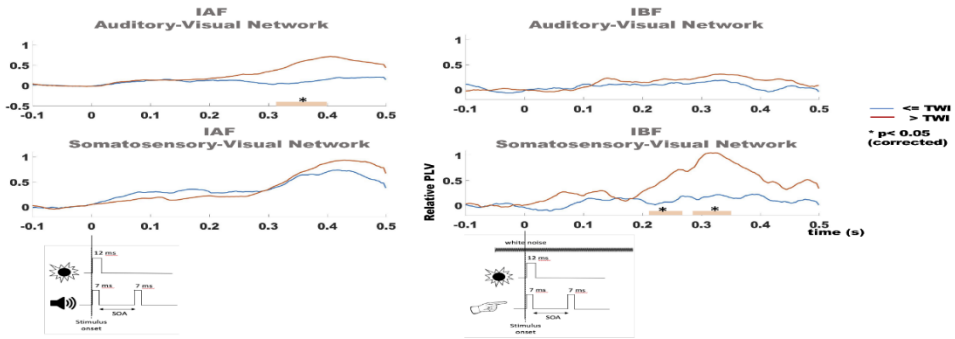

Figure 3. Phase Locking Value (PLV) Analysis in Source space:

Phase Locking Value (PLV) in the alpha (left most quadrants) and beta (right most quadrants) oscillatory activity for auditory-visual (upper quadrants) and somatosensory visual (lower quadrants) networks. For each quadrant, trials within (blue trace) and outside (red trace) each individual TWI are depicted as a function of time (ms) from visual stimulus onset.

In auditory-induced DFI, trials outside the TWI showed significantly higher PLVs in the alpha band for the auditory-visual (but not somatosensory visual) network between 310 and 400 ms post-stimulus.

In tactile-induced DFI, trials outside the TWI showed significantly higher PLVs in the beta band for the somatosensory visual (but not auditory-visual) network between 210 and 260 ms and again between 280 and 360 ms post-stimulus.

3.6. Experiment One: Discussion:

In the current study we characterised (to the best of our knowledge), for the first time, the temporal profile of the tactile-induced DFI, comparing it directly to the temporal profile of the auditory-induced DFI. We found that these temporal profiles do indeed appear to be comparable. In other words, they do not differ significantly, and they positively correlate with one another. Initially this would appear to suggest that similar mechanisms

may be at play in determining these effects. We thus tested which neurophysiological mechanism might best account for both the auditory and tactile-induced DFIs.

EEG results demonstrated that oscillatory processes relate to the two illusions in a frequency and network specific manner. Whilst replicating previous findings demonstrating a relationship between IAF and the auditory-induced DFI (Cecere et al., 2015; Keil & Senkowski, 2017), we could not produce this relationship between the IAF and tactile-induced TWI. Instead, a positive correlation between the tactile-induced TWI and the IBF was found, such that a faster IBF value predicted a shorter TWI. This was found both at sensor and source space level, exclusively over early visual areas. Moreover, in source space we found that visual (but not auditory or somatosensory) IAF explained the auditory-induced TWI (in line with a recent report by Keil and Senkowski, (2017)) and similarly only visual IBF explained the tactile-induced TWI.

To test for the specific interpretation that oscillatory correlates of the auditory and tactile-induced DFI represent not just a local occipital phenomenon but rather a reliable marker of the specific crossmodal network engendering the illusion we have looked at an index of connectivity between nodes of the network, namely PLV. Specifically, we investigated the modulation of signal strength between auditory-visual and somatosensory-visual networks in the alpha and beta bands following stimulus presentation.

We found enhanced PLV in alpha (but not beta) oscillations between auditory-visual (but not tactile-visual) nodes, while the same was found in beta (but not alpha) oscillations between tactile-visual (but not auditory-visual) nodes, confirming that oscillatory tuning to the particular version of the illusion reflects a marker of network specific activation.

PLV differences between trials within or outside the TWI occurred at a late time following stimuli presentation. However, it should be noted that by nature of experimental design, the second crossmodal stimulus was not locked to the first one but jittered by tens of milliseconds, which might have masked an early differential PLV onset.

This frequency and network specific PLV enhancement was found for trials not inducing the illusion. This finding might reflect temporal alignment to coherent temporal and quantity information across the senses within the temporal binding unit defined by the oscillatory cycle (Romei et al., 2012). This same mechanism may be time sensitive to quantity disparity information presented within the temporal binding unit defined by the oscillatory cycle, leading to altered integration processes across the senses, ultimately resulting in an illusory percept.

So, the question now remains, what neurophysiological mechanism might be in place to account for this set of results? A relevant model which might explain the current data is the *Communication Through Coherence* framework (Fries, 2005, 2015). In this model neural communication is subserved by neural synchronization between remote but functionally interconnected areas. Specifically, such neural synchronization is the result of alignment of post-synaptic neural activity to pre-synaptic input, creating temporal windows of optimal, preferred communication between involved areas. In this case, such temporal profiles observed in our study related to the auditory and tactile-induced DFI may be the result of top down directed alpha (7 – 12 Hz) and beta (12 – 25 Hz) influences (feedback connections) on primary sensory input (Fries, 2015), shaping the final illusory perceptual outcome.

From this perspective, if a crossmodal stimulus (in our case auditory or tactile stimuli) phase aligns oscillatory activity (in the alpha band or beta band respectively) in

visual areas, it will define the temporal windows corresponding to such oscillatory cycle lengths (of alpha or beta respectively) within which two consecutive stimuli may give rise to the illusory percept (in our case the TWI of the illusion). The illusory phenomenon will be engendered by a second crossmodal phase alignment attempt induced by the second cross sensory stimulus reactivating the visual trace being still processed by the ongoing phase alignment induced by the first multisensory pair. Thus, individual frequency peaks would characterize the temporal resolution of interregional synchronization within which the TWI phenomenon arise.

A closely related reference framework has been introduced by (Klimesch et al., 2007), who proposes that communication between remote, but interconnected areas can be achieved through travelling waves, these are neural oscillations allowing the transfer of information as measured through propagation between electrodes via a neural network (Klimesch et al., 2007; Muller et al., 2018). According to this framework, local oscillatory activity (i.e. resonance frequency) in auditory (often associated with alpha processes (Dohrmann et al., 2007a; Dohrmann et al., 2007b; Frey et al., 2014; Fujioka et al., 2011; Gleiss & Kayser, 2014; McKee et al., 1973; Mercier et al., 2013; Teplan et al., 2003; Weisz et al., 2011)) or somatosensory (often associated with beta processes (Baumgarten et al., 2015; Brovelli et al., 2004; Engel & Fries, 2010; Foffani et al., 2005; Kilner et al., 2003; McFarland et al., 2000; Paus et al., 2001; Rubino et al., 2006; Salenius & Hari, 2003; Zhang et al., 2008)) cortices will propagate towards the visual cortex accounting for the specific differential impact of alpha and beta oscillations on the auditory and tactile-induced DFI, respectively. This mechanism allows prompt rescaling of temporal sampling across the senses, optimizing cross sensory communication efficiency.

Under these circumstances, one expects the respective size of observed TWIs to reflect the length of the oscillatory cycle determining it, for example this should be approximately 100 ms when alpha oscillations mediate the auditory-induced TWI and approximately 60 - 70 ms when beta oscillations mediate the tactile-induced TWI. While this is the case for the auditory-induced DFI, the tactile-induced DFI instead shows a TWI comparable to the auditory version rather than the significantly shorter profile that should be expected.

In this case several issues may combine to account for the lack of one-to-one correspondence between beta cycle length and the length of tactile-induced TWI. First, it simply takes longer for signals from the hand to reach the brain than it does for signals from the ears (Von Bekesy, 1959). Such conduction time differences could total up to 15 ms which may in part account for the longer than expected tactile-induced TWI. Second, the tactile-induced DFI was far noisier than its auditory counterpart, with its overall goodness of fit being significantly lower. A possible reason for this noisier fitting may lie on the asymmetry in our experimental design. White noise was continuously played during the tactile but not auditory-induced DFI tasks, this was done in order for us to cancel out the small mechanical noise induced by the tactile stimulator. One potential solution to this could have been to use white noise across both versions of the illusion, or even better, intermix both versions within the same block while continuously playing white noise. Additionally, this might have taken care of a potentially induced bias in the allocation of intersensory attention (Pomper, Keil, Foxe, & Senkowski, 2015) across the two versions of the illusion.

However, it should be noted that by pairing white noise with the auditory-induced DFI, participants may have subsequently relied more on visual information (Hartcher-O'Brien, Di Luca, & Ernst, 2014), which may subsequently lead to a significant degradation of the auditory-induced effect. However, several reports have shown the DFI to be resistant to feedback training (Rosenthal et al., 2009) and that participants perceive the illusion independently of crossmodal spatial congruence (Innes-Brown & Crewther, 2009) or even with prior awareness of the illusion itself (Rosenthal et al., 2009), suggesting a minor role played by intersensory attention allocation in this particular task.

Therefore, given the comparative nature of our design looking at possible differences of the impact of auditory and tactile stimuli on DFI, it was imperative to control for the specific contribution of each sensory modality.

Playing white noise in the tactile-induced DFI might have contributed to the tactile-induced TWI being more skewed towards slower durations due to noisier curve fitting, leading to a less efficient temporal profile calculation of the effect. Another point to consider is that generally beta frequencies are much noisier than alpha frequencies. This may mean that in general tasks that are associated with these frequencies could simply be inherently noisier than tasks associated more with less noisy frequency bands such as alpha. This could explain why such a difference was found in the overall goodness of fit. As a result these aspects may in part provide an explanation as to the lack of a one-to-one relationship between the TWI and the beta cycle length. Nevertheless, these factors should not affect or alter the relationship between the tactile-induced TWI and the oscillatory marker as they represent a fixed level of noise that should be accounted for in the calculation of the absolute size of the tactile-induced TWI.

In conclusion, the specific mechanism subtending this outcome may be comparable across sensory modalities but simultaneously reflects the peculiarity of each sensory modality, including temporal resolution. In other words, auditory and tactile crossmodal induced visual illusions might have been caused by the specific oscillatory properties of each sensory signal's pairing. The different oscillatory tuning could be explained as the specific computational speed needed by the cross-sensory network to efficiently integrate information, thus representing the optimal quantum for temporal binding between a given cross-sensory pair when impacting visual processing specifically. In this respect, there is ample evidence that, in isolation, visual (Dugue et al., 2011; Ergenoglu et al., 2004; Frey et al., 2014; Gleiss & Kayser, 2014; Gulbinaite et al., 2017; Lange et al., 2014; Mercier et al., 2013; Minami & Amano, 2017; Romei, Brodbeck, et al., 2008; Romei et al., 2010; Romei, Rihs, et al., 2008; Ronconi et al., 2018; Samaha & Postle, 2015; Van Dijk et al., 2008; Wutz et al., 2018; Wutz et al., 2016) and auditory (Dohrmann et al., 2007a; Dohrmann et al., 2007b; Frey et al., 2014; Fujioka et al., 2011; Gleiss & Kayser, 2014; McKee et al., 1973; Mercier et al., 2013; Teplan et al., 2003; Weisz et al., 2011) sensory processing are governed by oscillatory activity in the alpha band, while somatosensory processing typically occurs within the beta band (Baumgarten et al., 2015; Brovelli et al., 2004; Engel & Fries, 2010; Foffani et al., 2005; Kilner et al., 2003; McFarland et al., 2000; Paus et al., 2001; Rubino et al., 2006; Salenius & Hari, 2003; Zhang et al., 2008). There is little empirical evidence highlighting the specific oscillatory nature of the interaction between multiple senses. We and other groups have shown that the impact of simple auditory stimuli on visual processing seems to be governed by the way sounds phase aligns alpha oscillatory activity in the occipital cortex (Frey et al., 2014; Gleiss & Kayser, 2014; Mercier et al., 2013; Romei et al., 2012; Teplan et al., 2003). Yet, it was unclear whether this was a general feature of crossmodal interactions

within the visual system or whether the specific cross-sensory input determines the fate of the visual response to the visual processing. In the current study we provide the first evidence highlighting the relevance of neural communication at the network level through frequency specific oscillatory activity.

4. Chapter Four: Experiment Two – Reducing speed of early occipital beta via a novel neuromodulation technique leads to an expansion in the temporal window for tactile-visual illusions:

4.1. Experiment Two: Abstract:

The presentation of simple auditory or tactile stimuli can significantly impact visual processing and even induce visual illusions. Such as the auditory-induced and the tactile-induced Double Flash Illusions. The auditory-induced DFI has reliably been shown to be driven by occipital oscillatory activity within the alpha band (Cecere et al., 2015; Cooke et al., 2019). Recent evidence has also suggested that the tactile version is driven by similar oscillatory activity, this time within the beta band (Cooke et al., 2019). We take this to mean that task-dependent visual oscillations reflect network-specific oscillatory properties favouring optimal, directional neural communication timing for sensory binding. For us to test this idea further we utilised a novel TMS technique aimed at facilitating functional connectivity. We aimed to stimulate the functional connection between the right-somatosensory cortex and the visual cortex with a view to reducing the speed of the beta processes subtending them. We believed this would significantly affect the timing of sensory bindings of the tactile-induced effect. Results showed a significant modulation of beta speed post-stimulation, alongside a corresponding modulation of the temporal window of illusion. We take this as further evidence that task-dependent visual oscillations reflect network-specific oscillatory properties favouring optimal, directional neural communication timing for sensory binding.

4.2. Experiment Two: Introduction:

Through our senses we can perceive and navigate our world, without the use of these vital and complex processes our environment becomes an intensely disorientating place (Goldstein & Morewitz, 2011; Jauregui-Renaud et al., 2008). In recent years research has demonstrated that these processes do not simply work in isolation (Ghazanfar & Schroeder, 2006; Kayser & Logothetis, 2007). They instead appear to rely heavily on a complex multisensory system; this mechanism is hugely important in binding together sensory information from different domains. This sensory binding subsequently acts to reduce the overall complexity of our perceived environment allowing for a prompt and efficient perception.

Often the way this system is investigated is through the use of multisensory illusions. These exploit its normal workings in order to induce erroneous perceptions. This enables us to manipulate certain parameters of the illusion in order for us to determine the conditions at which the illusory percept appears. One such effect is known as the Double Flash Illusion, of which there are two versions (the more commonly explored auditory-induced DFI and the less common tactile-induced DFI). When presented with a single flashing disc, participants can often perceive a second illusory flash. This is if the single flash is presented alongside a brief double beep (Shams et al., 2000, 2002) or a double tap to the participant's index finger (Violentyev et al., 2005). By carefully manipulating the parameters of this illusion (in this case the spacing of the double stimuli) we can obtain information regarding a multisensory temporal window of integration for these illusory tasks. In this case the TWI corresponds to the maximum spacing between paired stimuli (the Inter-Stimulus Interval) that still elicits an illusory response. This is usually found to be around 100 ms for both the auditory (Cecere et al., 2015; Cooke et al., 2019; Shams et al., 2002) and the tactile effect (Cooke et al., 2019).

This means that when beeps or taps are placed apart by more than this value the illusory effect begins to decay.

Previous research has provided strong evidence of a tight correlation between occipital Individual Alpha Frequency and the temporal profile of the auditory-induced DFI (Cecere et al., 2015; Cooke et al., 2019). Research demonstrates that a slower IAF typically tends to predict a wider TWI. Cecere and colleagues (2015) also utilised transcranial Alternating Current Stimulation to entrain local oscillatory processes to assess the overall influence these have on the illusory effect. They stimulated at a frequency slightly above (+ 2 Hz) or below (- 2 Hz) the IAF, aiming at increasing or reducing the speed of these processes. The overall aim here was to experimentally manipulate local visual processes only. It was found that when stimulating at a frequency faster than the IAF, the auditory-induced TWI was shown to decrease in magnitude. Conversely when stimulating at a frequency slower than the IAF, this value then increased. These changes in the TWI were thought to be due to the changes induced in the alpha speed. However, no concurrent EEG was provided to confirm that any effect was the direct consequence of the oscillatory activity modulation in the alpha band. Yet we have reasons to believe that the behavioural effects were a consequence of the entrained alpha activity as shown in recent research addressing this issue directly through concurrent tACS and MEG recordings (Minami & Amano, 2017).

The core finding of Cecere et al., (2015) brought the author to hypothesize that this could represent a generalised mechanism of crossmodal influences of other sensory modalities over visual processes. Accordingly, the properties of the auditory-induced DFI would have been set by the local oscillatory processes of the visual regions. As one of the

most prominent oscillatory activities here is the alpha rhythm, this was a plausible explanation of this phenomenon (Dugue et al., 2011; Ergenoglu et al., 2004; Frey et al., 2014; Gleiss & Kayser, 2014; Gulbinaite et al., 2017; Lange et al., 2014; Mercier et al., 2013; Minami & Amano, 2017; Romei, Brodbeck, et al., 2008; Romei et al., 2010; Romei, Rihs, et al., 2008; Ronconi et al., 2018; Samaha & Postle, 2015; Van Dijk et al., 2008; Wutz et al., 2018; Wutz et al., 2016).

However, recently, Cooke et al., (2019) provided evidence for a different account. If local visual processes were indeed important in setting the fate of the DFI illusion, we should also presumably find a similar correlation between these and the tactile version of the DFI effect. However no correlation between the TWI for the tactile-induced DFI and these processes could be found. Instead, a tight correlation between this TWI and the Individual Beta Frequencies were found. In this case a slower IBF value predicted a wider TWI.

Thus, instead of a multisensory mechanism whereby information is processed locally, we suggest that the properties of the functional connectivity between interconnected regions may play a role here. Evidence has already suggested that alpha frequencies tend to play a role in both unisensory and multisensory auditory tasks (Dohrmann et al., 2007a; Dohrmann et al., 2007b; Frey et al., 2014; Fujioka et al., 2011; Gleiss & Kayser, 2014; McKee et al., 1973; Mercier et al., 2013; Teplan et al., 2003; Weisz et al., 2011). Furthermore, evidence also exists suggesting that beta frequencies play a large role in unisensory somatosensory processing (Baumgarten et al., 2015; Brovelli et al., 2004; Engel & Fries, 2010; Foffani et al., 2005; Kilner et al., 2003; McFarland et al., 2000; Paus et al., 2001; Rubino et al., 2006; Salenius & Hari, 2003; Zhang et al., 2008). This could possibly

suggest that rather than local oscillatory processes, these processes instead originate in these pre-synaptic regions. Information transfer across these networks (in this case to the visual regions) are facilitated by the oscillatory processes linked to these areas.

Thus, we propose that the information generated in somatosensory areas are influencing the visual signal processing, thus giving rise to the DFI phenomenon. This could be brought about through a convergent oscillatory activity in the functionally connected network. Specifically, the way in which this mechanism might operate is the level of signal coherence between a pre-synaptic area generating the signal and a post-synaptic area receiving the signal through this concerted activity. This implies a temporal constraint between sensory signals and specifically a critical temporal window within which a signal from one sensory modality (in this case the somatosensory signal) influences the signal of another sensory modality (in this case the visual signal). This temporal constraint would be pace marked by the convergent oscillatory activity of the functional network. Therefore in the specific case of the auditory-induced DFI this timing would correspond to the length of an alpha cycle. Conversely, according to this view, for the tactile-induced effect the time it would take the somatosensory signal to reach the visual cortex would be at a slightly faster pace, (i.e. in the beta range).

Whilst the theory that we propose here could potentially explain the findings in the literature (Cecere et al., 2015; Cooke et al., 2019), prior to this investigation we did not have direct evidence of this. As such we wished to utilise a method whereby we can modulate the connection between these areas, basing this modulation on the timing associated with these oscillatory processes. By facilitating these connections based on this information we theorised that we would be able to fine-tune the network and subsequently manipulate its

processing speed. We also believed that this would give us the capability to alter the temporal profile of the illusory effect. Specifically, by manipulating the network between the somatosensory and visual regions basing this upon the beta processes subtending it, we believed that it was possible to reduce the speed of these processes. Subsequently we also expected to see a change in the properties of the TWI for the tactile-induced DFI, in this case a widening was predicted. In this investigation EEG recordings took place both pre- and post-stimulation. This was done so that we could provide direct evidence of the change in processing speed.

In previous research where such modulation has taken place in local areas (Cecere et al., 2015) researchers utilised tACS to modulate the associated processes. However for our investigation this method will not serve the purpose. This is because it would not be able to disentangle the differential contribution of distant nodes of the network and the timing of their communication. Instead we used a novel method of neurostimulation known as cortico-cortical Paired Associative Stimulation, which makes use of repeated pairs of Transcranial Magnetic Stimulation pulses over the target areas of a network at critical intervals to induce Hebbian plasticity of the network (Buch et al., 2011; Hebb, 1949; Rizzo et al., 2011; Rizzo et al., 2009). This method has been demonstrated in the past to be an effective method in modulating the functional connectivity between two interconnected areas of the brain (Buch et al., 2011; Chiappini et al., 2018; Rizzo et al., 2011; Rizzo et al., 2009; Romei et al., 2016).

Specifically, ccPAS uses TMS pulses to repeatedly stimulate both pre- and post-synaptic clusters (Rizzo et al., 2009), aimed at evoking Hebbian like principles of short term potentiation or indeed depression (Buch et al., 2011; Hebb, 1949; Rizzo et al., 2011). This

method has typically been used to stimulates across relatively local regions (most commonly the motor cortex). As a result relatively short space timing delays between pulses have been utilised within the literature (usually around 8 ms) (Buch et al., 2011; Rizzo et al., 2011; Rizzo et al., 2009). This corresponds to the documented monosynaptic timing of communication between pre-synaptic and post-synaptic regions within this motor area (Ferbert et al., 1992). Recently stimulation has occurred over wider distances (from Visual area 5 to Visual area 1), culminating in an average of 20 ms between pulses (Romei et al., 2016). This represents the temporal transmission of information between the target nodes of monosynaptic connections within these visual regions (Pascual-Leone et al., 2000; Silvanto et al., 2005). At the time of writing this is the longest time between pulses that has been used and reported as being successful in achieving modulation of a known feedback network.

This research has gone a great way in expanding our understanding of ccPAS, and how it can promote the plasticity of functional connections within motor or visual regions. This new information has resulted in a surge of new information-based approaches (Romei et al., 2016a). These are with a view to exploiting this novel method to study complex brain networks which are functionally interconnected (e.g. supporting crossmodal interactions) but are not necessarily directly connected. One example of such a functional connection is that between the somatosensory cortex and the visual cortex.

In ccPAS protocols one major issue when testing complex, longer-range networks is the identification of a critical timing accounting for the connection and communication between the two key regions. When targeting these longer-range networks, the first empirical question that should be asked is, how long does it take for information from the

pre-synaptic region to reach the post-synaptic region? This would be for us to set the parameters of the pulse timing so as to ensure modulation is even possible. In this case attempting to use a short inter-pulse timing similar to those used in previous studies assessing monosynaptic connections (i.e. 8 ms – 20 ms), would not necessarily be appropriate here. We need to ensure that we are still respecting Hebbian principles of consequentiality. In this case, should we use these parameters, the signal that is generated by the somatosensory cortex may have yet to even reach the visual area before the ccPAS stimulation takes place.

One solution to this issue is to uncover the temporal profile of signal propagations by stimulating the somatosensory cortex and testing how long it takes for the signal to have a significant impact on the oscillatory activity within the visual cortex. In this case, when utilising the tactile-induced DFI, perhaps an analysis of coherence between the somatosensory and the visual cortices could provide us with the most accurate estimation of this temporal profile. With this in mind our previous results appear to suggest that the temporal profile of signal propagation across this network corresponds to one complete cycle of beta (Cooke et al., 2019).

In this investigation, we aimed at providing causal empirical evidence that beta oscillations do play a role in controlling the functional connectivity between somatosensory and primary visual areas. Therefore, we sought to investigate the functional relevance and the plasticity of reentrant connections from the somatosensory regions to visual areas in the ability to perceive this tactile-visual illusion. This was done by testing the tactile-induced DFI concurrently to EEG recording before (BSL) and after applying the ccPAS, whose temporal

parameters were set to modulate communication coherence between these two nodes away from the individual beta frequency.

We propose that these distant and yet functionally connected (somatosensory and visual) regions communicate with one another through the use of beta activity. To test this hypothesis we based the timing of these ccPAS pulses on the specific properties of these beta processes. Specifically, we have reasoned that inducing a slowing down of beta oscillations may represent a valid model to test functional malleability of the targeted network. Moreover, as from a methodological point of view this represents a proof of principle study, we opted to achieve an easier goal by targeting a slow-down (as opposed to a speed-up) of the mechanism due to the brains natural tendency to slow down with age (Aurlien et al., 2004), hence making it easier for us to achieve our modulation. This does not mean that speeding up processes of functional connections cannot be achieved but should be addressed in future investigations once more fundamental aspects have been empirically settled.

In this case, we uncovered each person's IBF value (in ms). We considered this to represent the time it takes for the somatosensory signal to reach the visual cortex. Therefore, we theorised that a way to use ccPAS to slow down this timing of communication was to calculate a slightly slower timing to modulate the somatosensory to visual connection and use this as the time delay between pulses. This resulted in a delay between pulses of approximately 60 ms – 110 ms, an unprecedently long delay. This was however supported by the introduction of the information-based approach in which biologically inspired mechanisms have been taken into account to calculate this critical timing of interaction between the two nodes of the network. It is important to note that this

stimulation occurred offline, after first completing the illusory tasks participants underwent the TMS and then after a brief wait period, once again completed the illusory tasks. Our intention here was to stimulate the connection between the two regions at a value slightly slower than natural processing speed, hence we intended to fine-tune this network with the view of creating a significant (but temporary) reduction in the speed of the beta processes subtending these regions of the brain. What we also expect to find here is that reducing the speed of these processes will subsequently result in an overall widening of the tactile-induced TWI.

Furthermore, as the stimulation occurred exclusively on the right hemisphere, we only expect to see any changes in the task when the tactile stimuli are presented to the left hand. As we will always be measuring occipital beta whilst each task was taking place (either whilst tactile stimuli are being presented to the left hand or to the right hand), two different connections are assumed to be at play here. One that will subtend the right somatosensory cortex and the visual cortex (left-hand condition) and one that will subtend the left somatosensory cortex and the visual cortex (right-hand condition). This should lead to a differentiation of occipital beta tuning depending on which task is being completed at the time. We will be using the ccPAS method to only target one network, the one in use when the tactile stimuli are presented to the left hand (right somatosensory cortex to visual cortex). In this case post-ccPAS measures of the parameters, when the tactile stimuli are presented on the right hand should be the same as pre-ccPAS measures. Specifically we expect to see a reduction in post-ccPAS beta speed (and subsequently an increase in the size of the TWI) only when the network involved corresponds to the one targeted by the ccPAS, showing the state-dependent network specificity of the effect.

In this current research we selected a subset of participants who all took part in Experiment One. Participants who took part all perceived the illusory effect and the relationship between beta processes and the TWI for this tactile-induced illusion was still observed even in this smaller sample.

We first looked to assess the effectiveness of our modulation. Here we expected that post-ccPAS measurements of IBF would be significantly slower than pre-ccPAS measurements, signifying a reduction in processing speed. Crucially, this was expected to only be the case for when the tactile stimuli were presented to the left hand. Subsequently we also expected post-ccPAS measurements of the tactile-induced TWI to be significantly larger when compared to pre-ccPAS measurements. As before, this should have only been the case when the tactile stimuli were presented to the left hand. If this was indeed what was found then we could take this as further evidence for the role of the properties of the functional connectivity between interconnected regions in the processing of multisensory information.

This investigation also acted as a way of shedding further light on the overall capabilities of the ccPAS method. This is because we were using it in a way that had not yet been reported in the literature. Drawing upon the information-based approach, we have theorised that the communication timing of this particular network corresponds to the duration of one complete beta cycle. We then wish to utilise this information within a ccPAS paradigm, potentially allowing us to take advantage of the timing of this connection and produce a modulation of its processing speed based on these individual beta frequencies. Our intended usage of this ccPAS protocol is entirely novel, and we have yet to see a successful modulation of a longer-range network. As such, if we were to find positive results

here, this could act to greatly improve our understanding, firstly of how functionally interconnected areas of the brain communicate with one another. Secondly this would also inform our understanding of the capabilities of the ccPAS method, and how it can be used to produce a transient modulation of these long-range networks.

4.3. Experiment Two: Materials and Methods:

Participants:

A total of 17 participants volunteered to take part in this study which was approved by the ethics committee of the University of Essex. All of the participants who took part in this experiment were randomly selected from the same sample that was used in Experiment One; thus we already knew that they were susceptible to the illusory effects of the DFI.

Sixteen of the 17 participants stated by self-report that they were right handed (with 1 being left handed) the mean age of the sample was 21 (range: 18 – 25, 12) with the sample consisting of 12 females and 5 males.

Prior to taking part, participants completed a screening questionnaire ensuring they had no psychiatric or neurological history and normal (or corrected to normal) vision and somatosensation by self-report. This was to ensure no confounding effects and to prioritise participant safety during the TMS procedure.

Materials and Apparatus:

All visual stimuli were presented on a 17.5 inch cathode ray tube monitor via a Dell Optiplex 960 computer (Windows XP, resolution: 1280x1024) with a refresh rate of 85 Hz.

The tactile stimuli were provided via a tactile controller and mechanical solenoid stimulator (Heijo Research Electronics, London, UK). This would deliver a suprathreshold tap (upon the participant's index fingertip) by pushing a blunt plastic point against the participant's skin whenever a current was passed through the solenoid. During trials, white noise (approximately 50 dB) was played to participants through the speakers (these were situated either side of the monitor). This was done to mask the mechanic noise produced by the tactile stimulator and to ensure this was not heard by the participants. This was to avoid confounding the tactile experience by also inadvertently presenting participants with auditory stimuli. All experimental stimuli were presented via the software E-prime (version 2.0; Psychology Software Tools, Pittsburgh, PA).

For all participants enrolled in the final sample, EEG was recorded from 64 sintered Ag/AgCl electrodes mounted on an elastic cap (Easycap, Herrsching, Germany) alongside the ground electrode (located at position AFz) and the reference electrode (placed upon the right mastoid bone). The EEG signals were digitized at 500 Hz and amplified using a BrainVision Professional BrainAmp amplifier through the BrainVision Recorder programme (BrainProducts GmbH, Gilching, Germany). Before the recording began we ensured that all electrodes were set upon the participant's scalp at an impedance not exceeding 10 kΩ.

In all trials, participants were presented with a flashing disc with a diameter of 2 cm, displayed just below a central fixation cross, the disc flashed once for a duration of 12 ms. In each of the tasks the presentation of this single flashing disc was paired with a double "tap" sensation to the participant's index finger. Participants took part in two tactile-induced DFI tasks, one where tactile stimuli were presented to left index finger and one where they were presented to the right.

The two tactile stimuli were spaced apart by a varying range of ISI values, these ranged between 36 ms and 204 ms increasing with increments of 12 ms, this resulted in 15 different ISI values. Each ISI was presented 10 times, resulting in 150 randomly ordered trials in all of the task blocks. The time between trials included the presentation of the stimuli (as described above) plus a varying inter-trial interval. This corresponded to the elapsed time following the experimenter's input on the keyboard, this was upon hearing the participant's vocal response to the previous trial. This prompted the other varying interval, which ranged between 1000 ms and 1800 ms before the next trial started. In this case there were 5 different inter trial delays in steps of 200 ms, each occurring 30 times.

The TMS procedure was conducted via the use of a Master TMS unit (Magstim BiStim2, UK) working alongside a secondary slave unit (Magstim 2002, UK) the device was always set at a fixed intensity of 70% of the maximum level of intensity. Ideally a variable intensity would have been used but this was not implemented due to time constraints, thus we selected an intensity that we believed was high enough to reach threshold without causing any unnecessary risks to the participants themselves. Coils were placed over the right somatosensory cortex (C4) and on the visual cortex (Oz). The directionality of the protocol was determined by the timing of the magnetic pulse, the pulse from the coil at C4 always preceded the coil at Oz. Timing between paired pulses was determined by each individual participant's individual beta peak frequency in the visual cortex (as measured at channel Oz). As we wished to induce a reduction in the beta speed travelling from electrode C4 to Oz, working only on the information from the left-hand task we uncovered each persons' IBF value (after the pre-stimulation trial had finished), reduced it by 3 Hz, and then using this value (in ms), we could then manipulate the parameters of the TMS to match this corresponding time between pulses. The TMS protocol itself lasted approximately 15-

minutes and consisted of 90 paired pulses, with a 10 second delay separating each set of pairs. It is important to note that the procedure was offline (i.e. did not occur during the task but during a break between the first set of tasks and the second).

Experimental Design:

Upon EEG cap fitting completion, participants were seated approximately 57 cm away from the screen. EEG recording was manually started prior to the first block of trials beginning. Participants were subsequently instructed to fixate on a cross situated at the centre of the screen while the 150 flashing discs within the block were presented. This was in two blocks of trials, each time paired with two tactile stimuli, presented to the left hand in one block and the right hand in the other. To control for order effects (including fatigue or boredom), the order of the blocks was counterbalanced, with trial order being entirely random. Half of the participants first had the stimuli presented to their left hand (and then the right hand), and the other half experiencing the opposite order. Participants were asked to place their index finger immediately below the location of the flashing disc (as close as they could get whilst still remaining comfortable) this was in order to maximise spatial co-occurrence of the visual and tactile stimuli processing.

In all trials participants were asked to verbally report whether they perceived one flash or two flashes. This was done verbally, rather than via keyboard input so as to avoid motor interference from participants using their resting hand to respond to the stimuli. In this case focus should only be concentrated on the hand experiencing the tactile stimuli so as to maximise the illusory effect. Participants were instructed to provide unspeeded and

accurate responses. The verbal report was then input by the examiner via the “1” or the “2” key, which prompted the new trial to begin, only after the variable inter-trial interval.

Once these two tactile-visual tasks were completed participants had a brief waiting period whilst the experimenter analysed the EEG (using the methods as described below) to uncover the IBF value. This was then used to calculate the spacing of the TMS pulses. Subsequently all participants underwent a TMS procedure consisting of 90 paired pulses, with each pair being separated by a delay of 10 seconds. This protocol lasted a total of 15-minutes and once completed was followed be a waiting period of 30-minutes. This particular waiting period was selected as this was the time at which ccPAS modulation had been found to be at peak effect in previous research (Chiappini et al., 2018; Rizzo et al., 2011; Rizzo et al., 2009). After the waiting period had been completed participants were required to undergo the two tactile-induced DFI trials once more, before reaching the end of the procedure. The procedure can be seen below in Figure 1.

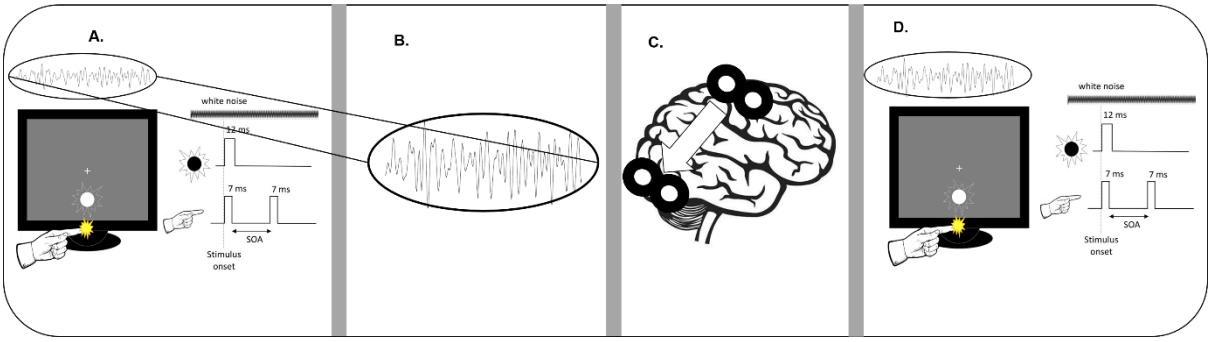

Figure 1. Experiment Two Procedure:

A. ***Pre-ccPAS DFI:*** *Whilst viewing the flashing disc (12 ms duration) participants also experienced two brief taps to their left of right index finger (both with a 7 ms duration). These tactile stimuli were separated by a variable ISI (36 ms - 204 ms). Participants were asked to ignore the tactile stimuli and state aloud whether they perceived one or two flashes.*

B. ***ccPAS timing calculation:*** *EEG was concurrently recorded during both DFI tasks. Peak beta frequency at area V1 (Oz) was uncovered (**f**), this was only taken during the left hand condition. This was subsequently converted to time **t** via the following formula **t** = 1000/(**f** - 3).*

C. ***ccPAS Procedure****: 15-minute TMS protocol takes place, whereby first coil is placed on the right somatosensory (C4) cortex and the second is placed on area V1 (Oz). Spacing between first coil pulse (C4) and second coil pulse (Oz) corresponds to time **t** uncovered in step D. There were 90 pulse pairs, with each pair being separated by a delay of 10 seconds.*

D. ***Post-ccPAS DFI:*** *Participants underwent the same tactile-induced DFI tasks (after a 30 minute waiting period), this was with identical parameters to the previous tasks.*

4.4. Experiment Two: Statistical Analysis

Behavioural data analysis

The participants' perceived illusory flashes across the different ISIs were used to calculate the tactile temporal windows of integration. This was done separately for both hands (and both pre- and post-ccPAS). This corresponded to the maximum ISI in which the visual illusion was reliably perceived. Therefore, we calculated the percentage of illusory trials (i.e. trials where two flashes were perceived) and plotted them as a function of the ISI values. This was done separately for both of the tactile-induced DFI tasks and was done both pre- and post-ccPAS, resulting in four different TWI values being collected. A psychometric sigmoid function *[y = a + b/(1 + exp(- (x - c) / d)); a = upper asymptote; b = lower asymptote; c = inflection point; d = slope]* was then fitted to each percentage distribution returning a

corresponding inflection point (centre c) of the fitted sigmoid. This value was taken to represent the point of decay of the illusion, which subsequently taken as an index of the TWI. Ergo we could assume that when stimuli pairs were spaced apart by more than this corresponding centre point the illusory response would begin to significantly decay.

EEG data analysis:

EEG activity was concurrently recorded during task execution, this was subsequently analysed to calculate individual beta frequency peaks, for each participant. By calculating the individual beta frequency peaks prior to TMS commencing we were able to base the pulse timing of the TMS directly on each person's individual beta frequency. This meant that each ccPAS protocol was tailored directly to the participant's individual neural activity. Pulse timing was only set using the data obtained from the pre-ccPAS data for the left hand only. However, EEG recording, and analysis took place separately in all four of the conditions that were tested.

For all participants, 64 channel EEG was recorded at a sampling rate of 500 Hz. The EEG signal was re-referenced offline to the average of all scalp electrodes. Data was then subsequently segmented into 2000 ms epochs, time locked to and preceding the visual stimulus onset. This resulted in 150 epochs of pre-stimulus oscillatory activity for both of the frequency bands assessed. This was done for both of the tactile-induced DFI tasks. Each single epoch was visually inspected for artefacts (from eye blinks, muscle contractions, electrical interference etc.) and was manually rejected where necessary. For each participant and for all of the recorded electrodes a full power spectrum was obtained through a Fast Fourier Transform (FFT) with a zero padded window (nominal frequency

resolution 0.125 Hz). Finally, for each participant and task (left pre-ccPAS, left post-ccPAS, right pre-ccPAS and right post-ccPAS) EEG segments were averaged. This allowed for calculation of the average peak frequency in the visual cortex, as calculated at electrode Oz. For each frequency band, the peak frequency was determined for each participant as the value corresponding to the maximum peak frequency within their frequency range. For alpha this was 7 Hz – 12 Hz and for beta this was 12 Hz – 25 Hz. Finally, for each participant the speed (in ms) of one single oscillatory cycle was calculated using the peak frequency data (in Hz) obtained in the alpha and beta bands over all 64 channels.

Difference in electrophysiological data pre- and post-ccPAS:

We calculated the IBF value (using the methods as described above) for both pre- and post-ccPAS conditions. This was done in order for us to assess the difference in beta processing speed (as measured in visual regions) between these pre- and post-ccPAS conditions. According to our hypothesis this should result in a reduction of beta speed post-ccPAS. Crucially as we are only stimulating between the right somatosensory area and the visual area (V1) we should expect changes to occur only when tactile stimuli were presented to the left hand (but not the right). If this is indeed the case then this would provide evidence that the modulation of the connection between somatosensory to visual regions leads to an effective change in this network's connectivity. This would also suggest that the modulation is specific to the stimulated network. In this case the contralateral non-stimulated network acts as a control condition. Here by modulating the functional connectivity of the network spanning the right hemisphere in a network specific manner, we intend to show that the homologous contralateral network subserving the same function for

the contralateral hand will not be affected by the modulation. In order to test for this a within-subjects ANOVA was performed, with corresponding Bonferroni corrected paired t-tests subsequently performed in order to test for simple main effects.

Difference in behaviour pre- and post-ccPAS:

We will calculate the TWI (using the method as described above), this is in order for us to assess the difference between these pre- and post-ccPAS tactile-induced DFI tasks. We will calculate these values for both the left hand and the right hand. According to our hypotheses, an attempt to slow down beta oscillations should also have an impact on the size of the TWI for the tactile-induced DFI, should beta oscillations play a causal role in this phenomenon. To this aim we stimulated the connection subtending the right somatosensory regions and V1 (over the inion, i.e. bilaterally), thus expecting any change to occur only when the tactile stimuli are presented to the left hand. If this is indeed found then this would demonstrate evidence of a causal relationship between IBF and the TWI for the tactile-induced DFI. In order to test for this a within-subjects ANOVA was performed, with corresponding Bonferroni corrected paired t-tests subsequently performed in order to test for simple main effects.

Coherence analysis:

We will also conduct an analysis of coherence between somatosensory and visual sensors in order to assess the change in this measure from pre to post-ccPAS. This will be done using the correlation/autocorrelation (also referred to as the Magnitude-squared Correlation Coefficient) method. This will be performed between the right somatosensory area (c4) and visual area V1 (Oz), using exclusively the pre-ccPAS IBF value. This analysis calculates the coherence via the formula:

$$Coh\ (c1, c2)\ (f) = |\ Cov\ (c1, c2)\ (f)\ |\ ^{2} / (\ |\ Cov\ (c1, c1)\ (f)\ |\ |\ Cov\ (c2, c2)\ (f)\ |\ )$$

In conjunction with:

$$Cov\ (c1, c2)\ (f) = \Sigma\ (c1, i\ (f) - avg\ (c1\ (f)\ )\ )\ (c2, i\ (f) - avg\ (c2\ (f)\ )\ )$$

Here, totalling is carried out via the segment number *i*. Formation of the average also relates to segments with a fixed frequency *f* and a fixed channel *c*. This was performed using BrainVision Analyzer (BrainProducts GmbH, Gilching, Germany). This should tell us the degree to which the two areas of the brain are communicating with each other using this key frequency. Here we expect post-ccPAS measures of coherence between right somatosensory cortex and V1 to be significantly lower than pre-ccPAS measures, in the condition where the tactile stimuli are presented to the left hand. A corresponding analysis will also be conducted between the left somatosensory region and area V1, using the pre-ccPAS measurement of the IBF value as calculated during the right hand condition. As before we expect no change between pre- and post-ccPAS conditions when the tactile stimuli are presented to the right hand.

4.5. Experiment Two: Results:

EEG correlates of tactile and auditory-induced DFI:

We first intended to re-confirm the correlation between beta frequencies and the TWI for the tactile-induced DFI, using this smaller sample of 17 participants. As was expected, we found that occipital IBF (in ms) positively correlates with the size of the TWI in the left tactile-induced DFI (*r = 0.55; p < 0.02*), such that faster IBFs accounted for shorter TWIs. This relationship also survived robust skipped correlations (Pernet et al., 2013) (*r = 0.55, CI = 0.20 : 0.79*). The same pattern of results was also found when the tactile stimulation was applied to the right hand. Once again a significant correlation was found between the TWI and occipital beta frequencies (*r = 0.52, p = 0.03*), as before this relationship survived robust skipped correlations (*r = 0.73, CI = 0.44 : 0.92*).

Pre-ccPAS vs. Post-ccPAS:

Difference in neuro-oscillatory activity:

We first wished to uncover the degree to which we were able to manipulate beta speed, and whether any change in beta speed was exclusive only to the condition whereby tactile stimuli were presented to the left hand. With this in mind a fully within-subjects ANOVA was conducted to compare the main effects of tactile stimulus placement (left or right) and TMS condition (pre-ccPAS or post-ccPAS) and to investigate the interaction between tactile stimulus placement and TMS condition on the speed of individual beta processes in the visual cortex. This analysis found a significant main effect for the TMS condition (*F (1, 16) = 8.961, mse = .74, p = .009*), however no effect was found for the tactile stimulus placement (*F (1, 16) = 1.552, mse = 3.35, p = .231*). This analysis did also find a

significant interaction between tactile stimulus presentation and TMS condition (*F (1, 16) = 31.143, mse = .58, p < .001)*.

Further to this, Bonferroni corrected paired t-tests confirmed that there was a significant difference between the pre-ccPAS IBF and the post-ccPAS IBF for the left-hand tactile stimulation: *t (16) = 5.38, p < 0.001*, with the left hand tactile stimulation leading to a slower IBF, in line with our hypothesis (*left IBF pre-ccPAS: 15.21 Hz (S.E.M.: 0.41); left IBF post-ccPAS: 13.55 Hz (S.E.M.: 0.34)*. This can be seen in Figure 2.

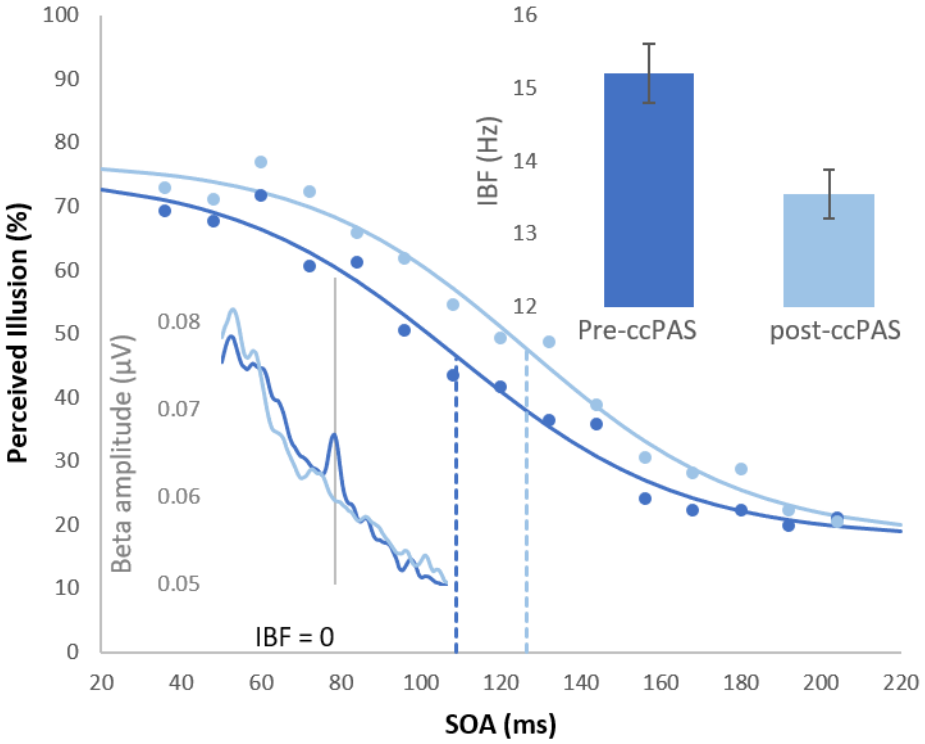

Figure 2: Difference in behavioural and electrophysical data pre- and post-ccPAS (left hand): *Sigmoid curve represents the best fit of the average probability of perceiving the tactile-induced double flash illusion plotted as a function of inter tap delays, both pre-ccPAS (darker blue) and post-ccPAS (lighter blue). Segmented lines represent the respective inflection points of the curve, this signifies the respective TWI of the two tasks. Each individual point represents the average percentage of illusory trials at each ISI.*

Upper inset: *Significant difference in beta frequency (Hz) between the pre-ccPAS (darker blue) and post-ccPAS (lighter blue) conditions.*

Lower inset: *Significant difference in IBF amplitude post-ccPAS between pre-ccPAS (darker blue) and post-ccPAS (lighter blue).*

Moreover, as we expected, no difference between pre- and post-ccPAS measurements for the right hand was found *t(16) = 1.01, p = 0.12* (*right IBF pre-ccPAS: 13.62 Hz (S.E.M.: 0.30); right IBF post-ccPAS: 14.03 Hz (S.E.M.: 0.34)*). This suggests that our stimulation was successful in temporarily slowing down occipital beta frequency and specifically only when the stimulated network was activated. This can be seen in Figure 3.

Interestingly the pre-TMS measurement of beta was higher when the left hand was stimulated compared to the right hand (*p = 0.007*). It is uncertain why this is the case, but as two different somatosensory regions are being utilised here it is perhaps not too surprising that the oscillatory processes subtending the connections differ from one another. Post-TMS this difference disappeared (*p = 0.296*), perhaps highlighting the reduction in the beta speed when the left hand is stimulated, but a lack of change for the right hand, bringing the two mean values closer together.

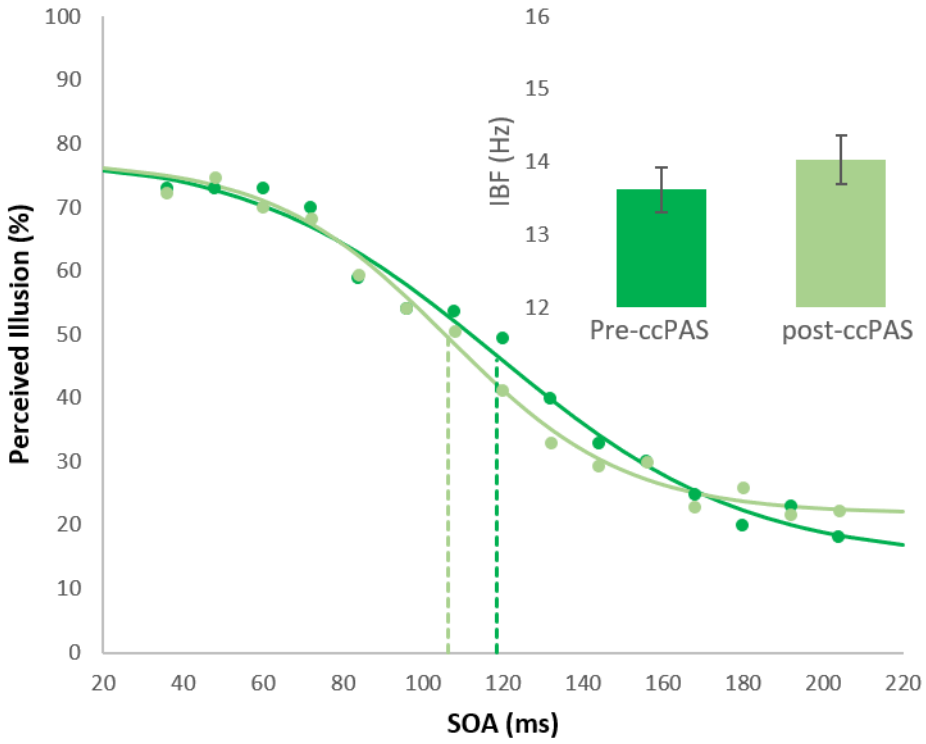

Figure 3: *Difference in behavioural and electrophysical data pre- and post-ccPAS (right hand): Sigmoid curve represents the best fit of the average probability of perceiving the tactile-induced double flash illusion plotted as a function of inter tap delays, both pre-ccPAS (darker green) and post-ccPAS (lighter green). Segmented lines represent the respective inflection points of the curve, this signifies the respective TWI of the two tasks. Each individual point represents the average percentage of illusory trials at each ISI.*

Upper inset*: represents the difference in beta frequency (Hz) between the pre-ccPAS (darker green) and post-ccPAS (lighter green) conditions, this was non-significant.*

The amplitude of these peak IBF values were extracted for each participant, both pre and post-ccPAS, when the tactile stimuli were presented to the left hand. This information is presented graphically and can be seen in figure 2. A paired t-test was conducted to compare the amplitude of the IBF peak pre- and post-ccPAS. Here it was found that the amplitude of the IBF value was significantly reduced post-ccPAS ($t(16) = 2.114, p = .05$).

Coherence Analyses:

Analysis of coherence in the condition whereby tactile stimulus was presented to the left hand suggested a reduced coherence between the somatosensory and the visual cortices at the original IBF value (*Pre-ccPAS: Mean: 0.041 (S.E.M.: 0.009); Pre-ccPAS: Mean: 0.019 (S.E.M.: 0.006)*). Paired t-tests confirmed that, for the left hand condition, post-ccPAS measures of coherence were significantly lower compared to pre-ccPAS measurements; $t(16) = 2.18$, $p =$ .045. There were no significant changes in coherence when the tactile stimuli were presented to the right hand (*Pre-ccPAS: Mean: 0.07 (S.E.M.: 0.03); Pre-ccPAS: Mean: 0.05 (S.E.M.: 0.02*), a paired t-test confirmed this to be the case ($t(16) = 1.24$, $p =$ *.231*). The pattern of results demonstrated that in the left hand condition 14 of the participants showed a reduced coherence between the somatosensory cortex and the visual cortex post-ccPAS at this IBF value, with only 2 of the remaining three showing an increase in their coherence. This information can be seen in figure 4.

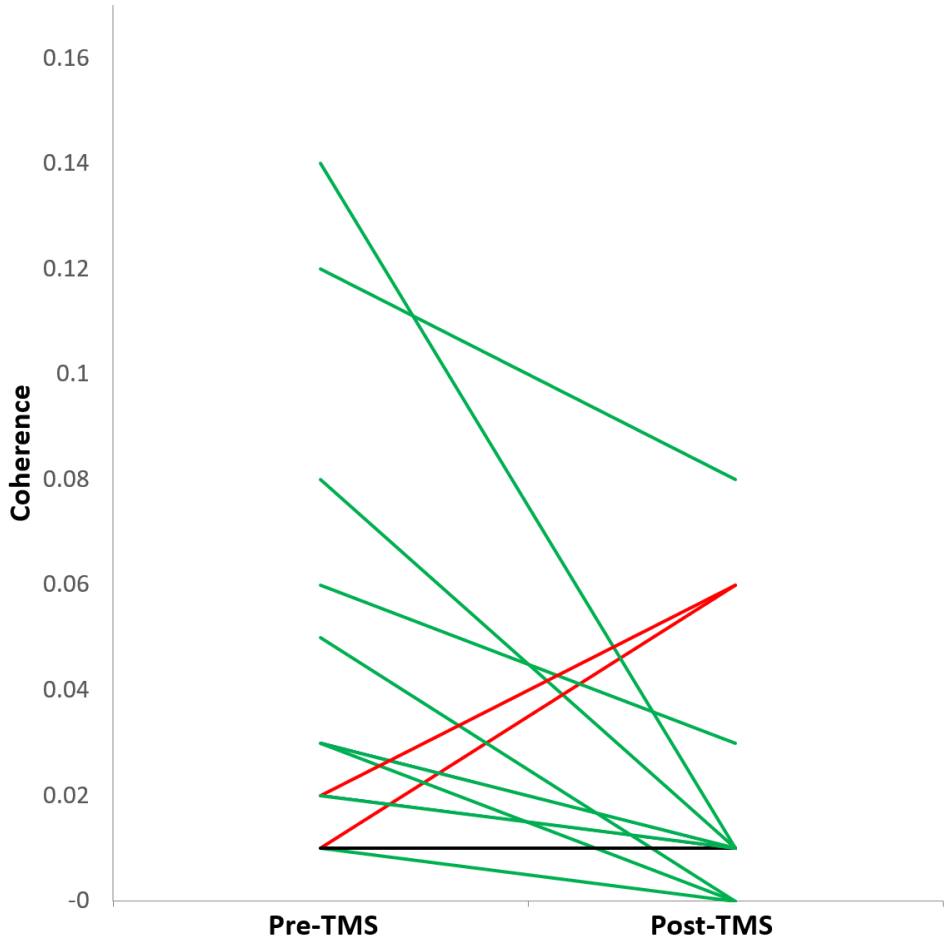

Figure 4. *Change in coherence pre- and post-ccPAS: Each line represents an individual participant and demonstrates their change in coherence between TMS conditions (pre- and post-). Colours represent direction of the change, with green indicating a reduction, red representing an increase and black representing no change in coherence between the somatosensory and the visual regions.*

Difference in behaviour:

In addition to a change in beta speed, we wished to then investigate whether any change at the EEG level could explain a change at the behavioural level as well in accordance with our working hypotheses. Specifically we tested whether there was a difference in TWI size post-ccPAS which again varied across hands. With this in mind a fully within-subjects ANOVA was conducted to compare the main effects of tactile stimulus placement (left or right) and TMS condition (pre-ccPAS or post-ccPAS) and to investigate the interaction between tactile stimulus presentation and TMS condition on the size of the

tactile-induced TWI. This analysis found neither main effect to be significant this was the case for both tactile stimulus placement, (*F (1, 16) = .69, mse = 401.32, p = .420*) and for TMS condition (*F (1, 16) = .43, mse = 365.10, p = .523*). This analysis, however, did importantly find a significant interaction between tactile stimulus presentation and TMS condition (*F (1, 16) = 14.878, mse = 311.89, p = .001*).

Further to this, Bonferroni corrected paired t-tests suggested that there was a significant difference between the pre-ccPAS TWI and the post-ccPAS TWI for the left-hand task: *t(16) = 4.01, p = .001* (*left TWI pre-ccPAS: 107.22 ms (S.E.M.: 4.95); left TWI post-ccPAS: 126.77 ms (S.E.M.: 6.21)*). This can be seen in Figure 2. As was expected this was not the case for the right hand *t(16) = 1.81, p = .09* (*right TWI pre-ccPAS: 119.72 ms (S.E.M.: 4.42); right TWI post-ccPAS: 106.22 ms (S.E.M.: 6.75)*). This can be seen in Figure 3. This pattern of results was in line with our hypothesis and subsequently suggests that by successfully reducing the speed of occipital beta we have been able to also induce a widening of the TWI for the tactile-induced DFI. This was only the case when the tactile stimuli were presented to the left hand. As this was not the case when the tactile stimuli were presented to the right hand we have also demonstrated the network specificity of our stimulation once again.

After Bonferroni corrections the pre-TMS measurement of the TWI was no different regardless of which hand was experiencing the tactile stimuli (*p = 0.022*). Post-TMS this difference remained (*p = 0.0173*), however it was much closer to reaching significance than pre-TMS comparisons.

Nonetheless we feel that these results provide tentative evidence for a causal relationship between occipital IBF and the temporal window of integration for the tactile-induced DFI.

4.6. Experiment Two: Discussion:

The major aim of this research was to further develop upon research demonstrated by Cooke et al., (2019). We wished to build upon the tentative evidence suggesting the role of functional connectivity in the processing of multisensory information by modulating this connectivity to see its effect on the temporal profile of the tactile-induced DFI.

We wished to provide evidence of a capability to experimentally reduce the speed of the beta processes subtending the connection between the somatosensory and the visual cortices using the ccPAS method of neuro-modulation. We based the stimulation timing on (what we believe to represent) the timing of the involved network reverberating in the beta band, and possibly subtending the critical time of communication for this connection.

As we were always measuring occipital beta whilst each tactile-induced task was taking place, two different connections were tested. One that subtended the right somatosensory cortex and the visual cortex (left-hand condition) and one that subtended the left somatosensory cortex and the visual cortex (right-hand condition). This should have led to a differentiation of occipital beta tuning depending on which task was being completed. As we were using the ccPAS method to target only the network in use for the left-hand condition (right somatosensory cortex to visual cortex) post-ccPAS measures of the parameters when tactile stimuli are presented to the right hand should not have been affected by the ccPAS protocol and therefore act as a network specific control measure.

In this case, comparisons of pre- and post-ccPAS measurements results showed a significant decrease in beta frequency in visual areas. This could suggest that we were able to reduce the speed of the beta processes subtending the connection between these two areas. Crucially this change was only seen for the condition where the tactile stimuli were

presented to the left hand, but not the right. This suggests that we were able to use the ccPAS method to modulate the beta processes subtending the functional connection. This could also highlight the specificity of the modulation technique that we used.

We then measured the size of the TWI both pre- and post-ccPAS. We had already found a reduced beta processing speed at electrode Oz (a value that we had theorised to represent the communication speed of the network subtending to this electrode from electrode C4). As a result, we believed that as we had reduced this value then we may also be able to observe a corresponding widening of the TWI post-ccPAS (compared with corresponding pre-ccPAS measures). As no change in beta processing speed was found for when the right hand was stimulated we should also expect to see no change in the temporal profile when this hand was stimulated. Again, what we found was once again in line with our hypothesis. We found that post-ccPAS measurements of the TWI were found to be significantly wider than pre-ccPAS measurements. We believe this may be taken as tentative evidence for the role of functional connectivity in multisensory tasks. Further supported by the fact that no change in the size of the TWI was observed when the tactile stimuli were presented to the right hand. This is consistent with what we had expected, given that we had found no change in beta processing speed post-ccPAS when the tactile stimulation was applied to this hand.

Finally analyses found that post-ccPAS measurements of the coherence between the somatosensory and the visual cortices appeared significantly reduced compared to pre-ccPAS measures, this was only the case for the left hand, and once again not the right. This reduced coherence may explain the results that we have found here. Rather than suggesting a particular enhancement in the coherence in the lower frequency (i.e. the new IBF post-

ccPAS) it could be the case that we have in fact reduced the coherence in the original IBF. This leads us to hypothesise that these pattern of results could be accounted for by mechanisms of Long Term Depression. Whereby the dominant coherent beta band subtending the connecting remote areas may have been depressed, rather than the new slower frequency band becoming actively enhanced. If this is the case the peaks that we are picking up post-ccPAS would not be new peaks as a result of an enhancement of coherence, rather slower pre-existing peaks that now become the dominant frequency as a result of the depression of the original peaks.

This could also possibly suggest that the findings that we uncovered here are not exactly what we were expecting. Indeed a significant reduction in beta speeds were found, however rather than this being as a direct result of the directionality and timing parameters of the ccPAS protocol and alternative explanation may characterise our results. What we may instead be recording here is a more general disruption of the key network as a response to inserting noise into the network via the ccPAS. Essentially we do not know whether the reduction in IBF speed that was observed was indeed due to the specific parameters of the stimulation we used, or if we are simply picking up on a general slowing down of processing speed associated with inserting random noise into the connection. We should now look to research this effect further by testing on a new subset of participants, creating a control condition to this current research.

One way in which this could be conducted is by running a similar study mimicking the protocol of the current study but using slightly different TMS parameters. These parameters should be devised specifically so as to not elicit any change in beta speed or TWI. In this case we could look to provide an identical investigation to the one presented

here; however we would use a slightly different TMS protocol. Instead of stimulating the connection at a reduced beta frequency, we could use the original beta frequency value itself. In other words, we would base the pulse timing upon the natural processing speed of the network (the IBF). As a result we should expect to see no changes in beta speed or in TWI size.

If we were to do this and we find these results this would add further evidence to suggest that properties of the functional connectivity between key regions play an important role in multisensory integration. Alternatively if we were to find similar results to those presented in the current study, we may instead conclude that the outcomes we have observed here are simply due to the insertion of noise into the network. Subsequently the reduction in beta speed (and consequential widening of the tactile-induced TWI) are simply due to a temporary slowing down of the communication speed in this network. Therefore by stimulating the network via ccPAS in any way, we would just insert noise into the system slowing down its communication speed, regardless of the specific pulse timings.

In conclusion, these findings provide some tentative evidence to support our theory of a complex neural-network of multisensory processing. We demonstrate promising evidence that may suggest that communication across this network is facilitated via domain specific neuro-oscillatory processes. We also demonstrate the roles these could play in multi-sensory processing, specifically in terms of the tactile temporal window of integration. We have also provided evidence that could demonstrate the potential efficacy of the ccPAS method in terms of modulating the properties associated with these functional connections. We have provided evidence that may suggest that this method could be used across longer-range networks, in addition to the short-term networks that have already been

demonstrated. Specifically we provide novel empirical evidence that may inform the literature about the specific communication timings of the network. We have also demonstrated that this method could potentially be used as a way of informing us about neuro-oscillatory processes, something that has not been done before. Finally we have also demonstrated evidence supporting the specificity of the method of modulation.

Crucially now we must look to provide a control condition to this current research. By performing an identical procedure, yet this time stimulating at the exact (theorised) communication speed of the network, we should expect to find no modulation of its processing speed. If this is indeed found this would provide further evidence for the efficacy of our research and of the method that we utilised. This could also go some way to discount an alternative explanation for our findings, i.e. we are simply causing a general slowing down of communication, due to the insertion of interfering noise via the ccPAS protocol rather than modifying the strength of communication through the modulation of coherence between the targeted areas.

5. Chapter Five: Experiment Three – Stimulating between somatosensory and visual cortices leads to no change in communication speed when stimulating at beta frequency:

5.1. Experiment Three: Abstract:

Presenting paired tactile stimuli alongside a single flashing disc can induce the perception of a second illusory flash. The temporal profile of this DFI has been linked to beta processes, with faster beta predicting a smaller TWI (Cooke et al., 2019). Evidence may suggest that differential properties of the functional connections subtending these interconnected areas set the fate of the illusion. Previous research used a ccPAS protocol to modulate the connectivity between somatosensory and visual regions. Basing stimulation timing on a value lower than that of normal processing speed (i.e. the speed of one complete beta cycle), with post-stimulation measurements highlighting a reduction in beta speed. Subsequently we also found a wider TWI for this illusion post-stimulation. We took these results as evidence that task-dependent visual oscillations reflect network-specific oscillatory properties. However, this investigation did not allow us to discount an alternative hypothesis, that we are instead recording the effects of an oscillatory slow-down as a result of inserting noise into the network. Thus, we now provide a control condition whereby participants undergo identical conditions yet TMS parameters are manipulated to elicit no change in beta speed (providing our previous conclusions were accurate). Indeed, no changes were found in beta frequency speed post-stimulation. We take this as evidence of the validity of previous research and that task-dependent visual oscillations do indeed reflect network-specific oscillatory properties.

5.2. Experiment Three: Introduction

Multisensory integration is an important process in which information from separate sensory domains are combined into one perceptual whole. This mechanism allows for our brains to combine the different information that we receive from the same sources in order to make sense of our environment. This ensures a prompt perception and efficient environmental navigation. It was once believed that the senses were processed in isolation, only being processed at late stage higher processing areas. However, we now know this to not be the case (Ghazanfar & Schroeder, 2006; Kayser & Logothetis, 2007), whereby many areas once thought of a being unisensory areas were found to also process multisensory information (Giard & Peronnet, 1999; Molholm et al., 2002; Watkins et al., 2006). Whilst our understanding of where multisensory information is processed in the brain is developing, how these areas work together to combine these information is less well understood. As such, this study acts as part of a comprehensive investigation into the underlying mechanisms behind multisensory processing.

When our brains are presented with two pieces of sensory information emanating from what it perceives to be the same source it will attempt to combine this information into the most logical perceptual whole. This normally acts to produce a prompt and efficient readout. However, when this information is incongruent, we often experience illusory phenomena as our brains struggle to make sense of the discordant information. Despite causing us to produce incorrect perceptual readouts, these illusions can be useful in experimental settings. This is because when they are induced in a controlled environment they become effective tools with which we can investigate the functionality of the multisensory system. By presenting discordant information and manipulating certain parameters (such as stimulus intensity or presentation timing), we can uncover certain

information regarding the precise conditions that lead to sensory information either being integrated together or to being perceived as separate.

One such illusion that has been used in this sense many times in the literature is known as the Double Flash Illusion of which there are two separate versions, the tactile-induced and the auditory-induced DFI. This effect leads participants to perceive a second illusory flash, this is when a single flash is presented alongside a brief double beep (Shams et al., 2000, 2002) or a double tap to their index finger (Violentyev et al., 2005).

By carefully manipulating the temporal parameters of this illusion we can obtain information regarding a multisensory temporal window of integration of these effects. Essentially, this measurement corresponds to the maximum delay between beep or tap pairs (the Inter-stimulus interval) that will still result in the perception of this second illusory flash. Research tends to find that this value to be comparable for both illusions and is often around 100 ms (Cecere et al., 2015; Cooke et al., 2019; Shams et al., 2000, 2002). This means that when these beeps or taps are spaced apart by less than 100 ms participants reliably perceive the second illusory flash. However when they are spaced apart by more than this value the illusory effect tends to decay.

Previous research has provided robust evidence of a tight correlation between occipital Individual Alpha Frequencies and the TWI for the auditory-induced DFI (Cecere et al., 2015; Cooke et al., 2019). Typically, it has been found that a slower IAF predicts a wider TWI indicating a higher likelihood of perception of the second illusory flash. By using tACS researchers subsequently demonstrated that local occipital activity tends to have a direct causal effect on the magnitude of the TWI. So much so that when the local occipital alpha frequencies were entrained to a value slightly above (+ 2 Hz) or below (- 2 Hz) the natural

processing frequency a direct corresponding modulation to the TWI value was observed. Here increasing alpha processing speed resulted in a decrease in the size of the TWI, with the opposite being found with a decrease in IAF. Given this research, it was theorised that local oscillatory activity sets the fate of the illusion. This was assumed because the visual cortex is often linked to alpha processes (Dugue et al., 2011; Ergenoglu et al., 2004; Frey et al., 2014; Gleiss & Kayser, 2014; Gulbinaite et al., 2017; Lange et al., 2014; Mercier et al., 2013; Minami & Amano, 2017; Romei, Brodbeck, et al., 2008; Romei et al., 2010; Romei, Rihs, et al., 2008; Ronconi et al., 2018; Samaha & Postle, 2015; Van Dijk et al., 2008; Wutz et al., 2018; Wutz et al., 2016), this manifests as a correlation between the temporal profile and these processes.

However, subsequent research has suggested that this may not in fact be the case. If local oscillatory activity is important then the tactile version of the effect should presumably also manifest as a similar correlation with these alpha processes. However, it was instead found that the tactile-induced effect tends to be linked rather with Individual Beta Frequencies in the occipital regions, again with slower frequencies predicting wider tactile-induced TWIs (Cooke et al., 2019). This begins to make sense when you consider that alpha frequencies tend to play a role in both unisensory and multisensory auditory tasks (Dohrmann et al., 2007a; Dohrmann et al., 2007b; Frey et al., 2014; Fujioka et al., 2011; Gleiss & Kayser, 2014; McKee et al., 1973; Mercier et al., 2013; Teplan et al., 2003; Weisz et al., 2011). Whereas, evidence has been found to suggest that beta frequencies play a role in somatosensory processing (Baumgarten et al., 2015; Brovelli et al., 2004; Engel & Fries, 2010; Foffani et al., 2005; Kilner et al., 2003; McFarland et al., 2000; Paus et al., 2001; Rubino et al., 2006; Salenius & Hari, 2003; Zhang et al., 2008). In this case this could suggest

that task-dependent visual oscillations reflect oscillatory properties (that are network-specific) favouring optimal, directional neural communication timing for sensory binding.

The idea here is that instead of local visual processes setting the fate of the illusion it is rather that this is affected by certain properties of the functional connectivity between the two interconnected regions. We theorised that the time it takes for information from the pre-synaptic region to reverberate to the post-synaptic region corresponds directly to the frequency associated with this pre-synaptic area. In the case of the auditory-induced DFI, the time it takes for one alpha cycle to occur corresponds exactly to the time it takes for information from the auditory cortex to the visual cortex. Similarly for the tactile effect, the time it takes for the key areas to communicate corresponds to one complete beta cycle (see previous chapter).

Drawing upon this theory and wishing to provide more compelling evidence we conducted an investigation modulating this connection to observe its effect on the TWI. Where Cecere et al., (2015) utilised a method known for manipulating local oscillatory activity (tACS), we used a different technique known as cortico-cortical Paired Associative Stimulation. Here, TMS coils are placed over two interconnected areas of the brain, pulsing in rapid succession. This acts to provide an effect similar to Hebbian like principles of Long Term Potentiation and Long Term Depression (Hebb, 1949), hence modulating the connections between these regions (Buch et al., 2011; Rizzo et al., 2011). This method has been reliably demonstrated to facilitate functional connectivity within cortices (Chiappini et al., 2018; Rizzo et al., 2011; Rizzo et al., 2009; Romei et al., 2016) with relatively short delays between TMS pulses (between 8 ms – 20 ms). These timings were informed by the

functional timing connecting areas of the motor cortex (Ferbert et al., 1992) or V5 and V1 (Chiappini et al., 2018; Romei et al., 2016).

In the previous chapter evidence was also provided to suggest that it could be used to stimulate these connections across cortices as well, with much larger pulse delays (60 ms – 110 ms); with these timings being informed by each person's individual beta frequency. These findings are potentially important for ccPAS protocols. This is because a major factor when testing complex, longer-range networks is identifying the critical timing accounting for the connection and communication between the two key regions. When targeting these longer-range networks, we must first ask, how long does it take for information from the pre-synaptic region to reach the post-synaptic region?

One solution to this issue, is to uncover the temporal profile of signal propagations by (in the case of a somatosensory to visual connection) stimulating the somatosensory cortex and testing how long it takes for the signal to have a significant impact on the oscillatory activity within the visual cortex. In our case, when utilising the tactile-induced DFI, perhaps an analysis of coherence between the somatosensory and the visual cortices could provide us with the most accurate estimation of this temporal profile. With this in mind our previous results suggested that the temporal profile of signal propagation across this network corresponds to one complete cycle of beta.

Thus, the previous research was devised specifically to investigate these transmission times in further detail. Here, investigators placed the TMS coils over the right somatosensory area (C4) and the visual areas (V1). Prior to this, each individual's IBF value was measured during the completion of the pre-ccPAS tactile task. This value was then slightly reduced, and this modified value (in ms) became the basis for the timing separating

the first pulse from the second. By stimulating using these precise parameters we intended to fine-tune the network and reduce the speed of the beta processes subtending it. Subsequently, we also wished to assess whether this modulation of beta speed would also result in a corresponding modulation of the tactile-induced TWI. Post-ccPAS measurements demonstrated that we did appear to be successful in this modulation and that we also were able to induce a corresponding widening of the TWI for this illusion.

We took this as evidence to potentially support our theory, and as further evidence for the role of the properties of the functional connectivity between interconnected regions in the processing of multisensory information. We also believe that this theory could develop the understanding of the capabilities of the ccPAS method, and how it can be used to produce a transient modulation of such long-range networks.

However, despite this promising evidence, we could not discount an alternative explanation for our findings. Instead of precise changes to the network's processing speed as a result of the specific modulation that was used, changes that we observed here may have instead been as a result of a general slowing down of neuro-oscillatory processing associated with inserting noise into the system. This subsequently could also result in a transient degradation of the multisensory system, leading to us observing a wider tactile-induced TWI post-ccPAS. Therefore we now wish to provide a control condition that can tease apart these alternative hypotheses and potentially provide support for the methods that were used in the original investigation.

In the original investigation the parameters of the stimulation were set so that we should expect to see a reduction in the IBF value and a subsequent increase in the size of the TWI. This was done by stimulating the network using a value that we theorised to be

slightly less than that of normal processing speed. The intention here was to fine-tune the network and reduce the speed of the beta processes subtending it. However, in the current experiment our intention is to reproduce (almost) entirely the previous procedure, without reducing the speed of these processes. This will be done by stimulating at the normal processing speed of this network (i.e. without first reducing the IBF value). We feel that by stimulating at the normal functioning speed of this network, we should be able to subject participants to very similar conditions, however we should not expect to induce any modulation of processing speed. Hence any change in this speed or a subsequent change in TWI size that we find post-ccPAS should not be as a result of the specific parameters of the stimulation that we are using. In other words, if we could find a significant difference post-ccPAS (compared to pre-ccPAS measures) then we can attribute these changes to simple noise insertion rather than the specific parameters of our stimulation.

In this investigation, participants will first complete a tactile-induced DFI task. They then will undergo a ccPAS procedure that will almost be identical to that conducted in the previous study. However, this time we will not perform the initial frequency reduction; instead basing the pulse timing on the exact value of the individual's IBF value. This means that whilst conditions will be similar to the previous investigation here we will instead stimulate the connection between the right-somatosensory cortex and the visual cortex at its normal processing speed. Using these exact parameters should subsequently yield no modulation and hence no reduction in the speed of the participants' IBF speed, should our postulations be correct. Furthermore this should also lead to no change in the size of the tactile-induced TWI. We will investigate this by comparing the change in IBF and TWI observed in this current study directly with those observed in the previous investigation.

If no reduction in the speed of the IBF and no subsequent widening of the TWI is found when comparing pre- to post-ccPAS measurements this would provide further evidence for the efficacy of the method used in the previous investigation. It would help inform our understanding of the capabilities of the ccPAS method, and how it can be used to produce a transient modulation of these long-range networks further, as it would go some way to discount the hypothesis that simple noise assertion accounted for our previous findings. This would also act as further evidence for the role that the functional connectivity between interconnected sensory areas plays in the processing of multisensory integration.

5.3. Experiment Three: Materials and Methods:

Participants:

A total of 17 participants volunteered to take part in this study which was approved by the ethics committee of the University of Essex. All of the participants who took part in this experiment were randomly selected from the same sample that was used in Experiment One; thus we already knew that they were susceptible to the illusory effects of the DFI.

Fifteen of the 17 participants stated by self-report that they were right handed, with 1 being left handed and 1 stating they were ambidextrous, the mean age of the sample was 26 years (range: 20 – 42) and consisted of 9 females and 8 males.

Prior to taking part, all participants completed a screening questionnaire ensuring that they had no psychiatric or neurological history and normal (or corrected to normal) vision, as well as normal hearing and somatosensation by self-report. This was to ensure no confounding effects and to prioritise participant safety during TMS.

Materials and Apparatus:

Visual stimuli were presented on a 17.5 inch cathode ray tube monitor via a Dell Optiplex 960 computer (Windows XP, resolution: 1280x1024) with a refresh rate of 85 Hz. The tactile stimuli were provided via a tactile controller and mechanical solenoid stimulator (Heijo Research Electronics, London, UK). This would deliver a suprathreshold tap (upon the participant's left index fingertip) by pushing a blunt plastic point against the participant's skin whenever a current was passed through the solenoid. During trials, white noise (approximately 50 dB) was played to participants through the speakers (these were situated either side of the monitor). This was done to mask the mechanic noise produced by the tactile stimulator and to ensure this was not heard by the participants. This was to avoid confounding the tactile experience by also inadvertently presenting participants with auditory stimuli. All experimental stimuli were presented via the software E-prime (version 2.0; Psychology Software Tools, Pittsburgh, PA).

For all participants enrolled in the final sample, EEG was recorded from 64 sintered Ag/AgCl electrodes mounted on an elastic cap (Easycap, Herrsching, Germany) alongside the ground electrode (located at position AFz) and the reference electrode (placed upon the right mastoid bone). The EEG signals were digitized at 500 Hz and amplified using a BrainVision Professional BrainAmp amplifier through the BrainVision Recorder programme (BrainProducts GmbH, Gilching, Germany). Before the recording began we ensured that all electrodes were set upon the participant's scalp at an impedance not exceeding 10 kΩ.

In all trials, participants were presented with a flashing disc with a diameter of 2 cm, displayed just below a central fixation cross, the disc flashed once for a duration of 12 ms. In

each of the tasks the presentation of this single flashing disc was paired with a double “tap” sensation to the participant’s left index finger.

The two tactile stimuli were spaced apart by a varying range of ISI values, these ranged between 36 ms and 204 ms increasing with increments of 12 ms, this resulted in 15 different ISI values. Each ISI was presented 10 times, resulting in 150 randomly ordered trials in all of the task blocks. The time between trials included the presentation of the stimuli (as described above) plus a varying inter-trial interval. This corresponded to the elapsed time following the experimenter’s input on the keyboard, this was upon hearing the participant’s vocal response to the previous trial. This prompted the other varying interval, which ranged between 1000 ms and 1800 ms before the next trial started. In this case there were 5 different inter trial delays in steps of 200 ms, each occurring 30 times.

The TMS procedure was conducted via the use of a Master TMS unit (Magstim BiStim2, UK) working alongside a secondary slave unit (Magstim 2002, UK) the device was always set at a fixed intensity of 70% of the maximum level of intensity. Ideally a variable intensity would have been used but this was not implemented due to time constraints, thus we selected an intensity that we believed was high enough to reach threshold without causing any unnecessary risks to the participants themselves. Coils were placed over the right somatosensory cortex (C4) and on the visual cortex (Oz). The directionality of the protocol was determined by the timing of the magnetic pulse, the pulse from the coil at C4 always preceded the coil at Oz. Timing between paired pulses was determined by each participant’s individual beta peak frequency in the visual cortex (as measured at channel Oz). In this investigation we wished to use a similar ccPAS protocol to the previous work, however we wished to use parameters that would lead to no change in IBF value. As such,

working only on the data collected during the illusory task we uncovered each persons' IBF value (after the pre-stimulation trial had finished). Then using this value (in ms) we could then manipulate the parameters of the TMS (prior to commencing the stimulation) to match this corresponding time between pulses. Our intention here was to stimulate the connection between the two areas using its natural processing speed, rather than a speed that is slower as was the case in the previous investigation. The TMS protocol itself lasted approximately 15-minutes and consisted of 90 paired pulses, with a 10 second delay separating each set of pairs. It is important to note that the procedure was offline (i.e. did not occur during the task but during a break between the first set of tasks and the second).

Experimental Design:

Upon EEG cap fitting completion, participants were seated approximately 57 cm away from the screen. EEG recording was manually started prior to the first block of trials beginning. Participants were subsequently instructed to fixate on a cross situated at the centre of the screen while the 150 flashing discs within the block were presented. Participants were asked to place their index finger immediately below the location of the flashing disc (as close as they could get whilst still remaining comfortable) this was in order to maximise spatial co-occurrence of the visual and tactile stimuli processing.

In all trials participants were asked to verbally report whether they perceived one flash or two flashes. This was done verbally, rather than via keyboard input so as to avoid motor interference from participants using their resting hand to respond to the stimuli. In this case focus should only be concentrated on the hand experiencing the tactile stimuli so as to maximise the illusory effect. Participants were instructed to provide unspeeded and

accurate responses. The verbal report was then input by the examiner via the “1” or the “2” key, which prompted the new trial to begin, only after the variable inter-trial interval.

Once this tactile-induced DFI task was completed participants had a brief waiting period whilst the experimenter analysed the EEG (using the methods as described below) to uncover the IBF value. This was then used to calculate the spacing of the TMS pulses.

Subsequently all participants underwent a TMS procedure. This lasted approximately 15-minutes and consisted of 90 paired pulses, with a 10 second delay separating them. Once this was completed a waiting period of 30-minutes was required. A wait time of 30-minutes was selected as this was the time at which ccPAS modulation had been found to be at peak effect in previous research (Chiappini et al., 2018; Rizzo et al., 2011; Rizzo et al., 2009). After the waiting period had been completed participants were required to undergo the two

tactile-induced DFI trials once more, before reaching the end of the procedure. The procedure can be seen below in Figure 1.

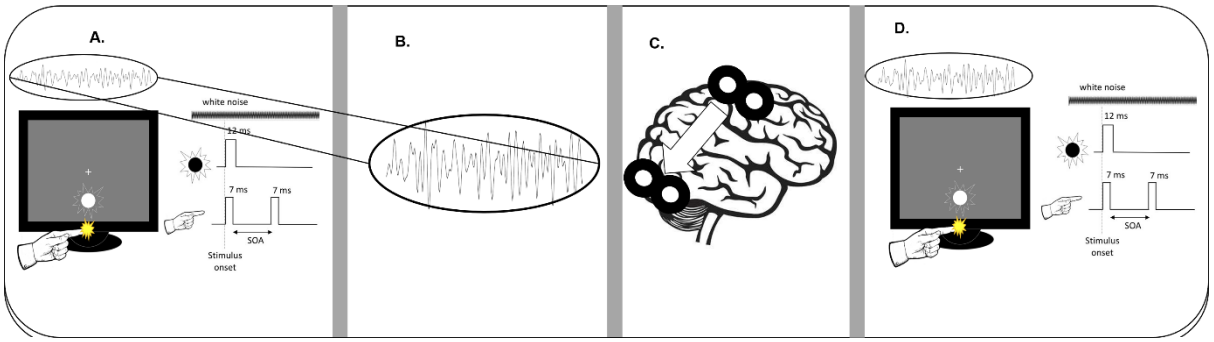

Figure 1. Experiment Three Procedure:

E. ***Pre-ccPAS DFI:*** *Whilst viewing the flashing disc (12 ms duration) participants also experienced two brief taps to their left of right index finger (both with a 7 ms duration). These tactile stimuli were separated by a variable ISI (36 ms - 204 ms). Participants were asked to ignore the tactile stimuli and state aloud whether they perceived one or two flashes.*

F. ***ccPAS timing calculation:*** *EEG was concurrently recorded during both DFI tasks. Peak beta frequency at area V1 (Oz) was uncovered (**f**), this was only taken during the left hand condition. This was subsequently converted to time **t** via the following formula **t** = 1000/**f**.*

G. ***ccPAS Procedure****: 15-minute TMS protocol takes place, whereby first coil is placed on the right somatosensory (C4) cortex and the second is placed on area V1 (Oz). Spacing between first coil pulse (C4) and second coil pulse (Oz) corresponds to time **t** uncovered in step D. There were 90 pulse pairs, with each pair being separated by a delay of 10 seconds.*

H. ***Post-ccPAS DFI:*** *Participants underwent the same tactile-induced DFI tasks (after a 30 minute waiting period), this was with identical parameters to the previous tasks.*

5.4. Experiment Three: Statistical Analysis:

Behavioural data analysis:

The participants' perceived illusory flashes across the different ISIs were used to calculate the tactile temporal windows of integration. This corresponded to the maximum ISI in which the visual illusion was reliably perceived. Therefore, we calculated the percentage of illusory trials (i.e. trials where two flashes were perceived) and plotted them as a function of the ISI values. This was done separately for both pre- and post-ccPAS trials, resulting in two different TWI values being collected. A psychometric sigmoid function *[y = a + b/(1 + exp(- (x - c) / d)); a = upper asymptote; b = lower asymptote; c = inflection point; d =*

slope] was then fitted to each percentage distribution returning a corresponding inflection point (centre c) of the fitted sigmoid. This value was taken to represent the point of decay of the illusion, which subsequently taken as an index of the TWI. Ergo we could assume that when stimuli pairs were spaced apart by more than this corresponding centre point the illusory response would begin to significantly decay.

EEG data analysis:

EEG activity was concurrently recorded during task execution, this was subsequently analysed to calculate peak beta frequency peaks, for each participant. By calculating the individual beta frequency peaks prior to TMS commencing we were able to base the pulse timing of the TMS directly on each person's individual beta frequency. This meant that each ccPAS protocol was tailored directly to the participant's individual neural activity.

For all participants, 64 channel EEG was recorded at a sampling rate of 500 Hz. The EEG signal was re-referenced offline to the average of all scalp electrodes. Data was then subsequently segmented into 2000 ms epochs, time locked to and preceding the visual stimulus onset. This resulted in 150 epochs of pre-stimulus oscillatory activity for both of the frequency bands assessed, this was performed separately both pre- and post-ccPAS. Each single epoch was visually inspected for artefacts (from eye blinks, muscle contractions, electrical interference etc.) and was manually rejected where necessary. For each participant and for all of the recorded electrodes a full power spectrum was obtained through a Fast Fourier Transform (FFT) with a zero padded window (nominal frequency resolution 0.125 Hz). Finally, for each participant and task (pre-ccPAS and post-ccPAS) EEG segments were averaged. This allowed for calculation of the average beta peak frequency in

the visual cortex, as calculated at electrode Oz. The peak beta frequency was determined for each participant as the value corresponding to the maximum peak frequency within the beta frequency range (i.e. 12 – 25 Hz). Finally, for each participant the speed (in ms) of one single beta cycle was calculated using this peak frequency data (in Hz).

Difference in electrophysical data pre- and post-ccPAS:

We calculated the IBF value (using the methods as described above) for both pre- and post-ccPAS conditions. This was done in order for us to assess the difference in beta processing speed (as measured in visual regions) between these pre- and post-ccPAS conditions. According to our hypothesis we should expect to see no change in beta speed post-ccPAS. In order to test for this a mixed-factor ANOVA was performed comparing the change in beta frequency in this current investigation with the change observed in the previous investigation. With a corresponding paired t-test in order to test for simple main effect for the control condition only (we already know the experimental condition was significant). We expect to find a significant interaction between study condition (control vs. experimental) and TMS condition (pre-ccPAS vs. post-ccPAS) on the speed of individual beta processes. We also expect to find no significant difference post-ccPAS in the speed of these beta processes. If our results are in line with our hypothesis then this would go some way to support the specificity of our ccPAS method.

Difference in behaviour pre- and post-ccPAS:

We calculated the TWI (using the methods described above), in order to assess the difference between these pre- and post-ccPAS tactile DFI tasks. A mixed-factor ANOVA will be performed in order to directly compare the change in the TWI size in this control investigation with the change observed in the previous experimental condition. Once again a corresponding paired t-test will be conducted in order to test for simple main effects for the control condition only (we already know the experimental condition was significant). We expect to find a significant interaction between study condition (control vs. experimental) and TMS condition (pre-ccPAS vs. post-ccPAS) on the size of the temporal window of integration for the illusion. We also expect to find no significant difference post-ccPAS in the size of the TWI. If this is indeed found then this would demonstrate further evidence of a causal relationship between IBF and the TWI for the tactile-induced DFI and would provide evidence to once again support the efficacy of the methods that we utilised in the previous investigation.

Coherence analysis:

Much like the previous investigation we will also conduct an analysis of coherence between somatosensory and visual sensors in order to assess any change in this measure from pre to post-ccPAS. This will be done using the correlation/autocorrelation (also referred to as the Magnitude-squared Correlation Coefficient) method via the use of BrainVision Analyzer (BrainProducts GmbH, Gilching, Germany). This will be performed between the right somatosensory area (c4) and visual area V1 (Oz), exclusively using the pre-ccPAS IBF value. This analysis calculates the coherence via the formula:

$$Coh\ (c1, c2)\ (f) = |\ Cov\ (c1, c2)\ (f)\ |\ ^{2} / (\ |\ Cov\ (c1, c1)\ (f)\ |\ |\ Cov\ (c2, c2)\ (f)\ |\ )$$

In conjunction with:

$$Cov\ (c1, c2)\ (f) = \Sigma\ (c1, i\ (f) – avg\ (c1\ (f)\ )\ )\ (c2, i\ (f) – avg\ (c2\ (f)\ )\ )$$

Here, totalling is carried out via the segment number *i*. Formation of the average also relates to segments with a fixed frequency *f* and a fixed channel *c*. This should tell us the degree to which the two areas of the brain are communicating with each other using this key frequency. Here we expect post-ccPAS measures of coherence between right somatosensory cortex and V1 to be the same as pre-ccPAS measures.

5.5. Experiment Three: Results

EEG correlates of tactile and auditory-induced DFI:

Our first aim was to ensure the key correlation that forms the basis of this report was still present in this smaller subgroup. That is the correlation between occipital beta frequencies and the tactile-induced TWI. Here we once again found that IBF (in ms) positively correlated with the size of the TWI of the tactile-induced DFI ($r = 0.63; p < 0.01$), such that faster IBFs accounted for shorter TWIs. This relationship was found to survive robust skipped correlations (Pernet et al., 2013) ($r = 0.63, CI = 0.30 : 0.85$).

Pre-ccPAS vs. Post-ccPAS:

Difference in Neuro-oscillations:

We wished to assess whether there was a different pattern of results to those displayed in the previous study. In comparison to the change in beta speed that was observed in the previous experiment, we expected to find no change in beta speed in this current work. To test for this we used a mixed-factor ANOVA to compare the main effects of study condition (experimental or control) and TMS condition (pre-ccPAS or post-ccPAS) and to investigate the interaction between study condition and TMS condition on the speed of individual beta processes. This analysis found a significant main effect for the TMS condition (*F (1,32) = 7.19, mse = 1.46, p = .011*). It also found a significant main effect for the study condition (*F (1,32) = 6.50, mse = 6.77, p = .016*). This analysis revealed a significant interaction between study condition and TMS condition (*F (1, 32) = 8.78, mse = 1.46, p = 0.006)*.

Further to this paired t-tests showed a non-significant difference between pre- and post-ccPAS measures of IBF in the control condition, *t (16) = 0.17, p = 0.87* (pre-ccPAS: 15.95 Hz (S.E.M.: 0.55); post-ccPAS: 16.03 Hz (S.E.M.: 0.63). This is indeed consistent with our hypotheses. These results can be observed in figure 2.

The amplitude of these peak IBF values were extracted for each participant, both pre and post-ccPAS. This information is presented graphically and can be seen in figure 2. A paired t-test was conducted to compare the amplitude of the IBF peak pre- and post-ccPAS. Here it was found that there was no difference in the amplitude of the IBF value post-ccPAS compared to pre-ccPAS measures (*t(16) = .85, p = 0.408*).

Difference in behaviour:

We wished to assess whether there was a different pattern of results to those displayed in the previous study. In addition to the widening of the TWI that was observed in the previous experiment, we expected to find no change in the size of the TWI in this current work. To test for this we used a mixed-factor ANOVA to compare the main effects of study condition (experimental or control) and TMS condition (pre-ccPAS or post-ccPAS) and to investigate the interaction between study condition and TMS condition on the tactile-induced TWI size. This analysis found a significant main effect for the TMS condition (*F (1,32) = 6.39, mse = 132.74, p = .017*). It also found a non-significant main effect for the study condition (*F (1,32) = 3.12, mse = 888.90, p = 0.87*). This analysis revealed an interaction between study condition and TMS condition that was found to be significant *F (1, 32) = 19.95, mse = 132.74, p < .001.*

Further to this a paired t-tests demonstrated that there was no statistically significant difference between pre- and post-ccPAS measures of TWI in the control condition, *t (16) = 1.99, p = 0.06,* (*pre-ccPAS: 106.92 ms (S.E.M.: 5.50); post-ccPAS: 101.51 ms (S.E.M.: 5.20)*). Once again this was found to be consistent with our initial hypotheses. These results can be observed in figure 2B and can be compared to the previous results that can be seen in figure 2A.

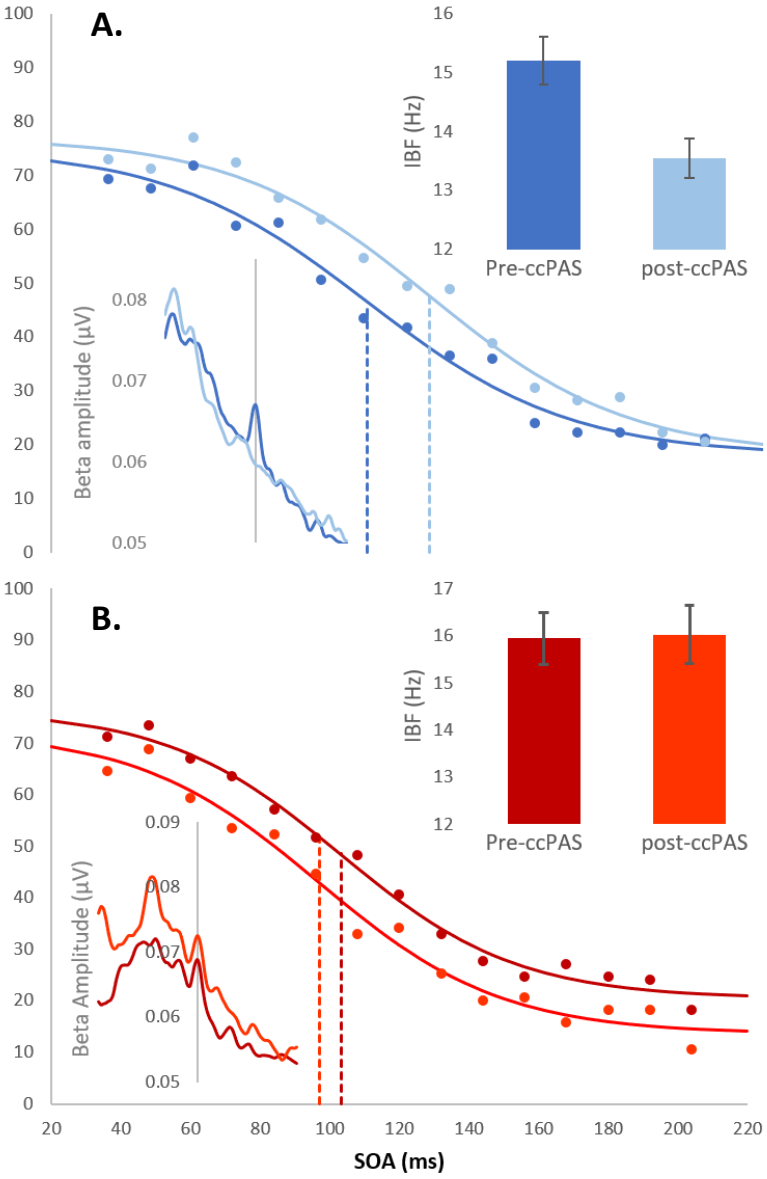

Figure 2A: Difference in behavioural and electrophysical data pre- and post-ccPAS (Experimental data): *Sigmoid curve represents the best fit of the average probability of perceiving the DFI pre-ccPAS (darker blue) and post-ccPAS (lighter blue), this is plotted as a function of inter-tap delay. Segmented lines represent the significant difference in TWI for the experimental condition.*

Upper inset: *Significant difference in beta frequency (Hz) between the pre-ccPAS (darker blue) and post-ccPAS (lighter blue) conditions.*

Lower inset: *Significant difference in IBF amplitude post-ccPAS between pre-ccPAS (darker blue) and post-ccPAS (lighter blue).*

Figure 2B: Difference in behavioural and electrophysical data pre- and post-ccPAS (Control data): *Sigmoid curve represents the best fit of the average probability of perceiving the DFI pre-ccPAS (darker red) and post-ccPAS (lighter red), this is plotted as a function of inter-tap delay. Segmented lines represent the non-significant difference in TWI for the experimental condition.*

Upper inset: *Non-significant difference in beta frequency (Hz) between the pre-ccPAS (darker red) and post-ccPAS (lighter red) conditions.*

Lower inset: *Non-significant difference in IBF amplitude post-ccPAS between pre-ccPAS (darker red) and post-ccPAS (lighter red).*

Coherence Analysis:

In the previous analysis we found a significant reduction in coherence between the somatosensory cortex and the visual cortex at the IBF value. Here we wished to perform the same analyses. In this case, should our postulations be correct, we should see no significant change in coherence between pre- and post-ccPAS conditions. This analysis of coherence did indeed suggest little change in coherence post-ccPAS (Pre-ccPAS: Mean: 0.034 (S.E.M.: 0.010); Pre-ccPAS: Mean: 0.028 (S.E.M.: 0.007)). Paired t-tests subsequently confirmed that there was no change in coherence post-ccPAS compared to pre-ccPAS measures; *t (16) = .47, p = .645*.

Unlike in the previous investigation (with a generally consistent reduction in coherence) the pattern of results in this investigation appear very random, with no consistent changes in coherence being observed. This information can be seen in figure 3.

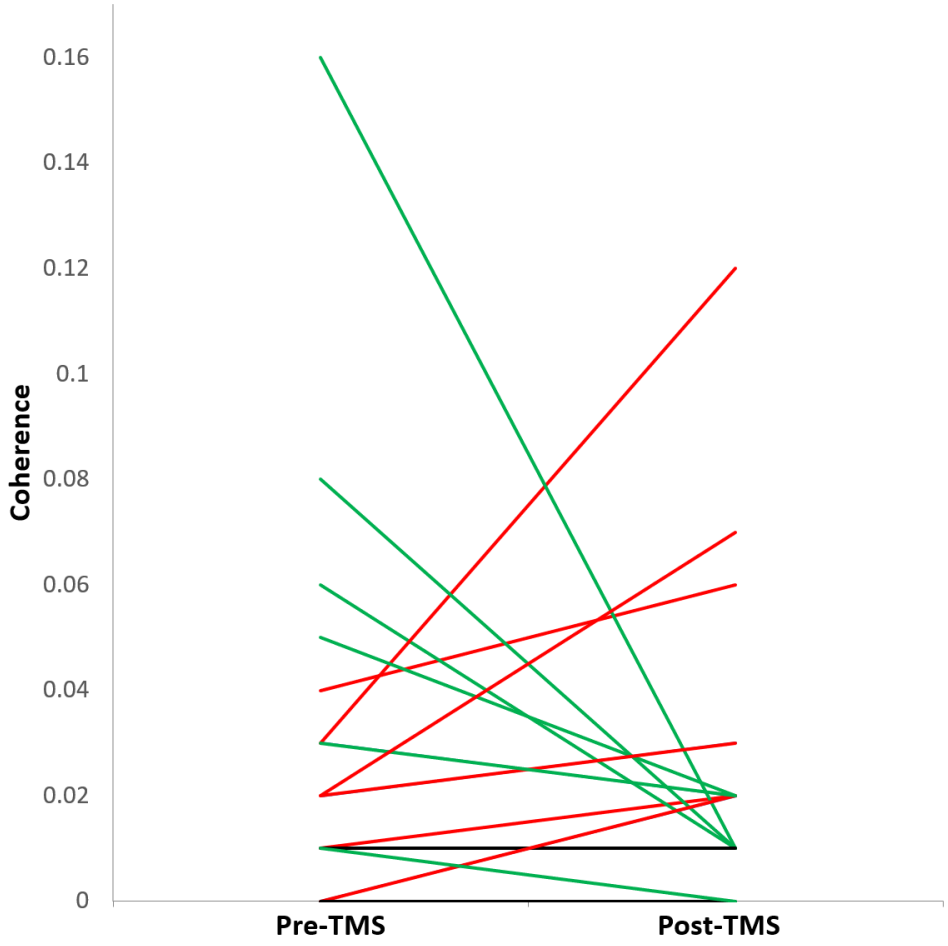

Figure 3: Change in coherence pre- and post-ccPAS: *Each line represents an individual participant and demonstrates their change in coherence between TMS conditions (pre- and post-ccPAS). Colours represent direction of the change, with green indicating a reduction, red representing an increase and black representing no change in coherence between the somatosensory and the visual regions.*

5.6. Experiment Three: Discussion:

The aim of this research was to further inform our understanding of a method of neuromodulation by providing a control condition to a previous investigation. This investigation had already yielded promising results in using this method to modulate functional connectivity based upon neuro-oscillatory processes. Without this control condition we were not able to justify discounting an alternative explanation for our results in the previous study. More specifically, the reduction in beta processing speed that we

observed in Experiment Two could simply have been the result of a general slowing down of neuro-oscillatory processes as a result of inserting noise into the system. Rather than as a result of the precise parameters of the stimulation. This control experiment looked to provide evidence to challenge this alternative explanation.

Thus we conducted an experiment whereby instead of stimulating at a timing slower than that of normal processing speed (and hence fine-tuning the system to this slower speed) we stimulated using the exact processing speed; a value that we hypothesise to correspond to the IBF value (Cooke et al., 2019). By stimulating at this frequency, we expected no modulation of the speed of the processes subtending the key network, and thus no change in beta processes post-ccPAS. However, should the previous changes (observed in Experiment Two) been bought about by this simple and crude noise insertion, we would expect to see the same pattern of results in this investigation as was found in the previous. We proposed this method as an elegant way to provide a differentiation of results and thus provide evidence for the efficacy of the key parameters that we used in the previous experiment.

Our results were indeed consistent with what we had initially hypothesised. Here, post-ccPAS measurements of IBF did not significantly differ from corresponding pre-ccPAS measurements. This is indeed different to what was found in the previous investigation whereby our stimulation did result in a significant slowing down of these beta frequencies. These findings are strongly consistent with our hypothesis; they point to the efficacy of our method in the previous investigation. Had the changes that we observed been due to a general slowing down of beta processes as a result of inserting noise into the system, presumably we would also have expected to observe a slowing down of the beta processes

here as well. This would be because we were still inserting noise into the system. Instead, finding no difference here points to the frequency specificity (alongside the previously reported network specificity) of our method of stimulation.

In addition, we wished to compare the size of the respective TWIs pre- and post-ccPAS, in order to observe any potential changes. As no change in beta speed was seen between the pre- and post-ccPAS conditions, we also expected to see no change in the size of the TWI. This would be in line with our hypothesis and could again suggest that properties of the functional connectivity between interconnected areas are important in subsequent properties of multisensory integration. Again, what we found was in line with our hypothesis, where post-ccPAS measurements of the TWI were found to be no different compared to the corresponding pre-ccPAS measurements. Once again different to the previous investigation where this difference was indeed found.

Finally, we wished to compare pre- and post-ccPAS measurements of the coherence between the somatosensory and the visual regions using the pre-ccPAS IBF value. Once again, as no change in beta frequency speed was found, we also expected to see no significant different in the coherence between these two regions post-ccPAS. Indeed these two conditions were found to not significantly differ from one another. Once again providing a differentiation to the previous results, whereby a significant change in coherence was found.

These results provide evidence of the specificity of the stimulation that we used. This suggests that the previous results may not simply be the result of a general slowing down of neuro-oscillatory processes due to inserting random noise into the system but were more likely to be as a result of the exact parameters of the stimulation itself. We also provide

further support for previous evidence that properties of the functional connectivity between areas set the fate of the tactile-induced DFI. This also supports evidence that the ccPAS method can be effectively used over longer-range networks and that the method can be used to investigate properties of neural-oscillatory processes. These represent two potentially important uses of the method that have not yet been reported in the literature and may eventually have greater benefits outside of pure research.

Based on this and previous investigations we conclude that properties of the connection between the somatosensory and the visual cortices (or auditory and visual cortices in the case of the auditory-induced effect) is an important factor in determining properties of the DFI. This in turn informs our overall understanding of how multisensory information is processed with our brains. Essentially, we believe that, in the case of the tactile-induced DFI, the time it takes for information from the somatosensory cortex to reverberate into the visual cortex corresponds directly to the speed of one complete beta cycle. But one must consider why this could indeed be the case?

One such theory suggests that communication across connected regions may be subserved by the neural synchronization of functionally interconnected areas regardless of the physical distance between them. In this case, the neural synchronization would be the result of the alignment of post-synaptic (visual processes) neural activity to the pre-synaptic input (in our case this would be somatosensory information). This subsequently acts to create a temporal window of optimal communication between the two areas involved. If this is indeed the case then such profiles observed in the tactile-induced DFI may be the result of top-down directed beta (13 - 25 Hz) influences on the primary sensory input (Fries,

2015). This then eventually acts to shape the final illusory perceptual outcome because of the quantity and temporal disparity between auditory or somatosensory and visual signals.

Travelling waves may also be another potential explanation for this phenomenon. These waves are said to facilitate communication between two remote, interconnected areas. In this model neural oscillations allow for the transfer of information by propagating from one region to the next via a complex neural network (Klimesch et al., 2007; Muller et al., 2018). According to this framework, local oscillatory activity (i.e. resonant frequency) in the somatosensory cortex will propagate towards the visual cortex accounting for the specific impact of these beta oscillations on the tactile-induced DFI.

As we have now provided some promising evidence for the overall efficacy of this method, eventually we could begin to consider other potential applications of this tool. Particularly when taking into account its apparent ability to modulate connectivity and multisensory perception.

This could involve examining the flexibility of the method in terms of manipulating the parameters of the TWI. In other words future research should now look at a potential capability of using this method to not just increase the size of the TWI but to decrease it too, potentially resulting in an increase in the precision of one's multisensory processing. The benefit of doing this is that the method could potentially be used as a way of providing an improvement to one's multisensory processing ability by reducing TWI size and hence multisensory accuracy. This potential application could be particularly useful in developing interventional approaches to neurological conditions that have been linked to both a general multisensory degradation, and more specifically a widening of multisensory temporal windows of integration.

Conditions that have been linked to this type of multisensory disruption include schizophrenia (de Gelder, Vroomen, Annen, Masthof, & Hodiamont, 2003; de Gelder et al., 2005; Haß et al., 2017; Ross et al., 2007; Stekelenburg, Maes, Van Gool, Sitskoorn, & Vroomen, 2013; Zvyagintsev, Parisi, & Mathiak, 2017), autism (Foss-Feig et al., 2010), dyslexia (Hairston, Burdette, Flowers, Wood, & Wallace, 2005; Virsu, Lahti-Nuuttila, & Laasonen, 2003), anorexia (Gaudio et al., 2014) and obesity (Scarpina et al., 2016). All of these conditions have been specifically linked specifically to a widening of the TWI (thus a degradation of the multisensory system) (Costantini, Scarpina, Migliorati, Mauro, & Marzullo, 2015; de Gelder et al., 2003; de Gelder et al., 2005; Foss-Feig et al., 2010; Gaudio et al., 2014; Hairston et al., 2005; Haß et al., 2017; Kwakye et al., 2011; Ross et al., 2007; Scarpina et al., 2016; Stekelenburg et al., 2013; Virsu et al., 2003; Zvyagintsev et al., 2017).

Thus, if future research could provide evidence that this ccPAS method could also improve connectivity between two interconnected regions of the brain, and subsequently increase the precision of the multisensory system, we could subsequently propose a clinical usage for this method. Whereby we use this method to restore the communication speeds between interconnected regions to something more resembling normality, with a view towards providing some form of treatment to those suffering with these conditions.

Of course this direction is admittedly rather speculative, and it is unknown at this stage whether any applications of this method would result in any major changes to individuals suffering with these conditions, beside simply affecting their ability to perceive this (and presumably other multisensory illusions). However, the reasoning here is that by reducing the size of an abnormally wide TWI and returning it to a value comparable to that of a healthy individual we may be able to fine-tune a person's multisensory processing

system. This could have some potential in reducing some of the effects of multisensory degradation associated with these conditions, hence potentially resulting in positive changes in behaviour and mental health.

In conclusion, we have provided a control condition to the previous experiment wherein the ccPAS method was used to reduce the speed of beta processes subtending a proposed multisensory network. In this previous experiment, the slowing down of these processes also led to a subsequent increase in the size of the TWI of the tactile-induced DFI. Furthermore a decreased coherence between the key regions was found pre-ccPAS compared to pre-ccPAS measurements. In the current experiment we intended to disentangle two explanations for these findings. One that the specific parameters of the modulation led to a fine tuning of the network and reduced the speed of the processes subtending them. The other that we were simply inserting noise into the system, resulting in a general slowing down, independent of ccPAS timing parameters. Thus a control was devised, stimulating at the natural processing speed (as opposed to a value slower than this), which we hypothesised would lead to no changes in IBF or TWI (as well as coherence). This is assuming that the previous results that had been observed were due to the parameters of the stimulation. In Experiment Three we found these expected results with no change in IBF speed, TWI size or coherence being found when comparing pre-ccPAS to post-ccPAS measures. This goes some way towards supporting our previous methods and suggests that the ccPAS method can indeed be used as a way of modulating functional connectivity between two distant, yet functionally interconnected regions of the brain.

6. Chapter Six: General Discussion:

6.1. Summary of Experiment One:

In Experiment One, we were able to provide promising evidence that it is in fact properties of the functional connectivity between cortices influencing both the auditory-induced and tactile-induced DFIs, rather than local oscillatory frequencies as we first assumed.

Initially we were able to characterise for the first time the temporal profile of the tactile-induced DFI and compared this directly with the known temporal profile of the auditory-induced DFI. We found, when pooling results together from an initial pilot study and in a larger experimental study, that the temporal profiles of the two illusory phenomena appear to be comparable. We found that they do not significantly differ from each other, and also demonstrated a correlation between the auditory-induced and the tactile-induced TWIs. This could perhaps suggest that similar mechanisms may be subtending these two illusion. These similarities suggested to us initially that the tactile-induced DFI may also be subtended by alpha frequencies, directly influencing properties of its TWI, much in the same way as has been found with the auditory-induced effect (Cecere et al., 2015).

One explanation for this previously uncovered relationship between alpha processes and the auditory-induced effect could be due to local visual oscillatory processes setting the fate of the illusion. Another could be that this is due to the properties of the functional connectivity (set by the pre-synaptic area, in this case the auditory cortex) between the two interconnected areas processing the incongruent information in the task. For the auditory-

induced DFI both of these explanations could manifest as a direct influence of alpha processes.

Due to the similarity between the two illusions, we assumed that the same underlying processes would subtend them, meaning that we also expected to find an influence of alpha on the temporal profile of the tactile-induced DFI. If we had indeed found the same effect then this would suggest that multisensory processes follow the rules of the cortex processing the affected sensory modality, in this case, the visual cortex. Accordingly, one would expect visual alpha oscillations to be playing a role in the processing of multisensory information independently of the sense affecting vision. Thus leading to comparable influences of visual alpha processes on the two differently induced illusions.

However, instead of this, EEG results appear to demonstrate that oscillatory processes relate to the two illusions in fundamentally different ways. Whilst we replicated previous findings and demonstrated a tight relationship between visual alpha processes and the auditory-induced DFI, we could not find this same relationship for the tactile-induced effect. Instead, a significant relationship between the tactile TWI and visual *beta* processes was found such that a higher beta frequency (or faster beta waves) accounted for a smaller TWI. These correlations were found both at sensor and at source space level. PLV analysis also suggested a greater connectivity between key areas of the brain at the corresponding frequencies (i.e. alpha for the auditory-visual effect and beta for the tactile-visual effect).

Given these findings we took this as tentative evidence that could suggest that different multisensory tasks are processed in fundamentally different, frequency specific ways. This appears to be highly dependent on which sensory modalities are currently engaged. In other words, we proposed that the temporal properties of these auditory- and

tactile-induced illusions might have been directly influenced by the specific oscillatory properties of each sensory signal's pairing. This different oscillatory tuning could be explained as the specific computational speed needed by the cross-sensory network to efficiently integrate information. In this investigation we showed that the impact of simple auditory stimuli on visual processing seems to be governed by the way sounds phase aligns alpha oscillatory activity in the occipital cortex (Frey et al., 2014; Gleiss & Kayser, 2014; Mercier et al., 2013; Romei et al., 2012; Teplan et al., 2003). Yet, prior to this it was unclear whether this was a general feature of crossmodal interactions within the visual system or whether the specific cross-sensory input determines the fate of the visual response to the visual processing. Here we take this as the first evidence highlighting the relevance of neural communication at the network level through frequency specific oscillatory activity.

Thus one could perhaps argue that whilst still being subtended by similar mechanisms, the specific network that is involved differs between tasks. This means that the two effects may still be processed similarly (hence the correlations and lack of significant differences between the two measurements of behaviour). However, the speed at which they are processed appears to differ based on the properties of the network subtending the two cortices involved with producing the illusory perception (hence the differential correlations between behaviour and neuro-oscillatory processes). As such what we have uncovered here appears to be similar mechanisms that are subtended by different network specific communication timings.

6.2. Summary of Experiment Two:

The main aim of Experiment Two was to provide further information regarding the relationship between neuro-oscillatory processes and the tactile-induced DFI. The ultimate goal here was to expand our understanding of the underlying mechanism behind the DFI tasks. With the ultimate view to provide us with further details of the mechanism underlying general multisensory processing.

We first wished to provide some evidence of a possibility to experimentally manipulate beta frequencies using the ccPAS method of neuro-modulation. As the results of Experiment One had suggested to us that instead of local oscillatory activity influencing the properties of the illusory effects, it was indeed properties of the functional connection *between* cortices that set the fate of the illusion. Thus, we wished to stimulate this connection with a view to reducing the speed of the beta processes that, according to our theory, subtends it. Whilst evidence exists to suggest a capability to use tACS to modulate local visual processes in order to modulate the auditory-induced DFI (Cecere et al., 2015), we wished to modulate properties of a functional connection, thus for our research a different methodology was required. Evidence exists to suggest that the ccPAS method can be used to modulate functional connectivity between two regions of the brain (Buch et al., 2011; Chiappini et al., 2018; Rizzo et al., 2011; Rizzo et al., 2009; Romei et al., 2016). However, this was the first time that the stimulation had occurred over such a long-range network. Furthermore, the method has not in the past been used in the investigation of neuro-oscillatory processes. Hence whilst we used an established (whilst still relatively new) method, we wanted to assess the capabilities of this technique beyond what had already been reported.

As stimulation took place exclusively on the right hemisphere we should only expect to see an effect when the tactile stimuli are presented to the participant's left hand, but not their right hand. During this investigation we were measured occipital beta whilst each task was taking place (either the left-hand or the right-hand task). As a result two different connections are at play here, one subtending the right somatosensory area and the visual cortex (as in the left-hand condition) and one subtending the left somatosensory area and the visual cortex (as in the right-hand condition). This should have led to a differentiation of occipital beta tuning depending on which task was being completed. As we were using the ccPAS method to exclusively target the network in use for the left-hand condition (i.e. right somatosensory to visual), post-ccPAS measures of the IBF speed and the TWI size should have been the same as pre-ccPAS measures when tactile stimuli were presented to the right hand. Specifically we expected to see a modulation of the tactile-induced DFI only when the network involved corresponded to the one targeted by the ccPAS, showing the state-dependent network specificity of the effect.

Crucially, our intention here was to reduce the speed of the beta processes subtending the connection. In this case we first measured each person's visual IBF while they performed the tactile-induced DFI task either with tactile stimuli being presented to either their left or their right hand. This IBF value (in ms) is what we hypothesised to correspond to the time it takes information from somatosensory regions to reach the visual regions. We then used IBF value that was uncovered when tactile stimuli were presented to the left hand and calculated, for each individual, a value that was 3 Hz slower than the original IBF value. We then used the duration of one cycle of this new modulated frequency value (in ms) to set the spacing of the paired TMS pulses. These were delivered exclusively between the right somatosensory cortex and the visual cortex. This was with a view to fine-

tune the communication of the network at a rather slower rate corresponding to a value slower than that of the IBF. In other words, the manipulation was aimed at reducing the speed of the beta processes subtending the connection between the somatosensory and the visual cortices. We theorised that this would manifest as a reduced beta frequency in visual areas post-ccPAS.

In line with our hypothesis, our results showed a clear decrease in beta frequency post-ccPAS, as measured in the visual cortex. This suggests that our method was successful in reducing the speed of the beta processes subtending the connection. Crucially, this effect of stimulation appears strictly state-dependent as it was only found for those blocks in which the tactile stimuli were delivered over the left hand. Instead, no difference was found when they were delivered to the right hand. This finding would be consistent with a network specific effect, as the modulation of the beta peak in expected directions can only be appreciated for the right (but not left) somatosensory to visual cortex network manipulation, the same network targeted by our ccPAS procedure.

Given previous findings of the correlation between beta processes and the tactile-induced DFI, we assumed that by modulating the speed of these beta processes we may also have been able to modulate certain aspects of the perceived illusion which we have shown to be related to the speed of beta oscillations, namely the size of TWI. If a change was found here then this provide support to out theory that the properties of the tactile-induced DFI are causally set by the properties of the functional connection subtending the two cortices. As we found that the length of IBF appears to be directly related to the size of the TWI, we also expected that a decrease in IBF speed following our ccPAS protocol should produce a corresponding widening of this window of integration. In addition, this effect was

expected to once again be state-dependent. This was as no change in beta speed was found in blocks where the tactile stimuli post ccPAS were delivered to the right hand, and hence this should lead to no change in TWI.

Again, what we found was in line with our hypothesis, we found that post-ccPAS measurements of the tactile-induced TWI appeared to be significantly wider than pre-ccPAS measurements. This was exclusively the case for when the tactile stimuli were presented to the left hand, but not the right, once again demonstrating the network specificity of this effect. In this instance we believe this may represent promising evidence that highlights the potential relevance of neural communication at the network level through frequency specific oscillatory activity.

Despite these promising results, at the conclusion of Experiment Two we did not have any particularly compelling evidence to discount one other alternative explanation for the pattern of these results. That is we could interpret the reduction in beta speed (and in turn the widening of the TWI) as a result of inserting noise into the network. This in turn would be independent of the precise timing that we used in this experiment. If this was to be the case then these findings tell us very little about the specific network and instead would suggest that we have simply induced a degradation of the TWI as a result of noise insertion. As a result we felt that it was imperative to conduct a further experiment, this time making use of a control condition to the ccPAS procedure. In other words a condition mimicking the stimulation whereby no changes are expected. The option that we decided to utilise was a method where we based the timing of the paired TMS pulses on the IBF value exactly, that is the normal timing that we believe the system to operate at (instead of a reduced value as we had used in this investigation). This would be beneficial as it would

mimic entirely the procedure that participants experienced during Experiment Two, yet as we were stimulating at normal processing speed we should expect to see no modulation of IBF or TWI post-ccPAS. Of course this would not be the case if the changes observed in Experiment Two were as a result of this possible noise insertion, in which case we should expect to see results similar to those found in the current investigation. Using this method to tease apart these two hypotheses, Experiment Three looked to investigate this further.

6.3. Summary of Experiment Three:

Experiment Three was purposely designed to be almost identical to Experiment Two. This was for us to allow a different set of participants to experience the same experimental conditions. Yet this time we utilised parameters for our stimulation that we believed would not result in any changes in beta frequency or TWI size post-ccPAS. This was to challenge the possibility that the changes observed in Experiment Two were solely down to inserting noise into the network. If we were to mimic the stimulation, with different TMS pulse timings and find different results we could use this as evidence for the frequency specificity of our neuro-modulation technique.

The key aspect of this investigation was to mimic the stimulation that had occurred in the previous study, however this time we had manipulated the parameters of the ccPAS protocol so that we would expect no change in IBF. Subsequently this would also lead to no change in the TWI post-ccPAS. This was with the overall goal of providing further evidence of the frequency specificity of our method of stimulation and to challenge the idea that noise insertion could be an alternative explanation for the findings in Experiment Two.

Based on the findings of Experiment One and Experiment Two we proposed that properties of the beta frequencies subtending the functional connections between the somatosensory and the visual cortices set the fate of the tactile-induced DFI effect. As such we proposed that by basing our stimulation timing on frequency slightly lower than this IBF value we should have been able to fine-tune the network and induce a reduction in the speed of these processes subtending the connection. Indeed the results in Experiment Two were found to be consistent with this. In Experiment Three we proposed that instead by stimulating at the exact speed at which we believe the system to communicate at (i.e. the IBF value) we should expect no modulation of the beta frequency across this connection. Additionally, we also expected to see no difference in the size of the TWI post-ccPAS (compared with pre-ccPAS measures).

In this instance the results did indeed show no difference in IBF value post-ccPAS (compared to pre-ccPAS), which was consistent with our hypothesis. This supports the idea that in Experiment Two we may indeed have been able to successfully use the ccPAS method to modulate beta frequency. Furthermore, this is consistent with the idea that beta modulation was not simply as the result of a general slowing down of beta processes caused by inserting noise into the system. This further supports the use and efficacy of the method that we used in Experiment Two, and in turn supports the conclusions that we made from the results of this experiment. Indeed, these results may suggest that if we wish to replicate our results from Experiment Two we would certainly need to use identical parameters to the ones that we used in that particular investigation.

As we had previously demonstrated no change in beta frequency, we also expected to find no change in the size of the TWI post-stimulation. As was expected, no change in the

size of the tactile-induced TWI was found, which was indeed consistent with our hypotheses. Once again, this provides further support for the efficacy of our stimulation technique used in Experiment Two. Crucially, as no change in IBF was found, we also found no change in TWI. Potentially suggesting that in the previous research we did indeed successfully utilise the ccPAS method to modulate beta frequency and that our stimulation appeared to be both frequency and network specific. Once again providing evidence highlighting the relevance of neural communication at the network level through frequency specific oscillatory activity.

6.4. Any issues that need to be addressed?:

The results that have been demonstrated across all three experiments are very promising. However as with all research there are some potential issues that could be addressed in future research. Whilst we do not believe that these issues could have greatly affected our findings the following section will look to assess these potential issues and suggest how future research along this line could look to implement solutions that could be used to streamline and further improve our methods.

One potential issue with Experiment Two could be that, despite an average difference in beta speed post-ccPAS compared to pre-ccPAS measurement, the ccPAS protocol did not always affect the participant in a predictable fashion. In this case we found that post-ccPAS measurements of a person's individual beta frequency was not always significantly lower than the corresponding pre-ccPAS measurement, and occasionally it would even be higher that the pre-ccPAS measurement, with 6 participants exhibiting only a negligible difference in beta frequency (< 1 Hz) and with 2 of these demonstrating a (very small) increase in their IBF post-ccPAS. This arguably could cast some doubt on the overall

reliability of our method of stimulation. Furthermore the inclusion of the participants who were unaffected by the stimulation potentially skewed our dataset. In other words, if we were able to ascertain the reason for this variability in effectiveness we could have potentially circumvented this issue and perhaps the difference between pre- and post-ccPAS measures, in both neuro-oscillatory processes and behaviour may well have been greater. This is without even taking into account how this variability may affect the validity of the results of Experiment Three, which also utilised the ccPAS method.

As such we should begin to consider the reasoning behind why such variation occurs, with a view to figuring out how to reduce this issue and potentially induce changes in these less susceptible participants as well. Indeed, one such potential explanation for this could simply be physical individual differences accounting for a variable success rate. In this case we may wish to consider natural variations in skull and scalp thickness as a potential cause of this range of stimulation effectiveness.

Research does indeed demonstrate the overall variability in natural skull thickness (Ruan & Prasad, 2001), with differences also potentially appearing to be linked somewhat to a person's biological sex. Researchers found that the average thickness of a male skull was around 6.5 mm on average, conversely the female skull was found to be on average around 0.6 mm thicker (Li, Ruan, Xie, Wang, & Liu, 2007). Further to this, research has also demonstrated that individuals also tend to differ in the thickness of their scalp alongside their skull (Hori, Moretti, Rebora, & Crovato, 1972) This not only refers to the thickness of the skin on a person's head, but to their hair as well, something that again naturally varies across the population. Overall scalp thickness has been found to once again vary across gender (again being thicker in women), and also changing with age, thickening up to the age

of 50 and then decreasing thereafter (Hori et al., 1972). These variations in skull and scalp thickness may have gone some way to produce a dampening of the overall influence of the ccPAS in some cases, this may subsequently account for the variable effectiveness of the method that was observed.

One factor that may be pertinent here is the intensity of the TMS pulses. Crucially we always used a fixed intensity level, this was set at a level of 70% of maximum. This was in order to achieve a healthy balance between TMS effectivity and participant safety. Perhaps however, something that we did not initially consider, is that there could be a minimum threshold intensity needed for the TMS to be effective. As a result of our fixed intensity level, it is perhaps possible that some people did not receive a pulse with an intensity that was high enough to achieve this minimum threshold of intensity. Conversely using an intensity level that is too high may also result in no changes being observed, this is because the positive effect is essentially cancelled out through a process known as the lateral inhibition phenomena, whereby increased activity in a neuron simultaneously decreases activity in surrounding neurons. This has been shown to result in no (or a negligible) net change in cortical activity in the stimulated region (Chiappini et al., 2018).

There is also evidence in the literature to suggest that some techniques used to measure and investigate brain activity are affected by individual skull and scalp thickness, this includes EEG or magnetoencephalography (Cuffin, 1993). Furthermore we already have evidence of TMS variability from our experiment, but previous work has also found a similar natural variation in TMS effectivity within the general population (Wassermann, 2002). Indeed, research has begun specifically to look into this variability, usually investigating measures of individual motor threshold, essentially this is a measure of the lowest electrical

energy needed to produce a small twitch when the motor cortex is stimulated (and can be measured through electromyography). These studies tend to suggest that one major factor in the motor threshold is the overall distance between the magnetic coil, and the cortex itself (Kozel et al., 2000; Stokes et al., 2007; Thielscher & Kammer, 2002). Essentially if one has a thicker skull or scalp that distance between the cortex and the coil is going to be greater, hence the importance of considering skull and scalp thickness in the use of TMS.

As a result, one could argue that to maximise the efficacy of our method we should be considering threshold intensity. This could be done by using the TMS to find the invoked motor or visual thresholds. This involves finding the lowest intensity stimulation that results in muscle activation (as measured through electromyography), or emergence of phosphenes when over the visual cortex. This however would increase the length of this already very lengthy procedure, potentially resulting in participant fatigue, which may subsequently affect neuro-oscillatory processes, and behavioural performance. It may also adversely affect drop-out rate of the investigation. Nonetheless should the ccPAS method described here be developed upon in future investigations, this point may be something that researchers could wish to consider in order to maximise the overall effectiveness of the technique.

Another aspect of our research that was found to have a high variability was the overall susceptibility to the illusions. In many cases, participants simply did not perceive the illusion at all. In other cases, participants perceived only one of the illusory effects, but not the other. For future research we may perhaps wish to find ways in which we can circumvent this issue by understanding exactly why this variability occurs, or by utilising other methods that could be analogous to the DFI effect yet with a higher reliability.

Another issue that we may wish to consider is the overall precarious nature of the perception of the illusion. It is important to note that before the experimental procedure began, we first performed a screening processes, this was a brief practice trial of both the auditory-induced and the tactile-induced DFI tasks. This was primarily for us to find participants who demonstrated a reliable illusory response. This enabled us to selectively use participants who experienced a strong and reliable illusory percept, and one that we could fit easily to the sigmoid function curve. Very often we would notice that people who demonstrated a reliable susceptibility to one illusion often did not demonstrate the same effect for the other. More often than not the more reliable illusion was the auditory-induced DFI. Indeed the tactile effect simply seemed to be vastly more precarious in its perception, which can be demonstrated by the significant difference in the overall level of goodness of fit. This may also have been somewhat affected by the concurrent use of white noise during the tactile-induced task (as was already discussed in a previous chapter). It should also be noted that whilst participants were screened prior to taking part and all those that were enrolled were found to experience both illusory effect in this screening task, occasionally their illusory susceptibility would reduce significantly during the experimental trials. This would sometimes get to the point where they had to be excluded from analysis. This demonstrates that not only was there a large variability between participants, there was a large variability within the same participant across different time periods. These issues meant that some participants were not eligible to take part in our research.

This raises an important question as to why there is such a variability in the overall perception of the illusion, not just between participants but also within participants across different tasks and even within the same task at different times. Understanding this point may subsequently lead to ways in which future research can be streamlined somewhat. This

could be done by either by maximising the likelihood of selecting participants that are already likely to perceive the illusion, tweaking the parameters of the task experience to maximise the likelihood of perception or by utilising a different task that is far more reliable yet one that still demonstrates a similar effect in terms of their relationships to neuro-oscillatory processes.

Variations among individuals in terms of their likelihood of experiencing the illusion have been found and discussed within the literature before. For example, research has found there to be a negative relationship between the power in the alpha band and the susceptibility to visual illusions (Lange et al., 2014). That is, people with a higher alpha power are less likely to experience the illusion than those with a low power. This was subsequently supported by the research carried out by Cecere et al. (2015). These researchers also found this negative correlation between alpha power and the susceptibility to the auditory-induced DFI. This could also explain why there is a variation in susceptibility within participants (not just between them), as neural activity (particularly alpha) has been shown to vary in the same participant depending on current task or their particular mental state (Payne et al., 2013; Pfurtscheller et al., 1996; van Diepen & Mazaheri, 2017; Zumer et al., 2014). This could suggest that a participant's illusory susceptibility may vary depending on their current state of mind.

Furthermore, the current literature has also suggested a link between the density of grey matter and the proneness to the auditory-induced DFI. Specifically it was suggested that participants who have a lower volume of grey matter in their early visual cortex tend to exhibit an overall higher proneness to the auditory-induced DFI (de Haas, Kanai, Jalkanen, & Rees, 2012). In addition to these other perhaps more surprising factors have also been

demonstrated to affect illusory susceptibility, this includes age (Innes-Brown et al., 2011; McGovern et al., 2014) and even factors as seemingly bizarre as musical capability (Bidelman, 2016).

One must also consider that for the DFI it is not simply low level activity that causes the effect, rather this mechanism is directly based on previous experience of one's environment. Whereby the integration and subsequent illusory perception is the result of how one would expect to perceive similar stimuli happening in similar real life circumstances. In other words the DFI is (at least partially) the result of past experiences where generally one would expect that when a sound is presented in close temporal proximity to a visual cue the two events are usually emanating from the same source. As such if a second sound is presented within a tight temporal window (without the corresponding visual stimulus), the past events experienced by our brain (whereby the two stimuli emanate from the same source) lead us to the conclusion that the second sound also corresponds to a second flash. As such an individual participant's past experience may directly affect their susceptibility to the illusory effect, as such it may simply be the case that many of our participants experienced different environmental conditions leading to a lower level of perceptual susceptibility to the illusion in their case. This could also explain somewhat the difference in susceptibility between the auditory-induced DFI and the tactile-induced effect. It could simply be the fact that in our environment it is more common for us to experience a visual-auditory pairing of stimuli than it is for us to experience a tactile-visual pairing, making the auditory-induced effect more likely for us to perceive based entirely on our past experiences of the world.

Clearly there could be a substantial number of variables that appear to affect a participants' ability to perceive these illusions; we must now work to find ways to reduce the influence of this variability. This would be beneficial as it would potentially mean we could expand the number of participants whom would be eligible for the study. This is as it would hopefully reduce the amount of participant wastage due to them not perceiving the illusion reliably, this would also be beneficial as we could reduce our level of selectiveness in terms of obtaining our sample.

In conclusion this section has suggested two potential issues that may be considered in future research. We may consider using a variable TMS intensity, possibly tailored to individual motor or visual thresholds in order to increase the likelihood of a significant effect of the stimulation. However we must first consider the risks associated with increasing TMS intensity. Indeed, perhaps we should only begin to consider using a variable intensity should we be able to develop any practical applications for the method or the theory. This would be with the view of increasing the reliability of the method of stimulation. One could argue that the best possible path to take would be to investigate the underlying reasons behind the general unreliability of the perception of the illusion. This could be beneficial as it may give us scope to provide conditions that may result in an increased likelihood of perception of this illusion in order for us to reduce participant wastage and avoid being overly selective when building our sample.

6.5. Considering future research:

Considering the promising nature of the findings demonstrated here, we must now consider potential directions in which the research can go. This would be with a view to

providing more details on the complex nature of the networks contained within the multisensory system. We should also look to consider potential applications of the ccPAS method, of which we have provided more evidence of its capability in the current investigation. Such ideas will now be discussed in further detail.

In this research we did not uncover any notable differences between the temporal profiles that were investigated, in other words we found that the TWI for the auditory-induced DFI did not significantly differ from the corresponding measurement for the tactile effect. In addition to this we also found there to be a significant relationship between these two temporal profiles. This would lead one to assume that the auditory and tactile effects are subtended by the same underlying processes. However, we also provided evidence to suggest that the two measures are subtended by different neuro-oscillatory processes.

Here we could argue that whilst still being subtended by similar mechanisms the specific network that is involved differs between tasks. This means that whilst the two effects are processed similarly, the speed at which they are processed differs based on the properties of the network subtending the two cortices involved with producing the illusory perception. As such what we have uncovered here appears to be similar mechanisms that are subtended by different network specific communication timings.

Regardless of the interpretation of these results there certainly appears to be a complex relationship between these different tasks. On the one hand they appear to be processed in fundamentally different ways, however on the other they appear to also be correlated with one another and they do not differ in their absolute magnitude. This suggests that we may not still understand fully the mechanisms subtending this multisensory network. As such future research could now look to investigate this

mechanism further by extrapolating the methods that we used in Experiment One to other multisensory tasks in order to further investigate these underlying mechanisms. If we were to conduct this research and find similar results this would hence provide further evidence for the theories that we have put forward in this current investigation. That is the role of functional connectivity in multisensory integration.

Given that there appears to be something of a dissociation between the temporal windows (at least in terms of their underlying mechanisms if not their absolute size), future research could now look to uncover more details on the temporal profiles of other multisensory tasks. These would be tasks whereby different sensory modalities to those presented here are involved, this would subsequently enable us to provide further details on this proposed complex unisensory and multisensory network. Subsequently, we could then use this information to further inform our understanding of the role played by the properties of the functional connection between the two cortices involved.

One potential effect that could investigated in this manner can be seen in the research conducted by Hotting and Roder in 2004. These researchers were able to demonstrate that, in a similar vein to the DFI tasks, participants could be induced into perceiving a second illusory *tap* to their index finger (Hotting & Roder, 2004). This effect only occurred when a single tap to the finger was simultaneously presented alongside a quick double beep sound (Hotting & Roder, 2004).

For this Double Tap Illusion (DTI), using the reasoning put forward in this report, we could perhaps expect to see a relationship between temporal properties of this DTI effect and alpha processes (in a similar vein to the auditory-induced DFI). This would be due to the auditory system's influence upon the somatosensory system, and with the auditory system

often being associated with alpha processes (Dugue et al., 2011; Ergenoglu et al., 2004; Frey et al., 2014; Gleiss & Kayser, 2014; Gulbinaite et al., 2017; Lange et al., 2014; Mercier et al., 2013; Minami & Amano, 2017; Romei, Brodbeck, et al., 2008; Romei et al., 2010; Romei, Rihs, et al., 2008; Ronconi et al., 2018; Samaha & Postle, 2015; Van Dijk et al., 2008; Wutz et al., 2018; Wutz et al., 2016).

Another potential effect can be observed in a study conducted by Bresciani and colleagues (2008). In this investigation it was found that irrelevant visual stimuli could influence the number of perceived taps or tones experienced, demonstrating the possibility of visual processes to influence tactile responses, as well as auditory responses (here we again may see a relationship between these illusions and alpha processes). In this case however these researchers also found that the number of tones perceived could also be influenced by the presence of an irrelevant double tactile or visual stimulus (Bresciani, Darnmeier, & Ernst, 2008). Specifically, it was found that participants could be induced into perceiving a second illusory beep, when paired with a brief double flash or a double tap to the index finger. In this case, once again we should expect to find something of a dissociation between the temporal profiles of these Double Beep Illusions (DBI). Theoretically, we should once again find an influence of alpha frequencies for the visual-induced DBI. The tactile version of the effect should, once again, be differentially influenced by beta frequencies, due to the influence of the processes in motor and tactile tasks (Baumgarten et al., 2015; Brovelli et al., 2004; Engel & Fries, 2010; Foffani et al., 2005; Kilner et al., 2003; McFarland et al., 2000; Paus et al., 2001; Rubino et al., 2006; Salenius & Hari, 2003; Zhang et al., 2008).

One potential direction could be to investigate other tasks that demonstrate roughly similar (but ultimately different) illusory effects. Potentially this may include simultaneity judgements (Harrar & Harris, 2008), sense of agency tasks (David, Newen, & Vogeley, 2008) and perhaps even the McGurk effect (McGurk & Macdonald, 1976). For example, much success has been demonstrated with the use of simultaneity judgements in past research in terms of using it to uncover information about a temporal window of integration (Powers, Hillock, & Wallace, 2009; Van Wassenhove, Grant, & Poeppel, 2007)

The evidence presented previously suggests that the illusory fission effect of the DFI does not appear to be exclusive to the domain of vision, with evidence also suggesting that the effect can also be induced in the auditory (DBI) and the tactile domain (DTI). One interesting question that could now be asked is what are the mechanisms that subtend *these* effects. The current research has implicated the connectivity between the sensory areas coding for the interaction between the influencing domain and the influenced domain. We should now move beyond the effects investigated here and investigate what the most effective communication mechanism between these newly proposed effects are (i.e. the DBI and the DTI effects). How does the brain orchestrate the activity of these areas in real time in order to produce a best possible perceptual outcome; In this case, the two illusory effects?

It is important to consider that for the DFI it is not simply low level activity that causes the effect, rather this mechanism is directly based on an individual person's previous experience of their environment. Whereby the integration and subsequent illusory perception is the result of how one would expect to perceive similar stimuli happening in similar real life circumstances, essentially resulting in the most logical (yet in this case

illusory) percept. In other words the DFI is the result of past experiences where generally one would expect that when an auditory (or of course a tactile) cue is presented in close temporal proximity to a visual cue the two events are usually emanating from the same source. If a second sound (or tap) is presented within a tight temporal window (without the corresponding visual stimulus), the past events experienced by our brain (whereby the two stimuli emanate from the same source) leads us to conclude that the second sound also corresponds to a second flash.

Consequentially we may wish to investigate how this complex combination of low-level neural functionality, adaptiveness and past experience leads us to perceive the corresponding DBI and DTI effects. In this case we could look to ascertain the exact values for the temporal profiles for these similar illusory effects, by repeating the methods of the current study on these aforementioned DTI and DBI effects. Subsequently we could look to infer the TWIs for these respective illusory tasks and attempt to uncover a relationship between the corresponding low level neural oscillations to further increase our understanding of the link between these processes and the multisensory integration system. If these results do show a dissociation between the influencing wave bands (in addition to what we have already demonstrated) this too would provide further evidence for the validity of our theory.

One must be somewhat pragmatic as to the interpretation of such results. Take for example the DTI effect, the idea here would be to look specifically how the auditory signal could influence the perception of the second illusory tap. The exact nature of the influence of this auditory signal could also be strongly influenced by other factors, such as the overall saliency of the stimuli. With this in mind, the nature of the relationship between any such

TWI and the oscillatory activity will also depend on the delicate balance between the individual participant's past experience and the functionality of the connection between the two key cortices involved in this illusory effect.

Another benefit to performing this research is that we could also look to investigate their comparative differences to one another, thus attempting to expand upon the evidence of a relationship between these windows. Once these other potential windows have been uncovered, we could then look to assess their properties and investigate them all in relation to one another, providing more information on any multisensory network that may be at play here.

In the case of the DTI effect, we could look to investigate how auditory information influences the perception of tactile information in the domain of time. This would inform our understanding of the underlying mechanisms of the multisensory system. Here we could possibly expect to see the influence of alpha in the profile of this effect. If we believe that in the DFI, alpha influences the temporal profile of this effect because of the influence of audition, and the importance of alpha in this domain, we may expect to find the same effect of alpha when investigating the corresponding DTI effect. Ascertaining the exact outcome here could be an empiric question worthy of investigation.

Furthermore we are already aware that abnormalities in the temporal profile associated with multisensory integration have been linked to abnormal behaviour resulting in certain medical conditions. These include conditions such as autism, obesity (Foss-Feig et al., 2010; Scarpina et al., 2016) or schizophrenia (Haß et al., 2017; Ross et al., 2007). However, in all of these cases only tasks whereby the visual system was influenced by the auditory system were utilised. Given the difference in certain properties of the two TWIs

that were investigated in this report (i.e. the auditory and the tactile-induced TWIs) it is also possible that these other temporal windows of integration could influence these conditions differently. Or alternatively, we may even uncover relationships to other conditions that have not yet been considered. Therefore, we are currently unaware if there is any connection between these conditions and the other potential temporal profiles that have been proposed here, and future research could look to investigate this further. This could also be conducted in partnership with the previous suggestion of investigating the DTI and DBI effects in order to investigate the TWIs, and subsequently link them to potential conditions that may arise because of abnormalities in their TWIs.

Another potential line of research stems from the fact that our research has demonstrated that multisensory temporal profiles differ greatly within the population. As such, one other potential future study could look to investigate how variations in these temporal windows influence other aspects of human behaviour. We could subsequently look to separate participants based upon the relative size of multisensory temporal window, perhaps separating them into two groups, those above the median and those below the median. This would be to ascertain whether the individual magnitude of the window itself has any specific behavioural function or advantages aside from their link to these illusions. For example, participants who have a larger temporal window may have a reduced sensory acuity. This could be as a result of having a wider period in which to integrate therefore being more susceptible to mistakenly overlapping sensory information and erroneously integrating them into a single perceptual whole. This could give rise to faulty perceptions and disorganised experiences of one's environment. This could explain the deficits associated with aging (Chan, Pianta, & McKendrick, 2014; Noel, De Niear, Van der Burg, & Wallace, 2016) and the link between schizophrenia (Haß et al., 2017; Ross et al., 2007) or

schizotypal personality traits (Ferri et al., 2018) and TWI. These people also may be more susceptible to the other illusory effects discussed previously because of their larger period in which they have to co-modulate sensory information. Nonetheless it would be highly interesting to investigate whether key differences in the temporal windows of integration correspond to any particular behavioural advantage or disadvantage depending on the relative size of these measures.

Finally, one potentially promising direction this research could go makes use of the ccPAS method as a way of manipulating connectivity between interconnected regions, and as a way of modulating multisensory task performance. In Experiment Two and Three we provided some promising evidence for the overall efficacy of this method as way of manipulating these factors, eventually we could begin to consider other potential applications of this tool.

This could involve examining the flexibility of the method in terms of manipulating the parameters of the TWI. Specifically, future research could now look at the possibility of using this method to not just widen the TWI but to shrink it too. One must consider the possibility that this TWI shrinkage may subsequently result in an increase in the precision of overall multisensory processing. The benefit of doing this is that the method may eventually be able to be used as a way of providing a fine-tuning of one's multisensory processing ability, which could in turn be particularly useful in developing interventional approaches to neurological conditions that have been linked to both a general multisensory degradation, and more specifically a widening of multisensory temporal windows of integration.

Conditions that have been linked to this multisensory disruption include schizophrenia (de Gelder et al., 2003; de Gelder et al., 2005; Haß et al., 2017; Ross et al.,

2007; Stekelenburg et al., 2013; Zvyagintsev et al., 2017), autism (Foss-Feig et al., 2010), dyslexia (Hairston et al., 2005; Virsu et al., 2003), anorexia (Gaudio et al., 2014) and obesity (Scarpina et al., 2016). All of these conditions have been specifically linked to a widening of the TWI (thus a degradation of the multisensory system) (Costantini et al., 2015; de Gelder et al., 2003; de Gelder et al., 2005; Foss-Feig et al., 2010; Gaudio et al., 2014; Hairston et al., 2005; Haß et al., 2017; Kwakye et al., 2011; Ross et al., 2007; Scarpina et al., 2016; Stekelenburg et al., 2013; Virsu et al., 2003; Zvyagintsev et al., 2017).

Thus, by providing evidence that ccPAS may also be able to improve connectivity between two interconnected regions of the brain, and subsequently modulate the multisensory system positively, we could subsequently propose a clinical usage for this method. Whereby we use this method, in affected populations, to restore communication between interconnected regions to something more resembling normality. This would be done with a view towards providing some form of treatment to those suffering with these conditions.

It has already been demonstrated within the literature that it is possible to induce a reduction in the size of the TWI (in a DFI task), via the use of neuromodulation, albeit with a different method that was used in Experiment Two and Experiment Three (Cecere et al., 2015). Research also exists to suggest that perceptual training on its own can lead to a reduction in TWI size (Powers et al., 2009). By giving participants five 1-hour simultaneity judgement tasks with feedback. This demonstrates that it is at least possible to reduce the size of a temporal profile of multisensory integration. This however does pose an interesting question, could we now use the ccPAS method to modulate the connection between two interconnected regions, modulating connectivity between them, resulting in more precise

multisensory integration? This could then potentially pave the way for ccPAS to be used in clinical settings, with it being used as a way of correcting multisensory deficits by improving the connectivity between two regions of the brain.

TMS in fact has been used in medical treatments before, most notably in neurological conditions such as depression (Avery et al., 2010; George et al., 2000; Horvath et al., 2010; Kolbinger et al., 1995; Lisanby et al., 2009). This method has been tested multiple times for its efficacy and its overall level of safety and has since been approved by the Food and Drug Administration in the United States for widespread use and treatment of this condition (Horvath et al., 2010). This method has also been used in the treatment of migraines (having achieved approval for use in the UK by the NHS) (Ahmed et al., 2015; Brüggenjürgen et al., 2016). Evidence also demonstrates that this method may also be beneficial for other neurological conditions such as aiding rehabilitation after head injuries (Paxman et al., 2018) and strokes (Naeser et al., 2005) and treating conditions such as Obsessive Compulsive Disorder (OCD) (Greenberg et al., 1997) and schizophrenia (Jin et al., 2005). However, evidence for this method being used for the latter two conditions is somewhat mixed (McIntosh et al., 2004; Sarkhel et al., 2010). As yet however, its usage in treating conditions beyond this is somewhat limited.

This allows for some scope in investigating TMS as a treatment to a variety of conditions. More specifically we believe that it would be interesting to investigate the potential clinical applications of the ccPAS method. As such this raise a series of potentially interesting questions; can future research demonstrate that the ccPAS method could be used to improve connectivity between interconnected regions of the brain? Could this result in a decrease in the size of the TWI? And could this method subsequently be used to correct

the size of the TWI in those individuals suffering with obesity (and of course other disorders linked to similar multisensory degradation)? And if so what would the effect of this be on the characteristics of the disorder itself?

Of course this direction is rather speculative, and many steps must be undertaken before these applications could even be investigated. Furthermore it is unknown at this stage whether any applications of this method would result in any major changes to individuals suffering with these conditions, beside simply affecting their ability to perceive this (and presumably other multisensory illusions). Of course we must also accept that we do not know the role multisensory degradation plays in these conditions (i.e. is it a cause or a symptom?) However, we could consider it a possibility that by using this method to enhance connectivity between regions, and potentially using this to fine-tune an individual's multisensory processing system we may be able to provide some reduction to some of the effects of multisensory degradation associated with these conditions without resorting to invasive surgery or debilitating medication.

6.6. Conclusion:

To conclude, in this study we set out to provide a complex investigation of the properties of both the auditory-induced and the tactile-induced Double Flash Illusions, mainly focusing on the latter of these two effects. The main aim here was predominantly to focus on providing specific details on the underlying mechanisms subtending the two illusory effects. This was with a view of informing our overall understanding as to the way in which multisensory information is processed in the brain.

We first wished to re-confirm previous findings that had suggested a tight functional relationship between occipital alpha frequencies and the temporal profile for the auditory-induced DFI (Cecere et al., 2015). In this instance, we were indeed able to replicate these previous findings, finding a significant correlation that was also shown to survive *Robust Skipped Correlations* (Pernet et al., 2013), we take this as evidence of the robustness of this effect.

We were also able to provide key details on the tactile-induced DFI, providing for the first time a measurement of its temporal profile (100 ms). We also provided evidence of a relationship between this TWI and the corresponding TWI of the auditory-induced effect. Incidentally these values were also found to not differ significantly from one another.

What we also found was evidence of visual *beta* frequencies playing a role in this tactile-visual processing, providing evidence of a tight relationship between peak beta frequency in the visual cortex and the TWI for this tactile-induced effect. This was found to be the case for when tactile stimuli were presented to both the left hand and to the right. *Robust Skipped Correlations* once again supported the robustness of these effects.

Instead of both illusory effects being determined by local visual processes we believe this may mean that there is a differential effect for both tasks. It could be that the functional connectivity between the two interconnected cortices set the fate of the illusory effects. We theorise that the processing speed of information subtending these connection could be set by the pre-synaptic region. Thus the time it takes for information from the auditory or somatosensory cortex to reverberate into the visual cortex could correspond to the time it takes for one cycle length in the wave band most associated with the pre-synaptic area. In

the case of the auditory-visual effect this would thus implicate alpha processes and beta processes would subsequently be implicated for the tactile-visual counterpart.

In Experiment Two we wished to stimulate the connection *between* the somatosensory cortex and the visual cortex to test for the specific hypothesis that the oscillatory frequency coding for the TWI is determined by the specific timing of network communication. In this research we were able to implement a modified version of a neuro-modulatory protocol known as ccPAS (originally introduced with the specific aim of modulating functional connectivity) in order to experimentally modify the connectivity between the target areas. This was done by specifically reducing the timing of communication between the two nodes of the target network which we thought was indexed by the speed of occipital beta frequencies. The manipulation of the ccPAS timing to reflect a slower pace of beta oscillations resulted in a corresponding reduction in beta speed, as measured at the visual cortex, which in turn was shown to subsequently correlate with an increase in the temporal size of the TWI for the tactile illusion. This once again provides evidence that it appears to be properties of the connection subtending the two interconnected regions that sets the fate of the illusory response, rather than local properties as was originally assumed.

Finally, in Experiment Three we also provided a control condition to this ccPAS protocol. In this case, instead of stimulating at a time slightly slower than normal processing speed (i.e. the cycle duration of one beta wave), we stimulated at a time directly corresponding to this value. As we were only stimulating at the normal processing speed of the network we theorised that we should expect no change in beta processing speed, nor should we expect a change in TWI size. The reasoning for including this condition was that

we wished to mimic the conditions of the previous stimulation, using a parameter that should result in no beta modulation. This was with a view of finding a differentiation of results and hence eliminating the possibility that previous findings only occurred as a result of a general slowing down of neuro-oscillatory processes associated with inserting noise into the system.

In this condition, in line with our expectations, no change in beta processing speed was found post-ccPAS. In addition, no change in the size of the TWI was found either. This suggests that the stimulation that we used in the previous investigation was strictly frequency specific and the changes that we observed we not simply due to a general slowing down of processing as a result of inserting noise into the system. This also provides further evidence of the role of functional connectivity in multisensory processing.

In this investigation we concluded that the specific mechanism subtending the specific parameters of the illusory effects may be comparable across sensory modalities but simultaneously they also reflect the peculiarity of each sensory modality that is being utilised, including temporal resolution. In other words, we theorise that auditory and tactile crossmodal induced visual illusions might have been caused by the specific oscillatory properties of each sensory signal's pairing. The different oscillatory processes linked to these effects could be explained as the specific computational speed needed by the cross-sensory network to efficiently integrate information, thus representing the optimal quantum for temporal binding between a given cross-sensory pair when impacting visual processing specifically.

In addition to providing information on these illusions and in turn general multisensory processing, we were also able to provide more understanding on the use of

the ccPAS method as a way of modulating long-range multisynaptic connections. Previous research has only demonstrated the effectiveness of the method in terms of shorter-range networks (Chiappini et al., 2018; Rizzo et al., 2011; Rizzo et al., 2009; Romei et al., 2016). Here however we have provided evidence to suggest that the method can also be used to stimulate at a longer-ranges between more remote, but still functionally interconnected areas of the brain (in this case, from the somatosensory cortex to the visual cortex). In providing this research we also demonstrate the specificity of the method. Finally we also provide evidence for the first time that this method can be used as a way of investigating certain properties of neuro-oscillatory processes.

8. Chapter Seven: References:

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