Neuronal Dynamics of Grapheme-Color Synesthesia

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Preface

This is an ad hoc Biology-Psychology thesis, and consequently the introduction incorporates concepts from both disciplines. It also provides a considerable amount of information on the phenomenon of synesthesia in general. For the reader who would like to focus specifically on the experimental section of this document, I include a "Background Summary" section that should allow anyone to understand the study without needing to read the full introduction. Rather, if you start at section 1.4, findings from previous studies and the overall aim of this research should be fairly straightforward.

I do not have synesthesia myself, but I have always been interested in it. Sensory systems are the only portals through which our conscious selves can gain information about the external world. But more and more, neuroscience research shows that our senses are unreliable narrators, merely secondary sources providing us with pre-processed results as opposed to completely raw data. This is a very good thing. It makes our sensory systems more efficient for survival- fast processing is what saves you from being run over or eaten every day. But the minor cost of this efficient processing is that we are doomed to a life of visual illusions and existential crises in which we wonder whether we're all in The Matrix, or everything is just a dream. Central to the neuroscience of consciousness is the question of color. Is color a feature of the external world, or is it a convenient illusion? Is the red that I see the same red that you see?

These endlessly interesting and needlessly irritating questions become even more complex when we examine them in the context of grapheme-color synesthesia. It is a case of sensory systems accidentally integrating in a way that creates a brand new phenomenological experience that we non-synesthetes can imagine, but may never truly know. This thesis is an attempt to deconstruct the neural mechanisms underlying synesthetic color perception, so while we may not know exactly what we're missing, we may begin to understand why we're missing it.

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Abstract

Grapheme-color synesthesia is a neurological phenomenon that causes individuals to perceive color when looking at achromatic letters or numbers. In the field of cognitive neuroscience, there is much interest in understanding the neural mechanisms underlying this phenomenon, as it has been associated with both cognitive benefits and brain disorders. This research has led to two primary questions: (1) What is the time-course of neuronal events related to synesthetic color perception? (2) Is attention necessary for synesthetic color perception to occur? To investigate these questions, the present study recorded the brain activity of ten grapheme-color synesthetes (and ten matched-controls) while they were presented with visual stimuli inducing synesthetic color perception. By comparing the event-related potentials (ERPs) elicited by these stimuli, we were able to isolate a neural correlate of synesthetic color perception in early visual processing. On some trials, these stimuli were rendered invisible using the attentional blink paradigm. By comparing the ERPs elicited by seen and unseen inducers, we also demonstrate that attention is necessary for the production of neuronal events related to synesthetic color.

Chapter 1: Introduction

1.1 The Phenomenon of Synesthesia

To John, the number 5 looks red. It is a red number. When he sees it on a piece of paper, when he hears the word "five" out loud, even when he pictures it in his head, he perceives the color red. And it's not just the number 5. Almost all numbers and letters elicit colors for John, such that reading a paragraph can be like an endless display of fireworks in his mind's eye. You might say that John sounds a little crazy- but you'd be wrong. He's not crazy, he's just synesthetic.

Synesthesia[1] is a rare perceptual phenomenon in which a particular stimulus consistently elicits a seemingly unrelated sensation or experience in addition to the expected one. That is, the triggering sensation/experience ("inducer") evokes an unrelated sensation or experience ("concurrent") with no conscious decision or attempt to recall it from memory (Johnson et al. 2013). The concurrent seems to 'hitchhike' on the inducer in a fast and automatic way. Synesthesia is typically developmental in nature, meaning synesthetes (individuals with synesthesia) report having these experiences from birth and have difficulty providing an explanation for them (Baron-Cohen et al. 2007). There have also been a number of cases of acquired synesthesia caused by hallucinogenic drugs (Simpson & McKellar 1955; Duffy 2001; Harrison & Baron-Cohen 1997) and neurological pathologies (Duffy 2001; Podoll & Robinson 2002), but these special cases of synesthesia will not be discussed here. For our purposes, the term "synesthesia" is meant to refer to the developmental form.

There are several different types of synesthesia that have been reported. Some of these include grapheme-color synesthesia (different letters/number/words elicit the perception of different colors), auditory-tactile synesthesia (different sounds elicit sensations on different parts of the body), and number-space synesthesia (numbers have specific locations in space, like a number line).

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[1]From the Ancient Greek *syn*- "together", and *aisthēsis*- "sensation"

1.1.1 Perceptual Reality

Synesthesia research began in 1812 with the first known description by Georg Sachs, given as a self-description in his medical dissertation (Sachs 1812). This led to a series of case studies (Figure 1.1) followed by many large-scale experiments to determine why synesthetes experience what they do. Despite its popularity in the late nineteenth century, there was a considerable reduction in the synesthesia literature beginning in the 1930s. Many believe this was related to the subjective nature of the phenomenon, given the emergence of behaviorism in the 1920s (Johnson et al. 2013). With no objective tests to validate the self-reports, it was impossible to distinguish synesthetes from people with vivid imaginations or people who were skilled at generating pseudo-synesthetic metaphors. However, synesthesia underwent a renaissance in the twentieth century, and since then several techniques have been developed that can distinguish genuine developmental synesthetes from non-synesthetes (Jewanski 2013).

The most reliable and commonly used behavioral paradigm to confirm the presence of synesthesia is known as the test of genuineness (TOG). Simply put, this paradigm involves asking synesthetes to report their associations for a large number of stimuli (the colors elicited by hundreds of letters/numbers/words, the tactile sensations elicited by hundreds of different sounds, etc.) and then retest them months or years later. The consistency of these tests tends to be very robust (see Figure 1.2 for an example), which is to say that scores for synesthetes almost never overlap the scores obtained by non-synesthetes in similar tests (Asher et al. 2006; Baron-Cohen et al. 1993, 1996; Ward et al. 2005). However, one drawback of this technique is that it works on the assumption that synesthetic associations are *generally* consistent, which is often (but not always) the case (Cytowic 2002; Eagleman et al. 2007).

Although the TOG is very useful, there are other methods that have been developed specifically for demonstrating the presence of grapheme-color synesthesia. One of these is the modified stroop task[2]. In this task, synesthetes are presented with

[2] In the standard stroop task, color words such as “red” and “blue” are presented to the participants, but they are sometimes printed in a color incongruent with the word (e.g. “red” printed in blue ink). Response times to name the color of the ink are severely decreased when the ink color is incongruent with the printed color name.

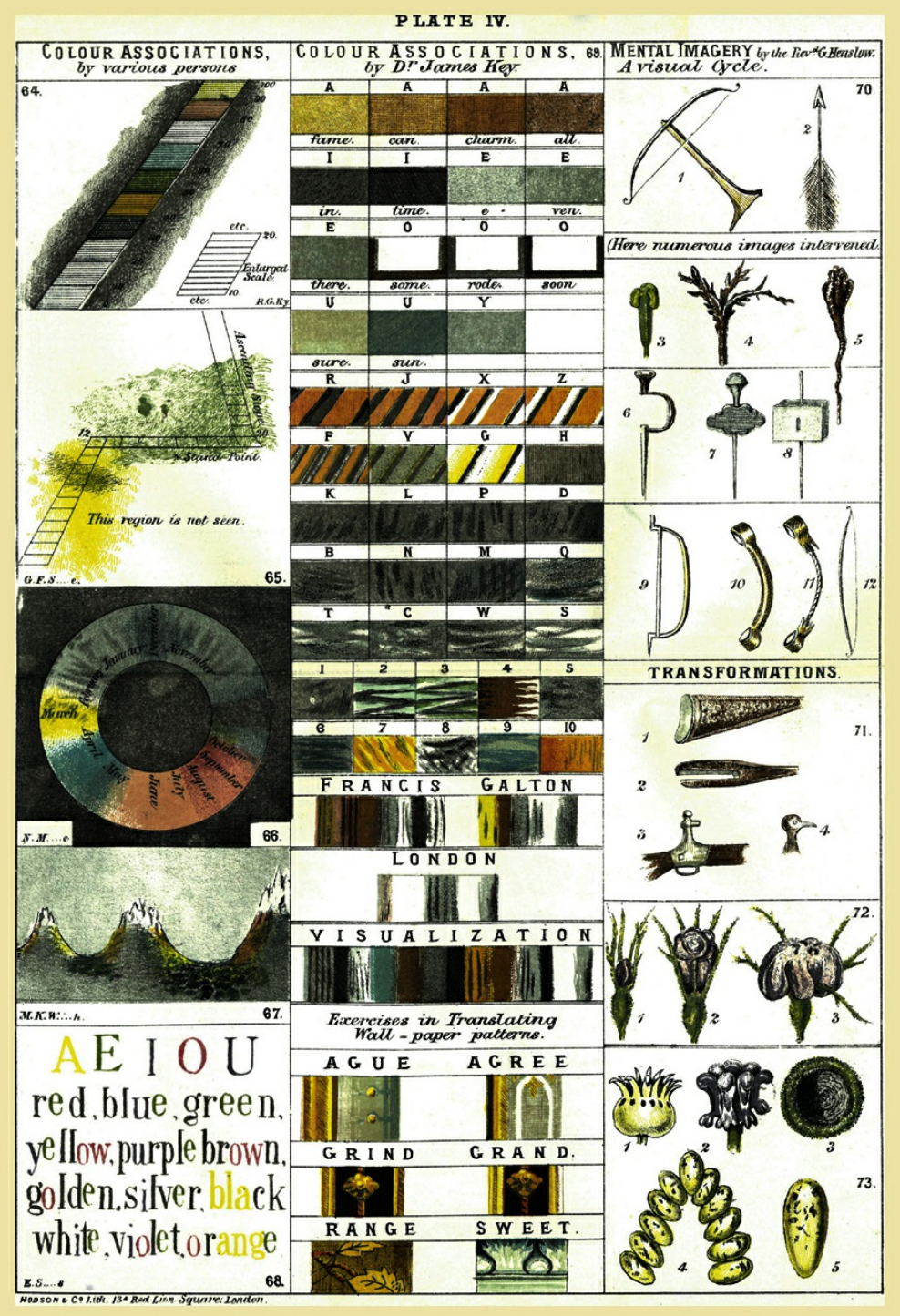

Figure 1.1 First Colored Print of Synesthesia (1883)

The first print of a synesthete's color associations and mental imagery as recorded by Sir Francis Galton in 1883. Reproduced from F. Galton (1883) Inquiries into human faculty and its development, plate IV.

letters that are printed in colors that are congruent (i.e. the same as their color association for that letter), incongruent (i.e. a different color from their color association) or neutral (black) and asked to name the printed color. When a grapheme is printed in an incongruent color, synesthetes take longer to name the color as compared to congruent or neutral stimuli (Blake et al. 2005; Mills et al. 1999). This difference in response times as a result of interference from synesthetic perception is commonly referred to as the synesthetic congruency effect. This effect has since been generalized to other types of synesthesia, including sound-taste synesthetes (Beli et al. 2005) and sound-color synesthetes (Ward et al. 2006).

Beyond the TOG and the synesthetic congruency effect, there are numbers of neuroimaging studies that have confirmed the authenticity of synesthesia (section 1.2). Overall, synesthesia is now accepted as a very real phenomenon, and research has since moved on to understanding how it occurs.

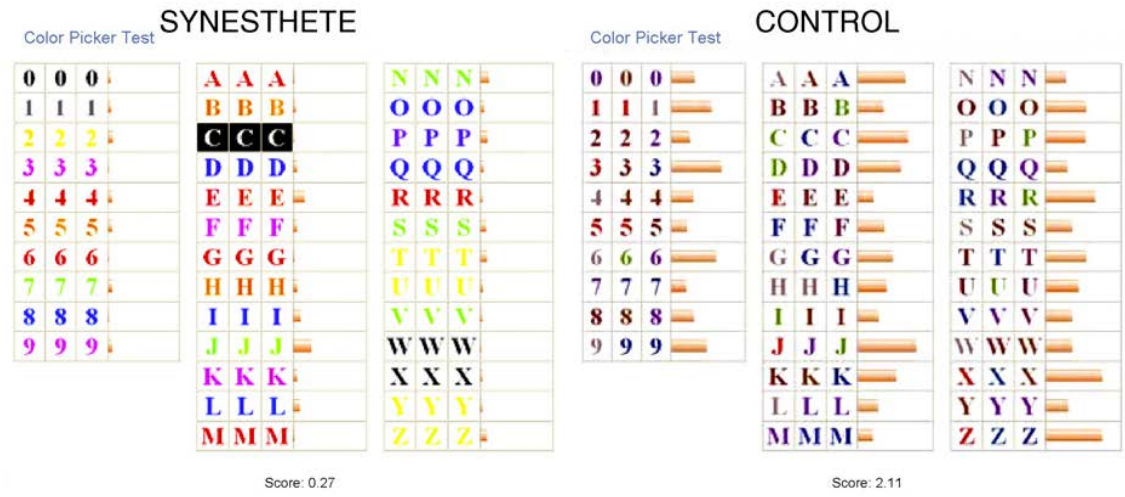

Figure 1.2 Example Results from Test of Genuineness

Test-retest reliability of a grapheme-color synesthete (left) and a trained control (right). The horizontal bars represent the amount of variance within the three different times they were asked to report color associations. Figure adapted from Eagleman et al (2006).

1.1.2 The Prevalence of Synesthesia

The question of what percent of the general population has any form of synesthesia has been largely debated in the literature, ranging from 0.24% (Ward et al. 2005) to 15% (Ginsberg 1923). However, many studies are subject to self-referral bias, meaning they rely on synesthetes making an effort to participate in the study, or depend on self-report. Simner et al. (2006) is often cited as the most accurate estimate in current literature as it avoids these confounds. They performed a large survey of university students and museum-goers, and then performed a series of TOGs on all potential synesthetes. They found 22 synesthetes with nine distinct forms of synesthesia, corresponding to a 4.4% population prevalence. They also found that grapheme-color synesthesia was the most common (1.4%) and have since replicated this finding (Simner et al. 2009: 1.3%).

Synesthesia has been widely believed to be a predominantly female condition, with female to male ratios ranging from 2:1 (Ward et al. 2005) to 6:1 (Rich et al. 2005). Again, there are concerns that these findings are the result of self-referral bias, as it has been shown that women are more likely to come forward to report atypical behavior (Johnson 2013). Simner et al (2006) found no female bias, which supports this hypothesis. Furthermore, this notion of a predominant female condition remains unsupported by studies of genetics and inheritance (see section 1.2.5).

1.1.3 Cognitive Benefits

Many researchers are interested in understanding synesthesia because of the cognitive benefits often associated with it. One of the commonly discussed benefits is enhanced creativity, with studies showing that synesthetes of any form are more likely to be involved in creative pursuits[3] (Rich et al. 2005; Rothen & Meier 2010a) and scoring significantly higher on quantitative tests of creativity (Mulvenna 2007; Ward et al. 2008). Another benefit commonly observed is an enhanced memory, with researchers finding that grapheme-color synesthetes have superior accuracy in word recall (Mills et al. 2006;

[3] See Appendix A for a list of famous musicians, writers, and artists that have reported having synesthetic experiences.

Yaro & Ward 2007; Simner et al. 2009; Brang et al. 2011; Gross et al. 2011). Beyond memory and creativity, it has also been demonstrated that synesthesia may lead to improvements in mental imagery (Barnett & Newell 2008; Brang & Ramachandran 2010), visuospatial skills (Simner et al. 2009) and mathematical skills (Ward et al. 2009) for specific synesthetic forms. That said, it should be noted that all of these studies are correlational in nature, and therefore one cannot conclude that synesthesia is the cause of these benefits. It could easily be the case that whatever factors are causing synesthesia could be causing these benefits as well.

1.1.4 Neuropsychology as a Tool

We have learned much in psychology and cognitive neuroscience by studying neurological patients with selective neural deficits to better understand intact brain function. This approach, known broadly as the field of clinical neuropsychology, has been extremely useful in the study of memory, attention, language, consciousness, and thought. However, phenomena that reflect a gain of function (rather than a loss) like synesthesia or savant syndrome are also excellent opportunities for understanding the intact brain, as theories of cognitive psychology and neural mechanisms should be able to predict both positive and negative deviations from normal function. Additionally, synesthetes are ideal subjects because they are not clinical cases- that is, they typically have no negative symptoms- unlike savants who are typically impaired socially (Johnson 2013).

1.1.5 Individual Differences: Projectors vs Associators

All synesthetes report that the inducer elicits the concurrent automatically (Beeli, Esslen, and Jäncke 2005; Dixon, Smilek, & Merikle 2004; Dixon et al. 2000; Mattingley et al. 2001; Odgaard, Flowers, & Bradman 1999) and consistently (Baron-Cohen, Wyke, & Binnie 1987; Simner & Logie 2007). However, recent studies have shown that synesthetes report differences in how they experience the concurrent. For example, some grapheme-color synesthetes report that when they see achromatic letters or numbers, they see the associated color as if it physically existed in their visual field. These synesthetes,

who see synesthetic colors externally, have been termed “projectors.” Other grapheme-color synesthetes report that their color perception occurs “in the mind’s eye”, in mental imagery rather than physically on the page or screen. These synesthetes, who experience their color associations internally, have been termed “associators”. Generally speaking, it seems that associator-type grapheme-color synesthesia is much more common than projector-type (Simner et al. 2009).

Behavioral studies of grapheme-color synesthesia have begun to account for this distinction, finding that different measures of synesthetic perception are more or less effective in distinguishing between associators and projectors (see van Leeuwen 2014 for a full discussion of this). However, studies investigating the neural basis of synesthesia have been lacking in this regard, which is unfortunate given that this distinction suggests a difference in the underlying neural mechanisms.

1.2 The Neural Basis of Synesthesia

1.2.1 Grapheme-Color Synesthesia as a Model

There are a number of reasons why most neuroimaging studies of synesthesia focus on those with the grapheme-color form. First, the neural mechanisms underlying the mechanisms of reading and color perception have already been investigated in depth using a wide range of methods. Second, as previously noted, grapheme-color synesthesia is the most common form (Simner et al. 2006) and therefore it is the most practical in terms of recruitment. Last, it is particularly convenient for studies using magnetic resonance imaging (MRI), a non-invasive imaging method that uses an oscillating magnetic field to temporarily excite hydrogen atoms so that their location can be identified, allowing information about the brain’s structure to be recorded (see Ashburner & Friston (2000) for full review of the technique). Because the oscillating magnet is very loud, visual stimuli like graphemes are ideal for these experiments as opposed to auditory stimuli that would be required to test chromesthesia (sound-to-color synesthesia).

1.2.2 Color Area V4

In 1973, the neurobiologist Samir Zeki discovered a region of neurons in the extrastriate cortex of non-human primates that selectively fired for particular colors. He called this area "V4" (Zeki, 1973). Following this discovery, J. C. Meadows reviewed all of the published evidence of acquired achromatopsia[4] in humans and found a correlation between the syndrome and a homologous region in the ventral occipital lobe (Meadows 1974). Since then, a number of neuroimaging studies have confirmed that V4 in humans is a region devoted to color processing. It should be noted that a minority of neurons in visual areas preceding V4 (V1 and V2) are also color selective, but as achromatopsia shows, intact V4 neurons are specifically necessary for conscious perception of color. Additionally, V4 is the first region along the visual pathway with neurons that are not selective for color in a retinotopic[5] manner (Zeki & Bartels, 2000). This makes V4 a likely candidate for being involved in synesthetic color perception since it does not involve any color processed at the level of the retina. Thus neuroimaging research into grapheme-color synesthesia began with the hypothesis that synesthetes may have abnormally increased activation in V4.

While many studies using functional magnetic resonance imaging (fMRI)[6] with a variety of paradigms and stimuli have found increased blood oxygen level dependent (BOLD) activity in V4 of synesthetes (Nunn 2002; Hubbard 2005; Steven 2006; van Leeuwen 2010), this finding is surprisingly inconsistent (see Aleman 2001, Weiss 2001 & 2005, Gray 2006, Rich 2006, and Rouw 2007 for failures to replicate). Several other brain areas have shown differential activity for synesthetes, but these results are also inconsistent between studies (see sections 1.2.7 and 1.3.3 for some discussion on why this might be the case). Two of the more replicable areas showing increased activity in

[4] Acquired (or cerebral) acrhomotopsia is a specific form of color blindness that is the consequence of cortical damage- typically as a result of illness or injury.
[5] When visual inputs are said to be "retinotopically mapped" in a particular brain area, this means that the neurons are organized in a way that mimics the organization of the visual field- such that damage to particular neurons would correspond to the loss of a particular part of the visual field.
[6] This technique measures levels of oxygenated and deoxygenated blood to assess activity of brain regions over time (one scan measures BOLD level over the course of one second).

synesthetes are the superior and inferior parietal lobules, which play a role in attention-based visual feature binding (Donner et al. 2002; Shafritz et al. 2002).

1.2.3 Connectivity Between Brain Regions

Area V4 not only receives inputs from V1/V2, it also has structural connections to a region known as the visual word form area (VWFA). This area is located in the fusiform gyrus anterior-lateral to V4 (Figure 1.3). A number of neuroimaging and brain recording studies have been performed using words and orthographically similar non-words to demonstrate that the VWFA is highly selective for visually presented words and letters[7] (McCandliss et al. 2003).

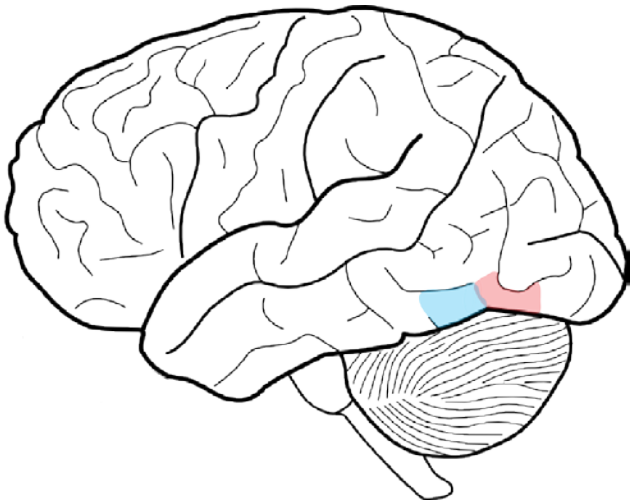

Figure 1.3 Diagram of V4 and the VWFA
Anatomical locations of the visual word form area (blue) and color area V4 (red). Note that these regions are actually located more ventrally than depicted in this diagram, with V4 more medial and the VWFA more lateral.

Because of the inconsistencies in synesthesia studies searching for differences *within* brain regions like V4, current theories of the neural mechanisms underlying synesthesia focus on differences *between* brain regions. These theories argue that synesthesia is the result of differences in cortical connectivity. Adjacent/nearby brain

[7] It should be noted that the identification of the VWFA has been more controversial than that of V4, partially due to the fact that single-cell and local field potential recordings in animal models to study V4, whereas the VWFA has only been examined using more macroscopic means.

regions tend to have more dense connectivity (with sparser long-distance connectivity) so as to optimize information transfer and wiring (Sporns et al. 2004). Thus, one could see how the idea of increased cortical connectivity causing synesthesia could be appealing, given that for the most common form of synesthesia, the brain areas related to the inducer and concurrent are directly adjacent (the VWFA and the V4 color area).

Differences in cortical connectivity are typically defined at the levels of structure and function. An example of a structural difference would be an increased number of physical connections between two brain regions, whereas an example of a functional difference would be a difference in the nature of the activity (more or less correlation in activation/inhibition) between the two regions.

Studies using diffusion tensor imaging (DTI), an MRI method that allows for the assessment of anatomical connections (see LeBihan et al. 2001 for full review of the technique), have found differences in structural connectivity in the brains of synesthetes relative to controls, both in overall white matter organization (Rouw & Scholte 2007) and gray matter density (Banissy et al. 2012; Weiss & Fink 2009). In particular, Rouw & Scholte looked at grapheme-color synesthetes and found increased structural connectivity between the letter-shape regions of the fusiform gyrus and color area V4.

However, differences between synesthetes and controls were also found in several other areas, so it is difficult to explain how one structural difference could be causing synesthesia when similar structural differences cause no visible phenotype. It is likely, then, that structural differences between other higher-order areas (in the frontal and parietal lobes) are also responsible for synesthetic perception. Researchers take the fact that certain trends in associations observed in synesthetes are similar to cross-modal associations also observed in non-synesthetes (i.e. higher pitch with brighter colors, or the color red with the letter R) as evidence that structural connectivity is one of the factors driving synesthesia. These observations suggest that synesthetes may simply express more of these normal cross-modal connections (Bargary & Mitchell 2008).

The evidence for functional connectivity differences between the brains of grapheme-color synesthetes and non-synesthetes comes from studies using fMRI. These studies assess functional connectivity between brain regions by looking at the correlation of BOLD activity between two regions at different times to see how well activity in one

region predicts activity in another region later in time (see Fox & Raichle 2007; Gusnard & Raichle 2001 for full review of the technique). The stronger the correlation, the more strongly the activity in one brain area depends on the activity of the other, and thus the more functionally connected those two regions are. As expected, Van Leeuwen et al. (2011) found increased functional connectivity between the regions of the visual word form area (VWFA) responsible for grapheme processing and color area V4.

A number of studies carried out since, have replicated this finding and in addition found increased functional connectivity between these visual regions and parietal areas (Sinke et al. 2012; Specht & Laeng 2011; Dovern et al. 2012). Researchers claiming that differences in functional connectivity also contribute to synesthesia, note that certain hallucinogens or psychedelic drugs (such as lysergic acid diethylamide- LSD) can induce a state of synesthesia where stimuli in one sensory modality cross-stimulate another (Nichols, 2004; Brang et al. 2008), suggesting that the same cross-modal connections may exist in all individuals but they are simply disinhibited in synesthetes.

Overall, it appears likely that, rather than differences within a single brain area, structural and functional connectivity differences are responsible for grapheme-color synesthesia. There are two important things to note from these studies. The first is that the evidence from fMRI supports the existence of both types of connectivity, and that these types are not mutually exclusive. A number of researchers have claimed that one or the other type is driving synesthesia but, given that functional connectivity is simply a correlation between activity in different regions, structural connectivity differences could be (and likely are) causally related to the differences in functional connectivity. Second, note that the studies of cortical connectivity show the potential for involvement of direct connections (between inducer/concurrent brain areas) and broader indirect connections (via higher order temporal or parietal regions). These factors (structural/functional and direct/indirect) are nicely summarized in figure 1.4.

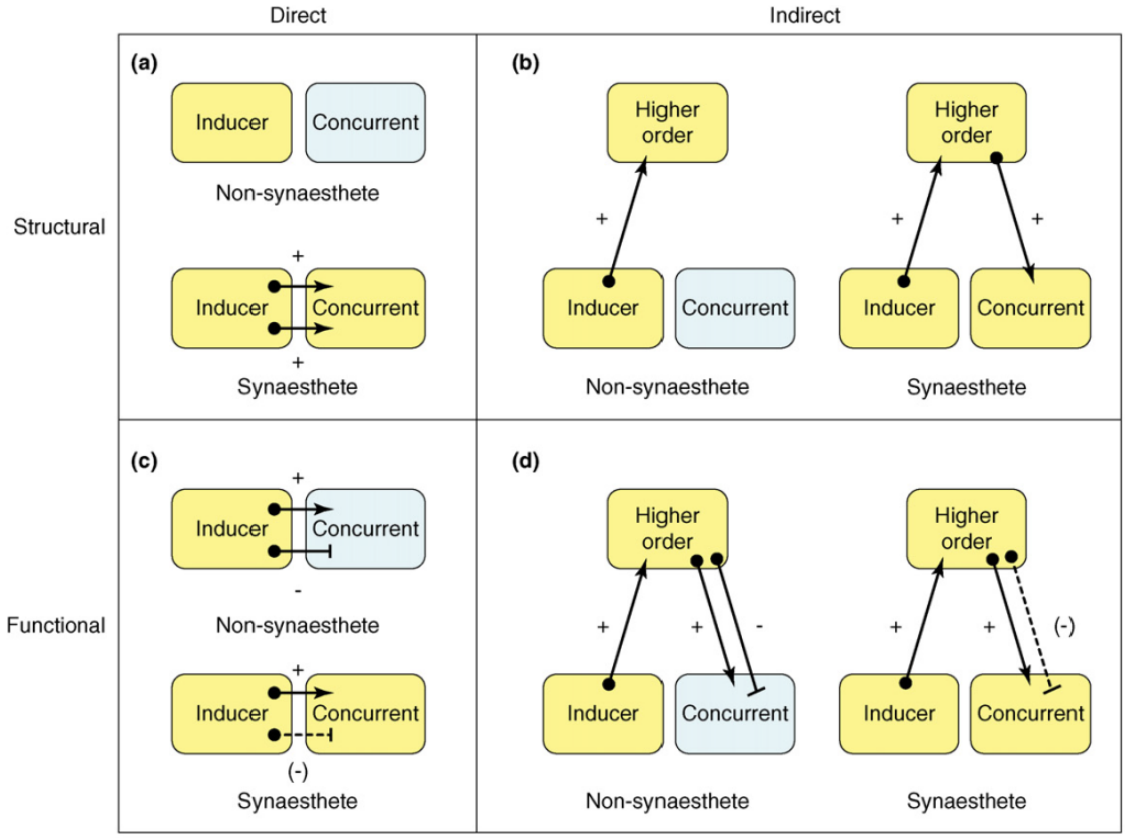

Figure 1.4 Models of Connectivity in Synesthesia

Diagram showing how the route of cross-activation resulting in synesthesia could be direct or indirect (columns) and how the underlying connectivity differences appear to be both structural and functional (rows). Yellow areas are active (starting in the inducer area) and blue areas are inactive. Excitatory connections are shown as arrows whereas inhibitory connections are blunt ended. Dashed lines represent structurally present but functionally ineffective connections. Adapted from Bargary & Mitchell (2008).

1.2.4 Genetic and Molecular Mechanisms

Developmental synesthesia appears to run in families (Jewanski et al. 2011). However, the particular grapheme-color associations do not, which is to say that family members don't necessarily agree on the colors of specific graphemes any more than unrelated synesthetes do (Barnett et al. 2008a). Furthermore, synesthesia type does not appear to be strongly familial. Genetic differences seem to relate to a susceptibility to synesthesia but don't specify the presence/absence of synesthesia in a deterministic way.

As previously mentioned, many studies have suggested that synesthesia has a female bias. Consequently, early studies proposed that the relevant genetic factors were X-linked dominant inheritance (Baron-Cohen et al. 1996). However, this has not been supported by any research on inheritance patterns and genetic linkage studies (Asher et al. 2009, Tomson et al. 2011), which find more than one example of male-to-male transmission of synesthesia. These studies did confirm genetic differences between affected and unaffected members of the same families, and genome-wide association data point to the involvement of multiple candidate genes[8], but none were located on the X chromosome.

In what ways could mutations in these candidate genes be influencing patterns of connectivity? There are three different developmental molecular mechanisms that mediate between genetics and cortical connectivity: Axon guidance, border formation, and pruning (Figure 1.5; see Bargary & Mitchell 2008 for full review).

When an axon grows, it extends and retracts filopodia that allow it to interact with external cues that guide its growth. One way that the direction of axon migration can be influenced is by extracellular signaling molecules that act as chemo-attractants and chemo-repellants by binding to receptors on the tip of the axon to promote extension or collapse. Mutations in genes coding for such signaling molecules (netrins, slit proteins, semaphorins) could be resulting in deviations in axon targeting (Wolpert 2012). Another way that the direction of axon migration can be influenced is by interactions with other cells. Thus mutations in transmembrane proteins like ephrins and cadherins (which mediate repulsive and attractive cell-cell interactions) could similarly be causing abnormal targeting (Figure 1.5- Middle). Lastly, connectivity could be influenced at the level of synaptic pruning. The development of the nervous system is not only on synapse formation, but also on the regulated disassembly of synapses. The mapping of connections early in development is rough, and genes coding for molecules like semaphorins and plexins are responsible for the fine tuning of these connections. Therefore, mutations in these genes could be causing less stereotypic pruning, leading to increased connectivity (Figure 1.5- Right).

[8] These genes were identified using genome wide association. These candidate genes are located at the following chromosomal regions: 2q24 (TBR1, SCN1A, SCN2A), 5q33 (DPYSL3), 6p12 (KIAA0319, DCDC2, EFHC1), and 12p12 (GRIN2B).

Further research in this line of questioning likely will depend on isolating candidate genes in synesthetes and then exploring the normal role of these genes in animal models of brain development.

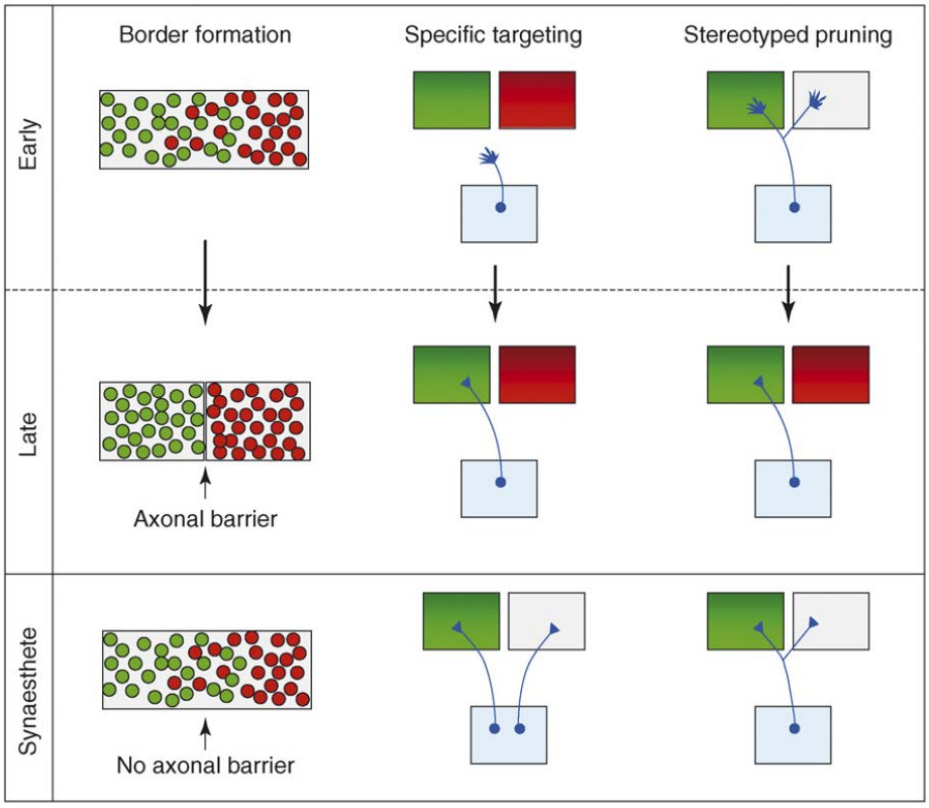

Figure 1.5 Cellular Mechanisms of Connectivity

Three example mechanisms that could underlie synesthesia. 'Early' and 'Late' refer to the stages of each process. **Left:** Formation of borders relies on differential expression of signaling proteins (red/green). **Middle:** Specific targeting of axons (middle) is mediated by chemo-attractive (green) and chemo-repulsive (red) molecules. **Right:** Many connections are pruned in a stereotyped manner dependent on the up-regulation of specific repulsive molecules (red). Adapted from Bargary & Mitchell (2008).

1.2.5 Models of Cortical Connectivity: Direct vs Indirect

Evidence from MRI/fMRI suggests that differences in connectivity drive grapheme-color synesthesia, and that both structural and functional connectivity differences between synesthetes and non-synesthetes exist between V4 and the VWFA But it has yet to be determined which type of connection (direct or indirect) between these two regions is responsible for synesthetic color perception. Three different models have been developed around this question:

The Cross-Activation Model

According to this model (Hubbard, 2007), excess direct connectivity between the regions of the visual word form area (VWFA) responsible for grapheme processing and V4 results in these two areas being co-activated in early grapheme processing. Consequently, by the time both perceptions (letter and color) reach higher level brain regions, they have already been bound together, such that the achromatic letter is perceived as colored.

The Disinhibited Feedback Model

This model (Grossenbacher & Lovelace, 2001) posits that connectivity differences in synesthetes cause disinhibited feedback from higher level areas in later stages of grapheme processing. In non synesthetes, these higher areas use top-down feedback to inhibit lower areas that are irrelevant to what is being perceived (i.e. inhibition of V4 when looking at an achromatic letter). In synesthetes, this inhibition of V4 may be lacking, such that after higher level brain regions receive input from the VWFA, V4 is also activated indirectly.

The Re-entrant Processing Model

A view that reconciles the previous two (Smilek et al., 2001), suggests that early cross talk between the VWFA and V4 and disinhibited feedback from higher-level areas are responsible for synesthetic perception.

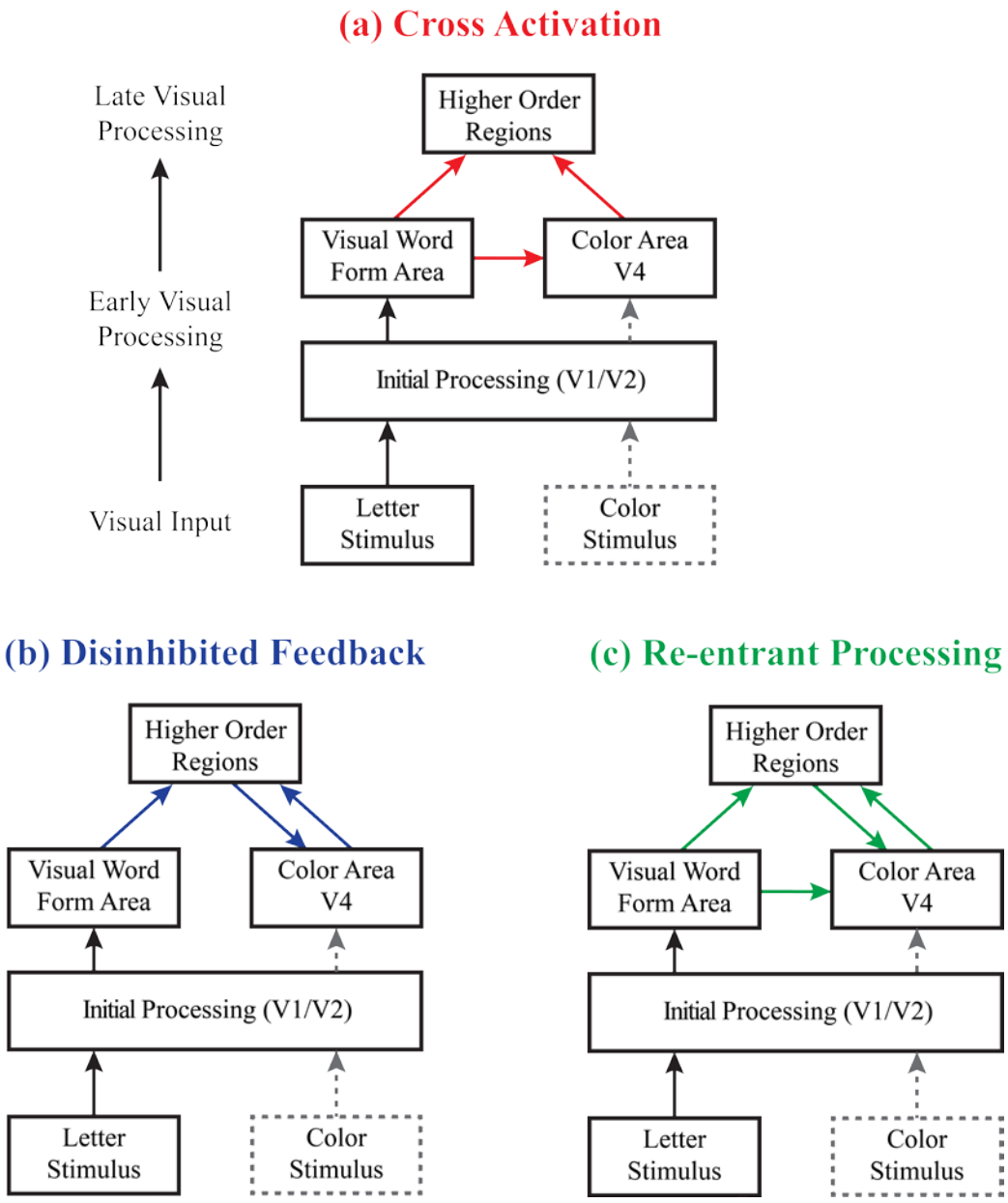

Figure 1.6 Models of Connectivity in Synesthesia

Three models of the connectivity differences resulting in grapheme color synesthesia. **(a)** The Cross-Activation Model: Activation of the VWFA causes direct stimulation of V4 during early visual processing. **(b)** The Disinhibited Feedback Model: Activation of the VWFA causes indirect stimulation of V4 during later visual processing. **(c)** The Re-entrant Processing Model: Activation of the VWFA causes stimulation of V4 via direct and indirect pathways.

1.2.6 Event-Related Potentials

Synesthesia researchers have sought to address the question of what connections (direct or indirect) are driving grapheme-color synesthesia by utilizing a brain recording method with high temporal resolution to determine *when* in stimulus processing synesthetic perception is occurring in the brain. Because the three proposed models have distinct predictions for the timing of neurological events related to synesthesia (early for cross-activation, late for disinhibited feedback, and both for re-entrant processing) the millisecond level analysis of event-related potentials (ERPs) can be very informative for this question. Here, I provide a brief introduction to this technique, and then I discuss ERP studies of grapheme-color synesthesia in the next section.

Event-related potentials (ERPs) are a measure of electrochemical brain activity recorded from electrodes placed on the scalp. They are derived by cutting out segments of electroencephalogram (EEG) activity at a specific event in time (i.e. when a stimulus was presented). By averaging together several segments “time-locked” to the onset of a specific stimulus, we can average out any electrical noise or activity representing neuronal events unrelated to that event (Figure 1.7). We can then compare the average of hundreds of ERPs elicited by one type of stimulus and compare it with the average of hundreds of ERPs elicited by another type of stimulus, allowing us to determine when brain activity differed between these stimuli at a millisecond by millisecond level of analysis (Luck 2014).

There are two main types of electrical activity produced by neurons: action potentials and postsynaptic potentials. Action potentials are spikes in voltage that travel down the length of the axon (lasting about one millisecond), whereas postsynaptic potentials are voltage changes caused by neurotransmitters binding to receptors on the membrane of the postsynaptic cell (and can last tens to hundreds of milliseconds).

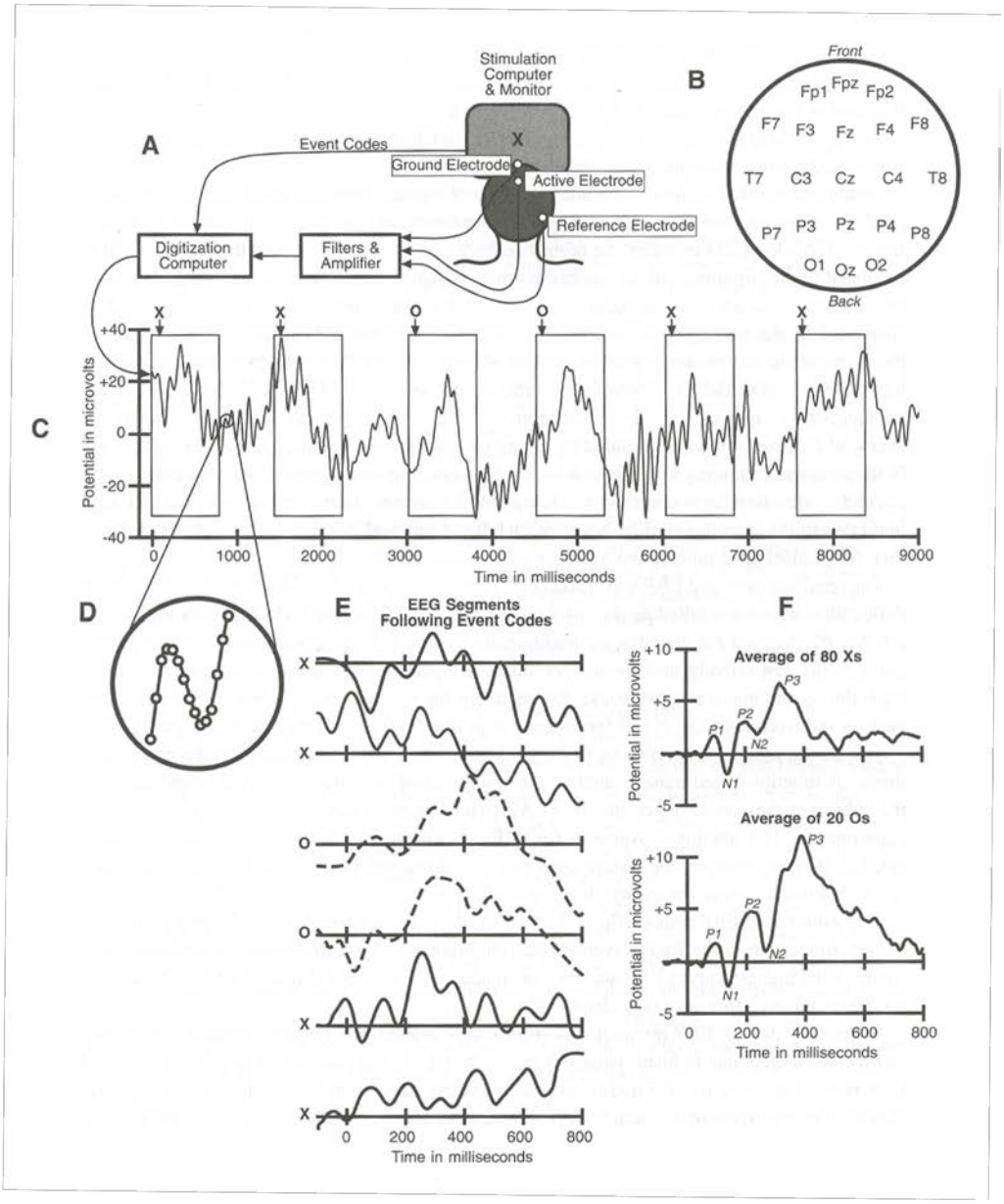

Figure 1.7 Diagram of ERP Recording

An example of an ERP experiment using the oddball paradigm. (a) The subject viewed frequent Xs and infrequent Os presented on a computer monitor while the EEG was recorded from several active electrodes (b) and reference/ground electrodes. The EEG output was filtered, amplified, and digitized to form a discrete set of digital samples (d). Event codes were also sent from the stimulus computer each time a stimulus was presented to mark its identity and timing in the continuous EEG (c). Each 900ms epoch following a stimulus presentation was extracted and lined up with respect to stimulus onset (e). Separate grand averages were then computed for the X epochs and the O epochs. Reproduced from Luck (2014).

In most cases, action potentials do not sufficiently summate to reach a level that is detectable by electrodes at the scalp[9]. Postsynaptic potentials, however, can last tens to hundreds of milliseconds, are largely confined to the dendrites and cell body, and occur almost instantaneously rather than travelling down the axon. Consequently, these potentials summate rather than cancel, making it possible to record them all the way at the scalp.

It is important to note that fMRI gives us the average activity of an indirect measure (hemodynamic response, as opposed to electrochemical activity) over the course of a few seconds, which is a relatively long period of time considering that neurons fire over the course of one millisecond. Therefore, ERPs have a significant temporal advantage. However, they also have a very significant spatial disadvantage. By placing several electrodes around the scalp, you can use mathematical tools to estimate the source of a particular ERP effect, but this estimation is very rough (cm^3 as opposed to mm^3 in MRI/fMRI). Consequently, both techniques should be used to investigate neurological phenomena in humans whenever possible.

1.2.7 Isolating a Neural Correlate of Synesthetic Perception

There are very few studies that have assessed brain activity in grapheme-color synesthetes using ERPs, and unfortunately their findings make it difficult to determine which model best fits the patterns of synesthetic brain activity. Some of these studies report only observing later ERP components (starting 250-300ms after stimulus onset) being affected as a result of synesthetic perception (Schiltz et al. 1992; Gebuis et al. 2009), such as the P300, and N400- supporting the disinhibited feedback model. However, others observe only early components being affected (starting before 200ms after stimulus onset), such as the N1 and N170 (Sagiv et al. 2003; Kadosh et al. 2007; Barnett et al. 2008; Niccolai et al. 2012), which would point towards the cross-activation model. So it appears that different studies are finding contradictory results. Other studies

[9] If two neurons have axons that run parallel to each other, and an action potential occurs at exactly the same time, the activity from these two neurons would summate. However, neurons do not often fire at precisely the same time, and consequently the current at a specific location on the axon flows out at the same time as the current is flowing in at that location on another axon- resulting in signal cancellation rather than summation.

(Brang et al. 2008, 2010, 2011; Goller et al. 2009) observe differences in both early and late components, supporting the re-entrant processing model.

There are at least three reasons why the results and interpretations of these studies are inconsistent. Firstly, some studies are single-subject case studies (Kadosh et al. 2007; Sagiv et al. 2003). While case studies are useful in informing us about what is possible in the brain, single subject ERP results are not very generalizable, especially given the individual variability that appears to exist in the phenomenon of synesthesia.

Second, most of these studies fail to measure or report whether their subjects are projectors or associators (1.1.5). This distinction is very significant given that their different phenotypes (seeing colors internally vs externally) are surely the result of different underlying neural mechanisms. Controlling for individual differences can obviously be very difficult when trying to have a large enough sample, given that synesthesia is a rare condition. However, there are now standardized questionnaires that have been developed (i.e. Eagleman et al. 2006) to quantify where a particular synesthete lies on the associator-projector spectrum. Ideally these metrics would be reported and used to split participants into different groups for analysis.

Most importantly, the inconsistency between ERP studies seems to stem from differences in the types of stimuli that are being used, and what comparisons are being made[10]. Only three of these studies actually measured ERPs time-locked to the actual graphemes that induce the perception of color (Brang et al. 2008, 2011; Nicolai et al. 2012), and those that did compared ERPs to these graphemes when they were congruent or incongruent with the semantic context (i.e. they visually presented sentences like "Yesterday the sky was a beautiful shade of 5", where 5 would be associated with the color congruent [blue] or incongruent [red] with the context). When comparing ERPs to grapheme inducers in congruent or incongruent contexts, these studies are not necessarily isolating the neuronal events generating synesthetic perception. In fact, because synesthetic color perception should be elicited by the inducer in both the congruent and

[10] Remember, an ERP is a stereotyped response to a particular stimulus. Let's say I wanted to see when normal color processing was occurring in the brain. It wouldn't be enough to record ERPs to a bunch of different colored stimuli, because these ERPs would reflect the brain's response to all of the features of those stimuli (color, shape, size, etc.). I would also need to record ERPs to achromatic stimuli of the same shape, size, etc. and compare the two different ERPs (color and no color) in order to isolate the timing of events *specifically* related to color perception.

incongruent contexts, the difference between them may actually be removing genuine effects of synesthetic color perception leaving only the brain's response to congruence/incongruence.

The other ERP studies of grapheme-color synesthesia measured activity time-locked to color patch stimuli in priming paradigms (Goller et al. 2009, Kadosh et al. 2007, Sagiv et al. 2003, Schiltz et al. 1992, Gebuis et al. 2009). For example, Nicolai et al. (2012) presented achromatic letters that were followed by color patches that were either congruent or incongruent with the synesthetic color elicited by the letter prime. They compared ERPs time-locked to incongruent color patches to those time-locked to congruent color patches to assess when in the processing of those color patches the preceding synesthetic color information would first show an influence. Similar to the context studies mentioned above, these types of studies are isolating a more indirect measure of synesthetic perception- perhaps even a consequence of synesthetic color perception, rather than synesthetic color perception itself.

In order to determine when in visual processing synesthetic color is being accessed (and thus inform which model is most appropriate), future studies should record ERPs to stimuli that induce synesthetic color perception and visually similar stimuli that do not induce synesthetic color perception. For example, studies of language use stimuli known as "false fonts" which are systematically made from letters by cutting them up and rearranging them (see section 2.1). ERPs to letters vs false fonts in grapheme-color synesthetes should show a difference that would not be observed in non-synesthetic controls, reflecting synesthetic color perception. Additionally, future studies should attempt to account for individual differences (between projectors and associators) by using established measures of synesthesia (i.e. Eagleman et al. 2006) to group subjects.

1.3 Attention and Synesthetic Color Perception

1.3.1 Studies of Behavior

There is another question that has been a large focus in the behavioral domain of synesthesia research: To what extent is attention necessary for synesthetic perception?

Like the research investigating the neural mechanisms underlying synesthesia, the results from this area are also rather inconsistent. This inconsistency seems to stem primarily from the fact that results from one type of behavioral measure suggests that attention is not necessary, whereas results from another behavioral measure suggest the opposite.

At the level of subjective report, most synesthetes report that their synesthetic experience is dependent on what stimulus is being attended to at the time, but once the inducer is attended, the experience is triggered involuntarily (Rich & Mattingly 2014). However, there are instances when synesthetes' attention is in fact captured initially by the synesthetic color of an inducer, suggesting that the synesthetic experience can also be pre-attentive. The studies reporting this finding describe a pop-out effect, meaning that the synesthetes can detect a target grapheme in an array of distractor graphemes (i.e. the letter "T" surrounded by a large number of "H"s; see Figure 1.8) significantly faster than controls, because the synesthetic color causes it to "pop out" from the surrounding distractors (Ramachandran & Hubbard 2001a; Palmeri et al. 2002). So, in these instances, synesthetic perception is arguably guiding attention, rather than depending on it.

Figure 1.8 Visual Search in Synesthetes

In the visual search paradigm, participants are asked to locate targets in an array of visually similar distractors as quickly as possible. Studies using this paradigm with grapheme-color synesthetes have found that synesthetes are significantly faster at this task because the colors induced by the letters cause the target to "pop out" (right), unlike in non-synesthetes (left).

Studies showing that attention is necessary for synesthetic perception all rely on the synesthetic congruency effect. As discussed in section 1.1.1, the synesthetic congruency effect is a widely used objective measure of synesthetic perception. Participants are asked to name the physical color of letters, and on "congruent" trials (the physical color of the letter matches the synesthetic color associated with the letter)

participants respond significantly faster than they do on "incongruent" trials (the physical color does not match the synesthetic color). This finding has been replicated in many different paradigms (Dixon et al. 2000; Mattingley et al. 2001; Rich et al. 2003, 2010). These studies have manipulated attention by forward masking the priming inducer (Mattingly et al. 2001), forward and backward masking[11] the inducer (Rich et al. 2003), and manipulating attentional load using a distracting task (Mattingly et al. 2006). All of these studies found that when attention was reduced, the synesthetic congruency effect was also reduced, supporting the notion that attention is necessary for synesthetic color perception. However, these studies still found a congruency effect when attention was reduced, so one could argue that they actually demonstrate that attention is related to synesthetic color perception, but not *necessary* for it. In order to create conditions in which participants were viewing inducers that were completely unattended, Mattingly et al. (2010) performed a study utilizing the attentional blink paradigm.

1.3.2 The Attentional Blink Paradigm

In the typical attentional blink paradigm, there are two targets ("T1" and "T2") embedded in a stream of distractor stimuli presented at a very fast rate (typically one image every 100ms). After the rapid stream of stimuli has ended, participants are asked to report the identity of T1 and T2. Typically participants do not have trouble reporting the identity of these two targets. However, when T2 is presented within 200 to 500ms after T1, participants' ability to identify T2 drops significantly (Raymond et al. 1992). Participants report that on many of these trials, they are completely unaware of T2. Theories from cognitive psychology have suggested that this phenomenon is the result of attentional resources being tied up in the processing of T1, such that T2 is completely unattended, despite the fact that it is present in the visual field[12].

[11] The backward masking paradigm involves presenting a target stimulus very briefly (i.e. 28ms) which is then immediately followed by second visual stimulus (a 'mask') presented for a longer period of time. Consequently, the target stimulus is not consciously perceived. A similar effect can be achieved presenting the mask before the target stimulus. This is known as forward masking.

[12] See Martins et al. 2008 for an interesting review on newer theories of the attentional blink. Overall, they suggest that the attentional blink is actually the result of attention being suppressed during T2 processing, rather than a lack of attentional resources.

Mattingly et al. (2010) modified this attentional blink paradigm to determine if the synesthetic congruency effect is eliminated in the absence of attention. In their paradigm, a grating (T1) and an achromatic letter (T2) were embedded in a stream of achromatic distractors. At the end of the stream, a color patch was presented that either matched or didn't match the color induced by T2. Initially, the researchers tried to have participants name the color patch, report the identity of T1, and report the identity of T2 for each trial, but they found that doing all three was too difficult. So, they divided their study into Task 1 (report the identity of T1 and T2), Task 2 (report the identity of T2 and name the color patch), and Task 3 (report the identity of T1 and name the color patch). They used Task 1 to ensure that there was an attentional blink, Task 2 to find the effect of congruency when participants were aware of T2, and Task 3 to see the effect of congruency when participants were unaware of T2.

They found that participants showed an attentional blink in Task 1, and a congruency effect in Task 2, but that this effect was eliminated in Task 3. They argue that these results support the conclusion that attention is necessary for synesthetic perception. However, this study is still open to interpretation, since participants did *not* actually need to attend to T2 on the Task 3 trials, and therefore they were essentially distractors- as opposed to targets that failed to be processed by attention. In other words, it could be the case that these T2s were actively suppressed (as opposed to just unattended) and the reason why no synesthetic congruency effect was observed. Ideally future studies using the attentional blink to investigate synesthetic perception would find a way to measure synesthetic perception on the exact same trials in which participants are experiencing the attentional blink.

1.3.3 Inconsistencies

Once again, we find that there is inconsistency between studies. These inconsistencies could be related to individual differences and differences in task. First of all, pop-out studies are mostly single-subject case studies, which again make things difficult given the large amount of variability in experience between synesthetes (van Leeuwen 2014). It could be the case that attention is not necessary for synesthetic perception in projector synesthetes but it is necessary for synesthetic perception in

associator synesthetes. Additionally the visual search paradigm is arguably not completely without attention, as a number of studies in the attention literature have shown that visual search involve feature-based attention guiding spatial attention (see section 4.2.2 for further discussion on this). On the other hand, the studies finding attention to be necessary are all showing findings from one measure of synesthetic perception: the synesthetic congruency effect. Perhaps synesthetic perception can occur in the absence of attention, but attention is necessary for the congruency effect to occur. A study using event-related potentials to directly measure synesthetic color perception might resolve this ambiguity in the research on synesthesia and attention.

1.4. The Present Study

1.4.1 Background Summary

In summary, grapheme-color synesthesia is an ideal model for understanding the neural mechanisms underlying synesthesia (1.2.1). It appears that there are no differences within the color processing area V4 that could explain the synesthetic experience (1.2.2), but there are differences in the structural and functional connections between areas such as V4 and the regions of the visual word form area (VWFA) responsible for grapheme processing, or higher level parietal regions responsible for feature binding (1.2.3). There are a number of developmental-genetic mechanisms that could result in these connectivity changes (1.2.4). These findings have led to the development of three different models (1.2.5) proposing what type of connections between V4 and the VWFA (direct or indirect) are involved in synesthetic color perception. The three models have testable predictions for the timing of neurological events related to synesthesia. However, the studies using high temporal resolution methods (1.2.6) to investigate this question have been largely inconsistent (1.2.7). Another area of interest for synesthesia researchers is the question of whether or not attention is necessary for synesthetic color perception. Unfortunately, the findings from studies investigating this question have also been somewhat contradictory (1.3), although, a recent study by Mattingly et al. (2010)

provided stronger evidence for the necessity of attention using the attentional blink paradigm (1.3.2).

These inconsistencies are likely the result of three different factors: (1) Several findings were from single subject case studies. (2) Most studies did not take into account or control for differences between associator and projector synesthetes (1.1.5). (3) None of these studies used stimuli/tasks that would directly measure synesthetic color perception in the brain. For studies investigating timing, the researchers compared ERPs to congruent vs incongruent stimuli, rather than directly isolating effects related to synesthetic color perception (1.2.7). For studies investigating attention, the contradictory evidence comes from two different behavioral effects, which are both indirect measures synesthetic color perception (1.3.3)

To correct for these inconsistencies, future studies should compare event-related potentials to letters (which induce color perception) vs false-fonts (letter-like stimuli that should not induce color perception) in order to isolate neuronal events strictly related to synesthetic color perception. Then, the availability of attentional resources could be manipulated to determine whether the neural correlates of synesthetic color perception are eliminated in the absence of attention. Ideally, these studies would be carried out on both associator and projector type synesthetes so that their underlying neural mechanisms could be compared and any differences could be controlled for.

1.4.2 Research Questions

Event-related potentials (ERPs) were recorded to letters and false-fonts in associator-type grapheme-color synesthetes and matched controls in order to investigate the timing of neural events directly related to synesthetic perception. By comparing ERPs time-locked to letters and ERPs time-locked to false fonts, we isolated a neural correlate of synesthetic color perception. These stimuli were presented using the attentional blink paradigm to determine whether or not attention is necessary for synesthetic perception. Additionally, ERPs to congruent vs incongruent color patches were recorded in an attempt to replicate the effects identified by previous studies and determine how these effects are influenced by the availability of attention.

1.4.3 Hypotheses

Question 1: What is the timing of neuronal events related to synesthetic color perception?

A. If the neural correlate of synesthetic perception is observed early in visual processing (within 200ms), then this would support the cross-activation model (Hubbard 2007).
B. If the neural correlate of synesthetic perception is observed late in visual processing (after 200ms), then this would support the disinhibited feedback model (Grossenbacher & Lovelace, 2001)
C. If neural correlates of synesthetic perception are observed both early and late in visual processing, then this would support the re-entrant processing model (Smilek et al. 2001).

Question 2: Is attention necessary for synesthetic perception?

A. If the neural correlate of synesthetic perception is present both for trials in which the participants were aware and unaware of the inducer, this would suggest that attention is not necessary for synesthetic perception.
B. If the neural correlate of synesthetic perception is present for trials in which the participants were aware of the inducer, but not for trials in which they were unaware, this would suggest that attention is necessary for synesthetic perception

Question 3: Can the effect of congruence found in previous ERP studies still be observed when synesthetes are unaware of the inducer?

A. If the effect of congruence found by previous studies is eliminated in the absence of attention, this implies that attention is necessary for the higher order processing of synesthetic experiences to occur.
B. If the effect of congruence is found even in the absence of attention, this implies that higher order processing of synesthetic experiences can occur subconsciously.

Chapter 2: Methods

2.1 Participants

A total of 20 current Reed College students (16 female; mean age 21) with normal-to-corrected vision and no history of brain injury participated in this study. Of these, 10 participants were grapheme-color synesthetes (8 female; mean age 21) and 10 were non-synesthetic controls matched for age and biological sex. In addition to being self-reported grapheme-color synesthetes, all synesthetic participants met the Eagleman et al. (2006) synesthesia battery criteria. All synesthetic participants had grapheme-color congruency test[13] scores less than 1.0 (mean = 0.61) and speed-congruency test[14] accuracies above 85% (mean = 94.44%). Control participants were also asked to complete the full synesthesia battery, and none of these individuals met the criteria to qualify as a grapheme-color synesthete (mean grapheme-color congruency = 2.71, mean speed-congruency test = 62%). See Appendix B for their individual color associations.

All 10 of the synesthetic participants were found to be associator synesthetes using the projector-associator (PA) scale of grapheme-color synesthesia. All participants were compensated a total of $50 for their participation. Funding was provided by the Initiative Grant of the Reed College Committee for Undergraduate Science Research. The Reed College Institutional Review Board approved all procedures.

During the experiment, one participant reported that the distractor and target false fonts (see section 2.3) had begun to elicit synesthetic color perception. Consequently, that participant's results (as well as the results from their matched control) were excluded from the final data set. The final data set therefore included 9 synesthetes and 9 matched-controls.

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[13]Eagleman et al. (2006): Synesthetes typically have a grapheme-color congruency test score below 1.0. A score of 0 would indicate perfect color selection test-retest accuracy for all letters and numbers presented.

[14]Eagleman et al. (2006): Synesthetes typically have a speed-congruency test accuracy above 85%.

2.2 Stimuli

The 26 letters of the Latin/Roman alphabet were created using Adobe Illustrator (Figure 2.1). The letters were black on white squares (500 x 500 pixels). Using these 26 letters, 52 false fonts were generated by systematically cutting and shuffling around basic elements of each letter (Figure 2.1). In addition to the letters and false fonts, four achromatic gratings oriented in different directions were created using Illustrator (example shown below in figure 2.3). All of these stimuli were presented in a classic attentional blink paradigm using Presentation (Neurobehavioral Systems, San Francisco CA). This software was also used to generate colored squares that were presented after each visual stream as explained below.

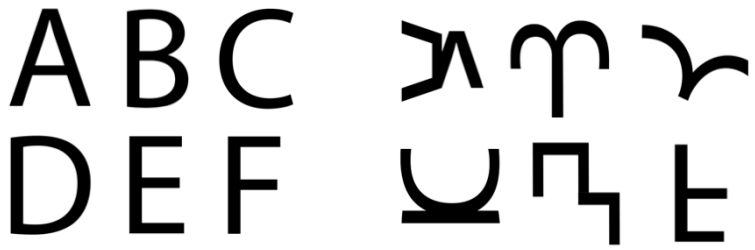

Figure 2.1 Example Stimuli
On the left, six letter stimuli created using Adobe Illustrator. On the right, six false fonts created systematically cutting and moving the elements of letter.

2.3 Procedure

At least one week after completing the synesthesia battery and a questionnaire created by the experimenter, participants attended two electroencephalography (EEG) recording sessions, each lasting approximately 2.5 hours (~2 hours of brain recording with intermittent breaks). The procedures of these two recording sessions were completely identical, and the sessions were held no less than 48 hours apart.

2.3.1 Synesthesia Battery

All participants (synesthetic and control) underwent the synesthesia battery (Eagleman et al. 2006), and then practiced the attentional blink task (see below) that they would perform in the EEG recording sessions. Control participants were informed of the phenomenon of synesthesia at the beginning of this session, and asked to complete the synesthesia battery to the best of their ability despite the fact that they were not synesthetic. The battery includes a number of computerized tasks and questionnaires that determine how consistently a participant associates a color with a specific grapheme and whether or not they are an associator or projector synesthete[15].

Upon completion of the synesthesia battery, synesthetic participants were then asked to complete an additional questionnaire created by the experimenter. This online questionnaire (created using SurveyMonkey, completed on a lab computer in the presence of the experimenter) presented all 26 letters and 52 false fonts created for use in this experiment. For each letter and false font, participants were asked to report their color association (if they had one) in RGB color space[16] (using a full range color wheel). See Appendix B for their individual color associations. They were also asked to rate the strength of each association and the consistency of each association on a scale from 0 to 3 (Appendix C).

All participants (synesthetes and controls) then performed a pilot version of the attentional blink task. This task was identical to the one described in Figure 2.2 below, except that it was shorter and no EEG was recorded.

2.3.2 Brain Recording Sessions

In the two EEG recording sessions, all participants (synesthetes and controls) performed a computerized attentional blink task while EEG was recorded (See Figure 2.2 for a detailed diagram). In one trial, a stream of 12-18 grey false font distractors was

[15] Recall that "associator" synesthetes report seeing the color in their 'mind's eye', whereas "projector" synesthetes report seeing the color in external space.

[16] RGB color space is the most commonly used color model identifying a specific color. Not unlike the human visual system, it defines a specific color as made up of three different color levels (red, green, and blue).

presented at a rate of 10Hz (100ms each). Embedded within the stream were two targets. The first target (T1) was a black grating that could be pointing in one of four directions. On half of the trials, a second target (T2) was one of four black letters. On the other half, T2 was one of four black false fonts.

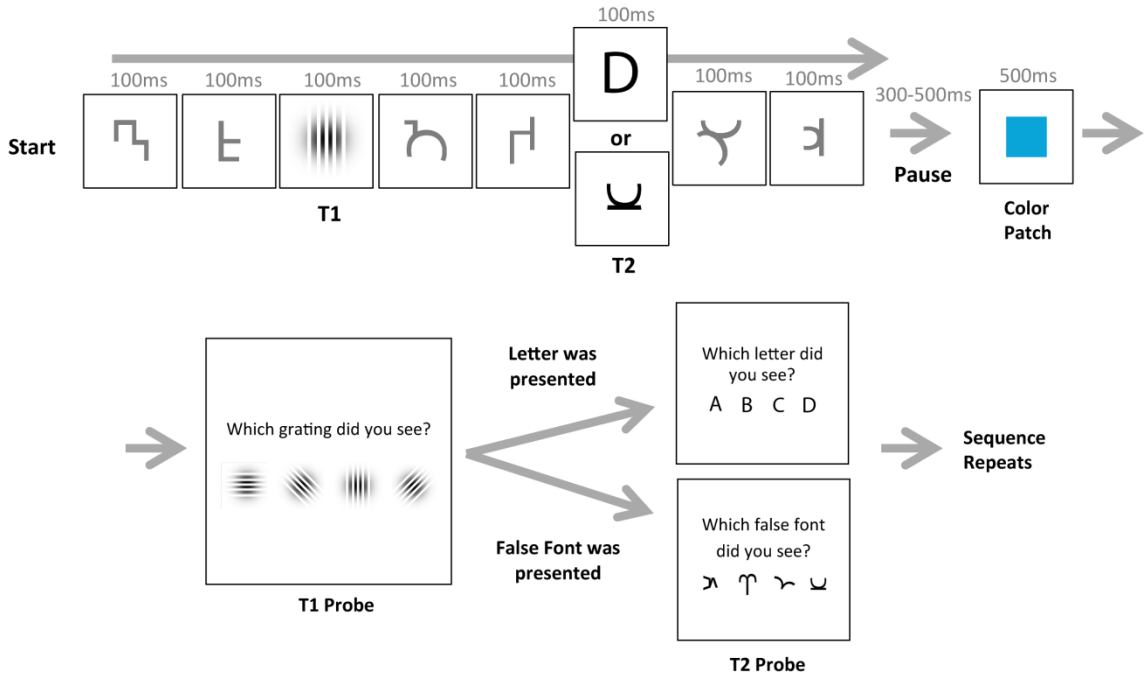

Figure 2.2 Diagram of the Attentional Blink Task

Each trial started with a stream of visual stimuli each presented for 100ms. This visual stream included gray false fonts, a black grating (T1) and either a black letter or a black false font (T2). At the end of the stream, a color patch was presented for 500ms that either matched or did not match the synesthete's color association with the letter presented at T2. After each stream the participant was asked to report the identity of T1 and T2 from four possible options (participants could also report "I'm not sure" for either target). This example depicts a T1-T2 SOA of 300ms.

For each synesthetic participant, the four possible target letters and false fonts were different (Figure 2.3). The letters used as targets were chosen by assessing the results of the questionnaire completed after the synesthesia battery. Only letters with associations rated at the highest level for strength and constancy were used as targets (Appendix C). This was done to maximize the likelihood that the letters would elicit synesthetic percepts. The false font targets were the ones directly corresponding to the

letters used. For each individual synesthete, no false fonts rated higher than a 1 for strength or constancy were used as false font targets or distractors to minimize the likelihood that the false fonts would elicit synesthetic percepts.

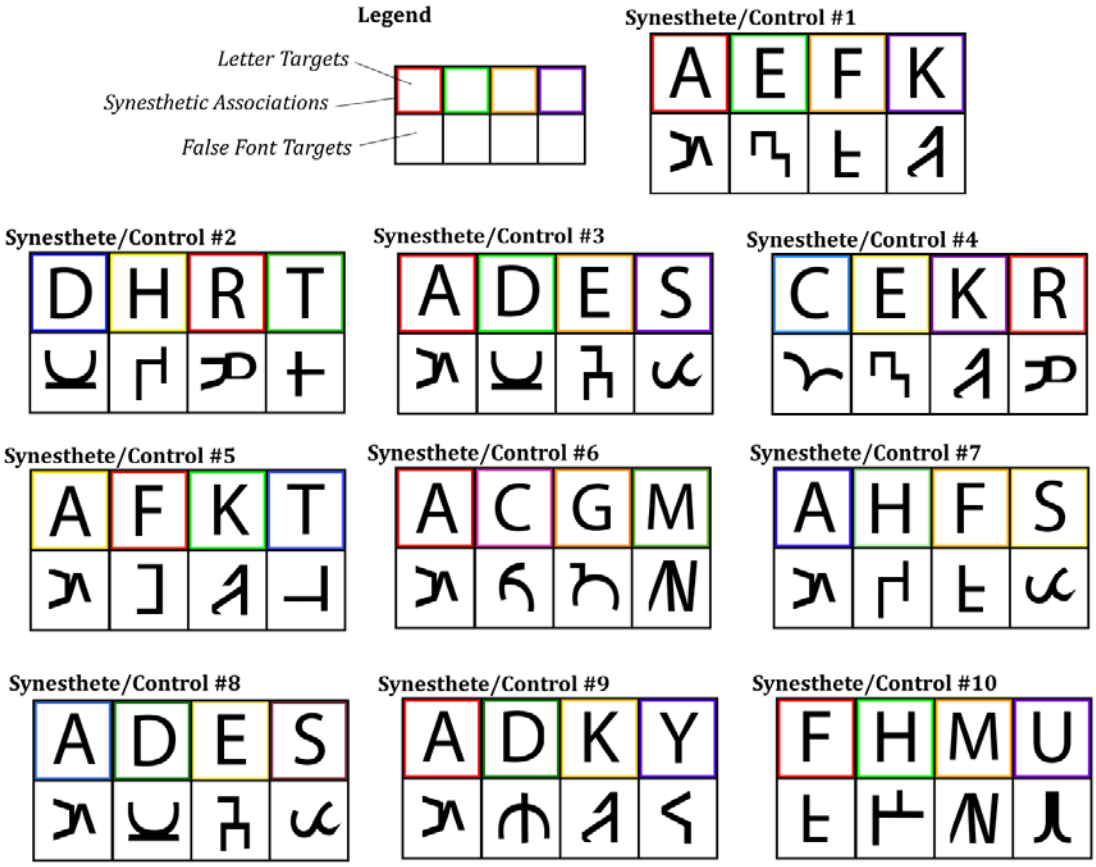

Figure 2.3 Target Stimuli for Individual Subjects

Letter and false font targets used for each synesthete and their matched control. For each synesthete, the letter targets chosen were rated as eliciting strong and consistent color associations, whereas the false fonts chosen were rated as eliciting no color associations. The figure depicts the individual color associations of each synesthete for the four letter targets.

Directly after the rapid stream of stimuli, a color patch that was either congruent with the color association of the letter in the stream (50%), or incongruent with the color association of the letter in the stream (50%). If a false font was presented in the stream, the color patch was either congruent or incongruent with the color association of the letter that the false font was made from.

After the presentation of the color patch, participants had 3 seconds to report the identity of T1 by pressing one of four buttons, each corresponding to a particular grating orientation. Then the identity of T2 was reported by pressing one of the same four buttons, now each corresponding to one of the four letters (if it was a letter trial) or one of the four false fonts (if it was a false font trial). The letter and false font trials were presented in a block format, such that participants would perform 28 letter trials and then 28 false font trials. When reporting T1 and T2, participants also had the option of pressing a fifth button corresponding to the response "I'm not sure". The response to the T2 probe would elicit a brief pause (300-500ms) before the start of the next trial.

The stimulus onset asynchrony (SOA)[17] of the two targets in the stream was varied between 5 different options: 100ms (9.3% of trials), 200ms (62.7%), 300ms (9.3%), 500ms (9.3%), and 800ms (9.3%)[18].

In total, participants completed 1120 trials in each session, with short breaks every 28 trials and longer breaks every 280 trials. The procedure in the two session was completely identical, and the second was always carried out within 48 hours of the first.

2.3.3 EEG Recording

In the EEG recording sessions, Participants were fitted with a 32-channel electrode cap (Figure 2.4). Eye blink artifacts were detected with an additional VEOG electrode attached to the face below the left eye, and two additional electrodes, each one adjacent to the left and to the right eyes for HEOG. Impedance levels were kept below 5kΩ. This was achieved with the use of a saline-based gel and some gentle rubbing with the wooden end of a Q-tip, in order to abrade away a thin layer of skin cells. Immediately after the session was finished, usually within 2.5 hours of participants' arrival, caps were removed and participants were able to wash their hair in the lab.

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[17] Stimulus onset asynchrony (SOA) is the amount of time between the onset of one stimulus and the onset of another stimulus.

[18] At the start of the experiment, the proportions were 100ms (10%), 200ms (80%) and 800ms (10%). However, participants were not performing poorly enough to gain enough unaware segments, so the 300ms and 500ms options were added to make the SOA less predictable. Therefore, two of the synesthetes (and their matched controls) were run under the original proportions, and the rest under the ones listed above.

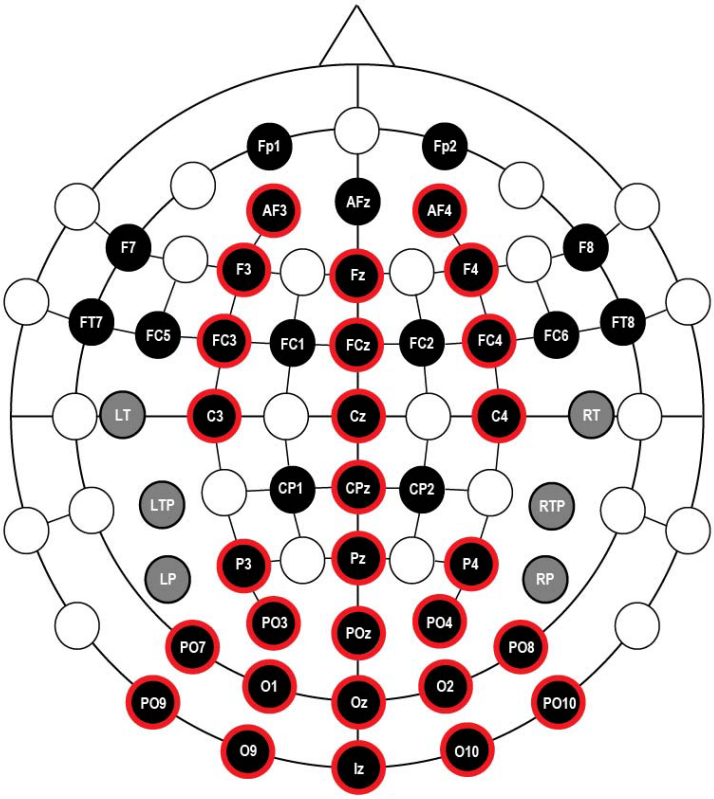


Figure 2.4 Electrode Locations

Twenty-eight of the electrodes used in this experiment (Red). The remaining electrodes used were VEOG, HEOGR, HEOGL, and Left/Right Mastoids.

2.4 Data Analysis

Electroencephalographic (EEG) data were processed using BrainVision Analyzer software (Brain Products, Germany). Artifacts (blinks, eye movements, facial muscle noise, etc.) were rejected semi-automatically (on average, 4% of trials were rejected due to artifacts). The final data set included 9 synesthetes and their matched controls. Based on an initial visual analysis of the waveforms elicited by T2, we measured the mean amplitudes in two time windows.

The first was a positive mean amplitude difference between 170ms and 230ms at fronto-central electrode sites. This positive difference between letters (stimuli inducing synesthetic color perception) and false fonts (similarly shaped stimuli that did not induce

synesthetic color perception) appeared to be present for synesthetes but not in matched controls. This effect had the same timing and scalp distribution as a previously established ERP component, the “Sensory Effect of Color”, found when comparing colored vs achromatic stimuli (Schoenfeld et al. 2003; Zinni et al. 2014; Pitts, Metzler, & Hillyard, 2014). The second effect was a negative mean amplitude difference between 200ms and 250ms at lateral-occipital electrode sites. This effect, which we refer to as the “N200/N250 Complex”, has been found for words vs false fonts both in previous studies by other labs (McCandliss et al. 2003), and in a recent experiment in our lab (unpublished observations). These two differences were submitted to a 4-way mixed model ANOVA, with several electrodes (6 for the first effect, 4 for the second effect), 2 conditions (aware/unaware) and 2 sessions (first/second) as within-subjects variables, and with group (synesthetes/controls) as our between-subjects variable.

In addition, ERPs time-locked to the color patch showed one effect: a negative mean amplitude difference between incongruent and congruent color patches in the 210ms and 310ms time window at frontal electrode sites present only for synesthetes but not matched controls. This effect had a similar polarity and scalp distribution (though slightly earlier latency) as the effect for incongruent vs congruent color patches shown in previous studies (Brang et al. 2008, 2010, 2011; Niccolai et al. 2012). For the purposes of this study, this difference was referred to as the “Incongruence Negativity”. Mean amplitude differences in this time window were subjected to a 5-way mixed model ANOVA with electrode (6), awareness (aware/unaware), stimuli (letter/false font), and session (first/second) as within-subjects variables and with group (synesthetes/controls) as our between-subjects variable.

Chapter 3: Results

3.1 Behavioral Results

Target 2 accuracies only for trials in which target 1 was correctly identified during the EEG recording sessions were submitted to a four-way mixed model ANOVA with three within-Ss variables: Session (2), Stimuli (letters/false fonts), and T1-T2 SOA[19] (100ms, 200ms, 300ms, 500ms, 800ms), and one between-Ss variable: Group (synesthetes / controls). This analysis revealed a significant main effect of SOA ($F(4,64) = 54.3$, $p < 0.001$) and no main effects of group ($F(1,16) = 0.45$, $p = 0.51$) or Session ($F(1,16) = 0.86$, $p = 0.37$). However, there was a marginally significant main effect of Stimuli ($F(1,16) = 4.66$, $p = 0.05$). Additionally, there was a significant interaction between SOA and Stimulus ($F(4,208) = 2.55$, $p < 0.05$). A series of paired t-tests (collapsed across group and session) were used to examine this interaction. These results are summarized in figures 3.1 and 3.2.

	100ms	**200ms**	**300ms**	**500ms**	**800ms**
Letters	90.67 (8.56) **A**	68.06 (11.82) **B**	76.33 (10.02) **C**	86.19 (10.57) **D**	91.63 (5.70) **A**
False Fonts	90.25 (8.21) **A**	63.25 (10.49) **E**	71.19 (15.94) **C**	80.06 (13.08) **D**	90.08 (7.28) **A**

Figure 3.1 Behavioral Results and Analysis

Mean % accuracy (±standard deviation) on target 2 for trials in which target 1 was correctly identified for the five different T1-T2 SOAs, collapsed across group and session. Cells sharing the same letter/color are not statistically different ($p > 0.1$) and cells with different letters/colors are statistically different ($p < 0.01$).

[19] Recall that T1-T2 Stimulus Onset Asynchrony (SOA) is the amount of time between the onset of the first target (one of four different gratings) and the onset of the second target (one of four different letters or one of four different false fonts). Previous studies have shown that when the T1-T2 SOA is 200ms-300ms, the ability of participants to perceive T2 drops significantly. This phenomenon is known as the attentional blink (section 1.3.2).

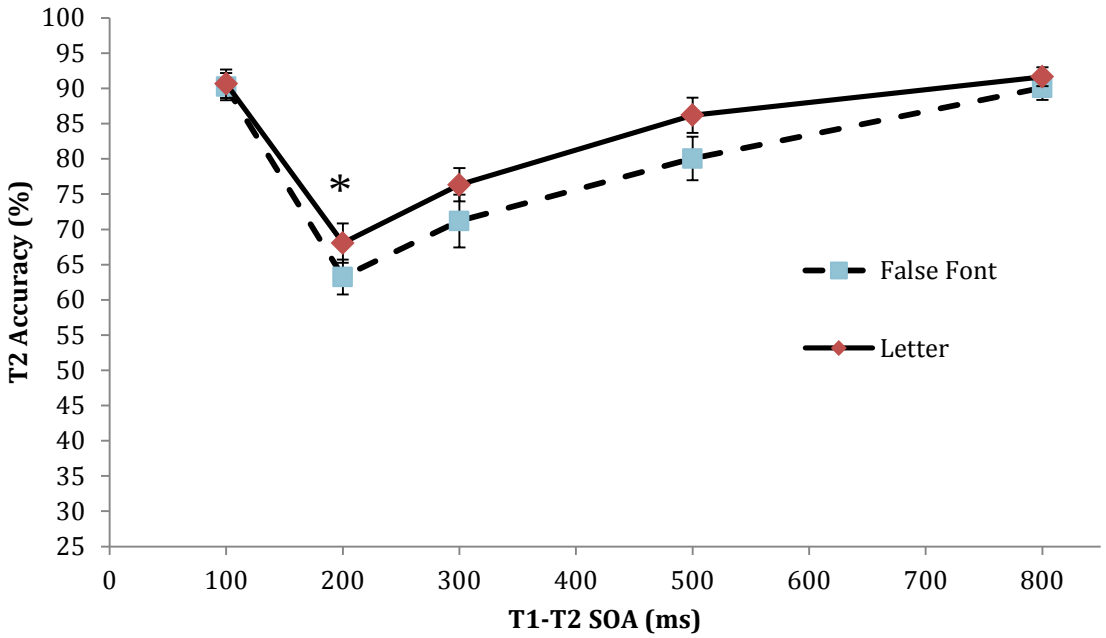


Figure 3.2 Overall Attentional Blink Effect

Mean % accuracy on target 2 for trials in which target 1 was correctly identified, collapsed across group and session. On each trial, participants had a 25% chance of answering correctly. At lag 2 (200ms T1-T2 SOA) participants performed significantly lower on false fonts than on letters ($t(17) = 2.64$, $p = 0.02$).

Overall, participants showed a typical attentional blink effect. Accuracy levels were high for 100ms and 800ms SOAs (~90%), and dropped when the T1-T2 SOA was 200ms (68% for letters, 63% for false fonts). Of note, participants performed significantly less accurately at the 200ms SOA for false fonts than letters. However, this letter vs false font difference was not statistically significant at any other SOA, though it was trending at the 500ms SOA ($t(17) = 2.04$, $p = .06$).

3.2 Electrophysiological Results

3.2.1 The Sensory Effect of Color (SEC)

ERPs were time-locked to target 2 (letter or false font). The results of the following analyses are shown in figures 3.3 and 3.4 for synesthetes and figures 3.5 and 3.6 for controls. Mean amplitude differences between waveforms elicited by letters versus false fonts (in the time window of the SEC) were submitted to a four-way mixed model ANOVA with three within-Ss variables: Session(2), Electrode (6, FC3, FCz, FC4, C3, Cz, C4), and Awareness (yes/no), and one between-Ss variable: Group (synesthetes/controls). This analysis revealed no main effect of Group ($F(1,16) = 0.27$, ns), Session ($F(1,16) = 0.48$, ns), Electrode ($F(5,80) = 0.49$, ns), or Awareness ($F(1,16) = 3.31$, ns). However, there was a significant interaction between Group and Awareness ($F(1,16) = 6.64$, $p < 0.05$). No other interactions were significant.

A series of paired t-tests (collapsed across session and electrode) were used to examine the Group X Awareness interaction revealing that the mean amplitude difference between letters and false fonts in synesthetes (M=1.18μV SD=0.39) was significantly greater for aware trials than unaware trials (M= -1.28μV SD=0.50; $t(8)=2.43$, $p < 0.05$). As for control participants, the mean amplitude difference between aware trials (M= -0.28μV SD=0.50) and unaware trials (M= -0.17μV SD=0.42) was not significant ($t(8)= -0.62$, ns). Independent means t-tests revealed that in aware trials, the mean amplitude difference between letters and false fonts was significantly greater in synesthetes than in controls ($t(16) = 2.36$, $p < 0.05$). However, in unaware trials, there was no significant difference between groups ($t(16) = -0.74$, ns).

Furthermore, single-sample t-tests were used to determine for which conditions (Aware and Unaware) the mean amplitude difference between letters and false fonts was significantly different from zero in each group. These t-tests (collapsed across electrode and session) revealed that, in synesthetes, the mean amplitude difference was significantly greater than zero for aware trials ($t(8) = 3.04$, $p < 0.05$), but not for unaware trials ($t(8) = -0.56$, ns). This difference was not significantly greater than zero in control participants for aware ($t(8) = -0.40$, ns) or unaware ($t(8) = 0.51$, ns) trials.

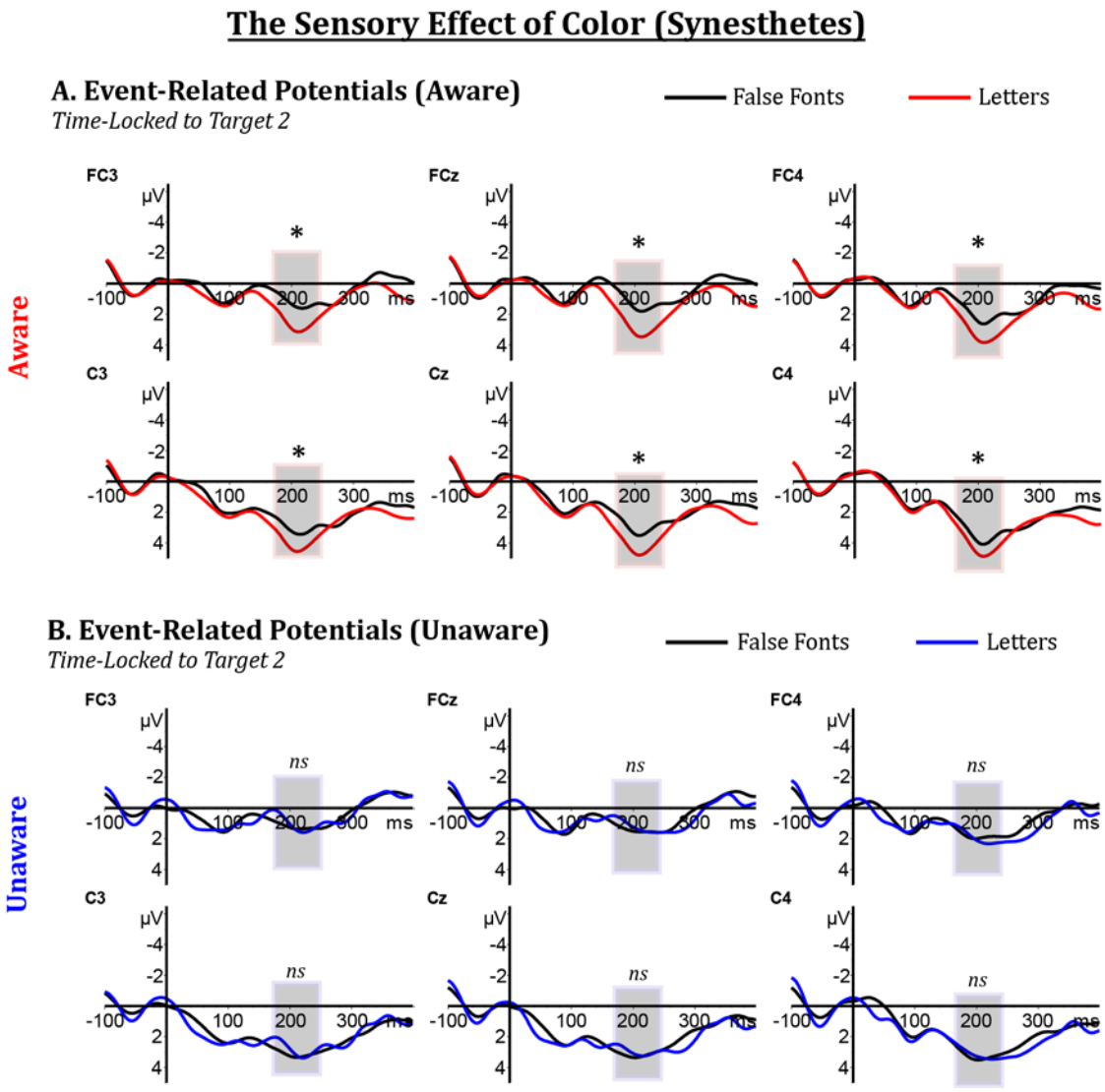


Figure 3.3 SEC Event-Related Potentials (Synesthetes)

Event-related potentials time-locked to the onset of target 2 (letters or false fonts) when participants correctly identified it **(A)** and when they were unable to correctly identify it **(B)** at six central scalp electrodes (FC3, FCz, FC4, C3, Cz, C4). Mean amplitude from 170ms to 230ms after stimulus onset was compared between letters and false fonts for aware and unaware trials. Stars denote a statistically significant difference in that time window, $p < 0.05$.

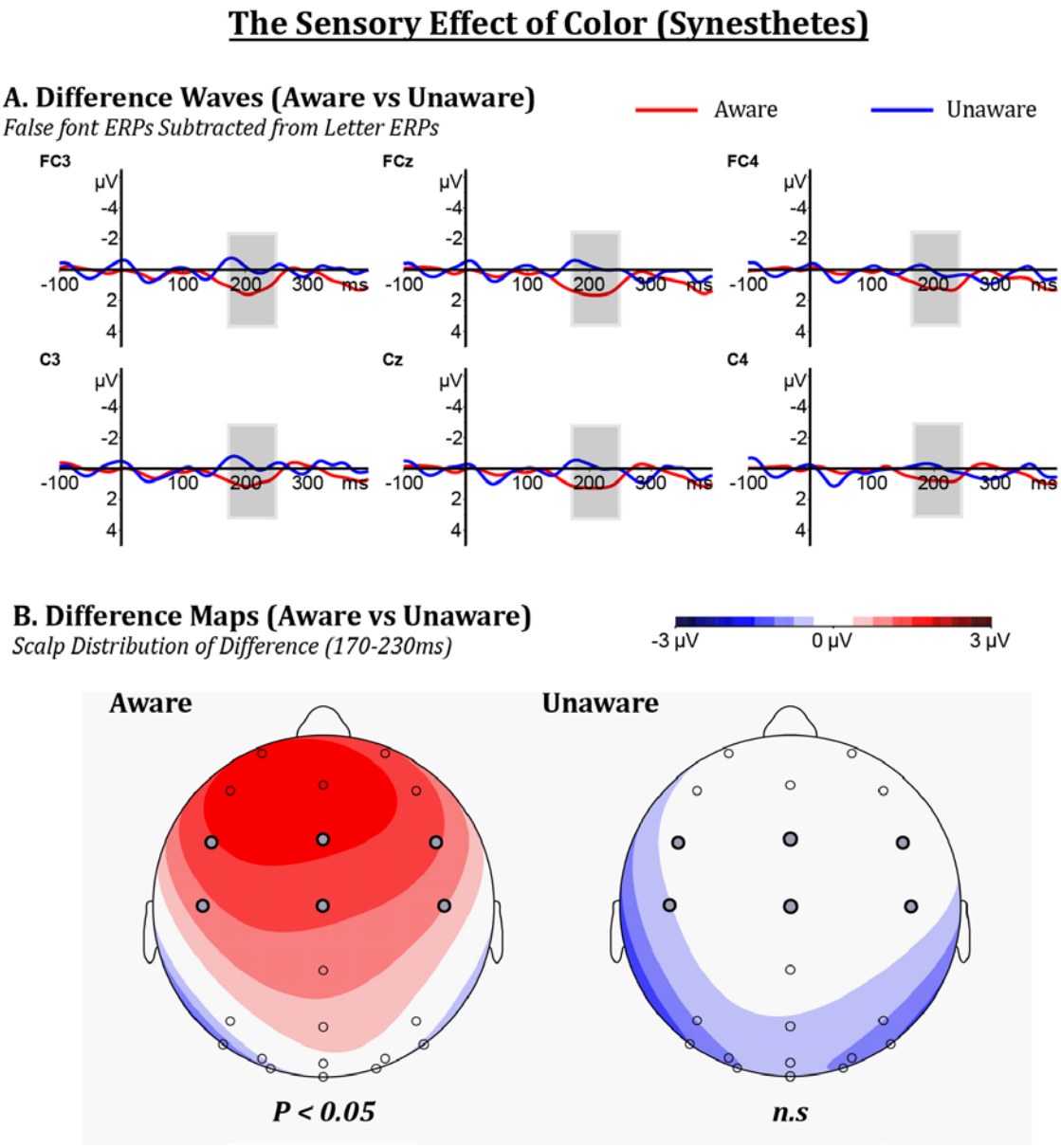


Figure 3.4 SEC Difference Waves & Maps (Synesthetes)

(A) Difference waves created by subtracting the amplitude of the ERPs to false fonts from the amplitude of the ERPs to letters at every time point. The difference from 170ms to 230ms after stimulus onset was significantly greater than zero for aware trials but not for unaware trials. **(B)** Difference maps showing the mean amplitude difference averaged across the 170ms-230ms time window for aware (left) and unaware (right) trials. Electrodes used in data analysis are bold and highlighted in gray.

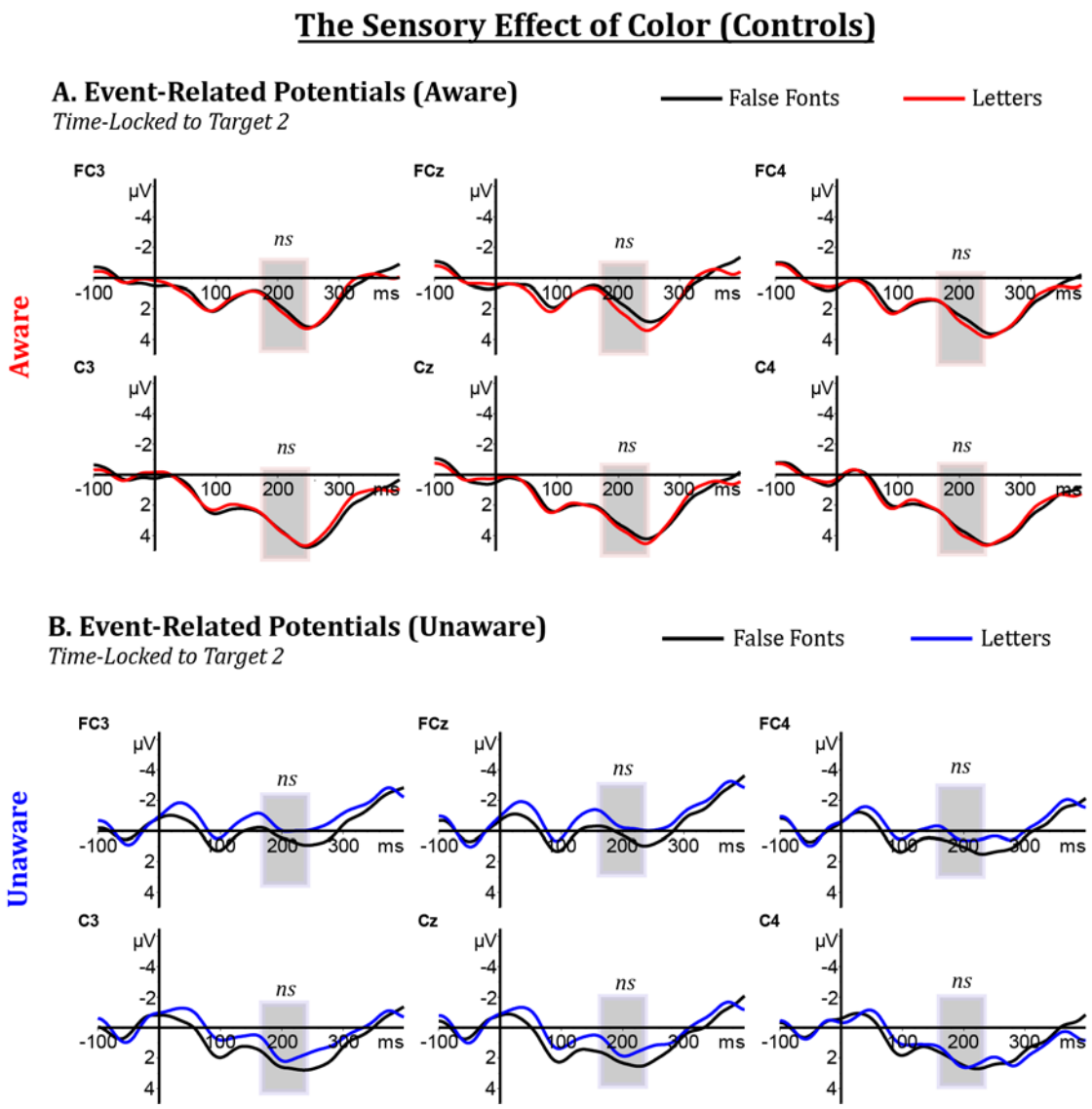


Figure 3.5 SEC Event-Related Potentials (Controls)

Event-related potentials time-locked to the onset of target 2 (letters or false fonts) when participants correctly identified it **(A)** and when they were unable to correctly identify it **(B)** at six central scalp electrodes (FC3, FCz, FC4, C3, Cz, C4). Mean amplitude from 170ms to 230ms after stimulus onset was compared between letters and false fonts for aware and unaware trials.

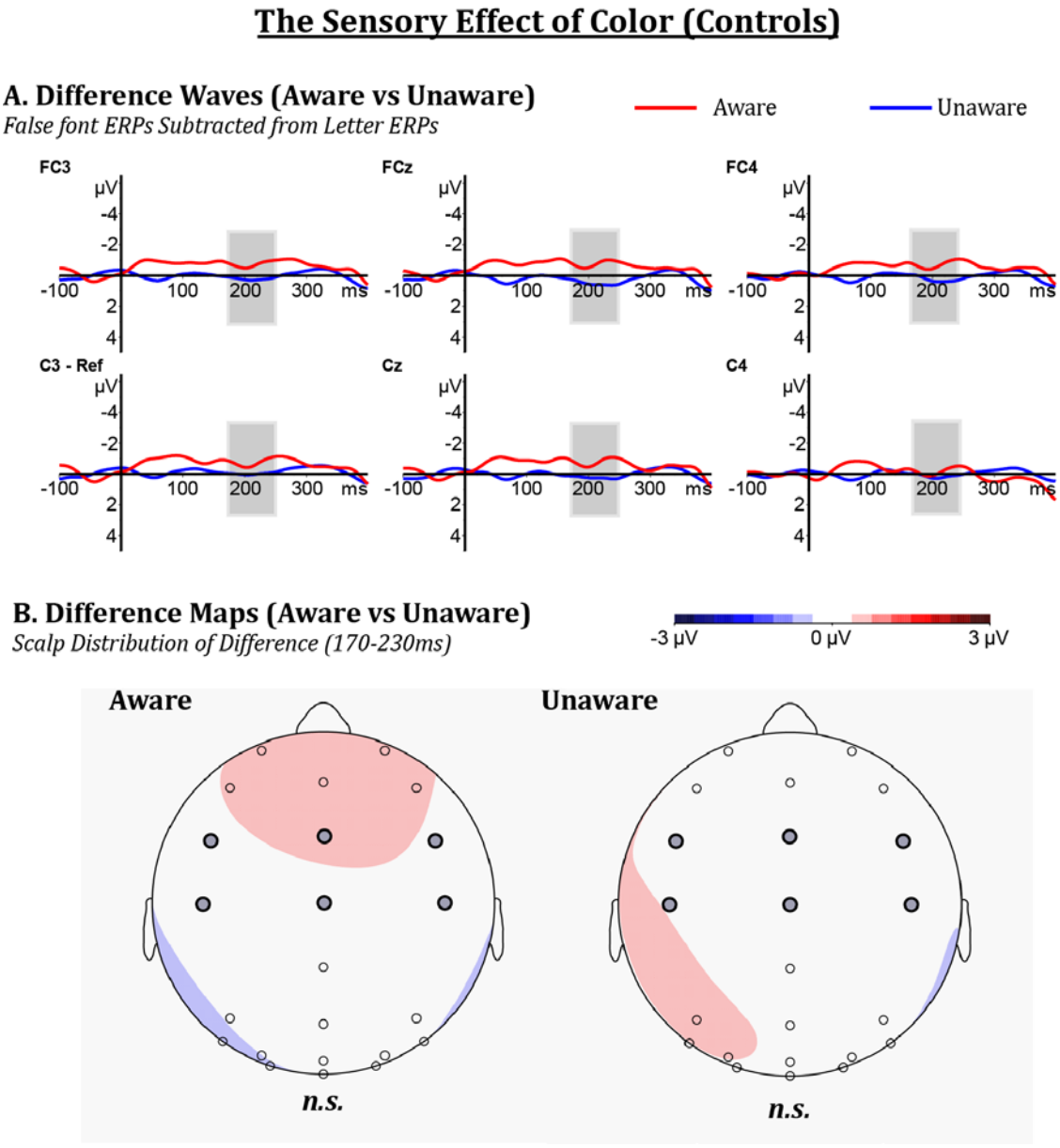


Figure 3.6 SEC Difference Waves & Maps (Controls)

(A) Difference waves created by subtracting the amplitude of the ERPs to false fonts from the amplitude of the ERPs to letters at every time point. The difference from 170ms to 230ms after stimulus onset was not significantly different from zero for aware or unaware trials. **(B)** Difference maps showing the mean amplitude difference averaged across the 170ms-230ms time window for aware (left) and unaware (right) trials. Electrodes used in data analysis are bold and highlighted in gray.

3.2.2 The N200/N250 Complex

These ERPs were time-locked to target 2 (letters or false-fonts). The results of the following analyses are shown in figures 3.7 and 3.8 for synesthetes and figures 3.9 and 3.10 for controls. Mean amplitude differences between waveforms elicited by letters versus false fonts from 200ms to 250ms were submitted to a four-way mixed model ANOVA with three within-Ss variables: Session(2), Electrode (4, PO7, PO8, PO9, PO10), and Awareness (yes/no), and one between-Ss variable: Group (synesthetes/controls). This analysis revealed no main effect of Group ($F(1,16) = 0.05$, $p = 0.82$), Session ($F(1,16) = 0.06$, $p = 0.86$), Electrode ($F(5,80) = 0.59$, $p = 0.62$), and Awareness ($F(1,16) = 0.08$, $p = 0.77$). Additionally, there were no significant interactions.

Single-sample t-tests were used to determine for which conditions (Aware and Unaware) the mean amplitude difference between letters and false fonts was significantly above zero in each group (Synesthetes and Controls). These t-tests (collapsed across electrode and session) revealed that the mean amplitude difference was significantly greater than zero for aware trials ($M=-1.4\mu V$ $SD=0.56$; $t(8) = -2.48$, $p < 0.05$) and unaware trials ($M=-0.98\mu V$ $SD=4.61$; $t(8) = -1.99\mu V$, $p < 0.05$) in synesthetes, as well as for aware trials ($M=0.85\mu V$ $SD=0.33$; $t(8) = -2.37$, $p < 0.05$) and unaware trials ($M=-1.20\mu V$ $SD=0.40$; $t(8) = -2.97$, $p < 0.05$) in controls. These results explain the lack of statistically significant effects in the four-way ANOVA, as this amplitude difference was present and equal in magnitude for both groups of subjects in both the aware and unaware conditions.

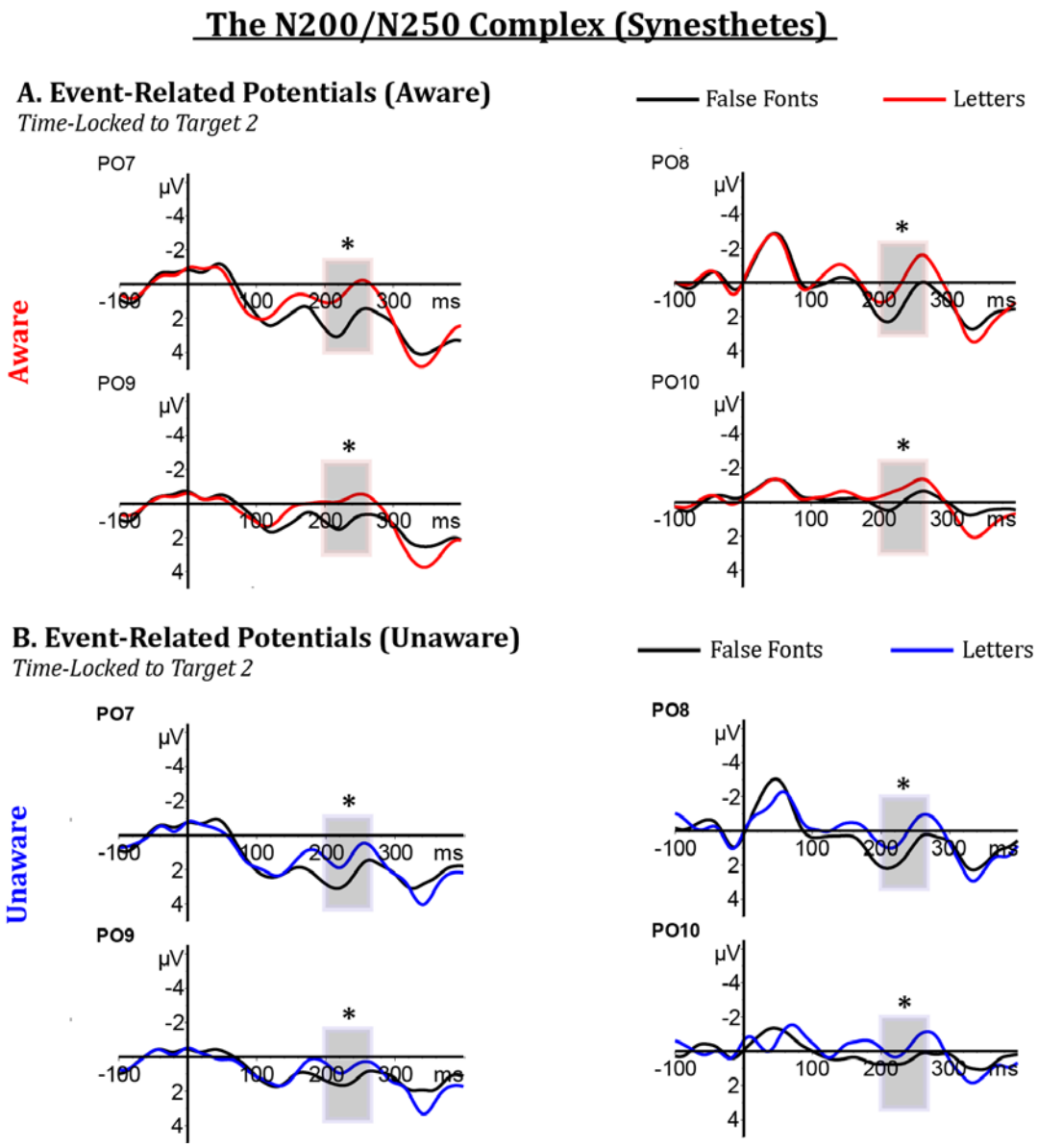


Figure 3.7 N200/N50 Event-Related Potentials (Synesthetes)

Event-related potentials time-locked to the onset of target 2 (letters or false fonts) when participants correctly identified it **(A)** and when they were unable to correctly identify it **(B)** at four occipital scalp electrodes (PO7, PO8, PO9, PO10). Mean amplitude from 200ms to 250ms after stimulus onset was compared between letters and false fonts for aware and unaware trials. Stars denote a statistically significant difference in that time window, $p < 0.05$.

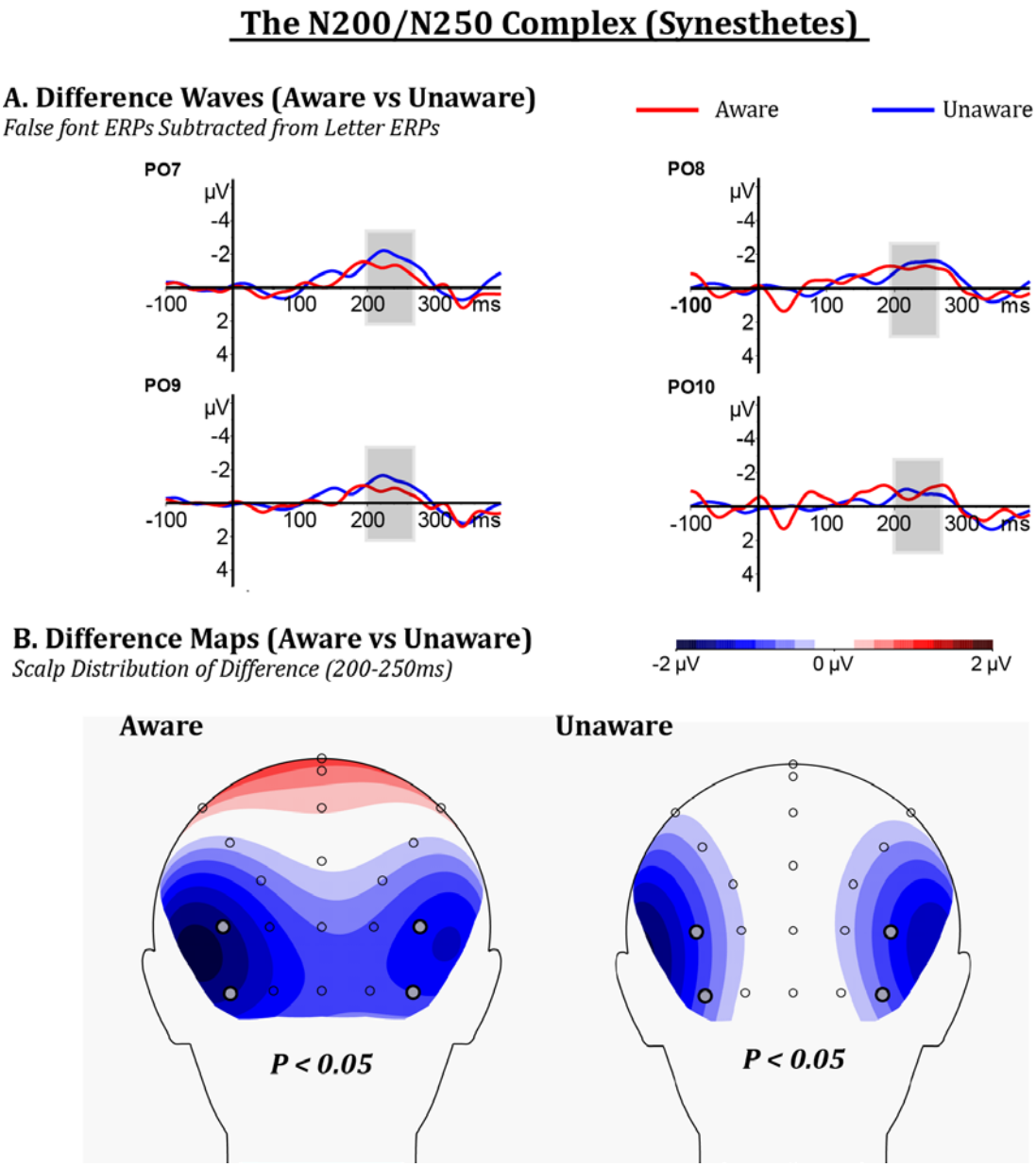


Figure 3.8 N200/N250 Difference Waves & Maps (Synesthetes)

(A) Difference waves created by subtracting the amplitude of the ERPs to false fonts from the amplitude of the ERPs to letters at every time point. The difference from 200ms to 250ms after stimulus onset was significantly greater than zero for both aware and unaware trials. **(B)** Difference maps showing the mean amplitude difference averaged across the 200ms-250ms time window for aware (left) and unaware (right) trials. Electrodes used in data analysis are bold and highlighted in gray.

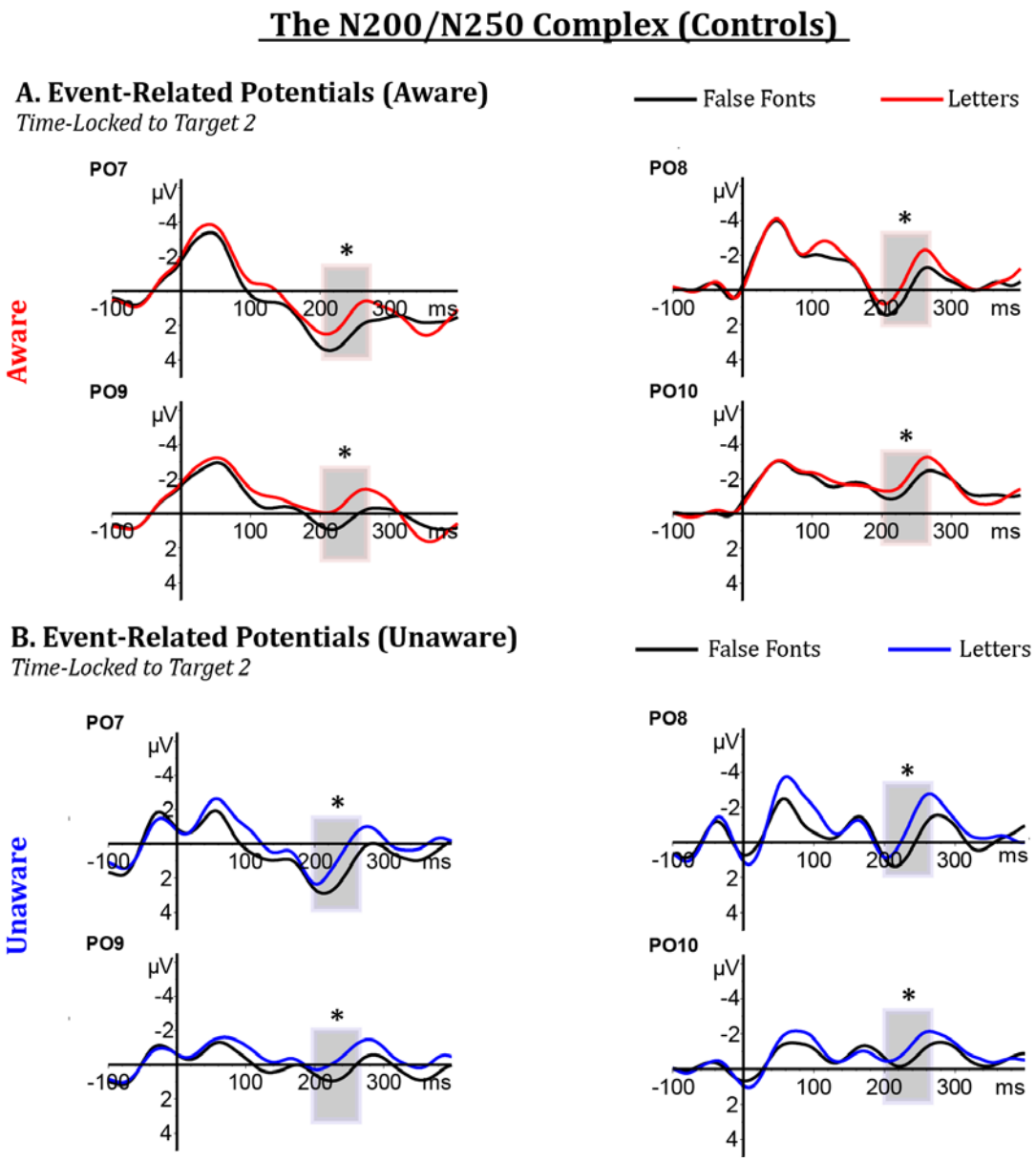


Figure 3.9 N200/N50 Event-Related Potentials (Controls)

Event-related potentials time-locked to the onset of target 2 (letters or false fonts) when participants correctly identified it **(A)** and when they were unable to correctly identify it **(B)** at four occipital scalp electrodes (PO7, PO8, PO9, PO10). Mean amplitude from 200ms to 250ms after stimulus onset was compared between letters and false fonts for aware and unaware trials. Stars denote a statistically significant difference in that time window, $p < 0.05$.

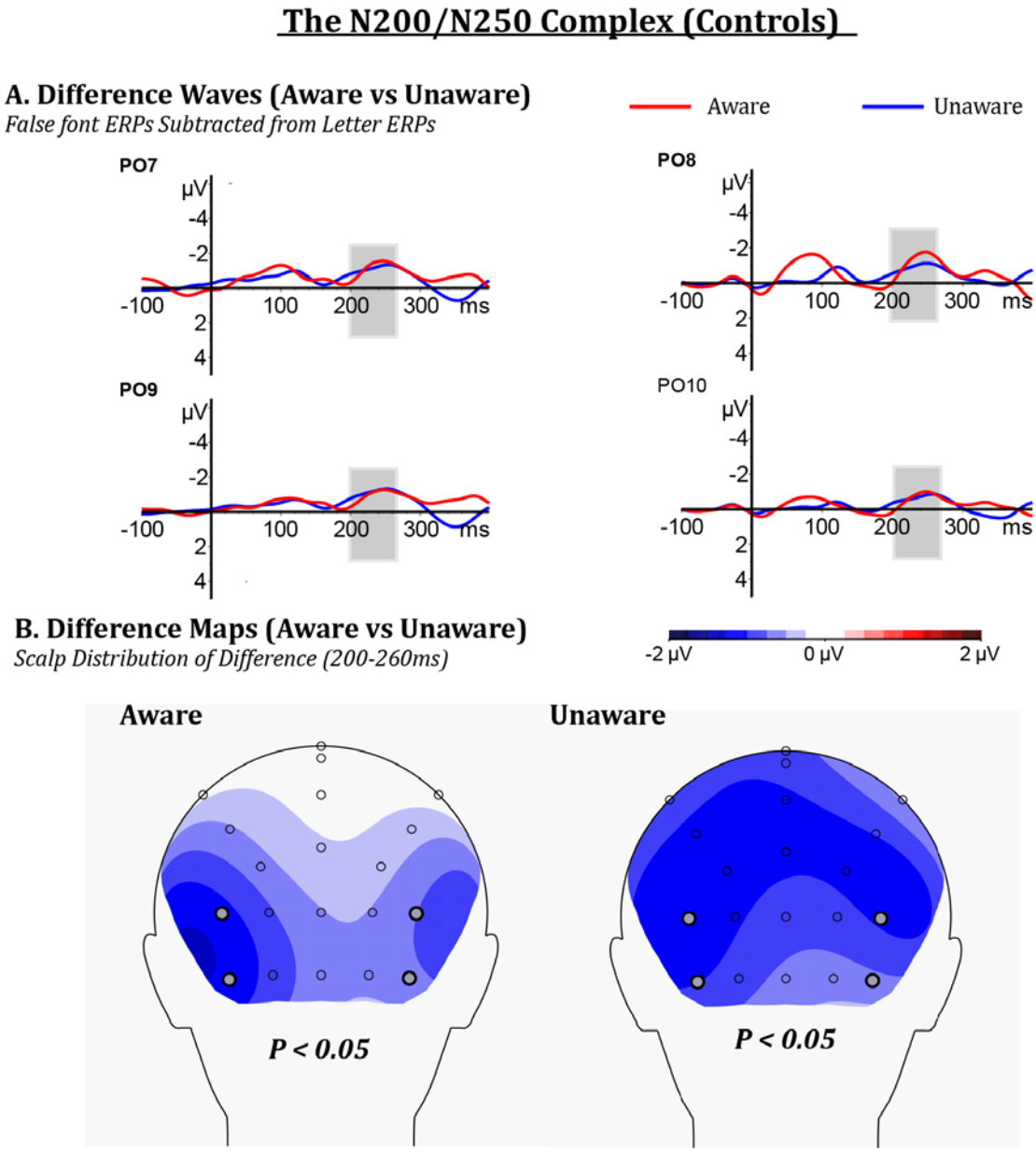


Figure 3.10 N200/N250 Difference Waves & Maps (Controls)

(A) Difference waves created by subtracting the amplitude of the ERPs to false fonts from the amplitude of the ERPs to letters at every time point. The difference from 200ms to 250ms after stimulus onset was significantly greater than zero for both aware and unaware trials. **(B)** Difference maps showing the mean amplitude difference averaged across the 200ms-250ms time window for aware (left) and unaware (right) trials. Electrodes used in data analysis are bold and highlighted in gray.

3.2.3 The Incongruence Negativity

ERPs were time-locked to the color patch presented after the rapid serial visual stream (congruent or incongruent with the synesthetic color of the letter in the stream). The results of the following analyses are shown in figures 3.11 to 3.14 for synesthetes (see Appendix B for these results for controls). Mean amplitude differences between waveforms elicited by congruent vs incongruent color patches from 210ms to 310ms were submitted to a five-way mixed model ANOVA with four within-Ss variables: Session(2), Electrode (6, F3, Fz, F4, FC3, FCz, FC4), Stimuli (letter/false font), and Awareness (yes/no), and one between-Ss variable: Group (synesthetes/ controls).This analysis revealed no main effect of Group ($F(1,16) = 2.62$, ns), Session ($F(1,16) = 1.40$, ns), Electrode ($F(5,80) = 0.32$, ns), Awareness ($F(1,16) = 0.35$, ns), or Stimuli ($F(1,16) = 0.51$, ns). There were two significant interactions observed: one between Group and Stimuli ($F(1,16) = 9.68$, $p < 0.01$) and another between Group, Stimuli, and Awareness ($F(1,683) = 11.55$, $p < 0.001$).

A series of paired t-tests (collapsed across session and electrode) were used to examine the Group X Stimuli X Awareness interaction, revealing that the mean amplitude difference in synesthetes for aware-letter trials (M=-0.70µV, SD=0.23) was significantly greater than for unaware-letter trials (M=-1.69µV, SD=0.78; $t(8) = 2.48$, $p < 0.05$), aware-false font trials (M=0.08µV, SD=0.31; $t(8) = -2.42$, $p < 0.05$), and unaware false font trials (M=0.16µV, SD=0.50; $t(8) = -2.54$, $p < 0.05$). There were no significant differences found between aware and unaware false font trials in synesthetes ($t(8) = -0.12$, ns). For control participants, t-tests revealed no significant differences between aware-letter, unaware-letter, aware-false font, and unaware-false font trials.

Single-sample t-tests were used to determine for which conditions (aware and unaware) and which stimulus types (letters and false fonts) the mean amplitude difference was significantly above zero in each group (Synesthetes and Controls). These t-tests revealed that in synesthetes, the mean amplitude difference for aware-letter trials was significantly greater than zero ($t(8) = -3.00$, $p < 0.05$). This difference was not significant in synesthetes for unaware-letter trials ($t(8) = -2.18$, ns), aware-false font trials ($t(8) = 0.27$, ns), or for unaware-false font trials ($t(8) = 0.33$, ns). Furthermore, this difference

was not significant in control participants for aware-letter trials (t(8) = 1.25, ns), unaware-letter trials (t(8) = 0.82, ns), aware-false font trials (t(8) = -1.26, ns), or for unaware-false font trials (t(8) = -0.92, ns).

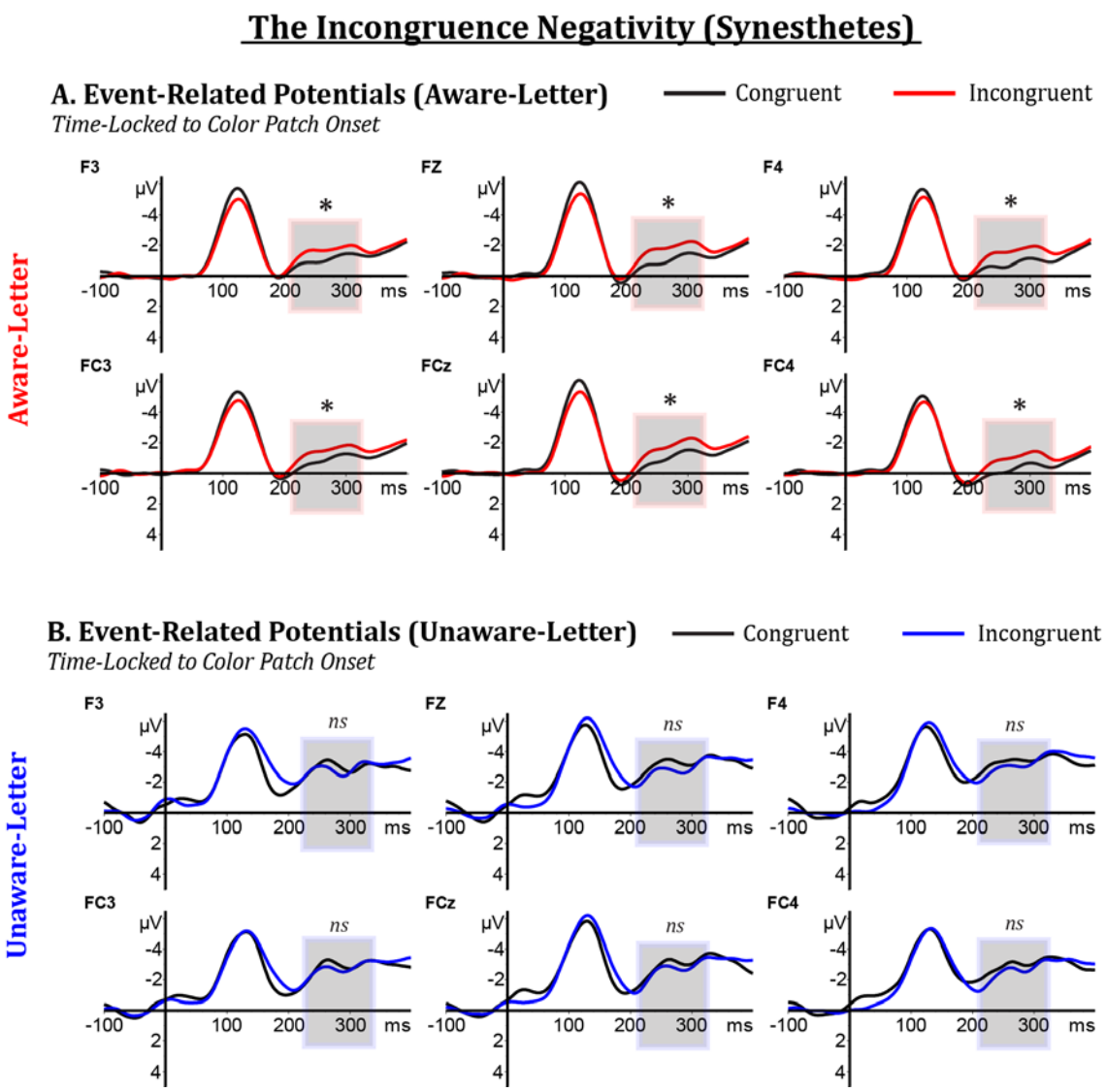


Figure 3.11 IN Event-Related Potentials (Letter Trials, Synesthetes)

Event-related potentials time-locked to the onset of the color patch (congruent or incongruent) when participants correctly identified T2 **(A)** and when they were unable to correctly identify T2 **(B)** at six frontal scalp electrodes (F3, Fz, F4, FC3, FCz, FC4). Mean amplitude from 210ms to 310ms after stimulus onset was compared between congruent and incongruent color patches for aware and unaware trials. Stars denote a statistically significant difference in that time window, $p < 0.05$.

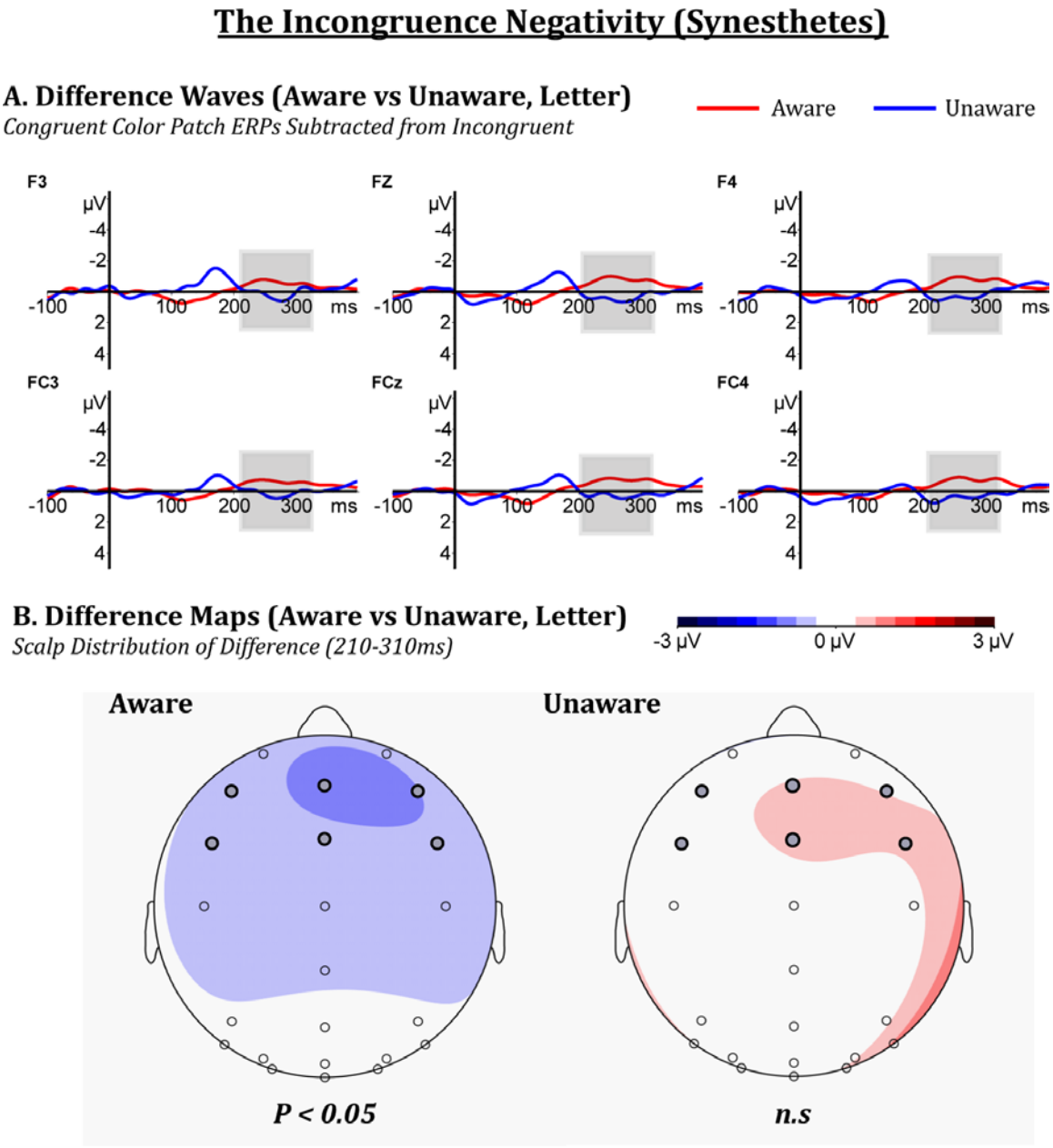


Figure 3.12 IN Difference Waves & Maps (Letter Trials, Synesthetes)

(A) Difference waves created by subtracting the amplitude of the ERPs to congruent color patches from the amplitude of the ERPs to incongruent color patches at every time point. The difference from 210ms to 310ms after stimulus onset was significantly greater than zero for trials in which T2 was seen, but not for trials in which T2 was unseen. **(B)** Difference maps showing the mean amplitude difference averaged across the 210ms-310ms time window for aware (left) and unaware (right) trials. Electrodes used in data analysis are bold and highlighted in gray.

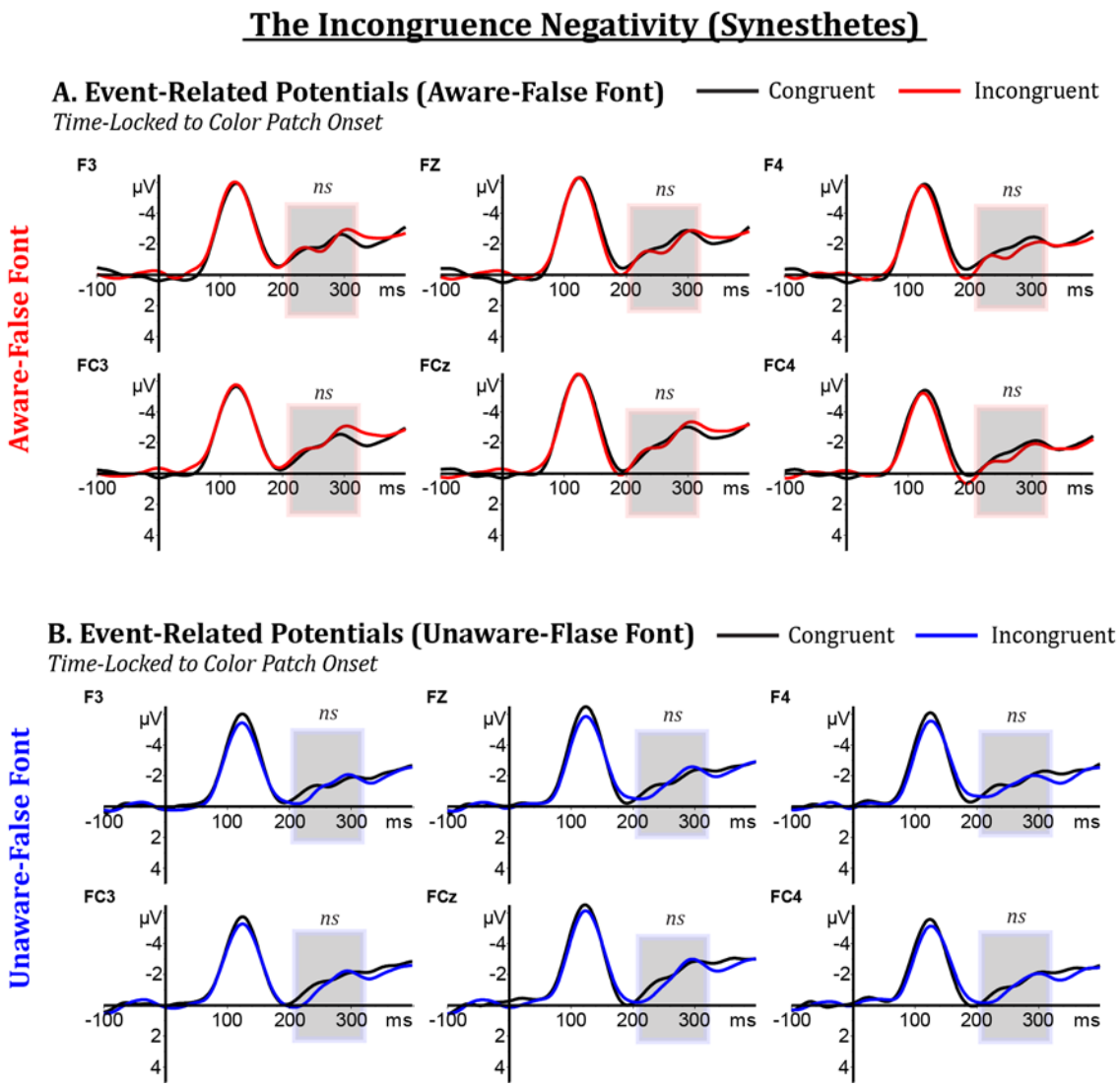


Figure 3.13 IN Event-Related Potentials (False Font Trials, Synesthetes)

Event-related potentials time-locked to the onset of the color patch (congruent or incongruent) when participants correctly identified T2 **(A)** and when they were unable to correctly identify T2 **(B)** at six frontal scalp electrodes (F3, Fz, F4, FC3, FCz, FC4). Mean amplitude from 210ms to 310ms after stimulus onset was compared between congruent and incongruent color patches for aware and unaware trials.

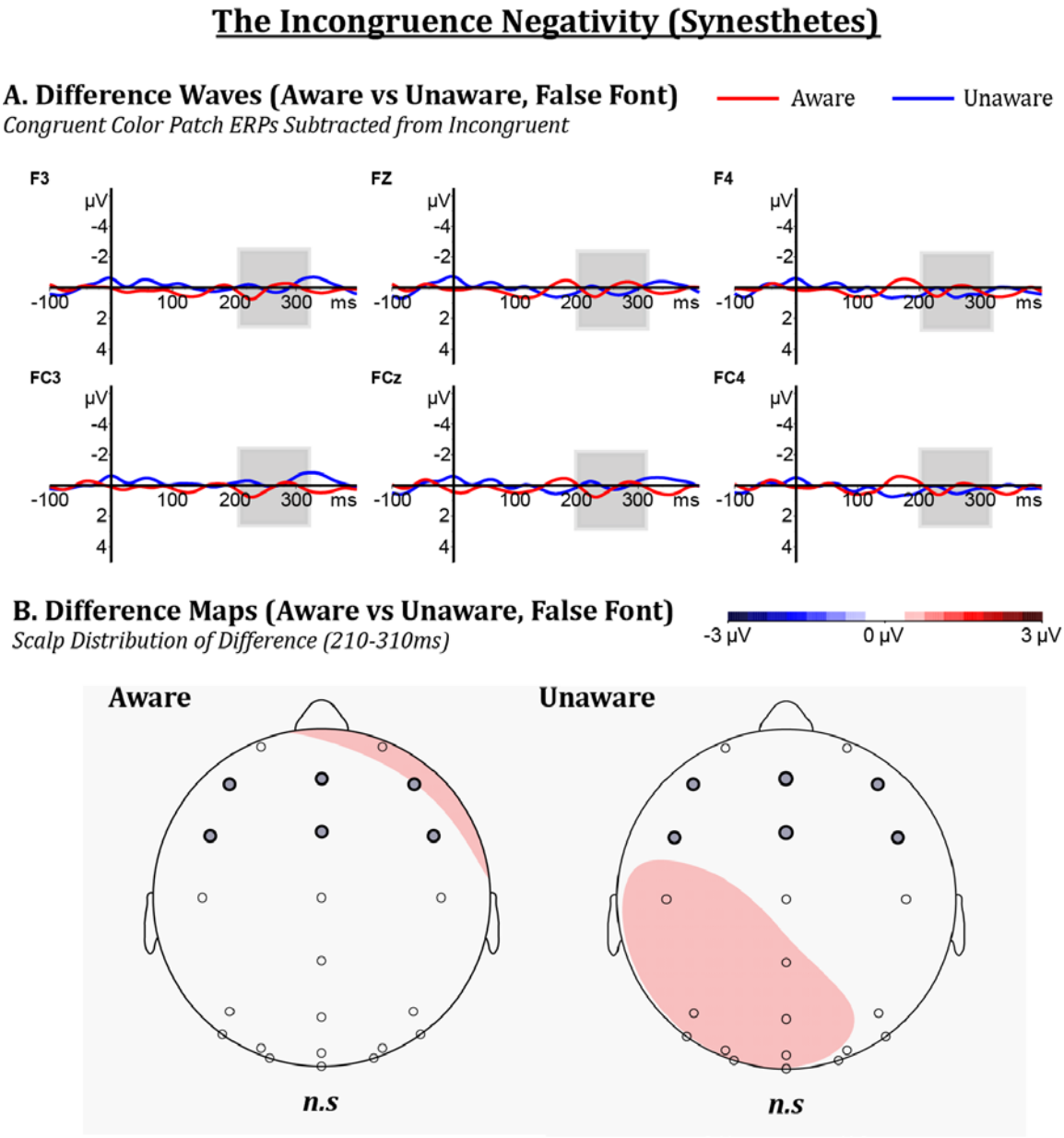


Figure 3.14 IN Difference Waves & Maps (False Font Trials, Synesthetes)

(A) Difference waves created by subtracting the amplitude of the ERPs to congruent color patches from the amplitude of the ERPs to incongruent color patches at every time point. The difference from 210ms to 310ms after stimulus onset was significantly greater than zero for trials in which T2 was seen, but not for trials in which T2 was unseen. **(B)** Difference maps showing the mean amplitude difference averaged across the 210ms-310ms time window for aware (left) and unaware (right) trials. Electrodes used in data analysis are bold and highlighted in gray.

Chapter 4: Discussion

4.1 Early Visual Processing and Synesthetic Color

4.1.1 Summary of Results

Event-related potentials (ERPs) were recorded to letters and false-fonts in associator-type grapheme-color synesthetes and matched controls in order to investigate the timing of neural events directly related to synesthetic perception. By comparing ERPs time-locked to letters and ERPs time locked to false fonts, we isolated a neural correlate of synesthetic color perception. This was an increased positivity for letters from 170 to 230ms after stimulus onset at fronto-central scalp electrode sites.

We can be relatively sure that this difference is strictly related to synesthetic color perception because it was completely absent in controls matched for stimuli, age, and biological sex. If this effect were reflecting the physical differences between letters and false fonts, it would be present in both groups.

Interestingly, an ERP effect with the same polarity, timing, and scalp distribution has previously been found when comparing colored stimuli to achromatic stimuli (Schoenfeld et al. 2003; Zinni et al. 2014; Pitts, Metzler, & Hillyard, 2014). Consequently, these researchers termed this ERP difference “The Sensory Effect of Color”. The first study to observe this effect (Figure 4.1) conveniently used EEG and MEG with fMRI, such that the neuronal source of this effect could be identified. They report its source to be in the ventral occipital cortex, the region containing V4. Taken together, these results suggest that the ERP difference in this study reflects color processing in V4, despite the fact that the stimuli were achromatic. They also suggest that synesthetic color processing and typical color processing appear to be fairly analogous in the brain.

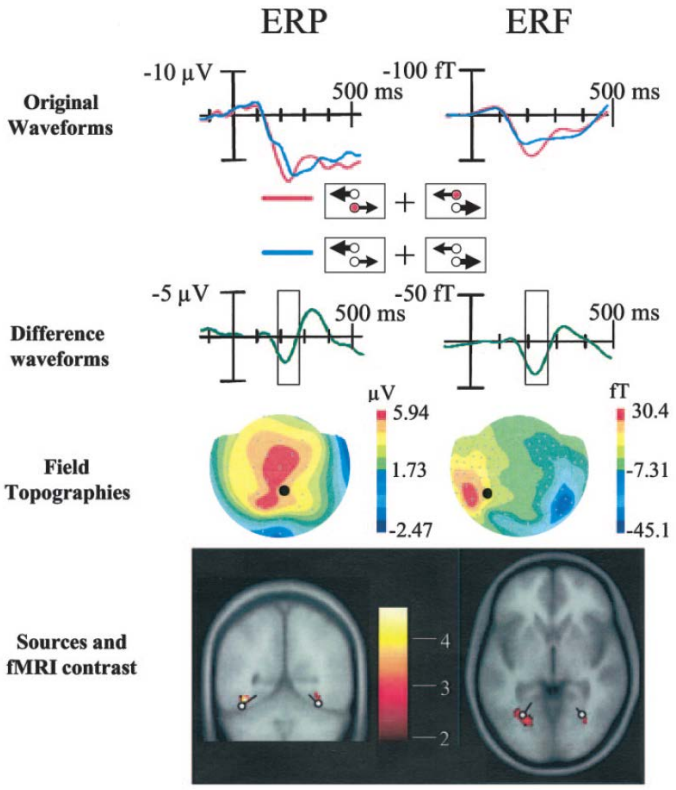


Figure 4.1 Results from Schoenfeld et al. 2003

The first study to identify the SEC, reported in 2003. This positive difference was observed at fronto-central scalp electrode sites for stimuli that were colored vs ones that were achromatic.

4.1.2 Models of Connectivity Revisited

The timing of this effect (170ms after stimulus onset) is relatively early in visual processing, and the source analysis from Schoenfeld et al (2003) suggests that this effect is generated in V4. Taken together, the timing and source of this effect suggest that it could be reflecting postsynaptic potentials at the dendritic inputs in V4 from connections with the VWFA in synesthetes. Overall, this points to the use of direct connectivity between the VWFA and V4 in associator-type synesthetic color perception, supporting the cross-activation model (1.2.5). This finding is in line with some ERP studies of grapheme-color synesthesia (Sagiv et al. 2003; Kadosh et al. 2007; Barnet et al. 2008) but contradicts others (Schiltz et al. 1992; Gebuis et al. 2009)- see section 4.4 for more discussion on this.

This finding can also be interpreted as providing some evidence for the re-entrant processing model, since it does predict the involvement of early direct connections. However, this model also argues for the involvement of slower, indirect connections being active in synesthetic color processing, and we found no evidence of slower neuronal events differing between letters and false fonts specifically for synesthetes.

Nevertheless, it could be the case that later effects were masked by the stimuli being presented rapidly in succession. After all, this effect was found 170ms after T2 was presented, and in our study a gray distractor false font was presented 100ms after T2. Neuronal events related to these distractors should have been subtracted out when comparing letters and false fonts, but it would still be important to replicate this experiment outside the attentional blink paradigm. Perhaps later neuronal events related to indirect connectivity would also be identified in such an experiment.

4.1.3 Individual Differences in Neuronal Correlates

A neural correlate of synesthetic color perception was isolated in the early visual processing stages of nine associator synesthetes[20]. How would these findings differ for projectors? One might predict that this effect would occur even earlier in time, given that synesthetic color perception of projectors seems to occur at a lower level of stimulus processing than it does for associators. Alternatively, it could be the case that the timing of this effect would not differ between projectors and associators, given that it is already being observed in early visual processing. Rather, this difference could be greater in amplitude in projectors, reflecting greater activation of V4 via direct connections, which could be causing the difference in phenotype. Lastly, one might also suppose that the perception of synesthetic color 'externally' (as in projectors) might be the result of feedback from other areas. If this were the case, we might even expect both the early difference observed for associators and a later difference reflecting this feedback- which would suggest that the re-entrant processing model is more suited to projector synesthetes.

[20] Remember, associators report internal synesthetic color perception (in their "mind's eye"), whereas projectors report external synesthetic color perception (physically seeing the colors in space).

4.2 Attention is Necessary for Synesthetic Perception

4.2.1 Summary of Results

Event-related potentials (ERPs) were recorded to stimuli inducing synesthetic color perception that were rendered invisible by a manipulation of attention. Attention was successfully manipulated using the attentional blink paradigm, such that participants were unable to successfully identify T2 on 32% of letter trials and 37% of false font trials in which T1 was correctly identified. When comparing ERPs to letters and false fonts correctly identified, a positive difference reflecting synesthetic color perception in early visual processing was isolated (4.1). When making this same comparison between trials in which letters and false fonts were not correctly identified, this effect disappeared. These results support the view that attention is necessary for synesthetic color perception, in line with the studies carried out by Mattingly et al. (2001, 2006; Rich et al. 2003, 2010) which utilized the synesthetic congruency effect. Note that these findings also have important implications for the neural mechanisms underlying synesthesia (this is discussed further in section 4.4).

4.2.2 Feature-Based Attention

These findings appear to contradict several studies claiming to find evidence of synesthetic color perception in the absence of attention (Ramachandran & Hubbard 2001a; Palmeri et al. 2002). These studies show synesthetic perception without attention by way of the visual search paradigm. They find that synesthetes are significantly faster at locating a target letter in an array of visually similar distractors (recall Figure 1.8) because the synesthetic colors cause the target to “pop out” and capture their attention. Thus, these authors conclude that attention is *not* necessary for synesthetic color perception, as this demonstrates attention being captured by the synesthetic color.

For many years, attentional models have argued that spatial selection is an inevitable prerequisite for the processing of feature information (Treisman & Gelade 1980; Hillyard & Anllo-Vento 1998; Cave & Bichot 1999). However, it has also been demonstrated that individual features like shape, color, or motion can guide spatial

attention to potential targets (Wolfe et al 1989, Wolfe 1994, Cave & Bichot 1999, Wolfe & Horowitz 2004). Imagine you are trying to locate a friend in crowd. It would be inefficient to spatially attend to every person and identify if they are the person you're looking for. Rather, it makes much more sense to consider the individual features of your target (red hair, blue sweater, etc.) and scan the crowd for that feature, then focus your spatial attention on any individuals matching the features you're looking for. This illustrates how one can attend to specific features of objects in an array without spatially attending to a specific member of that array. Although there is much less research on feature based attention than spatial attention, there are a fair number of neuroimaging studies showing that the two types of attention operate via distinct neural mechanisms- both spatially and temporally (see Schoenfeld & Stoppel 2014).

Thus, it is likely the case that these studies using visual search mentioned above, do not demonstrate synesthetic perception in the absence of attention- as participants are likely attending to the features of the members of the array at a global level. This feature based attention then automatically triggers synesthetic color perception, which in turn guides spatial attention to the target. Consequently, grapheme-color synesthetes would still have an advantage over non-synesthetes in this task, but not necessarily in the absence of attention.

4.3 Unconscious Letter Processing

4.3.1 Summary of Results

Letters and false fonts were presented to participants within the attentional blink. When comparing letter ERPs and false font ERPs, we observed an increased negativity for letters between 200 and 250ms after stimulus onset at bilateral posterior electrodes. We refer to this effect as the N200/N250 complex. This difference was found in both synesthetes and controls and in both aware and unaware trials. It could be the case that this difference reflects low level physical differences between the letters and false fonts (i.e. the number of intersections between lines). However, this seems unlikely given that each false font was made directly from the features of its corresponding letter, and the

effect was observed at 200ms post stimulus- long after basic stimulus features have been processed in V1. Rather, we suggest that this effect reflects differences in unconscious processing at a slightly later stage- in the visual word form area.

4.3.2 The Visual Word Form Area

Previous studies have found a very similar ERP difference when comparing words and false fonts (Figure 4.3), except that their effect was slightly earlier in time (140ms after stimulus onset, whereas ours began at 200ms). This difference is likely observed because of the fact that their stimuli were full words / false font strings as opposed to just individual letters and false fonts. Other studies have used fMRI to examine the source of this difference (McCandliss et al. 2003), finding that it can be localized to the region of the fusiform gyrus known as the visual word form area (VWFA). One such fMRI study also assessed how attention and awareness affect this difference by using the backward masking paradigm[21]. Consistent with our results, they showed that the VWFA activity is still present for stimuli that are rendered unaware.

It should also be noted that the ERP and fMRI studies found these differences to be left lateralized and localized in the left fusiform, but our effect was found to be bilateral. Perhaps this points to a difference in word and letter processing, wherein individual letters are processed bilaterally but word processing is left lateralized.

[21] Recall that in the backward masking paradigm, a target stimulus is presented very briefly (i.e. 28ms) and is then immediately followed by second visual stimulus (a ‘mask’) presented for a longer period of time. Consequently, the target stimulus is not consciously perceived.

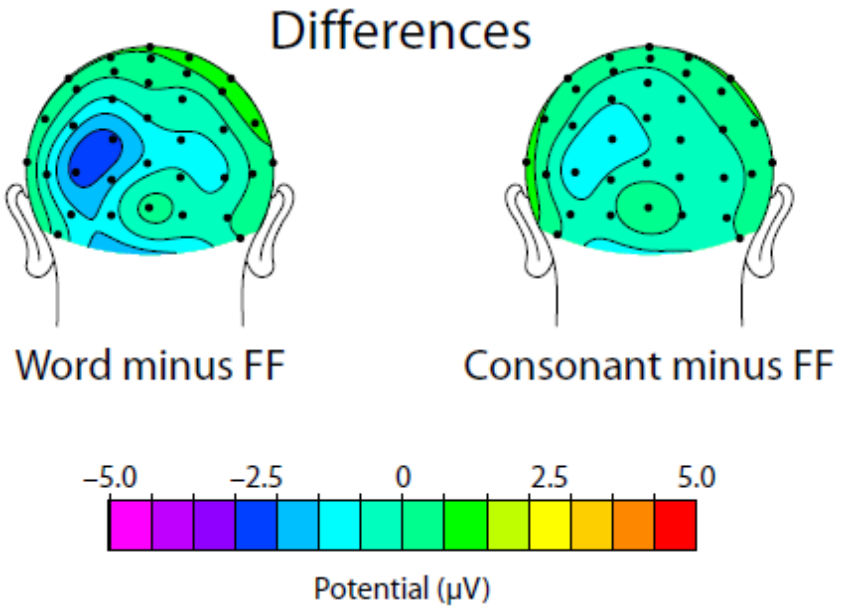


Figure 4.3 Results from Applebaum et al. 2009
Topographic distributions of the mean activity from 130 to 150ms for words minus false font strings (left) and consonant strings minus false font strings (right).

4.4 Attention and Neural Mechanisms

4.4.1 Early versus Late

As discussed in section 4.1.2, the main ERP effect observed here suggests that synesthetic color perception is occurring via direct connections between V4 and regions of the VWFA responsible for grapheme processing- as predicted by the cross-activation model. However, if the neural events underlying synesthetic color perception are occurring via *direct* connections, *early* in visual processing, then wouldn't we expect these effects to be pre-attentive? There has been a great deal of discussion among cognitive neuroscientists and psychologists regarding the "early versus late selection debate", with the evidence ultimately pointing to the fact that attentional mechanisms can be active in feature processing much earlier than we would expect- as soon as 100ms after stimulus onset(Zhang & Luck 2009). These effects of feature attention have been shown in the middle occipital cortex and regions of the posterior fusiform- the region containing V4 (see Schoenfeld & Stoppel 2014 for full review).

It appears that attention is necessary for the activation of these direct connections. At what processing stage is attention causing a change in activity? If neurons from top down attention centers responsible for feature binding (like the superior and inferior parietal lobules) are synapsing with a specific region to modulate activity, there are three possible regions in which this could be happening to influence synesthetic color perception (Figure 4.4). It could be the case that attention is modulating activity in the initial visual processing stages in V1/V2, causing a change in VWFA activity, and therefore causing cross-activation of V4 to occur (4.4a). Alternatively, attention could be modulating the activity of the VWFA itself, such that regions with increased direct connections (like V4 in synesthetes) are stimulated (4.4b). Lastly, it could be the case attention is modulating activity in the posterior fusiform, particularly in V4- such that the same amount of stimulation is reaching V4 from the VWFA in either case, but V4 activity is only influenced by that stimulation when it is being modulated by attention (4.4c).

We can identify which of these possibilities is most likely given the results from this study. If we were to look at an index of VWFA activity in the absence and presence of attention, these proposed mechanisms would have different predictions about what we would observe. Namely, mechanisms (a) and (b) would predict that an index of VWFA activity would be changed as a result of attention. But recall that the effect reflecting VWFA activity we isolated in this experiment, the N200/N250 complex, did not change when attention was limited by the attentional blink. Therefore, this supports mechanism (c), which would predict a change in V4 activity as a result of attentional modulation, but no change in VWFA activity. So if neuronal inputs from attention centers are modulating the amount of activity in a specific region to influence synesthetic color perception, they are likely doing so in V4.

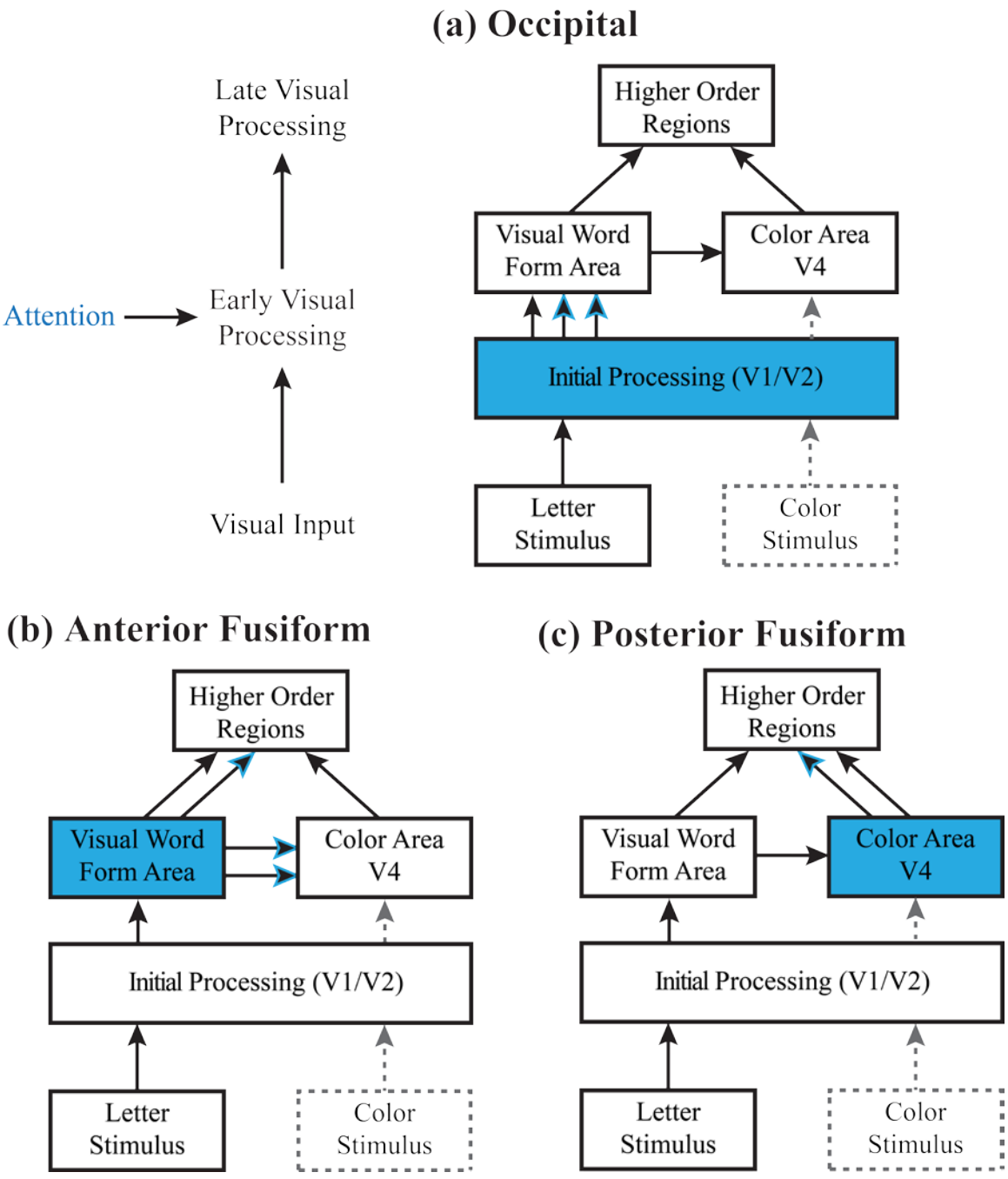


Figure 4.4 Proposals for Attentional Modulation Mechanism

Attentional modulation (blue) may be occurring in the occipito-temporal cortex **(a)**, the anterior fusiform **(b)**, or the posterior fusiform **(c)**, to cause a change in V4 activity.

4.4.2 Attention as a Binding Mechanism

The Binding Problem is a term used in cognitive neuroscience and philosophy of mind. It points out the computational problem of how brains segregate different pieces of information taken from different sensory inputs and allocates them to discrete "objects." Put another way, when looking at a blue square and a yellow circle, what neural mechanisms ensure that the square is perceived as blue and the circle as yellow? One hypothesis addressing how this is achieved is synchronization theory, which suggests that features of individual objects are bound via synchronization of the activity of different neurons (in this case, neurons responsive to color and shape).

So perhaps attention is acting as a binding mechanism to synchronize activity in the VWFA and V4, rather than modulating the amount of activity within V4. If this were the case, activity in each area would be unchanged, but their synchrony in time would be enhanced (Figure 4.5).

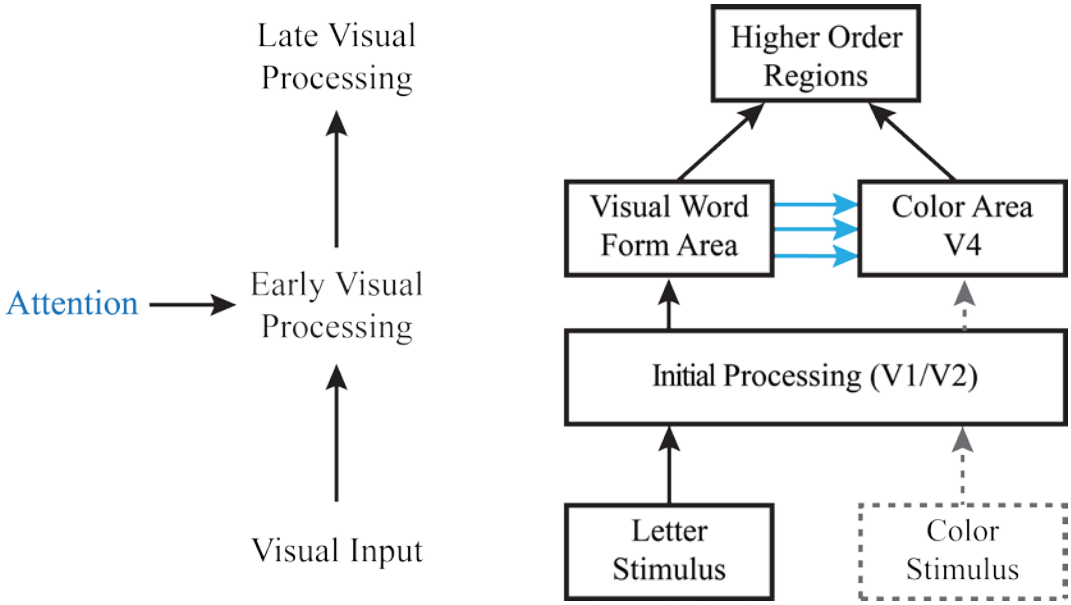


Figure 4.5 Mechanism of Feature Binding

Attentional modulation (blue) may be occurring at the connections between V4 and the VWFA to synchronize activity between them, rather than to influence the amount of activity in V4.

There have been a number of studies that support this theory, finding a relationship between rhythmic synchronous firing and feature binding. However, the findings of research in this area have been largely inconsistent (see Singer 2007 for a full review). That said, the idea of attention binding features by synchronizing their firing, and it is appealing in this case given that the SEC in synesthetes is likely reflecting postsynaptic potentials at inputs to V4 (as discussed in section 4.1.2) rather than activity of neurons within V4 itself. The rhythmic synchronous firing behavior of neuronal populations can be measured using EEG, but these analyses have not yet been performed on the data from this study.

4.5 Effects of Congruence

4.5.1 Summary of Results

By recording ERPs to color patches that were congruent or incongruent with synesthetic colors induced by the preceding letters, we were able to replicate an effect found in previous ERP studies of grapheme-color synesthesia. In our study, this was an increased negativity for incongruent color patches from 210 to 310ms after stimulus onset at frontal electrode sites. We term this difference the incongruence negativity (IN). This effect was only found in synesthetes when letters were presented in the stream, not for trials with false fonts. When the synesthetes were unaware of the letters as a result of the attentional blink, the IN was eliminated. This effect was not observed in controls for letter trials or false font trials, aware or unaware.

A similar effect has been found in previous studies, but the difference we observed began approximately 50-80ms earlier than those previously reported (Brang et al. 2008, 2010, 2011, Niccolai et al. 2012). There are a number of reasons why this might be the case. Firstly, the color patches in our study were completely task-irrelevant, unlike previous studies. Perhaps in previous studies this effect was delayed because the task required that participants use the information given by the color patch, whereas in our study participants merely saw them passively. Though, one could argue that we would

actually predict that task-relevant stimuli would be processed *more* quickly than those that are passively viewed.

Alternatively, maybe the fact that each time the color patch was presented it was following an extremely rapid stream of stimuli (one presented every tenth of a second) can explain this latency difference (forward masking). This is just speculation, but one could see how the rapid stream could prime faster processing of a visual stimulus that follows.

4.5.2 Semantic Processing

As discussed in section 1.2.7, comparing the difference between congruent and incongruent trails is somewhat problematic for isolating neural correlates of synesthetic perception. What process is the IN actually reflecting? It's quite possible that it is reflecting the knowledge that a feature of the preceding letter is semantically congruent or incongruent with the color patch (i.e. red-red vs red-blue). If this was the case, one could train control participants on the associations of the synesthetes and therefore, they should show the same effect, since they would also recognize congruent and incongruent trials. Another way to investigate this question would be to physically color the letters presented to controls, again making the experience more similar between synesthetes and controls, since controls would then also recognize congruent and incongruent trials.

In their 2011 ERP study, Brang et al. used one control group that saw physically colored numbers and another control group that was trained on the color perceptions of synesthetes. They visually presented numbers inducing synesthetic color perception at the ends of sentences, wherein the color perception could be congruent or incongruent with the context of the sentence. For example, they would use sentences like, "Yesterday the sky was a beautiful shade of 5", where the number "5" would induce a contextually congruent (blue) or incongruent (yellow) color perception.

When examining the IN effect (difference between incongruent and congruent trials), it appeared not only in synesthetes, but also in the two control groups. The results from Brang et al. 2011suggest that the IN observed in this study would also be present in controls if they were trained, showing that it is not necessarily reflecting purely synesthetic processing.

However, the results from Brang et al. 2011 may also have implications for the sensory effect of color observed in this study (4.1). When using their different control groups, these researchers found one effect that was present only in their twelve grapheme-color synesthetes: an increased positivity for incongruent graphemes from approximately 150ms to 250ms at frontal electrode sites (FC3 and FC4). Consequently, they conclude that this "P2 effect" likely reflects neural events underlying synesthetic perception (Figure 4.6).

This effect is very similar to the SEC observed here (3.2.1), in both timing and scalp distribution. The difference we observed was an increased positivity for achromatic letters inducing color as compared to false fonts that did not induce color, whereas their difference is an increased positivity for achromatic letters that were incongruent with the context. If we take the SEC to reflect increased activity in V4 (Schoenfled et al 2003), then one could see how interpretations from this study could also be in line with Brang et al's findings. When the induced color is congruent with the semantic context, perhaps the activation of relevant neurons in V4 has already been primed. So, incongruent letters may provoke a greater response in V4, relative to congruent ones. Consequently, they see evidence for increased V4 activity for incongruent trials, just as we do for letter trials.

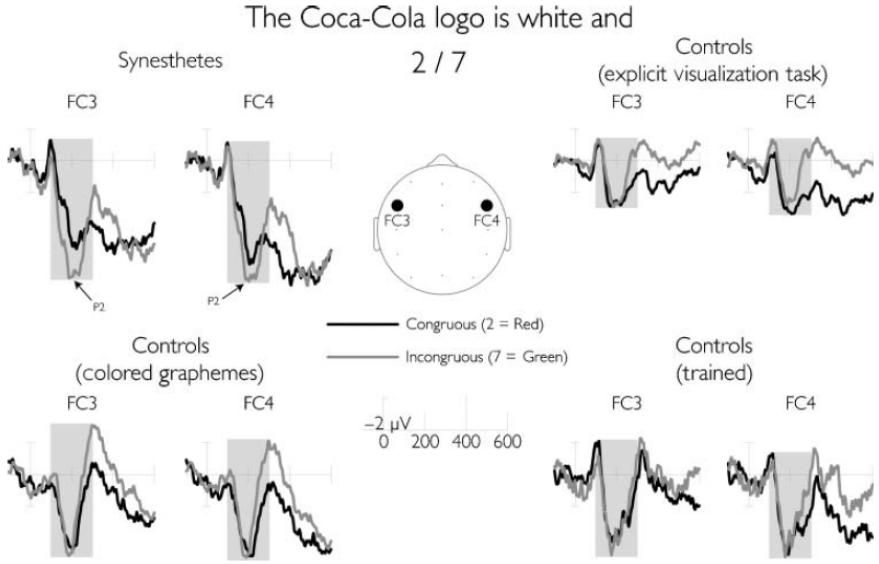


Figure 4.6 Results from Brang et al. 2011

The effect labelled "P2" was only observed in the twelve grapheme-color synesthetes, not in controls trained on the color associations or controls that saw physically colored graphemes. Its scalp distribution and timing suggest it may be related to the SEC.

4.6 Future Directions

Projector Synesthetes

This study should be replicated using projector synesthetes. As outlined in section 4.1.3, there are a number of predictions related to the amplitude and timing of the synesthetic SEC that could shed light on the connectivity differences likely underlying the differences in synesthetic color perception between associators and projectors. It could be the case that the cross-activation model is appropriate for associator synesthetes, but synesthetic color perception in projectors may be better represented by the re-entrant processing model. This study would be fairly easy to carry out, but recruiting a decent sample of projector synesthetes would be difficult.

Relative Strength

In the current study, we recorded the strength and consistency of each synesthete's individual letter and number associations using a 4-point scale (Appendix C). Only letters that elicited strong and consistent associations were used as targets, so as to ensure they would elicit color perception. In addition to being a good way to control for inter-subject differences in synesthetic associations, this also provides a unique opportunity to investigate the synesthetic SEC even further. This study could be replicated using three different types of letters: those with no color association, a weak color association, and a strong color association. If the effect isolated here does indeed reflect synesthetic color perception, then we would predict that letters reported as eliciting little to no color would also show little to no ERP difference from false fonts, and those eliciting weak associations might show ERP differences of intermediate magnitude to those eliciting strong associations.

One-Back Task

As discussed in section 4.2.3, one potential limitation of this study is that the letters and false fonts were presented within a stream of rapidly presented stimuli- so

other neural correlates of synesthetic color perception (perhaps any later ones) could have been masked. An easy follow up would be to present the letters and false fonts in a more traditional manner, while EEG is recorded so as to control for this limitation. Additionally, matched-control participants could be trained on the synesthetic color associations of the synesthetes or they could be shown physically colored letters (like in Brang et al. 2011) as discussed in section 4.4.2. For example, letters and false fonts could be presented in a simple one-back task (Figure 4.7).

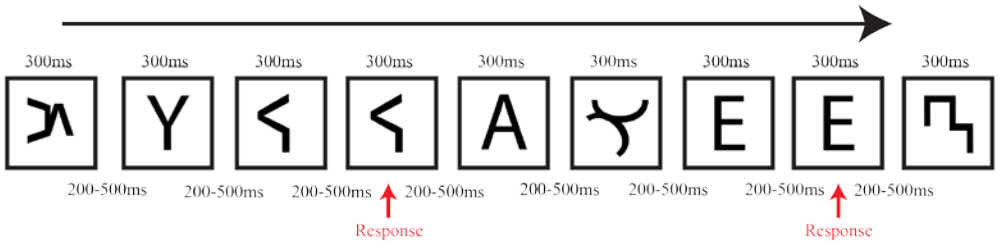


Figure 4.7 One-back Task Example

In a one-back task, participants attend to a series of stimuli (each presented for 300msec in this example) and respond (red arrows) whenever a stimulus is immediately repeated. ERPs to letters and false fonts would then be compared in synesthetes and matched-controls.

Attentional Scope

The current study demonstrated that synesthetic color perception is influenced by attention. An interesting follow-up study might further investigate the relationship between the synesthetic SEC and attention by manipulating attentional scope. A previous behavioral study using Navon figures (a large letter “A” made up of several small “B”s) with grapheme color synesthetes found that the synesthetic color perceived changes depending on whether attention is focused on the local “B” or the global “A.” (Palmeri et al. 2002). In this study, participants would be presented with Navon figures made up of letters and false fonts (Figure 4.8) in a one-back task while EEG was recorded. In one block of trials, participants would be asked to attend to the little letters and false fonts (local features) for the one-back task, and in the other block of trials they would be asked to attend to the big letters and false fonts (global features).

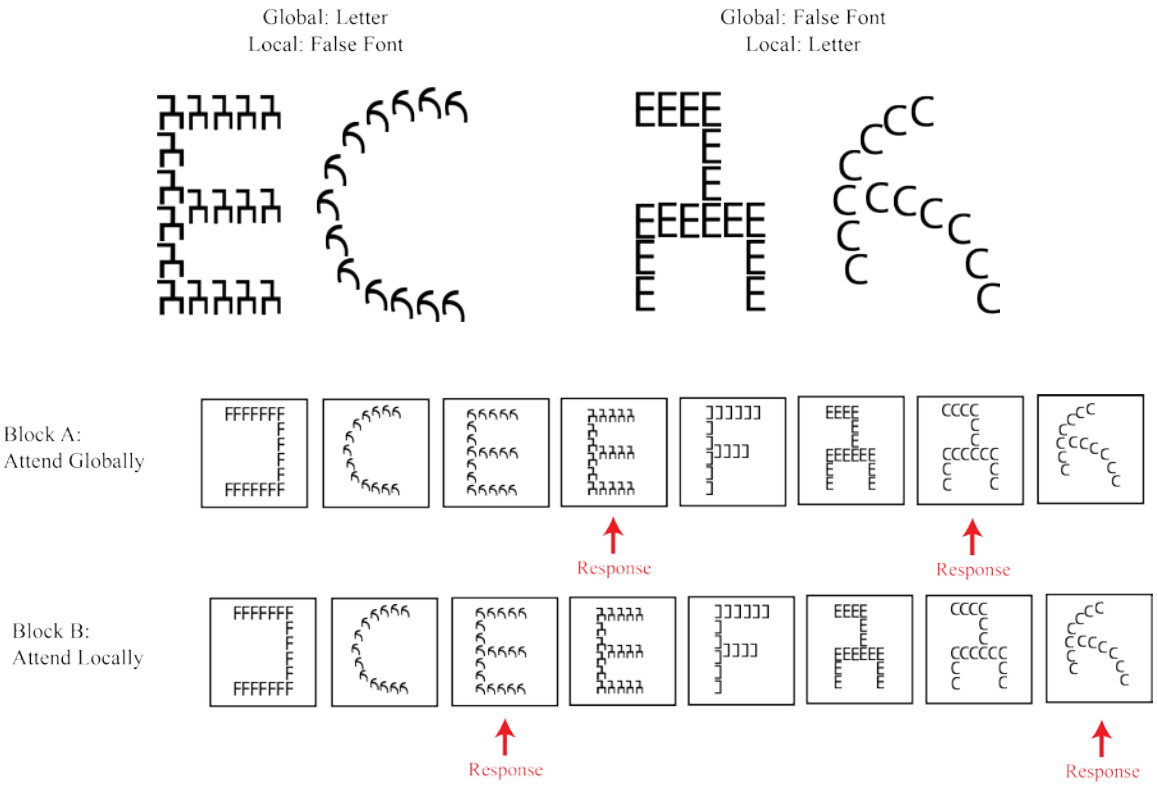


Figure 4.8 Attend Local vs Global Feature

Stimuli that should elicit color perception when attended globally but not locally (Top Left) and when attended locally but not globally (Top Right). In this design, participants would attend to either the global shape or local shape for the one-back task, responding when a letter or false font is repeated.

We would expect to see the synesthetic SEC when comparing ERPs when participants were attending to the letter (locally or globally) with ERPs when participants were attending to the false font (locally or globally). This would allow us to compare ERPs to the exact same stimuli overall, but comparing synesthetic color perception as elicited by attention. Because the stimuli would be physically identical between conditions, this should control for the concerns raised in 4.1.1.

4.7 Conclusion

ERPs to letters inducing synesthetic color and false fonts made from the same physical elements were presented to grapheme-color synesthetes and matched-controls in order to isolate a neural correlate of synesthetic perception. This effect was observed early in visual processing (170ms). Therefore, these results suggest that synesthetic color perception in associator synesthetes is the result of direct connectivity between the regions of the visual word form area responsible for processing graphemes and the V4 color area, as predicted by the cross-activation model. Additionally, ERP recording was combined with the attentional blink paradigm in order to determine whether attention is necessary for synesthetic perception. We found that in the absence of attention, the neural correlate of synesthetic perception was eliminated.

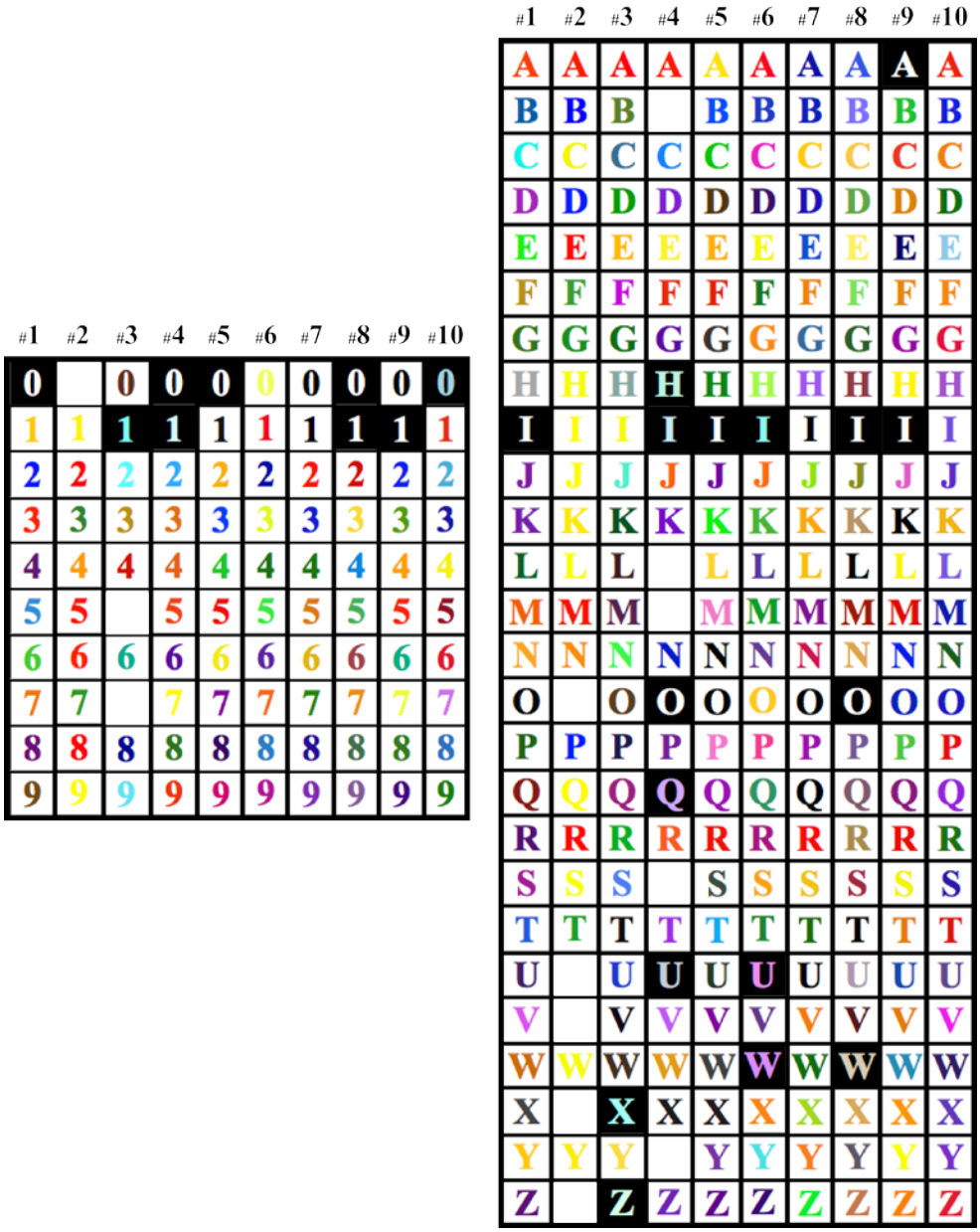
Taken together, these results suggest that synesthetic color perception in associators is the result of stimulation of V4 via direct connections from the VWFA, but V4 neurons are only competent to this signal when attentional resources are available. This could be the result of attentional mechanisms modulating activity within V4, or influencing synchrony between the two areas. Overall, these findings support previous behavioral research and provide some much-needed evidence for the underlying neural mechanisms of grapheme-color synesthesia.

Appendix A: List of Famous Synesthetes

Here are the names of well-known individuals who have explicitly stated they have some type of synesthesia, or for whom there is much evidence to suggest it:

Tori Amos
Rollo Armstrong
Steve Aylett
Amy Beach
Leonard Bernstein
Eugen Bleuler
Mary J. Blige
Sir Robert Cailliau
Stephanie Carswell
Antoine d'Abbadie
Marina Diamandis
Duke Ellington
Sam Endicott
Richard Feynman
Michel Gagné
Hélène Grimaud
Neil Harbisson
Robyn Hitchcock
David Hockney
Billy Joel
Elvin Jones
Kilford
Brooks Kerr
György Ligeti
Franz Liszt
Marian McPartland
Trash McSweeney
Olivier Messiaen
Marilyn Monroe
Stephanie Morgenstern
Vladimir Nabokov
Karl Robert Osten-Sacken
Itzhak Perlman
Joachim Raff
Nikolai Rimsky-Korsakov
Geoffrey Rush
Solomon Shereshevskii
Jean Sibelius
Ida Maria Børli Sivertsen
Patrick Stump
Daniel Tammet
Avey Tare
Sabriye Tenberken
Michael Torke
Vincent Van Gogh
Eddie Van Halen
Pharrell Williams
Stevie Wonder
Kanye West
Charli XC

Appendix B: Individual Color Associations



Appendix B. Individual Color Associations

Each column represents the associations for one synesthete. Empty boxes correspond to a participant reporting “no association” for that number or letter.

Appendix C: Association Strength & Consistency

Strength:

0- No association with this symbol
1- Weak association, I only vaguely see the color
2- Average association, I see the color somewhat clearly
3- Strong association, I see the color very clearly

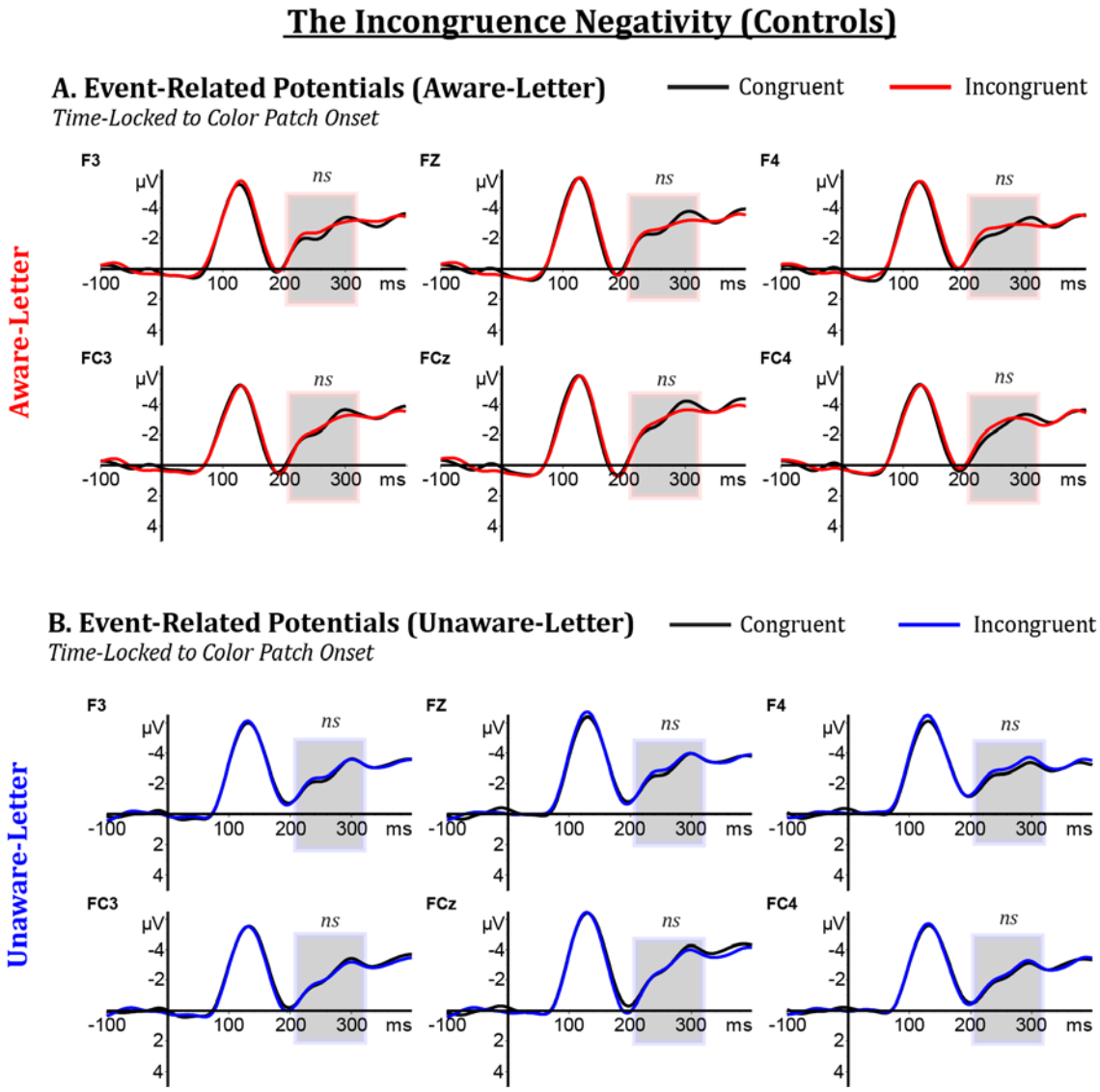
Consistency:

0- No association with this symbol
1- The color of this symbol **often** changes as a result of the context (i.e. other letters/numbers surrounding it)
2- The color of this symbol **sometimes** changes as a result of the context (i.e. other letters/numbers surrounding it)
3- The color of this symbol **never** (or almost never) changes as a result of the context (i.e. other letters/numbers surrounding it)

Appendix C Synesthetic Association Ratings

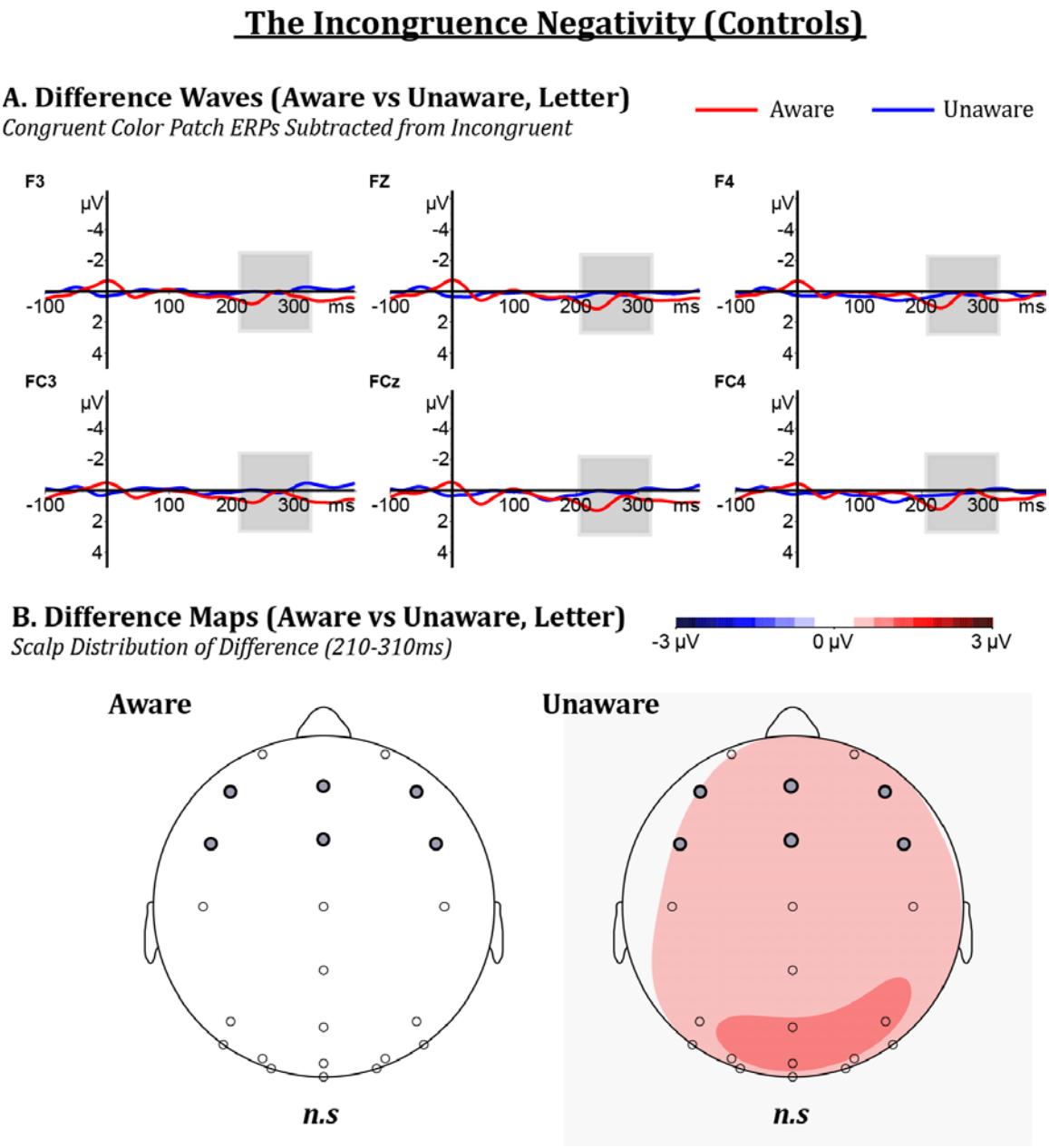
Rating options for strength and consistency of a synesthetic association for letters, numbers, and false fonts. Participants viewed the stimuli and reported their associations/ratings on a computerized survey. Note that the term “see” referred to either seeing the color in the mind’s eye or to physically seeing the color in space.

Appendix D: I.N. for Controls



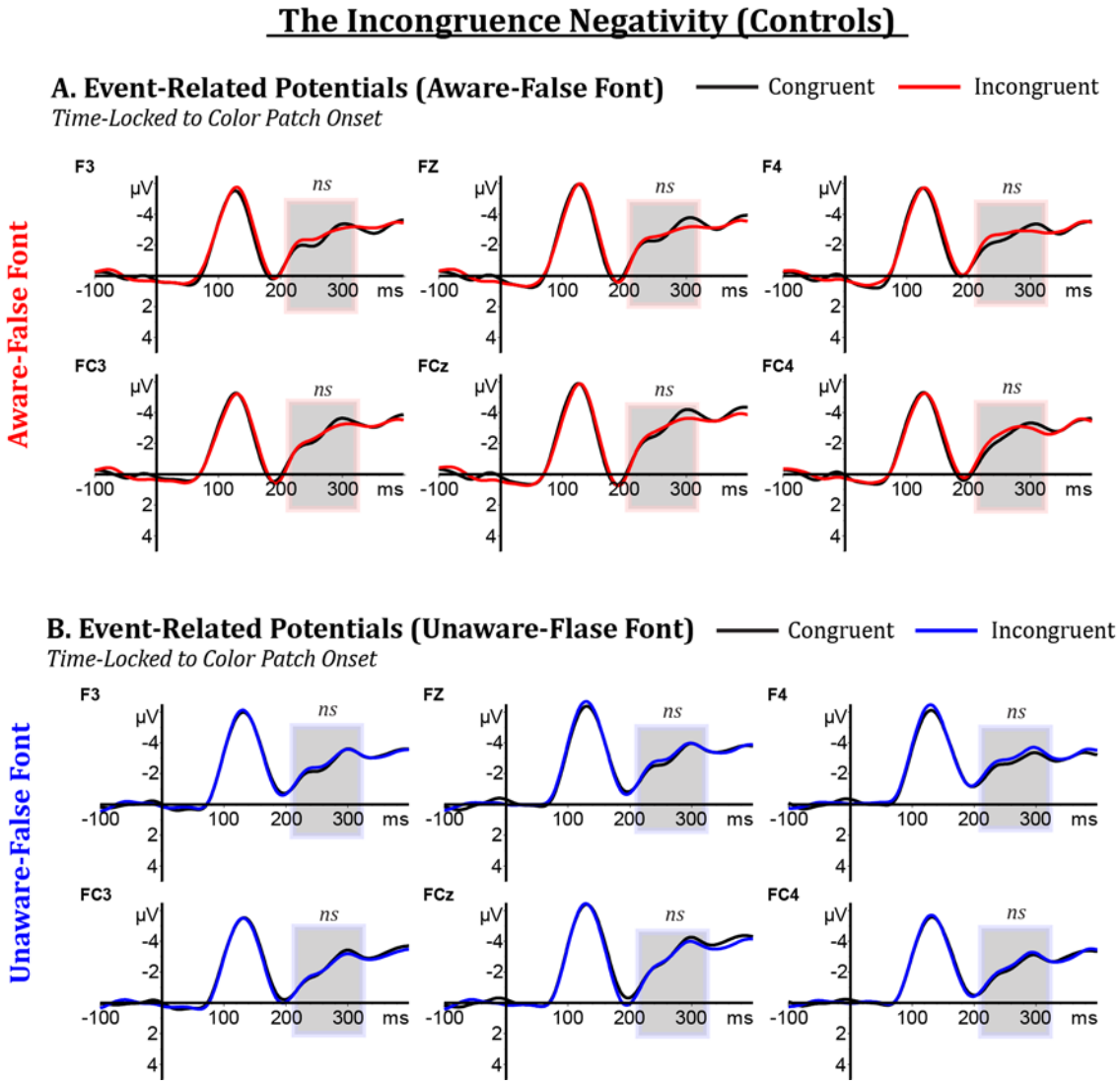
Appendix D.1 IN Event-Related Potentials (Letter Trials, Controls)

Event-related potentials time-locked to the onset of the color patch (congruent or incongruent) when participants correctly identified T2 **(A)** and when they were unable to correctly identify T2 **(B)** at six frontal scalp electrodes (F3, Fz, F4, FC3, FCz, FC4). Mean amplitude from 210ms to 310ms after stimulus onset was compared between congruent and incongruent color patches for aware and unaware trials.



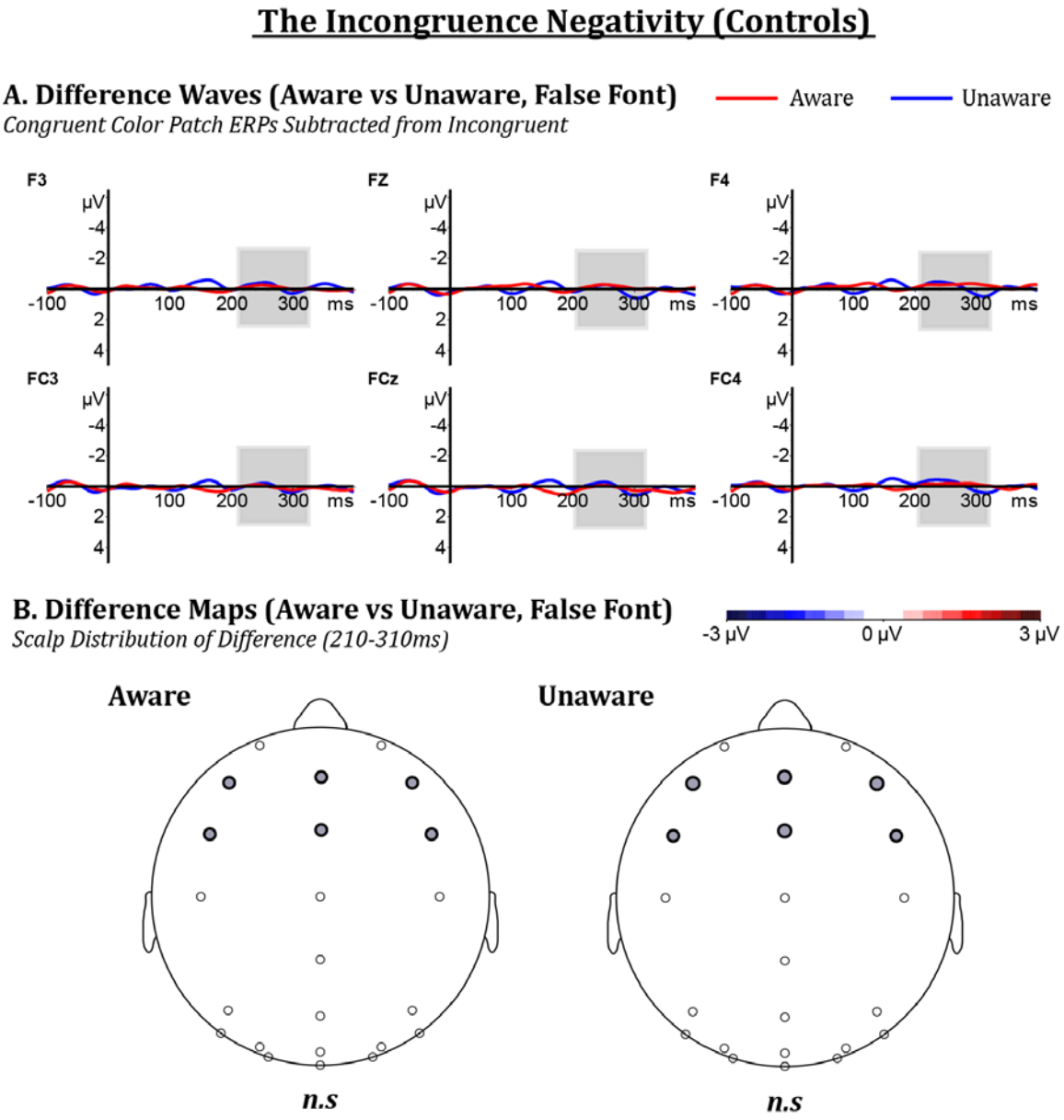
Appendix D.2 IN Difference Waves & Maps (Letter Trials, Controls)

(A) Difference waves created by subtracting the amplitude of the ERPs to congruent color patches from the amplitude of the ERPs to incongruent color patches at every time point. The difference from 210ms to 310ms after stimulus onset was not significantly different zero for trials in which T2 was seen or unseen. **(B)** Difference maps showing the mean amplitude difference averaged across the 210ms-310ms time window for aware (left) and unaware (right) trials. Electrodes used in data analysis are bold and highlighted in gray.



Appendix D.3 IN Event-Related Potentials (False Font Trials, Controls)

Event-related potentials time-locked to the onset of the color patch (congruent or incongruent) when participants correctly identified T2 **(A)** and when they were unable to correctly identify T2 **(B)** at six frontal scalp electrodes (F3, Fz, F4, FC3, FCz, FC4). Mean amplitude from 210ms to 310ms after stimulus onset was compared between congruent and incongruent color patches for aware and unaware trials.



Appendix D.4 IN Difference Waves & Maps (False Font Trials, Controls)

(A) Difference waves created by subtracting the amplitude of the ERPs to congruent color patches from the amplitude of the ERPs to incongruent color patches at every time point. The difference from 210ms to 310ms after stimulus onset not significantly different from zero for trials in which T2 was seen or unseen. **(B)** Difference maps showing the mean amplitude difference averaged across the 210ms-310ms time window for aware (left) and unaware (right) trials. Electrodes used in data analysis are bold and highlighted in gray.

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